Risk of endometrial cancer in asymptomatic postmenopausal women in relation to ultrasonographic endometrial thickness: systematic review and diagnostic test accuracy meta-analysis

Salvatore Giovanni Vitale, MD, PhD; Gaetano Riemma, MD; Sergio Haimovich, MD, PhD; Jose Carugno, MD, FACOG; Luis Alonso Pacheco, MD, PhD; Tirso Perez-Medina, MD, PhD; John Preston Parry, MD, MPH; Peter Török, MD, PhD; Jan Tesarik; Luigi Della Corte, MD; Luigi Cobellis, MD, PhD; Attilio Di Spiezio Sardo, MD, PhD; Pasquale De Franciscis, MD, PhD

OBJECTIVE: This study aimed to evaluate the risk of endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women concerning the endometrial thickness measured by stratified threshold categories used for performing subsequent endometrial sampling and histologic evaluation.

DATA SOURCES: MEDLINE, Scopus, ClinicalTrials.gov, SciELO, Embase, the Cochrane Central Register of Controlled Trials, LILACS, conference proceedings, and international controlled trials registries were searched without temporal, geographic, or language restrictions.

STUDY ELIGIBILITY CRITERIA: Studies were selected if they had a crossover design evaluating the risk of atypical endometrial hyperplasia and endometrial carcinoma in postmenopausal asymptomatic women and calculated the diagnostic accuracy of transvaginal ultrasonography thresholds (at least 3.0 mm) confirmed by histopathologic diagnosis.

METHODS: This was a systematic review and diagnostic test accuracy meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy and Synthesizing Evidence from Diagnostic Accuracy Tests guidelines. Endometrial thickness thresholds were grouped as follows: from 3.0 to 5.9 mm; between 6.0 and 9.9 mm; between 10.0 and 13.9 mm; and ≥14.0 mm. Quality assessment was performed using the Quality Assessment Tool for Diagnostic Accuracy Studies 2 tool. Publication bias was quantified using the Deek funnel plot test. Coprimary outcomes were the risk of atypical endometrial hyperplasia or endometrial carcinoma according to the endometrial thickness and diagnostic accuracy of each threshold group.

RESULTS: A total of 18 studies provided the data of 10,334 women who were all included in the final analysis. Overall, at an endometrial thickness threshold of at least 3.0 mm, the risk of atypical endometrial hyperplasia or endometrial carcinoma was increased 3-fold relative to women below the cutoff (relative risk, 3.77; 95% confidence interval, 2.26–6.32; I^2=74%). Similar degrees of risk were reported for thresholds between 3.0 and 5.9 mm (relative risk, 5.08; 95% confidence interval, 2.26–11.41; I^2=0%), 6.0 and 9.9 mm (relative risk, 4.34; 95% confidence interval, 1.68–11.23; I^2=0%), 10.0 and 13.9 mm (relative risk, 4.11; 95% confidence interval, 1.55–10.87; I^2=86%), and ≥14.0 mm (relative risk, 2.53; 95% confidence interval, 1.04–6.16; I^2=78%) with no significant difference among subgroups (P=.885). Regarding diagnostic accuracy, the pooled sensitivity decreased from thresholds below 5.9 mm (relative risk, 0.81; 95% confidence interval, 0.49–0.85) to above 14.0 mm (relative risk, 0.28; 95% confidence interval, 0.18–0.40). Furthermore, the specificity increased from 0.70 (95% confidence interval, 0.61–0.78) for endometrial thickness between 3.0 and 5.9 mm to 0.86 (95% confidence interval, 0.71–0.94) when the endometrial thickness is ≥14.0 mm. For 3.0 to 5.9 mm and 10.0 to 13.9 mm thresholds, the highest diagnostic odds ratios of 10 (95% confidence interval, 3–41) and 11 (95% confidence interval, 2–49), with areas under the curve of 0.81 (95% confidence interval, 0.77–0.84) and 0.82 (95% confidence interval, 0.79–0.86), respectively, were retrieved. The summary point analysis revealed that the 3.0 to 5.9 mm cutoff point was placed higher in the summary receiver operator curve space than the other subgroups, indicating increased endometrial carcinoma or atypical endometrial hyperplasia diagnosis using these cutoffs.

CONCLUSION: Both low and high endometrial thickness thresholds in postmenopausal asymptomatic women seem equally effective in detecting endometrial carcinoma and atypical endometrial hyperplasia. However, although using a 3.0 to 5.9 mm cutoff results in a lower specificity, the offsetting improvement in sensitivity may justify using this cutoff for further endometrial evaluation in patients with suspected endometrial malignancy.

Key words: atypical endometrial hyperplasia, cutoff, endometrial cancer, endometrial thickness, transvaginal ultrasonography

Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy diagnosed in developed countries.[1] It should be suspected in women presenting with postmenopausal bleeding (PMB) or with a thickened endometrium visualized by transvaginal ultrasonography (TVS).[2]

In the presence of PMB, several guidelines recommend using a sonographic cutoff value of 4.0 or 5.0 mm to recommend further investigation of the endometrium.[3,4] When the endometrial thickness (ET) is below these thresholds, the risk of EC is considered to be <1%.[5] More rarely, some patients diagnosed with uterine premalignant or malignant pathology are asymptomatic and do not present with PMB.[6,7] In contrast to the guidelines on the management of women with PMB, there is no clear consensus regarding when to screen for endometrial cancer in asymptomatic women with increased ET. Accordingly, it is appropriate to explore thresholds for evaluating postmenopausal women with endometrial thickening to prompt endometrial tissue sampling to increase the diagnostic accuracy, avoiding the risk of failure to diagnose EC when present.[8–10]

Postmenopausal patients may be incidentally diagnosed with a thickened endometrium in the absence of PMB when performing a pelvic ultrasound for other gynecologic indications or abdominal or pelvic complaints.[11] If applying the same ultrasonographic thresholds for ET currently recommended for symptomatic patients with PMB for further endometrial investigation to asymptomatic patients, these cutoffs would likely result in a lower specificity, with increased cost and inconvenience for millions of women worldwide.[12,13]

Early insights for this issue were proposed by Smith-Bindman et al[14] in 2004. Their decision-analysis based on a theoretical cohort concluded that, for asymptomatic postmenopausal patients, an endometrial biopsy should be carried out when the transvaginal ultrasonographic ET is at least 11.0 mm. They demonstrated that ET values above this threshold have a malignancy risk of 6.7%, which is comparable to the prevalence of endometrial cancer for women with PMB where ET is ≥5.0 mm (7.3%), a cutoff that remains a widely accepted threshold for recommending endometrial biopsy in symptomatic women.[14] Since Smith-Bindman et al's[14] research, several diagnostic accuracy studies have been conducted to determine the ideal sonographic threshold warranting biopsy for the early diagnosis of EC in asymptomatic women.

AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the risk of endometrial carcinoma (EC) and atypical endometrial hyperplasia in postmenopausal women without vaginal bleeding relative to endometrial thickness (ET) thresholds used in previous trials to guide endometrial histopathologic assessment.

Key findings

Using ultrasonographic ET, a threshold between 3.0 and 5.9 mm showed the highest sensitivity, whereas a threshold of ≥14.0 mm had the highest specificity. The summary point analysis showed increased chances of failing to diagnose EC or atypical hyperplasia using an ET threshold of 10.0 to 13.9 mm.

What does this add to what is known?

The use of a lower ultrasonographic endometrial threshold (3.0–5.9 mm) to recommend performing endometrial sampling maximizes balances for diagnostic accuracy and should be considered for further endometrial evaluation in asymptomatic postmenopausal women.

From the Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy (Dr Vitale); Obstetrics and Gynecology Unit, Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli," Naples, Italy (Dr Riemma, Dr Cobellis, and Dr De Franciscis); Department of Obstetrics and Gynecology, Laniado University Hospital, Netanya, Israel (Dr Haimovich); Division of Minimally Invasive Gynecology, Department of Obstetrics and Gynecology, University of Miami Leonard M. Miller School of Medicine, Miami, FL (Dr Carugno); Unidad de Endoscopia Ginecológica, Centro Gutenberg, Hospital Xanit Internacional, Málaga, Spain (Dr Alonso Pacheco); Department of Obstetrics and Gynecology, Puerta de Hierro Majadahonda University Hospital, Autonoma University of Madrid, Madrid, Spain (Dr Perez-Medina); Parryscope and Positive Steps Fertility, Madison, MS (Dr Parry); Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS (Dr Parry); Faculty of Medicine, Department of Obstetrics and Gynecology, University of Debrecen, Debrecen, Hungary (Török); Molecular Assisted Reproduction and Genetics, MARGen Clinic, Granada, Spain (Dr Tesarik); Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy (Dr Della Corte); and Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy (Dr Di Spiezio Sardo).

Received Dec. 17, 2021; revised July 5, 2022; accepted July 20, 2022.

The authors report no conflict of interest.

This work did not receive any grant or funding.

This study was registered in the International Prospective Register of Systematic Reviews (registration number: CRD42021241857) on April 9, 2021.

Corresponding author: Gaetano Riemma, MD.

0002-9378/$36.00

© 2022 Elsevier Inc. All rights reserved.

https://doi.org/10.1016/j.ajog.2022.07.043

Objective

This systematic review and diagnostic meta-analysis aimed to determine the risk of EC and AEH relative to the different ET thresholds by TVS reported in the literature. Recognizing trade-offs between sensitivity and specificity, an additional goal was to determine what ET would be the ideal balance for performing endometrial tissue sampling in asymptomatic postmenopausal women with increased ultrasonographic ET to increase the diagnostic accuracy for EC and balance costs.

Methods

We conducted a systematic review and diagnostic test accuracy (DTA) meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies[15] and Synthesizing Evidence from Diagnostic Accuracy Tests guidelines[16] on studies with a crossover design that evaluated the risk of AEH and EC in postmenopausal asymptomatic women and estimated the diagnostic accuracy of ultrasonography by comparing TVS ET thresholds with histopathologic diagnosis. The research protocol was designed a priori, defining methods for the literature screening, inclusion, and exclusion criteria before article examination, data extraction, tabulation, and analysis. The study was registered in the International Prospective Register of Systematic Reviews database (registration number: CRD42021241857) on April 9, 2021.

Data sources and search strategy

Electronic databases (MEDLINE, Scopus, SciELO, EMBASE, and LILACS) were searched from inception of each database without temporal limits and covered articles as early as March 1997 and as recently as May 2021. Search terms used were the following text words and Medical Subject Headings (MeSH): "endometrial carcinoma" or "atypical hyperplasia" and "asymptomatic" and "ultrasonography."

In addition, we searched CINAHL, PsycINFO, and AMED to retrieve other relevant articles and reduce publication bias. To capture further data, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform were also searched. Moreover, to search for abstracts of international and national conferences, the gray literature (National Technical Information Service and PsycExtra) was screened. In addition, the reference lists of all eligible articles and related reviews were examined to further screen for studies not included by electronic searches.

No language or geographic location restriction was applied. Commentaries, letters to the editor, editorials, and reviews were excluded from the search.

The electronic searches and the eligibility of the involved studies were independently evaluated by 2 authors (G.R. and S.G.V.). If disagreement arose, a third reviewer (P.D.F.) helped resolve questions of eligibility.

Study selection and data extraction

Studies were selected if they enrolled asymptomatic postmenopausal women who were evaluated for endometrial pathology by TVS and reported diagnostic accuracy data. As tests of diagnostic accuracy, included studies inherently had a crossover design where women served as their controls.

Studies that included premenopausal and/or perimenopausal women, studies that included women taking tamoxifen, hormonal therapy (HT), aromatase inhibitors, or any other selective estrogen receptor modulator or therapies with known effects on the endometrium, and studies that included women with active or a history of PMB were excluded. In addition, studies not reporting diagnostic accuracy data but only risk and/or prevalence of EC or AEH were also excluded.

The index test was TVS performed before endometrial sampling. The reference test used was the histopathologic analysis of endometrial biopsy specimens acquired from the same patient. Endometrial sampling was performed using any available technique to provide an adequate endometrial tissue sample.

The abstraction forms were created specifically for this DTA meta-analysis. Key characteristics recorded included patient descriptors, study duration, setting, ultrasonographic ET evaluated, features of the cohort and ET, outcomes evaluated, mean follow-up length, results, and quality elements.

All abstracts were screened, reviewed, and classified by 2 authors (G.R. and S.G.V.) independently. The concordance for plausible relevance was accomplished by consensus; the same 2 authors performed a full-text assessment of the eligible studies and independently extracted considerable data about the characteristics and the outcomes of interest described in the study. All the inconsistencies were discussed by the reviewers, and a consensus was reached by asking a third author (T.P.M.). If necessary, other unpublished data were obtained by establishing direct contact with the authors of the original articles whenever the methodology indicated that additional outcome data were reported.

Assessment of risk of bias

The methodology of the included studies was analyzed by 3 authors (L.D.C., S.H., and P.D.F.) through a qualitative instrument for data collection (Quality Assessment Tool for Diagnostic Accuracy Studies 2 [QUADAS-2]; University of Bristol, Bristol, United Kingdom), as recommended by the Agency for Healthcare Research and Quality.[17] This tool consists of 4 domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. All domains are assessed for risk of bias, and the first 3 domains are assessed for applicability concerns by indicating a low, high, or unclear risk.

The assessment of the risk of bias was independently judged by 3 authors (L.D.C, J.P.P., and S.H.). The disagreement was resolved by discussion with a fourth reviewer (P.D.F.).

Primary and secondary outcomes

The coprimary outcomes for this meta-analysis were the risk of EC and AEH according to each ET threshold for

recommending subsequent endometrial sampling, outlined by included studies, and DTA of TVS for each threshold using the following statistics: diagnostic odds ratio (DOR) and area under the curve (AUC) of the summary receiver operator curve (SROC) and summary estimates of the sensitivity and specificity. The secondary outcomes were the positive likelihood ratio (PLR) and negative likelihood ratio (NLR).

Data extraction and statistical analysis

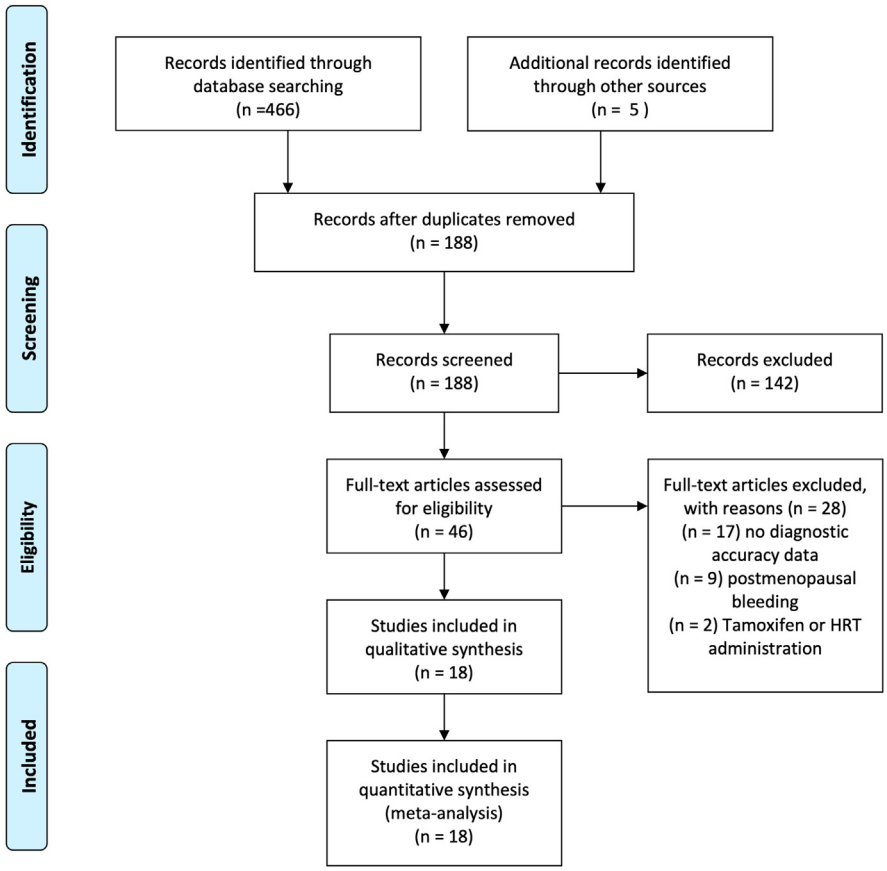
Statistical parameters—including true positive (TP), true negative (TN), false positive (FP), and false negative (FN)—were directly extracted from the study, and if not available, they were calculated and arranged in a 2×2 table; for these circumstances, we used the following formulas: sensitivity = TP/(TP+FN) and specificity = TN/(FP+TN).

When multiple ultrasonographic cutoffs were used in a single study, data were reported and analyzed for each included threshold.

Subsequently, to evaluate differences between lower and higher ET thresholds, we performed the analysis based on the ultrasonographic measurement of ET used as a threshold in qualified articles.

For each ET at the prespecified threshold, to calculate the overall DTA, we used the bivariate model according to Reitsma.[15] We evaluated the DOR through the DerSimonian-Laird random-effects model and the AUC of the SROC. The SROC and its derived AUC have been recommended to represent the performance of a diagnostic test, based on data from a meta-analysis.[18] The SROC represents the relationship between sensitivity and specificity across involved studies. The AUC ranges from 1 for a perfect diagnostic test that correctly identifies all cases and noncases of a known pathology to 0 for a test that is never able to correctly diagnose the disease.[18] Moreover, we obtained paired forest plots, showing the variation in accuracy between studies for sensitivity and specificity. The PLRs and NLRs were calculated through summary estimates of the sensitivity and specificity.

FIGURE 1
Flowchart of studies identified for diagnostic accuracy meta-analysis



Vitale. Endometrial thickness thresholds and risk of malignancy. Am J Obstet Gynecol 2023.

The bivariate method of Reitsma uses logistic regression on the TP, TN, FP, and FN values reported in the studies. We constructed SROCs and plotted confidence regions for each.[18] The average operating point for each test was identified on each curve, and pooled sensitivities and specificities were computed. In cases of insufficient data for estimating all variables, we simplified the SROC model by assuming a symmetrical shape of the SROC curve. We assessed the significance of the difference in test performance by using a likelihood ratio test comparing models with and without covariate terms for accuracy at equivalent threshold levels.

According to the available literature[14,19,20] and to apply the bivariate model, which requires a minimum of 4 datasets to run the analysis, threshold subgroups were divided as follows: ET between 3 and 5.9 mm, ET between 6.0 and 9.9 mm, ET between 10.0 and 13.9 mm, and ET ≥14.0 mm.

Heterogeneity was assessed using the Higgins I^2 index in which 0% means no heterogeneity and 100% represents the highest degree of heterogeneity.[21] Publication bias was assessed using the Deek funnel plot asymmetry test for each outcome and each subgroup, and a P value <.05 was considered to reflect significant publication bias. For all data analyses, Stata (version 14.1; StataCorp LLC, College Station, TX) with a *MIDAS* package was used to calculate relative risks (RRs), DORs, and AUCs, and the Review Manager (version 5.3; 2014; Nordic Cochrane Centre, Copenhagen,

TABLE 1
Main characteristics of studies included in diagnostic accuracy meta-analysis

Study, year	Design	Duration	Location	Patients	Primary outcome	Secondary outcomes	Endometrial thickness thresholds	Endometrial biopsy technique
Hefler et al,[19] 2018	Multicentric prospective	2015–2018	Austria	900	Endometrial cancer risk	Endometrial thickness	10.0 mm 12.0 mm 15.0 mm 20.0 mm	In-office hysteroscopic endometrial biopsy
Ozelci et al,[22] 2019	Monocentric retrospective	2012–2013	Turkey	266	Endometrial cancer risk	Endometrial thickness	6.0 mm 11.0 mm 16.0 mm 21.0 mm	In-patient hysteroscopy
Ghoubara et al,[20] 2018	Monocentric retrospective	2011–2015	United Kingdom	1995	Endometrial cancer risk	Diagnostic accuracy	10.0 mm	Pipelle or office hysteroscopy
Li et al,[23] 2019	Monocentric retrospective	2006–2016	United States	2898	Endometrial cancer risk	Diagnostic accuracy	11.0 mm	In-office hysteroscopic endometrial biopsy
Famuyide et al,[12] 2014	Monocentric retrospective	2007–2011	United States	154	Endometrial cancer rate	NA	10.0 mm	In-office hysteroscopic endometrial biopsy
Jiang et al,[24] 2019	Monocentric prospective	2013–2015	China	234	Diagnostic accuracy	Cutoff differences	11.0 mm	In-office hysteroscopic endometrial biopsy
Laiyemo et al,[25] 2016	Monocentric retrospective	2008–2010	United Kingdom	63	Diagnostic accuracy	Endometrial cancer risk	11.0 mm	In-office hysteroscopic endometrial biopsy
Seckin et al,[26] 2016	Monocentric prospective	2012–2014	Turkey	328	Best cutoff	Diagnostic accuracy for asymptomatic women	11.0 mm	Pipelle or D&C
Jokubkiene et al,[27] 2016	Monocentric prospective	2008–2010	Sweden	96	Intracavitary lesion number	SCSH attempt	5.0 mm	In-patient hysteroscopic surgery
Louie et al,[28] 2016	Monocentric retrospective	2008–2013	United States	435	Malignant pathology threshold for endometrial thickness	Risk of cancer or AEH	14.0 mm	Hysteroscopy
Fleischer et al,[29] 2001	Multicentric prospective	1998–2000	Europe-United States	1792	Idoxifene safety	Endometrial cancer risk	6.0 mm	Aspiration biopsy
Kasraeian et al,[30] 2011	Monocentric prospective	2009–2010	Iran	259	Cutoff value	Diagnostic accuracy	5.0 mm	In-office hysteroscopic endometrial biopsy
Yasa et al,[31] 2016	Monocentric retrospective	2003–2012	Turkey	276	Cutoff value	Endometrial cancer prevalence	8.0 mm 12.0 mm	In-office hysteroscopic endometrial biopsy
Cohen et al,[32] 1999	Monocentric prospective	1996–1998	United States	60	EC and AEH prevalence	Diagnostic accuracy	5.0 mm	Unspecificed or endocyte
Gouveia et al,[33] 2007	Monocentric retrospective	NR	Brazil	47	EC and AEH prevalence	Diagnostic accuracy	5.0 mm	Pipelle biopsy

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

(continued)

TABLE 1
Main characteristics of studies included in diagnostic accuracy meta-analysis *(continued)*

Study, year	Design	Duration	Location	Patients	Primary outcome	Secondary outcomes	Endometrial thickness thresholds	Endometrial biopsy technique
Güven et al,[34] 2004	Monocentric retrospective	NR	Turkey	97	EC and BMI correlation	Diagnostic accuracy	5.0 mm	D&C
Paraskevaidis et al,[35] 2002	Monocentric prospective	2000	Greece	59	Diagnostic accuracy	Mean endometrial thickness	9.0 mm	Karman biopsy
Tsuda et al,[36] 1997	Monocentric retrospective	NR	Japan	375	Diagnostic accuracy	EC and AEH prevalence	3.0 mm 4.0 mm 6.0 mm 8.0 mm	Endocyte

AEH, atypical endometrial hyperplasia; *BMI*, body mass index; *D&C*, dilation and curettage; *EC*, endometrial carcinoma; *NA*, not available; *NR*, not reported; *SCSH*, saline contrast sonohysterography.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

Denmark) was used both to generate paired forest plots of sensitivity and specificity and to draw SROCs.

Results

Study selection

We identified and evaluated 466 initial studies (Figure 1). Of these, 18 studies involving 10,334 patients, who underwent sequential TVS followed by histopathologic analysis through endometrial biopsy, were considered for inclusion in this meta-analysis (Table 1). We excluded 283 articles as duplicates, 17 for not providing diagnostic accuracy data for at least 1 ET threshold, 9 studies for including women with PMB, and 2 trials for not excluding women treated with hormone replacement therapy or tamoxifen.

Study characteristics

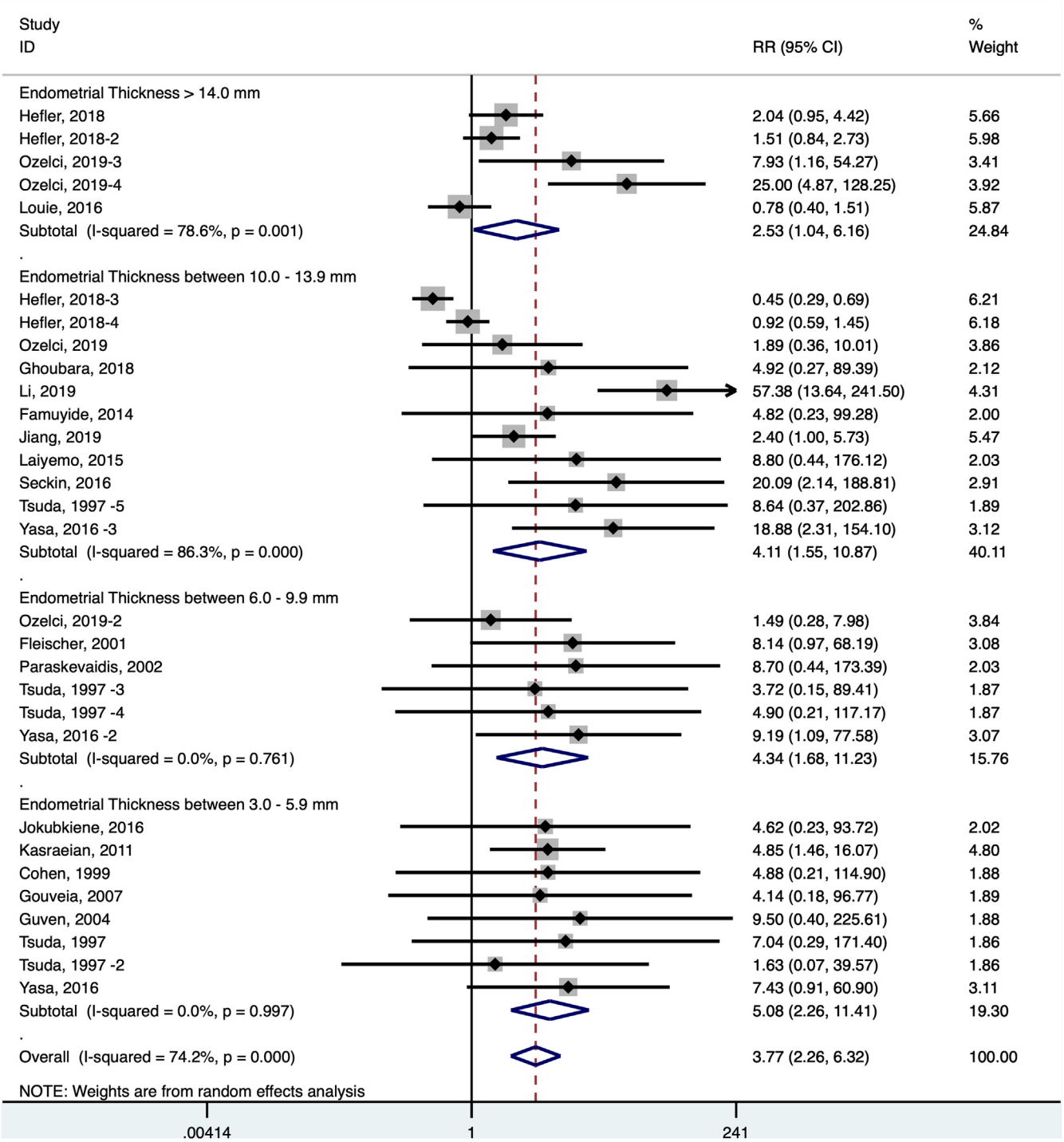
Among the 18 included studies, 14 analyzed a single cutoff,[12,20,23–30,32–35] whereas 4[19,22,31,36] evaluated multiple cutoffs (Table 1). All studies used a crossover comparison in which ultrasonographic ET was compared with subsequent endometrial biopsy followed by histopathologic examination (Table 2). For endometrial sampling, 11 of 18 studies (61%) used hysteroscopy, whereas the rest of the trials involved dilation and curettage (D&C), Pipelle, Vabra, Endocyte, or Karman or aspiration biopsy techniques (Table 1).

The ET thresholds evaluated by the 18 studies ranged from 3.0 mm to 21.0 mm. Of note, 8 studies[27,30–34,36] evaluated an ET threshold of <6.0 mm. Moreover, 4 studies[22,29,31,35,36] investigated a threshold between 6.0 and 9.9 mm. In addition, 10 studies[12,19,20,22–26,31,36] considered an ET cutoff between 10.0 and 13.9 mm, and 3 studies[19,22,28] performed a DTA analysis for thresholds of ≥14.0 mm.

Risk of bias

The methodological assessment of the included reports according to the QUADAS-2 is presented in Supplemental Figures 1 and 2. Overall, low scores relative to the risk of bias and applicability concerns were achieved for most included articles. Only 1 study

FIGURE 2
Endometrial carcinoma or atypical hyperplasia RR according to endometrial thickness



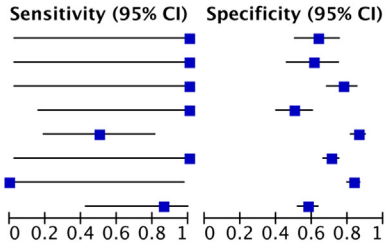
CI, confidence interval; *RR*, relative risk.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

FIGURE 3
Pooled sensitivity and specificity plots for endometrial thickness thresholds

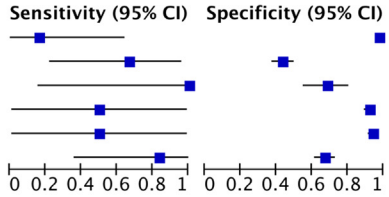
Endometrial thickness between 3.0 – 5.9 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Cohen, 1999	1	22	0	38	5.0	1.00 [0.03, 1.00]	0.63 [0.50, 0.75]
Gouveia, 2007	1	18	0	28	5.0	1.00 [0.03, 1.00]	0.61 [0.45, 0.75]
Guven, 2004	1	22	0	75	5.0	1.00 [0.03, 1.00]	0.77 [0.68, 0.85]
Jokubkiene, 2016	2	47	0	47	5.0	1.00 [0.16, 1.00]	0.50 [0.40, 0.60]
Kasraeian, 2011	5	36	5	218	5.0	0.50 [0.19, 0.81]	0.86 [0.81, 0.90]
Tsuda, 1997	1	110	0	264	3.0	1.00 [0.03, 1.00]	0.71 [0.66, 0.75]
Tsuda, 1997 -2	0	63	1	311	4.0	0.00 [0.00, 0.97]	0.83 [0.79, 0.87]
Yasa, 2016	6	114	1	155	4.0	0.86 [0.42, 1.00]	0.58 [0.51, 0.64]



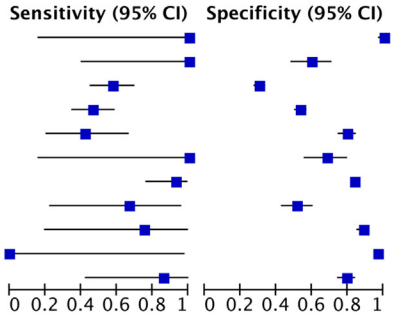
Endometrial thickness between 6.0 – 9.9 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Fleischer, 2001	1	41	5	1475	6.0	0.17 [0.00, 0.64]	0.97 [0.96, 0.98]
Ozelci, 2019	4	148	2	114	6.0	0.67 [0.22, 0.96]	0.44 [0.37, 0.50]
Paraskevaidis, 2002	2	18	0	39	9.0	1.00 [0.16, 1.00]	0.68 [0.55, 0.80]
Tsuda, 1997 – 4	1	30	1	344	6.0	0.50 [0.01, 0.99]	0.92 [0.89, 0.95]
Tsuda, 1997 -3	1	23	1	351	8.0	0.50 [0.01, 0.99]	0.94 [0.91, 0.96]
Yasa, 2016 -2	5	89	1	181	8.0	0.83 [0.36, 1.00]	0.67 [0.61, 0.73]



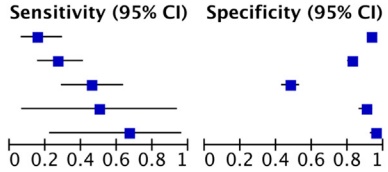
Endometrial thickness between 10.0–13.9 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Famuyide, 2014	2	0	0	107	10.0	1.00 [0.16, 1.00]	1.00 [0.97, 1.00]
Ghoubara, 2018	4	31	0	46	10.0	1.00 [0.40, 1.00]	0.60 [0.48, 0.71]
Hefler, 2018 -2	38	572	28	252	10.0	0.58 [0.45, 0.70]	0.31 [0.27, 0.34]
Hefler, 2018 -3	33	386	38	443	12.0	0.46 [0.35, 0.59]	0.53 [0.50, 0.57]
Jiang, 2019	8	54	11	210	11.0	0.42 [0.20, 0.67]	0.80 [0.74, 0.84]
Laiyemo, 2015	2	20	0	43	11.0	1.00 [0.16, 1.00]	0.68 [0.55, 0.79]
Li, 2019	25	463	2	2353	11.0	0.93 [0.76, 0.99]	0.84 [0.82, 0.85]
Ozelci, 2019 -2	4	64	2	68	11.0	0.67 [0.22, 0.96]	0.52 [0.43, 0.60]
Seckin, 2016	3	37	1	287	11.0	0.75 [0.19, 0.99]	0.89 [0.85, 0.92]
Tsuda, 1997 -5	0	13	1	361	10.0	0.00 [0.00, 0.97]	0.97 [0.94, 0.98]
Yasa, 2016 -3	6	56	1	213	4.0	0.86 [0.42, 1.00]	0.79 [0.74, 0.84]



Endometrial thickness > 14.0 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Hefler, 2018	7	61	38	794	20.0	0.16 [0.06, 0.29]	0.93 [0.91, 0.94]
Hefler, 2018 -4	14	151	38	697	15.0	0.27 [0.16, 0.41]	0.82 [0.79, 0.85]
Louie, 2016	16	210	19	192	14.0	0.46 [0.29, 0.63]	0.48 [0.43, 0.53]
Ozelci, 2019 -3	2	26	2	236	16.0	0.50 [0.07, 0.93]	0.90 [0.86, 0.93]
Ozelci, 2019 -4	4	12	2	248	21.0	0.67 [0.22, 0.96]	0.95 [0.92, 0.98]



CI, confidence interval; *FN*, and false negative; *FP*, false positive; *TN*, true negative; *TP*, true positive.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

was considered at high risk of bias and applicability of findings issues by the authors.

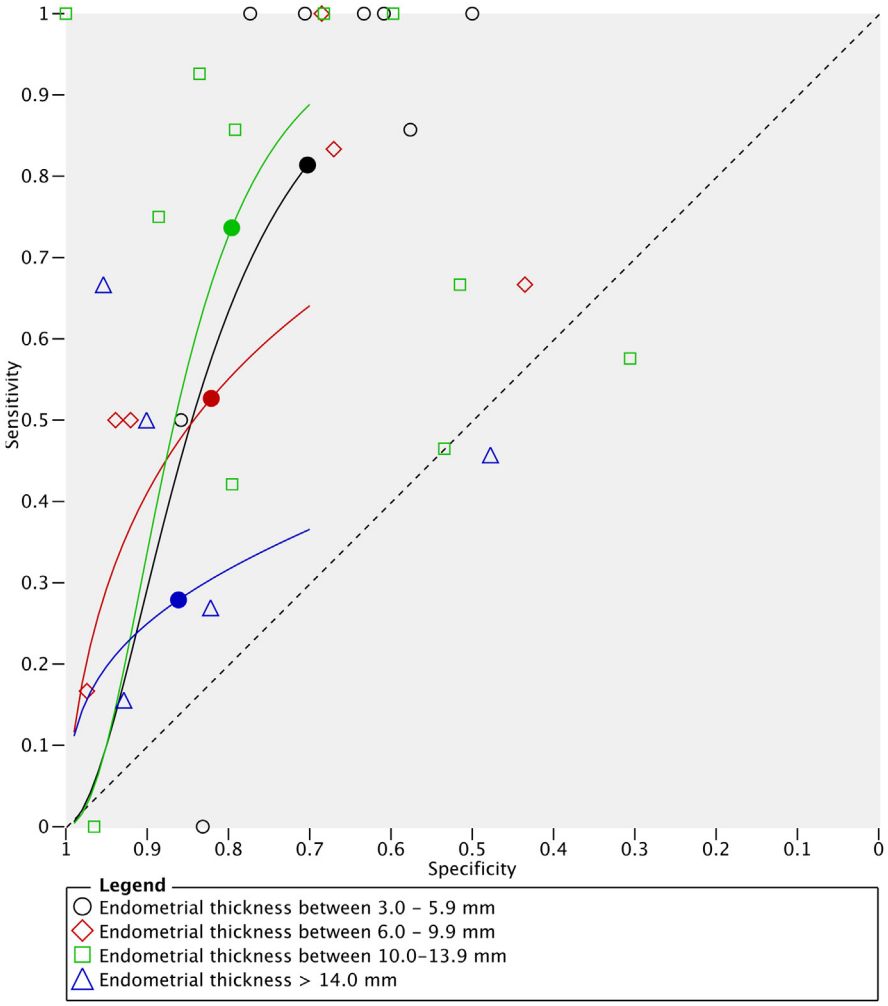
The Deek funnel plot asymmetry test was performed to evaluate the publication bias among the eligible studies. We found no significant publication bias in this meta-analysis for <5.9 mm (P=.38), between 6.0 and 9.9 mm (P=.27), between 10.0 and 13.9 mm (P=0.07), and ≥14.0 mm (P=.17) thresholds.

Synthesis of results

An ultrasonographic ET threshold for recommending endometrial sampling of at least 3.0 mm in asymptomatic postmenopausal women resulted in a 3-fold increased risk of finding AEH or EC at subsequent endometrial biopsy (RR, 3.77; 95% confidence interval [CI], 2.26−6.32; I^2=74%) compared with asymptomatic women with an ET <3.0 mm. This increased risk was also observed for ET thresholds between 3.0 and 5.9 mm (RR, 5.08; 95% CI, 2.26−11.41; I^2=0%), between 6.0 and 9.9 mm (RR, 4.34; 95% CI, 1.68−11.23; I^2=0%), between 10.0 and 13.9 mm (RR, 4.11; 95% CI, 1.55−10.87; I^2=86%), and ≥14.0 mm (RR, 2.53; 95% CI, 1.04−6.16; I^2=78%) (Figure 2). Overall, there was no significant risk difference among the cutoff subgroups (P=.885).

When the DTA meta-analysis was performed, the pooled sensitivity,

FIGURE 4
Summary receiver operator curves for endometrial thickness thresholds



Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

specificity, PLR, and NLR of TVS at a threshold for ET to subsequent endometrial biopsy between 3.0 and 5.9 mm were 0.81 (95% CI, 0.49–0.85), 0.70 (95% CI, 0.61–0.78), 2.7 (95% CI, 2.0–3.7), and 0.26 (95% CI, 0.08–0.86), respectively, with a DOR of 10 (95% CI, 3–41) and an AUC of 0.81 (95% CI, 0.77–0.84).

Conducting a DTA meta-analysis for ET thresholds between 6.0 and 9.9 mm resulted in a sensitivity of 0.53 (95% CI, 0.27–0.77) and a specificity of 0.82 (95% CI, 0.64–0.92), and the PLR and NLR were 3.0 (95% CI, 1.6–5.6) and 0.58 (95% CI, 0.35–0.94), respectively. Pooled DOR was 5 (95% CI, 2–13), with an AUC of 0.71 (95% CI, 0.67–0.75).

When analyzing the accuracy of ET thresholds between 10.0 and 13.9 mm, pooled sensitivity was 0.74 (95% CI, 0.54–0.87), and a specificity of 0.80 (95% CI, 0.62–0.91), a PLR of 3.6 (95% CI, 1.6–8.4), and an NLR of 0.33 (95% CI, 0.16–0.70) were retrieved. Moreover, the DOR was 11 (95% CI, 2–49), with an AUC of 0.82 (95% CI, 0.79–0.86).

Lastly, an ET ≥14.0 mm obtained a sensitivity of 0.28 (95% CI, 0.18–0.40), with a specificity of 0.86 (95% CI, 0.71–0.94), a PLR of 2.0 (95% CI, 1.1–3.7), and an NLR of 0.84 (95% CI, 0.75–0.94), resulting in a DOR of 2 (95% CI, 1–5) with an AUC of 0.45 (95% CI, 0.41–0.50).

At the lowest threshold (from 3.0 to 5.9 mm), pooled sensitivity reached the highest value, although pooled specificity was slightly lower (0.70) than for higher thresholds (0.82, 0.8, and 0.86, respectively), as also depicted by forest plots for sensitivity and specificity (Figure 3). As the threshold increased, pooled sensitivity decreased (fewer endometrial biopsies were performed, failing to diagnose some patients with AEH or EC), and specificity slightly increased (Figure 4). However, although the other SROCs demonstrated similar pathways, the curve design for an ET threshold of >14 mm showed the lowest diagnostic accuracy. The summary sensitivity and specificity points with 95% confidence bands for each threshold subgroup are displayed in Figure 5.

A clear overlap of the confidence bands for each 1 of the ET thresholds subgroups was present, showing no statistically significant difference between the investigated ET subgroups. However, the summary point for an ET ≥14.0 mm was positioned lower in the SROC space (Figure 5), suggesting that a worse diagnostic accuracy is expected when choosing higher cutoffs because of low sensitivity and the lowest AUC (0.45), relative to 3.0 to 5.9 mm, 6.0 to 9.9 mm, and 10.0 to 13.9 mm cutoffs (0.81, 0.71, and 0.82, respectively).

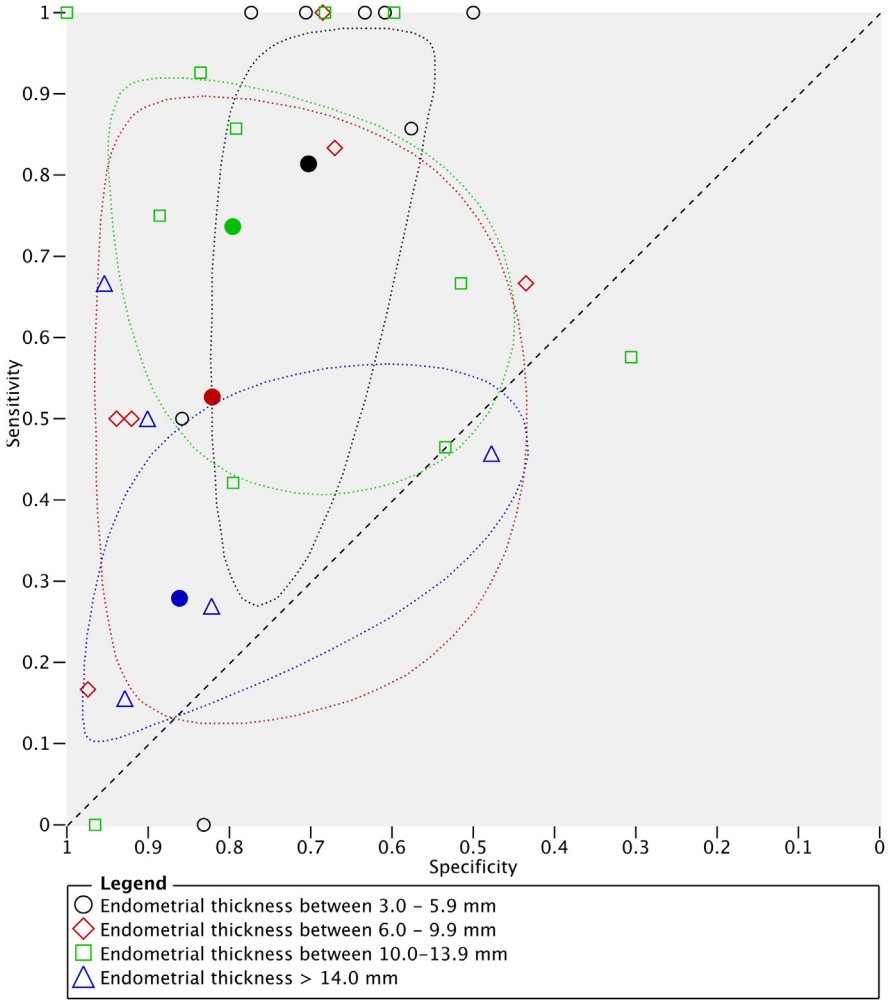
Comment

Principal findings

This systematic review and meta-analysis demonstrated that the risk of EC and AEH in postmenopausal asymptomatic women with an incidental ultrasonographic finding of ET of ≥3.0 mm is 3-fold higher than postmenopausal asymptomatic women with an ultrasound ET under the 3.0 mm threshold to perform endometrial sampling with histopathologic examination. This suggested that it is a higher yield to perform endometrial sampling with a histopathologic examination in women with these findings. However, no substantial risk difference was found compared with higher ultrasonographic thresholds for ET. Regarding the DTA analysis, choosing an ultrasonographic ET threshold between 3.0 and 5.9 mm

when deciding to sample the endometrium to screen for EC demonstrated higher sensitivity, although DOR and AUC were similar between 3.0 to 5.9 mm and 10.0 to 13.9 mm. The highest specificity was obtained with a TVS ET threshold of ≥14.0 mm, but this was associated with much lower sensitivity. Summary point analysis demonstrated the <6.0 mm cutoff point to be higher in the SROC space, showing that, despite a lower specificity, there were reduced chances of missing the EC or AEH diagnosis using these cutoff values.

FIGURE 5
Summary points on SROC curve spaces for endometrial thickness thresholds



Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

Comparison with existing literature

The prognosis of EC in asymptomatic postmenopausal women is similar to the cancer prognosis of women presenting with vaginal bleeding. However, screening of asymptomatic women for EC or AEH is currently not recommended, and when a thickened endometrium is incidentally found in asymptomatic patients, recommended ET thresholds to prompt endometrial tissue sampling are not well defined. Although a low ET threshold is less likely to miss EC, the associated high number to treat for EC or AEH detection can have meaningful implications for cost and patient experience.[37] In addition, the study based on a theoretical cohort by Smith-Bindman et al[14] and the United Kingdom Collaborative Trial of Ovarian Cancer Screening study[37] reported that adopting an ET threshold value >10.0 mm or 12.0 mm seemed to be a promising way to reduce the number of excessive second-level examinations while, consequentially, improving the early detection of cases of endometrial malignancy.

However, data retrieved in our meta-analysis showed no difference in the risk of EC or AEH between low and high ET thresholds. Moreover, the use of higher ET thresholds to recommend further endometrial investigation in asymptomatic postmenopausal women, although increasing the specificity of TVS to diagnose EC, decreased the number of women undergoing endometrial tissue sampling, therefore lowering the overall sensitivity of the diagnostic test (Figure 3).

Office hysteroscopy reduces cost and complexity relative to scheduling at-risk postmenopausal women to blind dilation and curettage performed in the operating room under general anesthesia.[38,39] The enhanced accuracy inherent to directly visualized biopsy of pathology is an important consideration, particularly when most studies used hysteroscopic sampling as the reference test. In-office hysteroscopic endometrial biopsy facilitates identification of cornual pathology, which would be more likely to be missed when blind sampling disproportionately assesses the posterior midline of an anteflexed uterus. The enhanced sensitivity relative to blind office sampling and the lower cost relative to a D&C in the operating room should be considered when considering modern thresholds for endometrial sampling. Several studies have confirmed the cost-effectiveness of the in-office hysteroscopic-guided endometrial biopsy under direct visualization in the management of postmenopausal women with EC[40] and other intrauterine conditions.[41,42] Although a visual approach should be

TABLE 2
Inclusion and exclusion criteria

Study, year	Inclusion criteria	Exclusion criteria
Hefler et al,[19] 2018	Asymptomatic postmenopausal women with an endometrium larger than 3 mm	Use of tamoxifen, known hereditary nonpolyposis colon cancer and Lynch syndrome
Ozelci et al,[22] 2019	Postmenopause and symptoms absent. ET ≥6 mm (double layer) without any symptoms	Premenopausal and perimenopausal women, patients on HRT, and patients with a history of uterine malignancy; tamoxifen use.
Ghoubara et al,[20] 2018	Postmenopausal women with incidental finding of ET >4 mm in the absence of bleeding	NA
Li et al,[23] 2019	ET ≥5 mm in asymptomatic postmenopausal women	NA
Famuyide et al,[12] 2014	Postmenopausal women with >4 mm ET on ultrasound and without uterine bleeding	NA
Jiang et al,[24] 2019	Postmenopausal endometrium ≥5 mm or uterine cavity lesion without history of postmenopausal bleeding	AUB
Laiyemo et al,[25] 2016	Postmenopausal women with thickened endometrium and without postmenopausal bleeding	NA
Seckin et al,[26] 2016	Asymptomatic thickened endometrium (>5 mm)	Abnormal vaginal bleeding, HRT, or tamoxifen use
Jokubkiene et al,[27] 2016	Postmenopause and no systemic or local HRT with absence of symptoms	Current hormonal treatment for breast cancer; history of irregular menstruation or abnormal vaginal bleeding either before or after menopause; gynecologic surgery on the uterus, ovaries or Fallopian tubes (including sterilization) other than cone biopsy, loop electrosurgical excision procedure, dilation and curettage, cesarean delivery or surgical termination of pregnancy; hormonal therapy obscuring time of menopause
Louie et al,[28] 2016	Menopausal, no history of postmenopausal bleeding, and had an ET of at least 4 mm	History of endometrial hyperplasia or carcinoma, tamoxifen use, oral or transdermal hormone replacement therapy, endometrial ablation, hereditary cancer syndrome
Fleischer et al,[29] 2001	Postmenopausal women who had not undergone hysterectomy	History of endometrial abnormality, undiagnosed vaginal bleeding, oral or vaginal HRT within 6 mo of use, use of therapies that interact with the estrogen, history of breast cancer
Kasraeian et al,[30] 2011	Nonbleeding women who were referred to the outpatient clinics for routine follow-ups or other gynecologic problems, including pruritus and dysuria	AUB, history of endometrial pathologies, including cancer or hyperplasia, and coexisting malignancies, hormone replacement therapy, tamoxifen and raloxifene
Yasa et al,[31] 2016	Asymptomatic postmenopausal patients	(1) AUB; (2) history of endometrial pathologies, such as hyperplasia or cancer; (3) history or current use of hormone replacement therapy; (4) use of raloxifene and/or tamoxifen
Cohen et al,[32] 1999	Asymptomatic postmenopausal women	Presence of active uterine bleeding
Gouveia et al,[33] 2007	Asymptomatic postmenopausal patients	Women with history of AUB or using HRT
Güven et al,[34] 2004	Asymptomatic postmenopausal patients	BMI≥30
Paraskevaidis et al,[35] 2002	Unselected asymptomatic postmenopausal women	NR
Tsuda et al,[36] 1997	Amenorrhea for at least 1 y	HRT usage

AUB, abnormal uterine bleeding; *BMI*, body mass index; *ET*, endometrial thickness; *HRT*, hormone replacement therapy; *NR*, not reported.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

preferred to blind techniques, in poor-resource settings, the use of an in-office Pipelle biopsy remains an inexpensive and worldwide available technique to assess for uterine malignancy without surgery when a suspicious ET is ultrasonographically measured.[43]

Considering the number of biopsies performed in included studies, lowering the cutoff to a minimum ET of 3 mm could result in 44.8% of women having endometrial biopsies. However, false positives for potential cancer create a meaningful emotional burden, and this rate could be meaningfully reduced if secondary screening were implemented for a cutoff of 4 or 5 mm, where only 12.7% or 9.5% of women require additional evaluation. As this degree of reassessment is comparable to the 11.3% seen in the United States after cervical cancer screening,[44] this seems an already acceptable rate for gynecologic malignancy, although risk factors and cost-effectiveness considerations may further refine decision-making.

For this reason, to maximize the diagnostic accuracy, even if ET should be considered first line before performing endometrial tissue sampling to discover EC or AEH, a more accurate prediction model should include common risk factors (age, body mass index, HT use, and personal and family history for gynecologic and colorectal cancers) and other minor factors to improve sensitivity and avoid performing lower yield endometrial biopsies. However, evidence about a wider and more inclusive prediction model is lacking, as only a few models have been developed for asymptomatic women.[45]

Strengths and limitations

A strength of this study was the high number of studies included for DTA analysis. A previous meta-analysis by Breijer et al[46] from 2012 noted the paucity of diagnostic accuracy trials for ultrasonographic diagnosis of asymptomatic endometrial malignancies. To date, several new studies have been added to the literature, enhancing statistical power and confidence in the available scientific evidence and justifying an updated meta-analysis. Moreover, to improve validity, we restricted the analysis to only studies evaluating the diagnostic accuracy of sonographic ET, avoiding the inclusion of trials without a reference test or without reporting the number of true negatives. Another strength worth highlighting is the exclusion of studies involving cohorts of women receiving hormone therapy or tamoxifen, considering the drug's impact on the ET and, as a consequence, biasing the results of the meta-analysis.

Although there are meaningful strengths to this meta-analysis, several limitations should be acknowledged. First, although multiple studies were included in the data synthesis, as EC and AEH had low prevalence in the evaluated studies, the 95% CIs for the pooled sensitivity are wide, reflecting inconsistency among studies. Second, there were discrepancies among the number of ET cutoffs evaluated by the included trials, as 3 studies investigated the accuracy of multiple thresholds on the same cohort of women. Moreover, all included studies had inherently a crossover design, and the associated inherent limitations should be applied to the results of this meta-analysis. Specifically, a carryover from the results of the first diagnostic examination on the effect of the endometrial sampling could be applicable, therefore increasing the number of incorrect diagnoses. Another limitation is related to the analysis of sensitivity and specificity for each ET threshold subgroup, in which the evaluated CIs were wide in amplitude for both the parameters. This limitation should be linked to the low incidence of EC and AEH in all included studies, to the different ethnicities involved in the studies, to the presence of interobserver variability (as in each study more than one operator oversaw the ultrasonographic examinations), and to the technical advances in both ultrasonographic imaging and endometrial sampling techniques across 24 years of scientific progress, which have been increasing the diagnostic accuracy for EC over time. In addition, only 1 study was conducted in a low-income environment, hindering broader generalizability. Lastly, it should be acknowledged that approximately 10% of endometrial malignancies are type 2, nonendometrioid, adenocarcinomas, which are related to endometrial atrophy and not to increased ET. In such cases, standard TVS cannot be useful as a predictive tool for asymptomatic women.[46]

Conclusions and implications

This systematic review and DTA meta-analysis showed limited differences in diagnosing EC or AEH in asymptomatic postmenopausal patients with incidental findings of ET when using multiple threshold groups. Sensitivity decreases with increased thresholds, whereas specificity increases when shifting from lower to higher cutoffs. Although the use of a threshold between 3.0 and 5.9 mm had the highest sensitivity, this should be balanced with cost and patient convenience as screening protocols when deciding which asymptomatic postmenopausal women with increased ET should have a subsequent biopsy. Given that a $\geq$14.0 mm threshold for screening for EC or AEH in asymptomatic women misses 72% of cases, a lower cutoff likely will achieve better balances for efficacy, economics, and patient preference. In contrast, it also should be acknowledged that the use of an excessively low threshold will come with meaningful financial and psychological costs. The emotional burden inherent to following up potential malignancy can take a substantive toll on patients. There are ethical implications to minimizing such burdens, particularly when these false positives are found in asymptomatic women undergoing EC and AEH screening. ■

REFERENCES

1. Sroczynski G, Gogollari A, Conrads-Frank A, et al. Cost-effectiveness of early detection and prevention strategies for endometrial cancer-a systematic review. Cancers (Basel) 2020;12:1874.

2. La Rosa VL, Garzon S, Gullo G, et al. Fertility preservation in women affected by gynaecological cancer: the importance of an integrated gynaecological and psychological approach. Ecancermedicalscience 2020;14:1035.

3. Practice Bulletin No. 149: endometrial cancer. Obstet Gynecol 2015;125:1006–26.

4. Palipana D, Fomin I, Russell E, et al. Investigating women with postmenopausal bleeding: the utility of endometrial thickness in transvaginal ultrasound. Aust N Z J Obstet Gynaecol 2020;60:773–5.

5. Alcázar JL, Bonilla L, Marucco J, 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;46:565–70.

6. Elfayomy AK, Soliman BS. Risk factors associated with the malignant changes of symptomatic and asymptomatic endometrial polyps in premenopausal women. J Obstet Gynaecol India 2015;65:186–92.

7. Gemer O, Segev Y, Helpman L, 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;219:181.e1–6.

8. Choi JK, Park SI, Kim TH, Ryu SY, Lee ED. Diagnostic hysteroscopy in asymptomatic postmenopausal women with sonographically abnormal endometrial findings. J Minim Invasive Gynecol 2016;23:S184–5.

9. Farfaras A, Cumashi E, Soulos P, Pavlakis E, Drakontaidis A, Skolarikos P. Asymptomatic, postmenopausal women with sonographically thickened endometrium. Pathologic findings following hysteroscopic evaluation. Climacteric 2011;14:129.

10. Ferrazzi E, Zupi E, Leone FP, et al. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. Am J Obstet Gynecol 2009;200:235.e1–6.

11. Wan OY, Cheung RY, Chan SS, Chung TK. Risk of malignancy in women who underwent hysterectomy for uterine prolapse. Aust N Z J Obstet Gynaecol 2013;53:190–6.

12. Famuyide AO, Breitkopf DM, Hopkins MR, Laughlin-Tommaso SK. Asymptomatic thickened endometrium in postmenopausal women: malignancy risk. J Minim Invasive Gynecol 2014;21:782–6.

13. Konstadatou A, Burk I, Drakontaidis A, Musa D, Skolarikos P. Endometrial thickness and pathologic findings following hysteroscopy in asymptomatic postmenopausal women. Maturitas 2012;71:S78.

14. 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;24:558–65.

15. Salameh JP, Bossuyt PM, McGrath TA, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ 2020;370:m2632.

16. Sotiriadis A, Papatheodorou SI, Martins WP. Synthesizing Evidence from Diagnostic Accuracy TEsts: the SEDATE guideline. Ultrasound Obstet Gynecol 2016;47:386–95.

17. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.

18. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med 2002;21:1237–56.

19. Hefler L, Lafleur J, Kickmaier S, et al. Risk of endometrial cancer in asymptomatic postmenopausal patients with thickened endometrium: data from the FAME-Endo study: an observational register study. Arch Gynecol Obstet 2018;298:813–20.

20. Ghoubara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol 2018;38:1146–9.

21. Higgins JPT; Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions, 2nd ed. Hoboken, NJ: Wiley-Blackwell; 2020.

22. Ozelci R, Dilbaz B, Akpınar F, et al. The significance of sonographically thickened endometrium in asymptomatic postmenopausal women. Obstet Gynecol Sci 2019;62:273–9.

23. Li Z, Li L. Risk of malignancies among asymptomatic postmenopausal women with thickened endometrium: a cohort study. Medicine (Baltimore) 2019;98:e14464.

24. Jiang T, Yuan Q, Zhou Q, et al. Do endometrial lesions require removal? A retrospective study. BMC Womens Health 2019;19:61.

25. Laiyemo R, Dudill W, Jones SE, Browne H. Do postmenopausal women with thickened endometrium on trans-vaginal ultrasound in the absence of vaginal bleeding need hysteroscopic assessment? A Pilot Study. J Obstet Gynaecol 2016;36:223–6.

26. Seckin B, Cicek MN, Dikmen AU, Bostancı EI, Muftuoglu KH. Diagnostic value of sonography for detecting endometrial pathologies in postmenopausal women with and without bleeding. J Clin Ultrasound 2016;44:339–46.

27. Jokubkiene L, Sladkevicius P, Valentin L. Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol 2016;48:390–6.

28. Louie M, Canavan TP, Mansuria S. Threshold for endometrial sampling among postmenopausal patients without vaginal bleeding. Int J Gynaecol Obstet 2016;132:314–7.

29. Fleischer AC, Wheeler JE, Lindsay I, et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol 2001;184:70–5.

30. Kasraeian M, Asadi N, Ghaffarpasand F, Karimi AA. Value of transvaginal ultrasonography in endometrial evaluation of non-bleeding postmenopausal women. Climacteric 2011;14:126–31.

31. Yasa C, Dural O, Bastu E, Ugurlucan FG, Nehir A, İyibozkurt AC. Evaluation of the diagnostic role of transvaginal ultrasound measurements of endometrial thickness to detect endometrial malignancy in asymptomatic postmenopausal women. Arch Gynecol Obstet 2016;294:311–6.

32. Cohen MA, Sauer MV, Keltz M, Lindheim SR. Utilizing routine sonohysterography to detect intrauterine pathology before initiating hormone replacement therapy. Menopause 1999;6:68–70.

33. Gouveia DA, Bahamondes L, Aldrighi JM, Tamanaha S, Ribeiro AL, Aoki T. [Prevalence of endometrial injury in asymptomatic obese women]. Rev Assoc Med Bras (1992) 2007;53:344–8.

34. Güven MA, Pata O, Bakaris S, Kafkasli A, Mgoyi L. Postmenopausal endometrial cancer screening: is there a correlation between transvaginal sonographic measurement of endometrial thickness and body mass index? Eur J Gynaecol Oncol 2004;25:373–5.

35. Paraskevaidis E, Papadimitriou D, Kalantaridou SN, et al. Screening transvaginal uterine ultrasonography for identifying endometrial pathology in postmenopausal women. Anticancer Res 2002;22:1127–30.

36. Tsuda H, Kawabata M, Yamamoto K, Inoue T, Umesaki N. Prospective study to compare endometrial cytology and transvaginal ultrasonography for identification of endometrial malignancies. Gynecol Oncol 1997;65:383–6.

37. Jacobs I, Gentry-Maharaj A, Burnell M, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol 2011;12:38–48.

38. Vitale SG, Haimovich S, Laganà AS, et al. Endometrial polyps. An evidence-based diagnosis and management guide. Eur J Obstet Gynecol Reprod Biol 2021;260:70–7.

39. Vitale SG. The biopsy snake grasper Sec. Vitale: a new tool for office hysteroscopy. J Minim Invasive Gynecol 2020;27:1414–6.

40. Moawad NS, Santamaria E, Johnson M, Shuster J. Cost-effectiveness of office hysteroscopy for abnormal uterine bleeding. JSLS 2014;18:e2014.00393.

41. Vitale SG, Carugno J, Riemma G, et al. Hysteroscopy for assessing Fallopian tubal obstruction: a systematic review and diagnostic test accuracy meta-analysis. J Minim Invasive Gynecol 2021;28:769–78.

42. Vitale SG, Parry JP, Carugno J, et al. Surgical and reproductive outcomes after hysteroscopic removal of retained products of conception: a systematic review and meta-analysis. J Minim Invasive Gynecol 2021;28:204–17.

43. Piatek S, Warzecha D, Kisielewski F, Szymusik I, Panek G, Wielgos M. Pipelle biopsy and dilatation and curettage in clinical practice: are factors affecting their effectiveness the

same? J Obstet Gynaecol Res 2019;45:645–51.

44. Irwin K, Montaño D, Kasprzyk D, et al. Cervical cancer screening, abnormal cytology management, and counseling practices in the United States. Obstet Gynecol 2006;108:397–409.

45. Alblas M, Velt KB, Pashayan N, Widschwendter M, Steyerberg EW, Vergouwe Y. Prediction models for endometrial cancer for the general population or symptomatic women: a systematic review. Crit Rev Oncol Hematol 2018;126:92–9.

46. Breijer MC, Peeters JA, Opmeer BC, 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;40:621–9.

Appendix

MEDLINE (accessed through PubMed)

("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("diagnostic imaging"[MeSH Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasonography"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasonographies"[All Fields]) AND ((("thicken"[All Fields] OR "thickened"[All Fields] OR "thickening"[All Fields] OR "thickenings"[All Fields] OR "thickens"[All Fields]) AND ("endometrium"[MeSH Terms] OR "endometrium"[All Fields] OR "endometriums"[All Fields])) OR ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrial"[All Fields] AND "cancer"[All Fields]) OR "endometrial cancer"[All Fields]) OR (("atypic"[All Fields] OR "atypical"[All Fields] OR "atypicalities"[All Fields] OR "atypicality"[All Fields] OR "atypically"[All Fields] OR "atypicals"[All Fields] OR "atypism"[All Fields] OR "atypisms"[All Fields]) AND ("hyperplasia"[MeSH Terms] OR "hyperplasia"[All Fields] OR "hyperplasias"[All Fields])))

Embase

asymptomatic AND ('ultrasonography'/exp OR ultrasonography) AND ('thickened endometrium' OR (thickened AND ('endometrium'/exp OR endometrium)) OR 'endometrial cancer'/exp OR 'endometrial cancer' OR (endometrial AND ('cancer'/exp OR cancer)) OR 'atypical hyperplasia'/exp OR 'atypical hyperplasia' OR (atypical AND ('hyperplasia'/exp OR hyperplasia)))

Scopus

TITLE-ABS-KEY (asymptomatic AND ultrasonography AND (thickened AND endometrium OR endometrial AND cancer OR atypical AND hyperplasia))

Cochrane Central Register of Controlled Trials

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

CINAHL, PsycInfo, AMED, and PsycExtra (accessed through EBSCO—IDEM for Italian Universities)

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia) AND Cerca anche nel testo completo degli articoli; Applica argomenti equivalenti

SciELO

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

LILACS

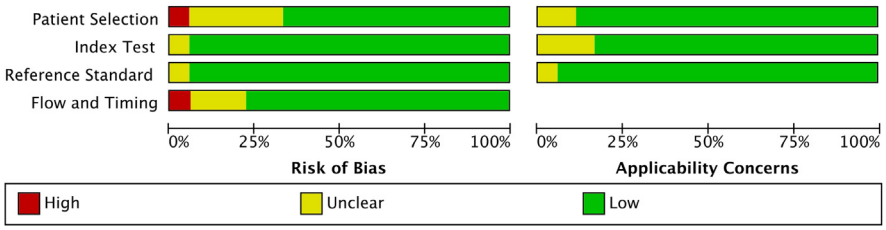
asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

ClinicalTrials, ClinicalTrials.gov and International Clinical Trials Registry Platform (accessed through Cochrane Central Register of Controlled Trials)

asymptomatic, asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

SUPPLEMENTAL FIGURE 1

Summary of risk of bias and applicability concerns (QUADAS-2 score)



QUADAS-2, Quality Assessment Tool for Diagnostic Accuracy Studies 2.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.

SUPPLEMENTAL FIGURE 2
Detailed risk of bias and applicability concerns (QUADAS-2 score)

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Cohen, 1999	?	+	+	+	?	?	+
Famuyide, 2014	+	+	+	+	+	+	+
Fleischer, 2001	+	?	+	+	+	?	+
Ghoubara, 2018	+	+	+	+	+	+	+
Gouveia, 2007	?	+	+	+	+	+	+
Guven, 2004	?	+	+	+	?	+	+
Hefler, 2018	+	+	+	+	+	+	+
Jiang, 2019	+	+	+	+	+	+	+
Jokubkiene, 2016	?	+	+	+	+	+	+
Kasraeian, 2011	+	+	+	+	+	+	+
Laiyemo, 2015	+	+	+	?	+	+	+
Li, 2019	+	+	+	+	+	+	+
Louie, 2016	+	+	+	?	+	+	+
Ozelci, 2019	+	+	+	+	+	+	+
Paraskevaidis, 2002	?	+	+	–	+	+	+
Seckin, 2016	+	+	+	+	+	+	+
Tsuda, 1997	–	+	?	?	+	?	?
Yasa, 2016	+	+	+	+	+	+	+

– High ? Unclear + Low

QUADAS-2, Quality Assessment Tool for Diagnostic Accuracy Studies 2.

Vitale. Endometrial thickness thresholds and risk for malignancy. Am J Obstet Gynecol 2023.