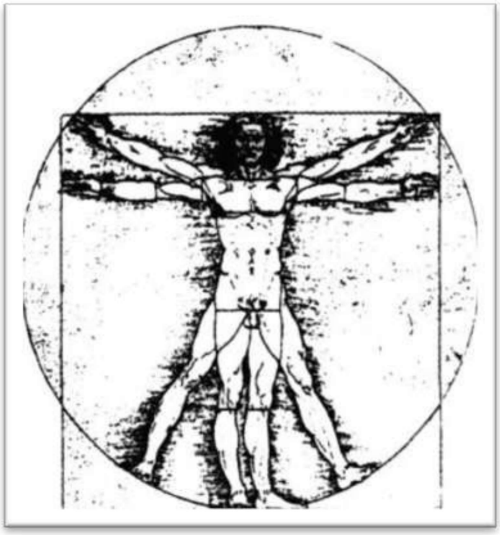
UDC: 61 ISSN 1409-9837

ЗАММ



МААМ

ACTA MORPHOLOGICA

INTERNATIONAL JOURNAL OF THE MACEDONIAN ASSOCIATION
OF ANATOMISTS AND MORPHOLOGISTS

Vol. 17 (1) 2020

UDC: 618.14-006-073.432.19-032:611.671]:618.173

ORIGINAL ARTICLE

ENDOMETRIAL THICKNESS ASSESSED BY TRANSVAGINAL ULTRASOUND AS A PREDICTOR OF THE RISK OF ENDOMETRIAL CANCER AND ATYPICAL ENDOMETRIAL HYPERPLASIA IN ASYMPTOMATIC POSTMENOPAUSAL PATIENTS

Tanturovski Mile[1], Jovanovska Viktorija[1], Stojovski Marjan[1], Tanturovski Dragan[1], Stojchevski Sasho[1], Aluloski Igor[1], Zafirova-Ivanovska Beti[2]

[1]Department for Gynecologic Oncology, University clinic of Gynecology and Obstetrics, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia;

[2]Institute of Epidemiology, Biostatistics and Medical informatics, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia

ABSTRACT

Introduction: Endometrial cancer (EC) is the most common gynecological malignancy in the developed world. It is estimated that 320000 new cases are diagnosed annually, accounting for up to 6% of all newly diagnosed malignant neoplasms. In spite of the associated controversies, transvaginal sonography and measurement of endometrial thickness are well-accepted, standard procedures in many gynecological office visits to date.

Objective: The study aim was to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer and atypical endometrial hyperplasia in asymptomatic postmenopausal patients.

Materials and methods: The databases of the Department of gynecological oncology at the University Clinic of Gynecology and Obstetrics in Skopje, in the period January – December 2015 were searched to identify asymptomatic postmenopausal patients undergoing endometrial sampling due to increased endometrial thickness.

Results: A total of 268 patient records that met the criteria were identified. The prevalence of endometrial cancer and atypical endometrial hyperplasia in the study were 5.2% and 2.2%, respectively. Endometrial thickness was a statistically significant independent predictor of the presence of endometrial cancer and atypical endometrial hyperplasia ($p<0.001$). The ROC curve analysis in our study had an AUC of 0.8 and identified a cut-off level to be ≥10mm which was associated with a sensitivity of 85.7%, specificity of 60.6%, PPV of 10.7% and NPV of 98.7% for the detection of endometrial cancer.

Conclusion: The proposed cut-off of ≥10mm for discriminating between "normal" and "pathological" endometrial thickness is clinically reasonable and of moderate diagnostic value. However, the cut-off value does not achieve the required high sensitivity with clinically acceptable low false positive rates. Nevertheless, transvaginal sonography for measuring endometrial thickness can be used to exclude pre-malignancy or malignancy in asymptomatic postmenopausal women with risk factors because of its low false negative rate.

Keywords: Endometrial cancer, atypical endometrial hyperplasia, endometrial thickness, asymptomatic postmenopausal patients.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world [1, 2]. It is estimated that 320000 new cases are diagnosed annually, accounting for up to 6% of all newly diagnosed malignant neoplasms.

In the Republic of North Macedonia, endometrial cancer is the second most common malignant neoplasm in women (after breast cancer), with an estimated 400 new patients diagnosed annually [1], and a corresponding age-standardized incidence rate of 24.3 per 100000 women.

Postmenopausal bleeding and endometrial thickening in postmenopausal women, assessed by transvaginal ultrasonography (TVUS) are indicative of an endometrial cancer diagnosis [3, 4]. The majority of patients with endometrial cancer present with postmenopausal bleeding and patients with postmenopausal bleeding have a 5-10% chance of having endometrial cancer. Nevertheless, up to 15% of endometrial cancers may manifest in asymptomatic patients [5].

It is well established [6, 7] that patients presenting with postmenopausal bleeding and an endometrial thickness >4mm should undergo further diagnostic evaluation to confirm or exclude endometrial cancer, while patients with endometrial thickness ≤4mm can be reassured without the need for further investigation, as the risk of endometrial cancer in that subgroup is less than 1%. [8]. Consensus is lacking, however, for asymptomatic patients with increased endometrial thickness. This is mostly due to the fact that a universal cut-off value for endometrial thickness that warrants histologic sampling has not been established. A number of studies have used low thresholds (less than 10mm) for endometrial thickness, which provided adequate sensitivity, while simultaneously steeply increasing the number-to-treat needed to diagnose a patient with endometrial cancer [9-12]. Smith-Bindman et al. [13] published data from a theoretical cohort of 10000 postmenopausal women designed to determine an optimal endometrial thickness threshold that should be considered abnormal in the absence of vaginal bleeding. The authors found that the risk of endometrial cancer in patients with postmenopausal bleeding id 7.4% if the endometrium is thicker than 5mm and 0.07% if the endometrium is thinner than the cut-off. A threshold of 11mm yielded the same stratification of endometrial cancer risk in patients in the asymptomatic group; the risk of endometrial cancer was 6.7mm in patients with endometrial thickness > 11mm and 0.002% in patients with endometrial thickness ≤11mm. Furthermore, the authors concluded that using the conventional 4mm cut-off to define an abnormal transvaginal endometrial ultrasonography in asymptomatic patients would increase the number of false-positive results beyond the number of true-positive test results [13]. Jacobs et al. published data of a nested case-control study [14] of a large cohort of patients undergoing transvaginal ultrasonography in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) with a primary endpoint of detecting endometrial cancer and atypical endometrial hyperplasia. The authors demonstrated that endometrial thickness of 10 and 20 mm were associated with a number-to-treat needed to detect endometrial cancer/atypical endometrial hyperplasia (AEH) of 17 and 6, respectively. The authors concluded that the role of population screening for endometrial cancer remains uncertain and that the burden of diagnostic procedures and false-positive results can be reduced by limiting screening to a high-risk group of patients.

In spite of the associated controversies, transvaginal sonography and measurement of endometrial thickness are well-accepted, standard procedures in many gynecological office visits to date [15]. Given that the histological evaluation of asymptomatic patients with endometrial thickness >4mm is relatively common in our institution, we conducted a retrospective analysis to better define the rationale for further diagnostic evaluation of asymptomatic postmenopausal patients with increased endometrial thickness. The objective of the study was to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer and atypical endometrial hyperplasia in asymptomatic postmenopausal patients.

MATERIALS AND METHODS

This retrospective study was conducted at the Department of gynecologic oncology at the University clinic of gynecology and obstetrics, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia. We searched the Clinic's patient registers from January until December 2015 for eligible postmenopausal patients that were admitted at our outpatient department for endometrial sampling. Exclusion criteria were: (1) postmenopausal bleeding; (2) endometrial thickness less than 4mm; (3) history of endometrial hyperplasia/cancer; (4) history of tamoxifen use; (5) incomplete patient records; (6) current hormone replacement therapy use; (7) known history of hereditary non-polyposis colon cancer (HNPCC); (8) inadequate endometrial sample for histopathology. The following data were extracted from the patient records: age at sampling, age at menarche, age at menopause, number of pregnancies, parity, history of hypertension and diabetes, endometrial thickness and the histology from the endometrial sampling. Post-menopause was defined as the absence of periods for at least 12 months prior to the sampling. Each patient had a transvaginal ultrasonography scan done by the attending physician no more than 14 days prior to the sampling, in accordance with the standard operating procedures of the Department. The endometrial thickness was measured in the sagittal plane, using a conventional transvaginal probe in a standardized fashion. The endometrial sampling was done by dilatation and curettage (D&C) with or without previous hysteroscopic evaluation (at the discretion of the attending). All histological samples were evaluated at the Department of histopathology at the University clinic for oncology and radiotherapy, University Ss. Cyril and Methodius, Skopje, Republic of North Macedonia.

The data was anonymized and entered into a database. The statistical analysis was carried out using the SPSS statistical software package version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). A value of $p<0.05$ was considered statistically significant. Standard descriptive statistics were done and data was displayed using frequencies, percent, mean and standard deviation (SD), where appropriate. Based on the histopathology reports, two separate binary outcome variables were created: presence of EC and presence of EC/AEC, based on the argument that there is a high rate of underdiagnosed malignancies and/or progression to cancer in patients with atypical endometrial hyperplasia [16, 17]. To check for possible confounders, we carried out logistic regressions to test the association of the analyzed factors with the outcomes.

The diagnostic performance of endometrial thickness was evaluated by plotting receiver-operating characteristic (ROC) curves and calculated the area under the curve (AUC). Sensitivity, specificity and Youden's index were calculated for each point on the ROC curves. The point with the highest Youden index was selected as the optimal cut-off in our data. We then calculated the positive and negative predictive value (PPV and NPV) of the test using the selected cut-offs and calculated the relative risk of the patient having EC or EC/AEC when the endometrium thickness is above the cut-off.

RESULTS

We identified a total of 268 patient records that fitted the inclusion and exclusion criteria. Table 1 summarizes the relevant demographic and clinical patient characteristics. All patients were Caucasian. The mean age at the moment of endometrial sampling was 61.2±7.1 years, with an interval of 11.3±7.2 years from menopause to sampling. Patients had an average of 36.8±4.6 reproductive years, 3.2±1.8 pregnancies and 2.1±1 delivery. Eleven (4.1%) of the patients were nulligravidae, and fourteen (5.2%) od the patients were nulliparous.

Over half of the patients (162, 60.4%) had hypertension and 31 (11.9%) had diabetes. The mean endometrial thickness was 9.3mm with a standard deviation of 3.2mm and a range from 5-23mm.

Table 1. Summary of the relevant demographic and clinical patient characteristics

Parameter	No. patients n=268
TVUS Endometrial thickness (mm), mean±SD [range]	9.3±3.2 [5-23]
Age at sampling (years), mean±SD	61.2±7.1
Age at menarche (years), mean±SD	13.1±1.5
Age at menopause (years), mean±SD	50±4.4
Interval from menopause to sampling (years), mean±SD	11.3±7.2
No. of reproductive years	36.8±4.6
Number of pregnancis	3.2±1.8
Number of deliveries	2.1±1
Nulligravidity, n (%)	11 (4.1%)
Nulliparity, n (%)	14 (5.2%)
Hypertension, n (%)	162 (60.4%)
Diabetes, n (%)	32 (11.9%)

A vast majority of the evaluated patients had benign endometrial lesions (248 patients or 92.6%), 6 patients (2.2%) had atypical endometrial hyperplasia and 14 patients (5.2%) had endometrial cancer. The various histological findings are outlined in detail in Table 2.

Table 2. Distribution of histological diagnoses in the studied population

	n (%)
Atrophic endometrium	135 (50.4%)
Endometrial polyp	70 (26.1%)
Other benign conditions (endometritis, leiomyoma...)	28 (10.5%)
Simple endometrial hyperplasia	13 (4.8%)
Complex endometrial hyperplasia without atypia	2 (0.8%)
Complex endometrial hyperplasia with atypia	6 (2.2%)
Endometrial cancer	14 (5.2%)
Endometroid adenocarcinoma	8 (2.9%)
Mixed serous and mucinous adenocarcinoma	4 (1.5%)
Serous adenocarcinoma	1 (0.4%)
Clear cell carcinoma	1 (0.4%)

The univariate logistic regression revealed a statistically significant association of endometrial thickness with both the presence of EC ($p<0.001$) and EC/AEC ($p<0.001$). The other factors were not significantly associated (Table 3).

The distribution of benign endometrial lesions, atypical endometrial hyperplasia and EC for different levels of endometrial thickness are shown in Figure 1. As expected, the proportion of premalignant/malignant endometrial lesions increases with increased endometrial thickness.

Table 3. Univariate logistic regression for determining the association between the clinical parameters and EC or EC/AEH in the studied population

Parameter	p (EC)	p (EC/AEH)
Endometrial thickness	<0.001	<0.001
Age at sampling	0.14	0.39
No. of reproductive years	0.92	0.3
Interval from menopause to sampling	0.18	0.78
Nulligravidity	0.07	0.19
Nulliparity	0.14	0.33
Hypertension	0.8	0.67
Diabetes	0.58	0.78

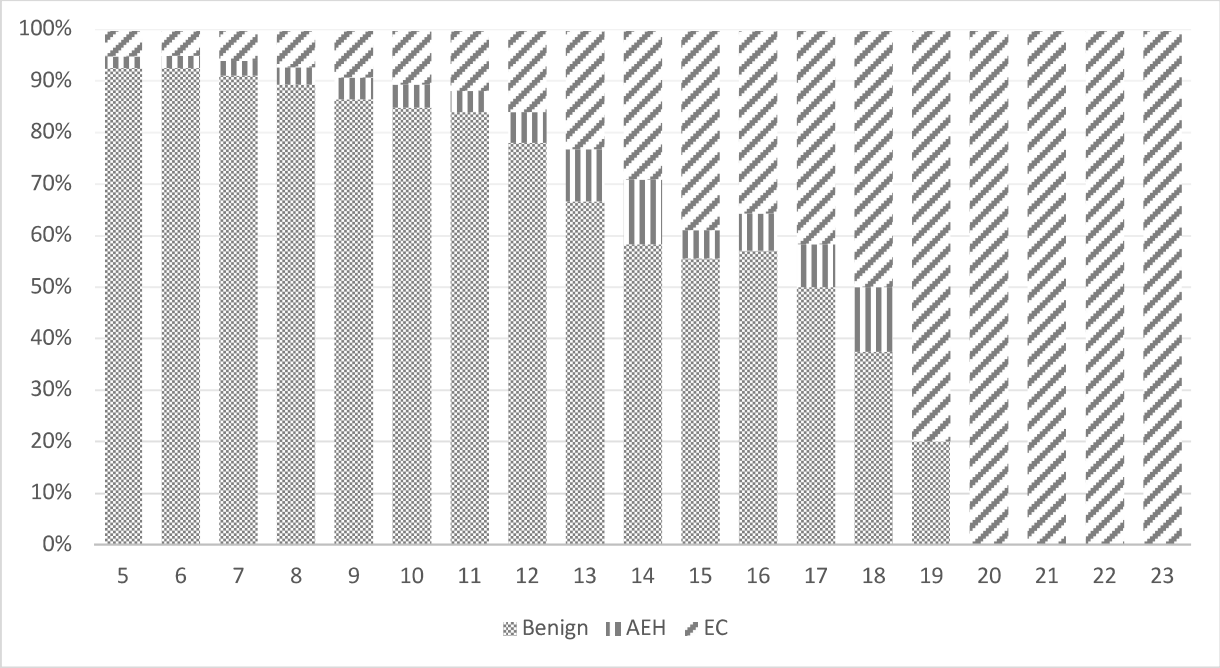


Fig. 1. Distribution of benign endometrial lesions, AEH and EC for different levels of endometrial thickness.

In order to evaluate the diagnostic performance of endometrial thickness measured by transvaginal sonography for the detection of EC and EC/AEC, two ROC curves were plotted (Figures 2 and 3). The AUC was 0.8 for detection of both EC (95%CI 0.66-0.94, $p<0.001$) and EC/AEC (95%CI 0.7-0.91, $p<0.001$).

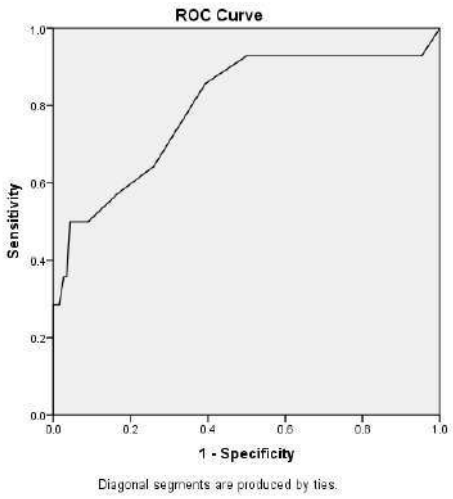


Fig. 2. ROC curve curve of transvaginal ultrasound measurement of endometrial thickness in asymptomatic postmenopausal for the detection of EC.

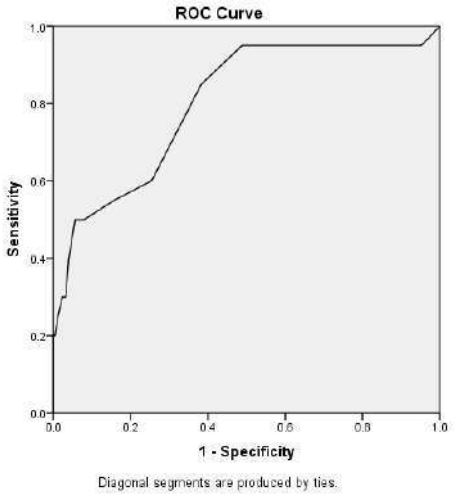


Fig. 3. ROC curve curve of transvaginal ultrasound measurement of endometrial thickness in asymptomatic postmenopausal for the detection of EC/AEH.

The results for the diagnostic performance of different cut-off points for endometrial thickness in the detection of EC and EC/AEH are summarized in Table 4 and 5 respectively. The optimal cut-off points for endometrial thickness measured by transvaginal sonography (selected using the Youden index) in our series was 10mm, yielding a sensitivity of 85.7% and 85%, specificity of 60.6% and 61.7%, PPV of 10.7% and 15.2% and NPV of 98.7% and 98.1% for the detection of EC and EC/AEH, respectively. The risk for EC and EC/AEH using the cut-off was 10.7% and 15.2%, respectively.

Table 4. Diagnostic performance for different cut-offs for endometrial thickness in the detection of EC in asymptomatic postmenopausal patients

Cut-off point (mm)	Sensitivity	Specificity	PPV	NPV	Youden index
≥5	93.3%	4.5%	5.2%	92.3%	-2.2%
≥6	92.9%	4.7%	5.1%	92.3%	-2.4%
≥7	92.9%	22.0%	6.2%	98.2%	14.9%
≥8	92.9%	35.4%	7.3%	98.9%	28.3%
≥9	92.9%	50.0%	9.3%	99.2%	42.9%
≥10	85.7%	60.6%	10.7%	98.7%	46.3%
≥11	64.3%	74.0%	12.0%	97.4%	38.3%
≥12	57.1%	83.5%	16.0%	97.2%	40.6%
≥13	50.0%	90.9%	23.3%	97.1%	40.9%
≥14	50.0%	93.3%	29.2%	97.1%	43.3%
≥15	50.0%	95.7%	38.9%	97.2%	45.7%
≥16	35.7%	96.5%	35.7%	96.5%	32.2%
≥17	35.7%	97.2%	41.7%	96.5%	33.0%
≥18	28.6%	98.4%	50.0%	96.2%	27.0%
≥19	28.6%	99.6%	80.0%	96.2%	28.2%
≥20	28.6%	100.0%	100.0%	96.2%	28.6%

Table 5. Diagnostic performance for different cut-offs for endometrial thickness in the detection of EC/AEH in asymptomatic postmenopausal patients

Cut-off point (mm)	Sensitivity	Specificity	PPV	NPV	Youden index
≥5	95.2%	4.6%	7.5%	92.3%	-0.1%
≥6	95.0%	4.8%	7.5%	92.3%	-0.2%
≥7	95.0%	22.6%	9.0%	98.2%	17.6%
≥8	95.0%	36.3%	10.7%	98.9%	31.3%
≥9	95.0%	51.2%	13.6%	99.2%	46.2%
≥10	85.0%	61.7%	15.2%	98.1%	46.7%
≥11	60.0%	74.6%	16.0%	95.9%	34.6%
≥12	55.0%	84.3%	22.0%	95.9%	39.3%
≥13	50.0%	91.9%	33.3%	95.8%	41.9%
≥14	50.0%	94.4%	41.7%	95.9%	44.4%
≥15	40.0%	96.0%	44.4%	95.2%	36.0%
≥16	30.0%	96.8%	42.9%	94.5%	26.8%
≥17	30.0%	97.6%	50.0%	94.5%	27.6%
≥18	25.0%	98.8%	62.5%	94.2%	23.8%
≥19	20.0%	99.6%	80.0%	93.9%	19.6%
≥20	20.0%	100.0%	100.0%	93.9%	20.0%

DISCUSSION

The study present data from 268 asymptomatic postmenopausal women with endometrial thickness >4mm. The prevalence of EC and AEH in the study were 5.2% and 2.2%, respectively. Endometrial thickness was a statistically significant independent predictor of the presence of endometrial cancer and atypical endometrial hyperplasia ($p<0.001$).

Schmidt et al. reported a similar prevalence of endometrial cancer (4.9%) in a prospective study of asymptomatic postmenopausal women [18], while Giannella et al. [19] in a similar prospective study found the prevalence of EC to be 2.1%. Data on the prevalence of EC in asymptomatic postmenopausal women with thickened endometrium from retrospective studies varies widely form 1.3-13.2% [4, 20, 21].

Transvaginal sonographic scans are frequently performed for various clinical indications. Therefore, the accidental finding of thickened endometrium in asymptomatic postmenopausal women is a relatively common occurrence and represents a diagnostic conundrum in many primary gynecologic practices. Historically, the cut-off points for endometrial thickness that warrant patient refferal for further histological (often invasive) evaluation have been the same as the ones used for patients with postmenopausal bleeding (i.e. 5mm) [9-12].

While the data from patients with postmenopausal bleeding points toward clear clinical recommendations, a cut-off point for endometrial thickness in asymptomatic postmenopausal women that would provide acceptable trade-off between cancer detection and unnecessary biopsies prompted by an incidental finding has remained debatable.

The ROC curve analysis in our study had an AUC of 0.8 and identified a cut-off level for EC/AEH to be ≥10mm which was associated with a sensitivity of 85.7% and 85%, specificity of 60.6% and 61.7%, PPV of 10.7% and 15.2% and NPV of 98.7% and 98.1% for the detection of EC and EC/AEH, respectively. Using that cut-off as the basis for the decision for endometrial sampling would "miss" 2 cases of EC and 1 case of AEH which account for 15% of all premalignant/malignant endometrial lesions in our series, but would also reduce the number of D&C procedures by 58%.

Kasraeian et al. [22] conducted a prospective observational cohort study on 259 asymptomatic postmenopausal. When using 5 mm as a cut-off point to detect EC, the authors reported sensitivity of 100 %, specificity of 84.4 %, PPV of 2.43 %, and NPV of 100 %, and an AUC of 0.853, indicating moderate accuracy. A recent metanalysis conducted by Alcazar et al on aggregated data from 4751 women had a prevalence of EC and/or AEH of 2.4%. The authors stated that the relative risk of EC and/or AEH was 2.59 with endometrial thickness ≥11 mm. They also observed high heterogeneity between studies (I2: 57.3%, P = 0.016). Two large cohort studies, the theoretical cohort by Smith-Bindman et al. [13] and the UKCTOCS study [14], suggest that choosing a cut-off value well above the one used for patients with postmenopausal bleeding, i.e. >10-12mm seems to be a viable strategy to decrease the needed number-to-treat for the early detection of EC cases. Our data compares favorably with these series. It should be noted, however, that the risk for EC in our series is higher (10.7%) than the risk for EC published in the theoretical cohort (6.7%) and the UKCTOCS study (5.9%). The UKCTOCS study has achieved sensitivity of 84.3 % and specificity of 89.9 % with a cutoff of 6.75 mm, but only after stratifying the study population into a low-risk and high-risk groups, using a logistic regression model [14]. The authors have concluded that the burden of diagnostic procedures and false-positive results can be reduced by limiting sonographic screening for EC to a high-risk population.

Conversely, Breijer et al. in their systematic review including 32 studies with data of over 11100 patients, concluded that endometrial thickness should not be used as a screening tool for EC or AEH in asymptomatic postmenopausal women [10]. Similarly, Yasa et al. in a retrospective study of 276 consecutive asymptomatic perimenopausal women found that endometrial thickness does not seem to be an effective diagnostic tool for the early detection of EC because it had a low diagnostic performance in asymptomatic postmenopausal women. Furthermore, a retrospective study on 2673 consecutive patients found that 44% of office hysteroscopies aimed at diagnosing EC were not indicated.

It can be argued that, although of low yield, pre-symptomatic diagnosis of EC might impact the course of the disease and improve survival in these patients. In a series of 313 EC patients (190 symptomatic and 123 asymptomatic with suspicious endometrium detected by ultrasound), Gerber et al. [25] found no prognostic advantage for screened patients compared to symptomatic patients with bleeding episodes lasting less than 8 weeks prior to diagnosis. Duration of bleeding had also no impact on EC prognosis in a study of 304 EC patients [26]. In a large group of 133 asymptomatic and 410 symptomatic patients with EC, the authors found that symptoms were not related to stage or age at diagnosis and the presence or absence of symptoms was not associated with improved survival.

Survival advantage from EC diagnosis in asymptomatic postmenopausal patients was also demonstrated in a large Israeli Oncology Group study adequately powered for survival measures [28].

The authors stated that there was no difference between asymptomatic EC patients and EC patients with postmenopausal bleeding in the 5-year recurrence-free survival (79.1% vs. 79.4%; p = 0.85), disease-specific survival (83.2% vs. 82.2%; p = 0.57), or overall survival (79.7% vs. 76.8%; p = 0.37). Therefore, operative hysteroscopy/curettage procedures in asymptomatic patients with sonographically diagnosed endometrial polyps or thick endometrium are rarely indicated and should be reserved for patients whose ultrasonographic findings demonstrate significant change over time [28].

Our study is not free of limitations. First its retrospective nature being subject to selection bias due to unmeasured confounders. Second, the study was conducted on a gynecologic-oncology department in a tertiary referral center. Although referral for histological diagnosis of asymptomatic thickened endometrium in the Republic of North Macedonia is liberal, it can be assumed that not all women with thickened endometrium were referred. Therefore, it can be hypothesized that due to the selection bias of a register study, we overestimated the risk for cancer compared to a general screening situation. Additionally, our cohort comprised of an above-average number of patients with comorbidities that were referred to our department they could not be treated safely in a secondary care center. The fact that many of those comorbidities are also risk factors for endometrial cancer might explain the high percentage of diagnosed cancers in our study. Lastly, we only evaluated the endometrial thickness and disregarded any additional data from the ultrasonography reports, such as specific morphology and/or Doppler evaluation, which could have revealed more information.

CONCLUSION

This retrospective cohort analysis found that an increased endometrial thickness, measured by transvaginal sonography, is a significant and independent risk factors for the presence of EC in asymptomatic postmenopausal women, which is in line with previously published data from the UKCTOCS trial and a theoretical cohort. No association was found between EC and related conditions such as diabetes and hypertension. The proposed cut-off of ≥10mm for discriminating between “normal” and “pathological” endometrial thickness is clinically reasonable and of moderate diagnostic value. However, the cut-off value does not achieve the required high sensitivity with clinically acceptable low false positive rates. Nevertheless, transvaginal sonography for measuring endometrial thickness can be used to exclude pre-malignancy or malignancy in asymptomatic postmenopausal women with risk factors because of its low false negative rate. Additionally, it is a preoperative diagnostic tool that might provide the surgeon with additional information important for the choice of surgical procedures, or as an alternative to endometrial sampling in postmenopausal women who cannot undergo invasive procedures. A well-designed large prospective study is required to reach consensus about the optimum endometrial thickness cut-off to initiate an investigation in asymptomatic postmenopausal women with incidental finding of thickened endometrium.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
3. Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. J Obstet Gynaecol. 2004;24(7):736–41.
4. Yasa C, Dural O, Bastu E, Ugurlucan FG, Nehir A, Iyibozkurt AC. Evaluation of the diagnostic role of transvaginal ultrasound measurements of endometrial thickness to detect endometrial malignancy in asymptomatic postmenopausal womenArch Gynecol Obstet. 2016;294(2):311–6.
5. National Institutes of Health (NIH) National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program (SEER). Bethesda (MD); [Accessed April 2020]. Available from: https://seer.cancer.gov/
6. American College of O, Gynecologists. ACOG Committee Opinion No. 440: the role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding Obstet Gynecol. 2009;114(2 Pt 1):409–11.
7. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(1):160–7.
8. Royal College of Obstetricians and Gynaecologists (RCOG). 2016. Management of Endometrial Hyperplasia Green-Top Guideline No. 67 [Accessed April 2020]. Available from: https://www.rcog.org.uk
9. Fleischer AC, Wheeler JE, Lindsay I, Hendrix SL, Grabill S, Kravitz B et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol. 2001;184(2):70–5.
10. Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2012;40(6):621–9.
11. Ates S, Sevket O, Sudolmus S, Ozel A, Molla T, Dane B et al. The value of transvaginal sonography in detecting endometrial pathologies in postmenopausal women with or without bleeding. Minerva Ginecol. 2014;66(4):335–40.
12. Jokubkiene L, Sladkevicius P, Valentin L. Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol. 2016;48(3):390–6.
13. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol. 2004;24(5):558–65.
14. Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol. 2011;12(1):38–48.

15. Gentry-Maharaj A, Sharma A, Burnell M, Ryan A, Amso NN, Seif MW et al. Acceptance of transvaginal sonography by postmenopausal women participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Ultrasound Obstet Gynecol. 2013;41(1):73–9.
16. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up. Hum Reprod. 2013;28(5):123–6.
17. Smith PP, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: a prospective cohort study. J Minim Invasive Gynecol. 2014;21(5):799–803.
18. Schmidt T, Breidenbach M, Nawroth F, Mallmann P, Beyer IM, Fleisch MC et al. Hysteroscopy for asymptomatic postmenopausal women with sonographically thickened endometrium. Maturitas. 2009;62(2):176–8.
19. Giannella L, Mfuta K, Setti T, Boselli F, Bergamini E, Cerami LB. Diagnostic accuracy of endometrial thickness for the detection of intra-uterine pathologies and appropriateness of performed hysteroscopies among asymptomatic postmenopausal women. Eur J Obstet Gynecol Reprod Biol. 2014;177:29–33.
20. Famuyide AO, Breitkopf DM, Hopkins MR, Laughlin-Tommaso SK. Asymptomatic thickened endometrium in postmenopausal women: malignancy risk. J Minim Invasive Gynecol. 2014;21(5):782–6.
21. Saatli B, Yildirim N, Olgan S, Koyuncuoglu M, Emekci O, Saygılı U. The role of endometrial thickness for detecting endometrial pathologies in asymptomatic postmenopausal women. Aust N Z J Obstet Gynaecol. 2014;54(1):36–40.
22. Kasraeian M, Asadi N, Ghaffarpasand F, Karimi AA. Value of transvaginal ultrasonography in endometrial evaluation of non-bleeding postmenopausal women. Climacteric. 2011;14(1):126–31.
23. Alcázar JL, Bonilla L, Marucco J, Padilla AI, Chacón E, Manzour N et al. Risk of endometrial cancer and endometrial hyperplasia with atypia in asymptomatic postmenopausal women with endometrial thickness ≥11 mm: A systematic review and meta-analysis. J Clin Ultrasound. 2018;46(9):565–570.
24. Scrimi F, Wiesenfeld U, Galati EF, Monasta L, Ricci G. Hysteroscopic chasing for endometrial cancer in a low-risk population: risks of overinvestigation. Arch Gynecol Obstet. 2016;293(4):851–6.
25. Gerber B, Krause A, Müller H, et al. Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding. Eur J Cancer. 2001;37(1):64–71.
26. Kimura T, Kamiura S, Yamamoto T, Seino-Noda H, Ohira H, Saji F. Abnormal uterine bleeding and prognosis of endometrial cancer. Int J Gynaecol Obstet. 2004;85(2):145–50.
27. Seebacher V, Schmid M, Polterauer S, et al. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. BMC Cancer. 2009;9:460.
28. Gemer O, Segev Y, Helpman L, Hag-Yahia N, Eitan R, Raban O et al. Is there a survival advantage in diagnosing endometrial cancer in asymptomatic postmenopausal patients? An Israeli Gynecology Oncology Group study. Am J Obstet Gynecol. 2018;219(2):181.e1–181.e6.