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Title: Determining a threshold measurement of Endometrial Thickness for Asymptomatic Postmenopausal Women: A tertiary centre case series

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ajo.13604

Acknowledgments : Funding received from Norman Beischer Medical Research Foundation, 2018 NBMRF Grant

Conflicts of Interest: None to disclose

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Keywords: Endometrial thickness, endometrial hyperplasia, post-menopausal

Manuscript word count: 2462 words

Abstract word count: 250 words

Figure count: One

Table count: Three

Conflicts of interest: None to declare

Abstract:

Background: An incidental finding of a thickened endometrium on ultrasound in the post-menopausal patient without bleeding is a common presentation to gynaecological services, however there is limited evidence to guide clinical practice as to when hysteroscopic evaluation and endometrial sampling is required.

Aims: To determine the endometrial thickness at which endometrial sampling is indicated in asymptomatic post-menopausal women referred with thickened endometrium on ultrasound.

Materials and Methods: A single-centre retrospective case series of postmenopausal women without bleeding undergoing hysteroscopy was conducted. Logistic regression was used to examine the association between a range of variables and pre-malignant or malignant pathology and endometrial thickness. The optimal endometrial thickness threshold was identified to maximise model sensitivity.

Results: A total of 404 postmenopausal women were included in this study, having undergone a hysteroscopy at the study site between 1st July 2008 and 30th June 2018. The mean(SD) age of patients at presentation was 65(9.09) years and the mean BMI was 29.86 kg/m^2(6.52). Of these women, 9(2.2%) were diagnosed with endometrial carcinoma and 7(1.7%) had endometrial hyperplasia with atypia. The most common histopathological finding was of a benign endometrial polyp 153(37.9%). When including hyperplasia with or without atypia in histopathology of interest, a cut-off of ≥9mm provides the greatest sensitivity (83.3%) and specificity (63.8%) for a diagnosis of pre-malignant or malignant pathology (classification accuracy of 64.8%; AUROC: 0.7358, 95%CI: 0.6439, 0.8278) in this cohort.

Conclusions: Using an endometrial thickness of ≥9mm can be used as a cut-off for endometrial sampling in post-menopausal women without bleeding.

Introduction

The incidental finding of thickened endometrium, defined as >4mm on pelvic ultrasound in the post-menopausal patient, is a common reason for gynaecology services referral.

It is widely accepted that post-menopausal bleeding(PMB) and an endometrial thickness(ET) >4mm, requires endometrial sampling, given the concern for endometrial cancer(EC)[1]. However, in the absence of bleeding, there remains no clear consensus whether these patients need endometrial sampling.

In Australia, despite EC being the most common gynaecological malignancy, with a 1 in 40 lifetime risk,[2] routine screening is not recommended.[3] The incidence of endometrial thickening on ultrasound is much higher than the incidence of EC, suggesting that this ultrasound finding is usually not sinister.[4] Although up to 15% of women with EC will not present with vaginal bleeding[5], there is no evidence of a survival benefit in diagnosing EC prior to clinical presentation with bleeding.[6] Nevertheless, the incidental finding of a thickened endometrium on ultrasound provokes anxiety for both the practitioner and patient, and thus referral for investigation.

A retrospective case series(n=83) concluded that it is reasonable to use a 10mm ET cut off or the presence of risk factors as the threshold for endometrial sampling, with a 1.2% detection rate of EC in this asymptomatic population.[7]

The Society of Obstetricians and Gynaecologists of Canada(SOGC) published guidelines in 2010 recommending against routine endometrial sampling in the absence of bleeding if ET is <11mm unless other ultrasound findings are present.[4] A recent committee opinion piece published by American College of Obstetrics and Gynaecology(ACOG) highlighted the lack of guidance regarding management of these patients and suggested an individualised approach to investigation based upon risk factors.[8]

Of the five general gynaecology units within our institution the management of postmenopausal women with an asymptomatic thickened endometrium varies. Several units recommend investigating all women with an ET>4mm, regardless of symptoms, whilst others used different thresholds (5mm or 10mm) in the absence of bleeding. Other risk factors such as diabetes, obesity, tamoxifen usage or sonographic abnormalities also influence the decision to investigate. Given the lack of consensus on management, this study aimed to determine a reasonable ET threshold that should prompt assessment in asymptomatic postmenopausal women.

Materials and Methods

This retrospective review of all postmenopausal women attending for hysteroscopy (both inpatient and outpatient) at a single site tertiary institution in Australia occurred over ten-years (1st July 2008 - 30th June 2018). There is no specific identifier code for this outpatient clinical referral at our institution. Therefore, all women >50years of age who underwent hysteroscopy during the study period were identified and their medical records reviewed. Postmenopausal status was confirmed from review of the notes, and only asymptomatic women without PMB were included. For all eligible patients, data pertaining to age, years since menopause, BMI, diabetes status, tamoxifen usage, indication for imaging, location where ultrasound was performed (tertiary or non-tertiary), and ultrasound approach (transvaginal or transabdominal) were documented. ET and additional sonographic endometrial findings were recorded.

Our primary aim was to determine the optimal threshold to recommend hysteroscopy and endometrial sampling in postmenopausal women without bleeding. Secondary outcomes included incidence of endometrial hyperplasia(EH) and EC(adenocarcinoma and other), and investigation of additional risk factors to consider when determining the threshold for endometrial sampling.

Analyses were conducted in Stata/IC v16.1(StataCorp LLC, College Station, Texas, USA). Logistic regression was used to examine the association between potential explanatory variables and pre-malignant or malignant pathology. These logistic regression models were primarily univariate, using specified subgroups from the analysis sample. A p-value of <.05 was used as the threshold for statistical significance, with no adjustment

made for multiple comparisons due to the exploratory nature of the analyses. The optimal ET threshold was identified to maximise model sensitivity using the cutpt package.[9] Exploratory analyses were performed comparing performance (as area under receiver operator curve[AUROC]) in the presence of polyps on ultrasound, scan location(tertiary or non-tertiary) and ultrasound view (transabdominal or transvaginal, or a combination) using the algorithm implemented in Stata as proposed by DeLong, DeLong, and Clarke-Pearson. [10] Missing data was accounted for by a pairwise deletion approach.

The project was approved by the Mercy Health Human Research Ethics Committee (HREC) (Reference number 2018-059).

Results

Of the 2692 files reviewed of women >50 years undergoing hysteroscopy, 425 postmenopausal women without PMB were identified. Of these, 404 patients had a recorded preoperative sonographic ET.

Study population characteristics are presented in Table 1. The mean(SD) age of patients at presentation was 65(9.09) years, and the median(IQR) years since menopause was 11(5,20). The mean BMI of women was 29.86 kg/m^2(6.52), with 137(44.8%) women being obese and 55(13.8%) women having a diagnosis of diabetes. Sixteen(4%) women were taking tamoxifen at the time of their ultrasound. The most common reason for

presentation was an incidental finding of thickened ET after pelvic/back pain (n=181, 44.8%). The ET on ultrasound ranged from 1-38mm, with a median(IQR) of 7.95mm(6, 11). Along with thickened endometrium, 329(81.4%) women had concurrent US findings of additional endometrial abnormalities; 120(29.7%) were found to have a cystic endometrium, 97(24.0%) had an endometrial polyp, and in 12(3.0%) the presence of endometrial fluid was noted. The most common histopathological finding was of a benign endometrial polyp (n=153, 37.9%) (Table 2). Nine(2.2%) women were diagnosed with endometrial carcinoma and 9(2.2%) had EH; 7(1.7%) women were found to have atypical EH, and 2(0.5%) non-atypical EH. Thirty (7.4%) women had histopathological results of an inadequate sample; importantly, all of these patients had macroscopic evidence of atrophy at time of hysteroscopy. The range of ET for those with EH or EC (n=18) was 6.7mm to 25mm, median(IQR) 12.3mm(9,14).

Using a cut-off of ≥10mm provides the greatest sensitivity (77.8%) and specificity (68.7%) for a diagnosis of EC (classification accuracy of 68.9%; AUROC: 0.7325, 95%CI: 0.5865, 0.8784) (Figure 1a). However, when including EH in histopathology of interest, a cut-off of ≥9mm provides the greatest sensitivity (83.3%) and specificity (63.8%) for a diagnosis of pre-malignant or malignant pathology (classification accuracy of 64.8%; AUROC: 0.7358, 95%CI: 0.6439, 0.8278) in this cohort (Figure 1b). The cut point of 9mm in the subpopulation of women without ultrasound features of a polyp or endometrial fluid or cystic endometrium (n=177) performed similarly, with a sensitivity of 85.71% and specificity of 66.47% and correctly classified 67.23% (AUROC: 0.7609 (95%CI: 0.6165, 0.9054)).

The presence of an endometrial polyp on ultrasound did not alter these accuracy analyses ($\chi^2(1)=0.15$, p=.70). Three cases with ultrasound evidence of an endometrial polyp had EC diagnosed; the ET for these 3 cases ranged from 8-24.5mm and one case with ultrasound evidence of polyp and ET<9mm had EC.

When evaluating the full cohort, the incidence of malignancy with ET <9mm is 0.85%(95%CI: 0.10%, 3.03%). The incidence of EH or EC with ET <9mm is 1.27%(95%CI: 0.26%, 3.67%). Diabetes and obesity were significant risk factors for EC. All patients with EC had a BMI greater than 30kg/m^2. When women with diabetes were excluded, the incidence of malignancy with ET <9mm decreased to 0.50% (95%CI: 0.01%, 2.73%), and the incidence of EH or EC with ET <9mm remained the same. There were no cases of EH or EC in women taking tamoxifen. There was no statistical evidence of a relationship between tamoxifen use and mean ET(p=0.25). The mean ET of individuals on tamoxifen was 10.3mm, compared to 8.8mm for those not on tamoxifen(mean difference 1.5mm, 95%CI: -1.1 to 4.1mm).

There was a significant association between increased ET and EC(p=0.002), with every 1mm increase in ET resulting in a 10% increased risk of pre-malignant or malignant pathology (OR 1.100; 95%CI: 1.036, 1.167) (Figure 1c). This association between ET and malignant pathology was similar regardless of years since menopause. Specifically, when dichotomizing years since menopause into <2, <5 and <10 years there was no evidence that the association between greater ET and malignant pathology was altered.

Our results showed no significant association between increased likelihood of EC and age at presentation (p=0.97), however there was a significant relationship with years since menopause (p=0.027). We found that every 5-years since menopause incurred an almost 40% increased risk of pre-malignant or malignant endometrial pathology (OR 1.370; 95%CI: 1.037, 1.809) (Figure 1d).

Discussion

Main findings:

In our cohort of postmenopausal women without vaginal bleeding who underwent hysteroscopy and endometrial sampling, the incidence of EC with ET <9mm was 0.85%, and the incidence of EH or EC at this same cut-off was 1.27%. These risks are similar to those reported with the accepted ET cut-off of >4mm necessitating endometrial sampling for women with PMB.[11]

Amongst women with PMB an ET >4mm is used as the threshold for investigation as an ET less than this poses a <1% risk of EC [1]. If this ET cut-off of > 4mm is applied to our cohort, 333 of 351(95.4%) patients would undergo unnecessary hysteroscopy and endometrial sampling (18 patients with ET>4mm were diagnosed with EH or EC). If this ET cut-off was altered to >9mm for asymptomatic postmenopausal women, 147 patients would undergo hysteroscopy, and 132(89.9%) would have benign histopathology. In increasing the threshold to ET>9mm in this asymptomatic group, 201 unnecessary interventions would be avoided. Indeed, in applying the cut-off of 9mm to this cohort, one case of atypical EH and two cases of EC would remain undiagnosed. However, if additional risk factors were taken into account and used to indicate need for sampling, these three cases would have undergone hysteroscopic investigation.

Strengths and Limitations:

In our cohort, 13.8% of women had diabetes mellitus, 44.8% were obese, and the median time since menopause was 11 years. The strength of the current study is the large sample size compared to similar reports, allowing investigation of these potential risk factors. Obesity, diabetes, and increased time since menopause were important risk factors for endometrial pathology. If patients with a BMI>30 were excluded, there were no patients diagnosed with malignancy. If those with diabetes were excluded, the incidence of EH or EC was 0.5%. These findings should prompt a policy of individualisation of the suggested ET threshold in the presence of risk factors.

For analysis, atypical and non-atypical EH were grouped together as premalignant pathology as there were small numbers in each subgroup. Although it is widely recognised that atypical EH carries a more than 5-fold greater risk in progression to malignancy compared to EH without atypia[12], guidelines recommend similar management in the post-menopausal population, as risk of occult pathology or progression to atypical EH or EC is up to 20%.[13]

The weaknesses of our study include its retrospective design, and our methods of identifying the cohort. Unfortunately, at our institution, there is no identification code for a presentation of thickened endometrium in the absence of PMB. As such, the only means of identifying our cohort was to review hysteroscopy data. Thus, we do not know any details of the cohort of women who did not have a hysteroscopy performed. Studies performed in the setting of PMB which have utilised a 4mm cut off, have then undertaken follow-up to ensure that this conservative approach did not result in women being missed.[8,14] Reassuringly, during our file review of all hysteroscopies performed during the study period, we identified no cases that involved a woman originally managed without hysteroscopy and sampling but later presenting with symptoms and having a malignancy identified.

Due to the retrospective data collection, some data was incomplete, such as age of menopause, BMI, diabetes status, and potentially tamoxifen use. This limits the inferences made about these risk factors. Further, there was a lack of consistency regarding the ultrasound approach and

definitions used to define abnormalities. Several ultrasounds were not done in a tertiary centre and there were no standardised definitions, making it difficult to compare and standardise ultrasound findings between patients.

Interpretation of Results:

Our findings are in line with recent studies that have found an ET >10-11mm should be used as an indication of endometrial sampling. A prospective study of 81 women showed that using an ET≥10mm had a sensitivity of 100% and specificity of 60% for the diagnosis of atypical EH or EC.[15] This study however had a smaller sample size and therefore did not account for individual risk factors. A larger prospective registered study included a total of 900 women with thickened endometrium.[16] This study reported the risk of atypical EH and EC to be 7.9% when using a cut off of 11mm. It is noted that the risk of EC or atypical EH in this study is significantly higher than in our cohort. This study included referrals from 26 departments with an ET >3mm. It is assumed with this referral pathway that not all women with thickened endometrium were referred, and therefore due to selection bias the risk of EC would be overestimated.

The largest prospective study[17] followed 1926 asymptomatic postmenopausal women with 1792 undergoing endometrial sampling. Of women with ET≤6mm (n=1750), 1 woman had EC, and 4 had atypical EH. Of women with an ET >6mm (n=42) who were sampled, 1 woman had EC. A comparison of the available evidence is shown in Table 3.

The SOGC guidelines recommend other positive findings on ultrasound such as increased vascularity, heterogeneity of the endometrium or particulate fluid should be investigated.[4] Our study investigated ultrasound findings such as cystic endometrium, endometrial polyps, endometrial fluid, ovarian abnormalities and fibroids. Of all women, only 49 had no other ultrasound findings. Of these women, 2.04% had a malignancy and 6.12% had either EH or EC (95% CI: 1.28, 16.87%). Given the small sample size when other ultrasound findings were excluded, further research is needed. Three (3.09%) cases with ultrasound evidence of a polyp were diagnosed with EC. 24% of ultrasounds reported an endometrial polyp, however the finding of a benign polyp was more common on histopathology, with 59.4% having this finding. There is a wide variation in the literature with benign endometrial polyps found on hysteroscopy, ranging from 24.7-59.1%[8,18,19,] in keeping with our study. It is likely, given 3 out of the 9 women diagnosed with EC had the finding of a polyp on ultrasound, that this sonographic finding still warrants histological assessment. It must be noted however, that based on ET >9mm alone, two of these cases would have been identified as being at increased risk of EC.

As Smith-Bindmann et al concluded, there is no perfect cut off at which no cancer will be missed.[5] However the data from this study strengthen the recommendation against routine hysteroscopic evaluation of asymptomatic women with ET<9mm. This ET can be used as the threshold for endometrial sampling in a postmenopausal woman without bleeding. To improve the sensitivity of a cut-off, women with additional risk factors

such as obesity, diabetes, increased time since menopause, or other ultrasound findings may benefit from individualisation and possible sampling at lower ET. A large, multi-centre prospective study that evaluates these risk factors in combination with the ideal ET is required to make further definitive recommendations for clinical practice.

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20.

21. **Table 1: Descriptive Characteristics of study population (n=404).** Data are shown as n (%) unless otherwise indicated

22.

Characteristic	n (%)
Age at presentation (years), mean (SD)[$]	65.31 (9.09)
Presentation type	
Unknown	37 (9.2%)
Incidental screening	85 (21.0%)
Incidental pelvic/back pain	181 (44.8%)
Incidental other bleeding	5 (1.2%)
Incidental GI bloating	34 (8.4%)
Incidental patient concern	7 (1.7%)
Incidental other	55 (13.6%)
BMI (kg/m^2), mean (SD)[#]	29.86 (6.52)
BMI, WHO categories[#]	
Underweight (<18.5 kg/m^2)	1 (0.3%)
Normal weight (18.5-24.9 kg/m^2)	64 (20.9%)
Overweight (25-29.9 kg/m^2)	104 (34.0%)
Obese (≥30 kg/m^2)	137 (44.8%)
Diabetic[&]	
No	345 (86.3%)
Yes	55 (13.8%)
Menopause duration (years), median (IQR)[@]	11 (5, 20)

Endometrial thickness (mm), mean (SD)	8.94 (5.24)
Endometrial thickness (mm), median (IQR)	7.95 (6, 11)
Other ultrasound findings^	
Nil other	75 (18.6%)
Cystic endometrium	120 (29.7%)
Endometrial polyp	97 (24.0%)
Endometrial fluid	12 (3.0%)
Ovarian abnormality	64 (15.8%)
Other	28 (6.9%)
Fibroid	135 (33.4%)

23.

24. $ age was unable to be calculated for n=17 patients; # BMI was missing for n=98 patients; & diabetes status was missing for n=4 patients; @ menopause duration was missing for n=118 patients; ^ categories are not mutually exclusive.

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26.

27. **Table 2: Histopathology results of cohort (n=404)**

28.

Histopathology	n (%)
No histopathology/Inadequate sample*	90 (22.2%)
Benign Endometrium	76 (18.8%)
Benign Polyp	153 (37.9%)
Benign polyp and endometrium	57 (14.1%)
Other benign	10 (2.5%)
Endometrial hyperplasia without atypia	2 (0.5%)
Endometrial hyperplasia with atypia	7 (1.7%)
Endometrial malignancy	9 (2.2%)

29.

30. Table 3: Comparison of existing evidence and cut-offs used for endometrial thickness

31.

Study and size (n)	Study Design	ET</=6mm	ET>6mm	ET<9mm	ET>/=9mm	ET<10mm	ET>10mm	<11mm	>/=11mm
Fleischer et al (n=1792 biopsies)	Prospective multi-centre drug trial. Asymptomatic postmenopausal women prior to commencing tamoxifen for osteoporosis prevention	N=1750 biopsied 1 EC (0.06%) 4 AEH (0.23%)	N=42 biopsied 1 EC (2.38%) 0 AEH						
Aggarwal et al (n=83)	Retrospective single-centre case series of asymptomatic postmenopausal women with thickened endometrium					* N=55 2 EC (3.64%) 1 AEH (1.81%)	* N=28 0 EC 0 AEH		
Ghoubara et al (n=81)	Prospective case series, Asymptomatic postmenopausal women with ET >4mm					& N=46 0 EC 0 AEH	& N=35 3 EC (8.57%) 1 AEH (2.86%)		
Helfer et al (n=900)	Prospective register study, Asymptomatic postmenopausal women with ET>3mm							N=481 4 EC (0.83%) 8 AEH (1.66%)	N=419 28 EC (6.68%) 5 AEH (1.19%)
Stewart et al, (n=404)	Retrospective review of Asymptomatic Postmenopausal women undergoing hysteroscopy where ET was known			N=246 2 EC (0.81%) 1 AEH (0.40%)	N=158 7 EC (4.43%) 6 AEH (3.80%)				

32

ET, Endometrial Thickness; EC, Endometrial Cancer; AEH, Atypical endometrial hyperplasia.

* Note 1: Cutoff </=10mm and >10mm

& Note 2: Cutoff <10mm and >/=10mm

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37.

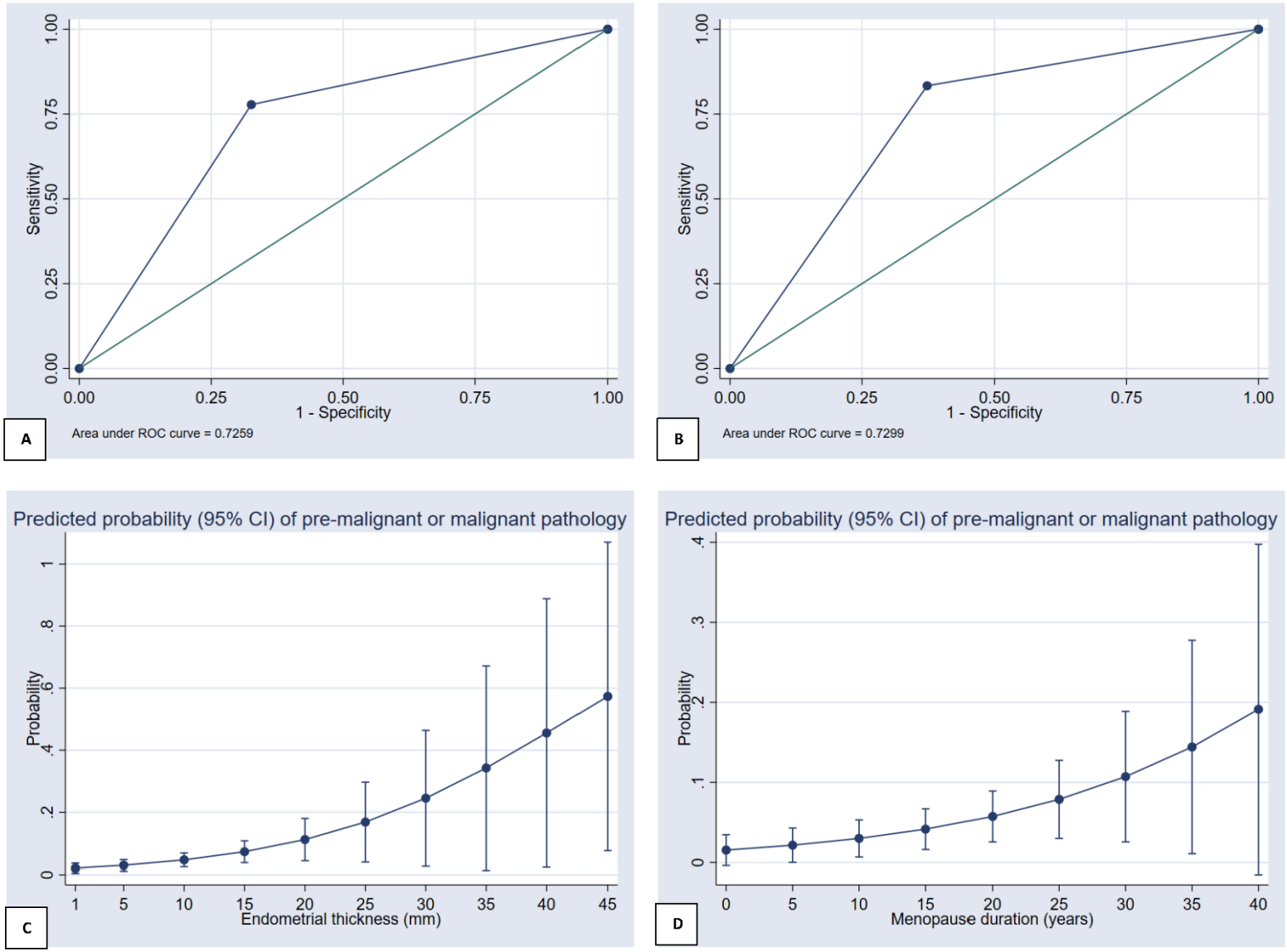

Figure 1: (a) Sensitivity and Specificity of a 10mm endometrial thickness cut-off for diagnosis of endometrial malignancy; (b) Sensitivity and Specificity of a 9mm endometrial thickness cut-off for a diagnosis of pre-malignant or malignant endometrial pathology; (c) Predicted Probability of pre-malignant/malignant endometrial pathology with increasing endometrial thickness; (d) Predicted probability of pre-malignant/malignant endometrial pathology and years since menopause