Gynecologic and Obstetric Investigation

Research Article

Gynecol Obstet Invest 2022;87:54–61
DOI: 10.1159/000522524

Received: September 9, 2021
Accepted: January 11, 2022
Published online: February 11, 2022

The Risk of Endometrial Malignancy and Other Endometrial Pathology in Women with Abnormal Uterine Bleeding: An Ultrasound-Based Model Development Study by the IETA Group

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Keywords
Abnormal uterine bleeding · Endometrial neoplasms · Endometrial disease · Ultrasonography · Prediction model

Abstract
Objectives: The aim of this study was to develop a model that can discriminate between different etiologies of abnormal uterine bleeding. ***Design:*** The International Endometrial Tumor Analysis 1 study is a multicenter observational diagnostic study in 18 bleeding clinics in 9 countries. Consecutive women with abnormal vaginal bleeding presenting for ultrasound examination (n = 2,417) were recruited. The histology was obtained from endometrial sampling, D&C, hysteroscopic resection, hysterectomy, or ultrasound follow-up for >1 year. ***Methods:*** A model was developed using multinomial regression based on age, body mass index, and ultrasound predictors to distinguish between: (1) endometrial atrophy, (2) endometrial polyp or intracavitary myoma, (3) endometrial malignancy or atypical hyperplasia, (4) proliferative/secretory changes, endometritis, or hyperplasia without atypia and validated using leave-center-out cross-validation and bootstrapping. The main outcomes are the model's ability to discriminate between the four outcomes

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and the calibration of risk estimates. ***Results:*** The median age in 2,417 women was 50 (interquartile range 43–57). 414 (17%) women had endometrial atrophy; 996 (41%) had a polyp or myoma; 155 (6%) had an endometrial malignancy or atypical hyperplasia; and 852 (35%) had proliferative/secretory changes, endometritis, or hyperplasia without atypia. The model distinguished well between malignant and benign histology (*c*-statistic 0.88 95% CI: 0.85–0.91) and between all benign histologies. The probabilities for each of the four outcomes were over- or underestimated depending on the centers. ***Limitations:*** Not all patients had a diagnosis based on histology. The model over- or underestimated the risk for certain outcomes in some centers, indicating local recalibration is advisable. ***Conclusions:*** The proposed model reliably distinguishes between four histological outcomes. This is the first model to discriminate between several outcomes and is the only model applicable when menopausal status is uncertain. The model could be useful for patient management and counseling, and aid in the interpretation of ultrasound findings. Future research is needed to externally validate and locally recalibrate the model.

Introduction

The development of diagnostic criteria that facilitate early referral of women to correct care is one of the most important research areas for endometrial cancer [1]. Blind sampling of endometrial tissue and hysteroscopy is traditional diagnostic tools for women with abnormal uterine bleeding, but they are invasive, associated with potential morbidity, and not always effective [2–6]. Blind sampling may miss localized intracavitary lesions [3, 7] and hysteroscopy provides information only on the uterine cavity, not on the myometrium or ovaries.

Transvaginal ultrasound is the recommended diagnostic tool to triage patients with abnormal uterine bleeding [8–11]. Several ultrasound-based models estimate the risk of endometrial cancer [12–18], and a few have been validated [19–21]. However, all are for postmenopausal women, whereas many women presenting at a bleeding clinic are perimenopausal. Moreover, a distinction between benign and malignant lesions may be too crude, as most patients with abnormal uterine bleeding have benign conditions that require a specific management.

The International Endometrial Tumor Analysis (IETA) group published a consensus statement on the assessment of ultrasound findings in the endometrium and uterine cavity [22] and set up large prospective multicenter studies to correlate ultrasound findings with intracavitary pathology [23–25]. The current aim was to develop and internally validate a model that estimates the probability of different pathologies in the uterine cavity in women with abnormal uterine bleeding, including perimenopausal women. The primary aim was to distinguish between malignancy and any benign condition, the secondary aim was to distinguish between different benign conditions.

Materials and Methods

In this observational study, 26 sonologists recruited consecutive patients with abnormal uterine bleeding between January 1, 2012, and December 31, 2015, in 19 centers (online suppl. Table S1; see www.karger.com/doi/10.1159/000522524 for all online suppl. material) in nine European countries. These were secondary or tertiary centers with a unit specialized in gynecological ultrasound, including some oncological referral centers.

The inclusion criteria were abnormal, nonpregnancy related, uterine bleeding (i.e., postmenopausal bleeding, heavy menstrual bleeding, intermenstrual bleeding, bleeding during continuous hormonal therapy (e.g., gestagen only, tibolone, tamoxifene), or abnormal bleeding during sequential estrogen-gestagen therapy). Exclusion criteria were (1) ultrasound examination failed or not performed, (2) missing histology combined with follow-up of less than 1 year, unknown follow-up time, or unknown endometrial thickness, (3) final diagnosis outside the scope of this study (online suppl. Fig. S1). It was recommended to scan premenopausal women not using hormonal therapy shortly after the last day of menstruation, but patients scanned at another time were not excluded.

Women had their history taken and underwent clinical and transvaginal gray scale and color or power Doppler ultrasound examination. Sonohysterography with saline or gel was added according to each center's local protocol. All data were entered into a dedicated web-based datasheet [26].

The outcome is histological category (based on required management): (1) atrophy, (2) endometrial polyp or intracavitary myoma, (3) endometrial malignancy or atypical hyperplasia, (4) proliferative or secretory changes, endometritis or hyperplasia without atypia. The histology was obtained from endometrial sampling, D&C, hysteroscopic resection, or hysterectomy (hysteroscopic resection in case of localized intracavitary lesions (endometrial polyp, intracavitary myoma), sampling per local guidelines in the absence of a localized intracavitary lesion). When multiple sampling methods were used in one patient, the clinically most relevant histological result was used in the statistical analysis (e.g., malignancy prioritized over myoma). The interval between ultrasound and histological sampling was maximally 120 days. The pathologist was not blinded to clinical and ultrasound information. In case no histology was available (22%), the outcome was based on follow-up (≥1 year) and ultrasound findings at inclusion (online suppl. Appendix S2).

Predictors

The candidate predictors were limited (to obtain 14 events for the smallest outcome category per variable) and selected based on

expert opinion. We chose age, body mass index, and endometrial characteristics at unenhanced ultrasound assessed at the inclusion scan. The ultrasound predictors were endometrial thickness, presence of a bright edge, color Doppler score, nonuniform echogenicity of the endometrium (including heterogeneous, asymmetrical, and cystic echogenicity), nonuniform cystic appearance of the endometrium, invisible endometrium. We adhered to IETA terms and definitions for the ultrasound predictors ([22], online suppl. Appendix S3). Blinding the assessment of one predictor to the value of others was not possible, but examiners were not aware of the histological diagnosis.

Statistical Analysis

To predict the probability of each of the four histological outcome categories, we used multinomial loglinear lasso (see online suppl. Appendix S2). As the patients attending the participating bleeding clinics are predominantly perimenopausal, a piecewise linear effect of age allowed the risks of each outcome category to change rapidly before or after the age of 50 years (see online suppl. Appendix S2).

To evaluate a model's ability to discriminate between the histological outcome categories, we present *c*-statistics (minimum value 0.5, optimally 1) for malignant vs. benign, pairwise *c*-statistics between all outcomes, and the polytomous discrimination index (the minimum value 0.25, optimally 1) [27]. To evaluate whether predicted probabilities are accurate, we present observed/expected ratios (ideally 1) and calibration slopes (ideally 1) [28]. All reported estimates are optimism-corrected (cluster bootstrap or leave-center-out cross-validation [see online suppl. Appendix S2]).

We compared the clinical utility of an increased malignancy risk according to the model to that of using sonographic endometrial thickness alone to decide which patients should undergo urgent office endometrial sampling (i.e., office sampling without delay with request for a quick reply by the pathologist, and if the histology result does not indicate malignancy, further testing to exclude a missed lesion). We also compared the model to office endometrial sampling in all women. Clinical utility is quantified as Net Benefit [29, 30]. Net Benefit considers the benefit of a true positive test result (in this case malignancy detected) versus the harm of a false-positive test result. We investigated scenarios where the acceptable number of urgent office biopsies yielding a benign result to detect one malignancy varied between 7 and 249.

We performed subgroup analyses of model performance by hormonal therapy and menopausal status. As the majority of women in our study is of perimenopausal age and abnormal bleeding was an inclusion criterion, we expect misclassification of menopausal status (postmenopausal defined as more than 12 months of amenorrhea in women older than 40 years provided that the amenorrhea was not explained by pregnancy, medication, or disease). We indicate this by using the terms "presumed" pre- or postmenopausal. In presumed postmenopausal women, we compared sensitivity and specificity regarding intracavitary malignancy of the unenhanced ultrasound model with that of endometrial thickness measurements alone. We dealt with missing data by imputation (online suppl. Appendix S2) and performed various sensitivity analyses to assess the robustness of our conclusions, e.g., to excluding women without histology (online suppl. Appendix S2).

Results

Of 2,856 women with abnormal vaginal bleeding presenting, 8 had no ultrasound, 354 had no histological outcome and <1-year follow-up, 77 had a diagnosis outside the study scope (e.g., retained products of conception) (online suppl. Fig. S1). The sample used for analysis consisted of 2,417 women.

The median age was 50 years (interquartile range, 43–57, range 19–94) (Table 1). The majority of (presumed) postmenopausal (753/1,002) and premenopausal (1,001/1,415) women were not using hormonal therapy. The median endometrial thickness was 9.0 mm (interquartile range 6.0 mm to 13.7 mm). Atrophy was found in 414 (17%) women, a polyp or myoma in 996 (41%), malignancy or atypical hyperplasia in 155 (6%), and proliferative or secretory changes, endometritis or hyperplasia without atypia in 852 (35%) (Table 1). The patients attending bleeding clinics differed between the centers (online suppl. Table S2): Skåne University Hospital has an outpatient bleeding clinic dedicated to postmenopausal women, Ospedale Luigi Sacco had most polyps or myomas, while University Hospitals Leuven had most proliferative or secretory changes.

The model and detailed instructions to calculate predicted probabilities for each outcome category can be found in appendix (online suppl. Tables S3, S4; online suppl. Appendices S3 and S5). The estimated effects of predictors were stable in our sensitivity analyses (online suppl. Appendix S5; online suppl. Tables S5–S7).

The model discriminated well between benign and malignant diagnoses in all centers (Fig. 1), with an overall optimism-corrected *c*-statistic of 0.88 (95% CI: 0.85–0.91). The model performed well in postmenopausal women (on or not on hormonal therapy) and in premenopausal women on hormonal therapy (*C*-indexes 0.71–0.89; online suppl. Fig. S2), but slightly worse in premenopausal women not using hormonal therapy (0.67, 95% CI: 0.55–0.80).

Using endometrial thickness ≥4.5 mm to indicate malignancy in postmenopausal women with measurable endometrium (n = 903), 72% of the women were classified as high risk, sensitivity was 97% and specificity was 32% (Table 2). When using the model's predicted malignancy risk ≥1.6%, also 72% of the women were classified as high risk, with slightly higher sensitivity (98%) and slightly lower specificity (29%). The sensitivities and specificities for other thresholds are presented in online supplementary Table S8. In contrast to endometrial thickness, the model can be applied in all women, including those with invisible or unmeasurable endometrium.

Table 1. Demographic background data, potential predictors, and outcomes (n = 2,417)

Age, years	50 (43–57)
BMI, kg/m^2	25 (22–29)
Postmenopausal	1,002 (41)
No hormonal therapy	753 (31)
Estrogen-only hormonal therapy	100 (4)
Any other hormonal therapy	149 (6)
Premenopausal	1,415 (59)
No hormonal therapy	1,001 (41)
Any hormonal therapy	414 (17)
Histology	
Atrophy	414 (17)
Atrophy (histologically confirmed)	224 (9)
Tentative diagnosis of atrophy (no histology)	190 (8)
Endometrial polyp, intracavitary myoma	996 (41)
Endometrial polyp (histologically confirmed)	749 (31)
Intracavitary myoma (histologically confirmed)	223 (9)
Tentative diagnosis of polyp or myoma (no histology)	24 (1)
Endometrial malignancy, atypical hyperplasia	155 (6)
Malignancy (histologically confirmed)	137 (6)
Atypical hyperplasia (histologically confirmed)	18 (1)
Proliferative or secretory changes, endometritis, hyperplasia without atypia	852 (35)
Proliferative endometrium (histologically confirmed)	304 (13)
Secretory endometrium (histologically confirmed)	306 (13)
Hyperplasia without atypia (histologically confirmed)	148 (6)
Endometritis (histologically confirmed)	22 (1)
Tentative diagnosis of proliferative or secretory endometrium (no histology)	72 (3)
Unenhanced ultrasound characteristics	
Visible endometrium	2,175 (90)
If visible	
Presence of bright edge	495 (23)
Color score	
No flow (1)	1,038 (48)
Minimal flow (2)	674 (31)
Moderate flow (3)	382 (18)
Abundant flow (4)	81 (4)
Single dominant vessel	500 (23)
Nonuniform echogenicity	993 (46)
Nonuniform cystic echogenicity	407 (19)
Endometrial thickness, mm	9.0 (6.0–13.7)

Results are presented as median (IQR) or n (%). IQR, interquartile range.

Table 2. Sensitivity and specificity with regard to malignancy/atypical hyperplasia for sonographic endometrial thickness and for the unenhanced ultrasound model in postmenopausal women with a measurable endometrium (n = 903)

	Classified as high risk, n/N (%)	Sensitivity (95% CI), %	Specificity (95% CI), %
Endometrial thickness, ≥4.5 mm	650/903 (72)	97 (93–99)	32 (29–35)
≥1.6% predicted risk of malignancy/atypical hyperplasia by unenhanced model	650/903 (72)	98 (94–99)	29 (26–33)

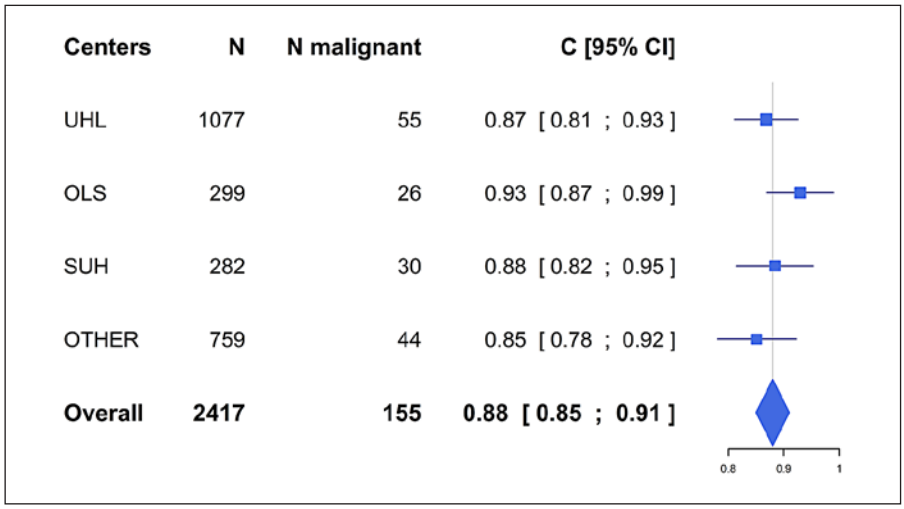

Fig. 1. *C*-statistic (any benign condition vs. malignant) per center and overall (optimism-corrected).

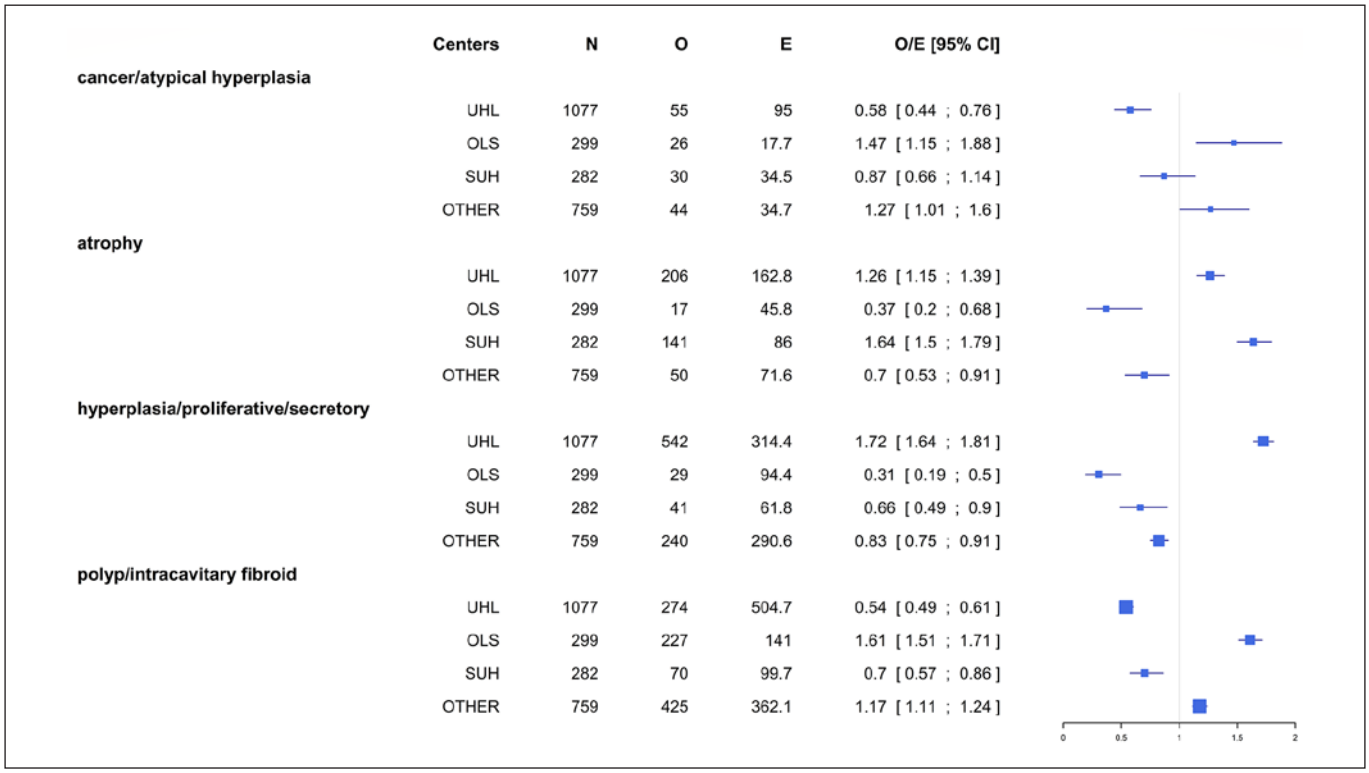

Fig. 2. Observed and expected number of cases in each outcome category. If the observed number of cases is higher than the expected number, then the model underestimates the probability of that outcome.

The model discriminated well between all categories (polytomous discrimination index 0.67, 95% CI: 0.63–0.75; online suppl. Fig. S3) with c-index ranging from 0.76 (95% CI: 0.74–0.79) for polyp or myoma versus proliferative or secretory endometrium to 0.94 (95% CI: 0.92–0.96) for atrophy versus malignancy.

Despite good discrimination, the model overestimated or underestimated the risk of certain histological outcomes in individual centers (Fig. 2). For example, in Ospedale Luigi Sacco, the observed number of atrophies and proliferative or secretory endometria was lower than expected, while the observed number of polyps and myo-

mas was higher. The risk of malignancy was higher than expected in postmenopausal women not on hormonal therapy and the risk may be lower for others, but the number of malignancies per group was too small for firm conclusions (online suppl. Fig. S4). The optimism corrected calibration slopes indicate negligible overfitting (online suppl. Table S9).

If one is willing to perform a maximum of 20 urgent office biopsies to detect one malignancy in (presumed) postmenopausal women, then using the model was the superior to endometrial thickness (cut-off 3, 4.5, or 7 mm) and to endometrial sampling in all women, in all centers (online suppl. Fig. S5). In contrast, if one is willing to perform more than 20 urgent office biopsies to detect one malignancy in (presumed) postmenopausal women, there was no universal best strategy, but the model was among the best strategies in each center. In (presumed) premenopausal patients, the best strategy differed from center to center (online suppl. Fig. S6).

Discussion

This model, combining age, BMI, and endometrial thickness with six other easy and clearly defined ultrasound characteristics discriminates very well between: (1) atrophy, (2) endometrial polyp or intracavitary myoma, (3) endometrial malignancy or atypical hyperplasia, and (4) proliferative or secretory changes, endometritis or hyperplasia without atypia. It can be used in perimenopausal women and women with an invisible or unmeasurable endometrium. The predicted risks of a certain outcome category may be an under- or overestimation for a specific patient. Despite this, the model is superior to doing a biopsy in all postmenopausal women and to endometrial thickness measurements (with 3, 4.5, or 7 mm cut-off) if one is willing to perform a maximum of 20 urgent biopsies to detect one malignancy, and competitive to the other strategies if one is willing to perform more biopsies. The IETA 1 study is the largest study to date to relate ultrasound characteristics to different conditions in the uterine cavity using a uniform terminology.

Limitations

A limitation is that not all patients had a diagnosis based on histology. Some diagnoses based on ultrasound and follow-up may be incorrect, but the exclusion of cases without histology did not change the effects of the included predictors. Another limitation is that our model over- or underestimated risks for certain outcomes in some centers. The regression equations that we present have been re-estimated on data from all centers, which may reduce the issue, but external validation is necessary to verify this. It is reassuring that the model had good discrimination and clinical utility in postmenopausal women in all centers, despite miscalibration.

Interpretation

The population in the participating clinics was predominantly perimenopausal and postmenopausal in Skane University Hospital. Caution is needed for premenopausal women not using hormonal treatment. The endometrium grows rapidly after menstruation. In the (late) secretory phase, the endometrium is well vascularized on color Doppler [31]. This may lead to ambiguous ultrasound findings and unreliable model predictions. Further validation in women seen shortly after the last day of menstruation is needed.

Others, too, have created models to predict malignancy in postmenopausal women with abnormal uterine bleeding [12–15, 17–20]. They also found thicker endometrium, older age, high color content of the endometrial scan and nonuniform echogenicity of the endometrium to increase the risk of malignancy. Ferrazzi et al. [32] also found that thinner endometrium and older age are indicators of endometrial atrophy in women with postmenopausal bleeding. Others also found that localized intracavitary lesions present at ultrasound with a hyperechoic line surrounding the central endometrial complex (corresponding to our "bright edge") [33], and the "pedicle artery" sign [34] (corresponding to our "single dominant vessel"). Others [35, 36] have described and compared sonographic characteristics of different types of lesions in the uterine cavity, but to our knowledge, we are the first to demonstrate that a model combining features distinguishes very well between four types of endometrial histology.

The outcome category with the highest predicted probability is the most likely diagnosis. However, a patient may also have an increased predicted probability for another histology when compared to the baseline risks (in this study 41% for polyp or myoma, 35% for proliferative or secretory changes, 17% for atrophy, and 6% for malignancy). This indicates that the patient has characteristics indicative of both outcomes, and they should be considered as differential diagnoses.

If future research confirms the utility of our model, it may be used to help select women to the appropriate care pathway: endometrial sampling without delay if the risk of malignancy is high with request for a quick reply by the pathologist (and if malignancy is not confirmed, further

testing to exclude a missed lesion); hysteroscopic resection if a polyp or an intracavitary submucous myoma is likely; blind office endometrial sampling if proliferative or secretory endometrium, endometritis or hyperplasia without atypia is the likely diagnosis; and perhaps no sampling at all if endometrial atrophy is likely and if the risk of malignancy is below a certain threshold (e.g., 1.6%). Experts in gynecological ultrasound may not need a model to make a correct diagnosis of endometrial and other intracavitary pathology, but our model may be of value for gynecologists less experienced in ultrasonography and for intermediate-level sonologists, after validation with such users. The model could be implemented in apps or ultrasound machine software to facilitate calculations during scanning.

Conclusion

Our model based on age, BMI, and ultrasound characteristics discriminates well between four types of endometrial lesions. The clinical and ultrasound variables in our model should be routinely investigated, reported, and used for diagnosis after every ultrasound examination because of abnormal uterine bleeding. The risk estimates may give a clinician extra support for the diagnosis and may also be used in patient counselling, if future external validations demonstrate the clinical utility of the model.

Acknowledgments

We acknowledge the data collection carried out by Catherine Van Pachterbeke, Alberto Rossi, Caroline Van Holsbeke, Marek Kudla, Ekaterini Domali, Attila Jakab, Valentina Chiappa, Iryna Tsikhanenka, Antonia Testa, Marta Szajnik, Francesca Rizzello, Danilo Dordoni, and Daniela Fischerova. We are grateful to the patients who consent to the use of their data for research. Laure Wynants is a post doc fellow of the FWO (Scientific Research Fund Flanders). Dirk Timmerman is senior clinical investigator of the FWO.

Statement of Ethics

The study protocol was reviewed and approved by the Leuven Ethics Committee (S52897/ML7087). All patients provided oral or written informed consent (depending on the center).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by Flemish Governmental grant IWT: TBM IETA (Grant No. 130256) and KU Leuven Internal Funds (Grant No. C16/15/059) and funds administered by Skåne University Hospital, two Swedish governmental grants (regionalt forskningsstöd and by the Swedish state under the agreement between the Swedish Government and the County Councils, the ALF-agreement. Laure Wynants is a postdoc fellow of the FWO (Scientific Research Fund Flanders). Dirk Timmerman is senior clinical investigator of the FWO. The funders had no role in data preparation or the writing of the manuscript.

Author Contributions

T.V.D.B., D.T., T.B, L.V., F.P.G.L., E.E., and B.V.C. conceived the IETA study. T.B., F.P.G.L., L.V., M.A.P., P.S., J.L.A., A.V., R.F., E.E., T.V.D.B., and D.T. collected data for the IETA study. L.W. designed the data analysis plan and conducted the analysis with the help of J.Y.B., B.V.C., B.D.C., and R.H. L.W. drafted the initial version of the manuscript, which was revised for important intellectual content by all co-authors. All authors approve of the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are not publicly available due to sensitive nature of patient health data but are available from T.V.D.B. upon reasonable request.

References

1 Wan YL, Beverley-Stevenson R, Carlisle D, Clarke S, Edmondson RJ, Glover S, et al. Working together to shape the endometrial cancer research agenda: the top ten unanswered research questions. Gynecol Oncol. 2016 Nov;143(2):287–93.
2 Word B, Gravlee LC, Wideman GL. The fallacy of simple uterine curettage. Obstet Gynecol. 1958;12(6):642–8.
3 Van den Bosch T, Cornelis A. Endometrial malignancy missed by office sampling. Aust N Z J Obstet Gynaecol. 1998;38(1):123–4.
4 Epstein E, Ramirez A, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. Acta Obstet Gynecol Scand. 2001;80(12):1131–6.
5 Epstein E, Skoog L, Valentin L. Comparison of endorette and dilatation and curettage for sampling of the endometrium in women with postmenopausal bleeding. Acta Obstet Gynecol Scand. 2001 Oct;80(10):959–64.
6 Epstein E, Valentin L. Managing women with post-menopausal bleeding. Best Pract Res Clin Obstet Gynaecol. 2004 Feb;18(1):125–43.

7 Van den Bosch T, Vandendael A, Van Schoubroeck D, Wranz PA, Lombard CJ. Combining vaginal ultrasonography and office endometrial sampling in the diagnosis of endometrial disease in postmenopausal women. Obstet Gynecol. 1995 Mar;85(3):349–52.
8 Valentin L. Imaging techniques in the management of abnormal vaginal bleeding in non-pregnant women before and after menopause. Best Pract Res Clin Obstet Gynaecol. 2014 2014/07/01/;28(5):637–54.
9 Colombo N, Creutzberg C, Amant F, Bosse T, Gonzalez-Martin A, Ledermann J, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016 Jan;27(1):16–41.
10 Haldorsen IS, Salvesen HB. What is the best preoperative imaging for endometrial cancer? Curr Oncol Rep. 2016 Apr;18(4):25.
11 Munro MG, Critchley HOD, Fraser IS, FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet. 2018;143(3):393–408.
12 Epstein E, Skoog L, Isberg PE, De Smet F, De Moor B, Olofsson PA, et al. An algorithm including results of gray-scale and power Doppler ultrasound examination to predict endometrial malignancy in women with postmenopausal bleeding. Ultrasound Obstet Gynecol. 2002 Oct;20(4):370–6.
13 Opolskiene G, Sladkevicius P, Valentin L. Ultrasound assessment of endometrial morphology and vascularity to predict endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥4.5 mm. Ultrasound Obstet Gynecol. 2007 Sep;30(3):332–40.
14 Opolskiene G, Sladkevicius P, Valentin L. Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥4.5 mm. Ultrasound Obstet Gynecol. 2011 Feb;37(2):232–40.
15 Dueholm M, Møller C, Rydbjerg S, Hansen ES, Ørtoft G. An ultrasound algorithm for identification of endometrial cancer. Ultrasound Obstet Gynecol. 2014 May;43(5):557–68.
16 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 Jun;126:92–9.
17 Dueholm M, Hjorth IMD, Dahl K, Hansen ES, Ørtoft G. Ultrasound scoring of endometrial pattern for fast-track identification or exclusion of endometrial cancer in women with postmenopausal bleeding. J Minim Invasive Gynecol. 2019 Mar - Apr;26(3):516–25.
18 Dueholm M, Hjorth IMD, Dahl K, Pedersen LK, Ørtoft G. Identification of endometrial cancers and atypical hyperplasia: development and validation of a simplified system for ultrasound scoring of endometrial pattern. Maturitas. 2019 May;123:15–24.
19 Sladkevicius P, Opolskiene G, Valentin L. Prospective temporal validation of mathematical models to calculate the risk of endometrial malignancy in patients with postmenopausal bleeding. Ultrasound Obstet Gynecol. 2017;49(5):649–56.
20 Sladkevicius P, Valentin L. Prospective validation of two mathematical models to calculate the risk of endometrial malignancy in patients with postmenopausal bleeding and sonographic endometrial thickness ≥4.5 mm. Eur J Cancer. 2016 May;59:179–88.
21 Plotti F, Capriglione S, Terranova C, Montera R, Scaletta G, Lopez S, et al. Validation of REM score to predict endometrial cancer in patients with ultrasound endometrial abnormalities: results of a new independent dataset. Med Oncol. 2017 April 07;34(5):82.
22 Leone FP, Timmerman D, Bourne T, Valentin L, Epstein E, Goldstein SR, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. Ultrasound Obstet Gynecol. 2010 Jan;35(1):103–12.
23 Epstein E, Fischerova D, Valentin L, Testa AC, Franchi D, Sladkevicius P, et al. Ultrasound characteristics of endometrial cancer as defined by International Endometrial Tumor Analysis (IETA) consensus nomenclature: Prospective Multicenter Study. Ultrasound Obstet Gynecol. 2018 Jun;51(6):818–28.
24 Sladkevicius P, Installé A, Van Den Bosch T, Timmerman D, Benacerraf B, Jokubkiene L, et al. International Endometrial Tumor Analysis (IETA) terminology in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm: Agreement and Reliability Study. Ultrasound Obstet Gynecol. 2018 Feb;51(2):259–68.
25 Van Den Bosch T, Verbakel JY, Valentin L, Wynants L, De Cock B, Pascual MA, et al. Typical ultrasound features of various endometrial pathologies described using International Endometrial Tumor Analysis (IETA) terminology in women with abnormal uterine bleeding. Ultrasound Obstet Gynecol. 2021 Jan;57(1):164–72.
26 Installe AJ, Van den Bosch T, De Moor B, Timmerman D. Clinical data miner: an electronic case report form system with integrated data preprocessing and machine-learning libraries supporting clinical diagnostic model research. JMIR Med Inform. 2014 Oct 20;2(2):e28.
27 Van Calster B, Vergouwe Y, Looman CW, Van Belle V, Timmerman D, Steyerberg EW. Assessing the discriminative ability of risk models for more than two outcome categories. Eur J Epidemiol. 2012 Oct;27(10):761–70.
28 Van Hoorde K, Vergouwe Y, Timmerman D, Van Huffel S, Steyerberg EW, Van Calster B. Assessing calibration of multinomial risk prediction models. Stat Med. 2014 Jul 10;33(15):2585–96.
29 Van Calster B, Wynants L, Verbeek JFM, Verbakel JY, Christodoulou E, Vickers AJ, et al. Reporting and interpreting decision curve analysis: a guide for investigators. Eur Urol. 2018;74(6):796–804.
30 Long B, Clarke MA, Morillo ADM, Wentzensen N, Bakkum-Gamez JN. Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: systematic review and meta-analysis. Gynecol Oncol. 2020;157(3):624–33.
31 Jokubkiene L, Sladkevicius P, Rovas L, Valentin L. Assessment of changes in endometrial and subendometrial volume and vascularity during the normal menstrual cycle using three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol. 2006 Jun;27(6):672–9.
32 Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, Dordoni D. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding. an Italian Multicenter study. Ultrasound Obstet Gynecol. 1996 May;7(5):315–21.
33 Baldwin MT, Dudiak KM, Gorman B, Marks CA. Focal intracavitary masses recognized with the hyperechoic line sign at endovaginal US and characterized with hysterosonography. Radiographics. 1999 Jul-Aug;19(4):927–35.
34 Timmerman D, Verguts J, Konstantinovic ML, Moerman P, Van Schoubroeck D, Deprest J, et al. The pedicle artery sign based on sonography with color Doppler imaging can replace second-stage tests in women with abnormal vaginal bleeding. Ultrasound Obstet Gynecol. 2003 Aug;22(2):166–71.
35 Hulka CA, Hall DA, McCarthy K, Simeone JF. Endometrial polyps, hyperplasia, and carcinoma in postmenopausal women: differentiation with endovaginal sonography. Radiology. 1994 Jun;191(3):755–8.
36 Davis PC, O'Neill MJ, Yoder IC, Lee SI, Mueller PR. Sonohysterographic findings of endometrial and subendometrial conditions. Radiographics. 2002 Jul-Aug;22(4):803–16.