Ultrasound features of endometrial pathology in women without abnormal uterine bleeding

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Ultrasound features of endometrial pathology in women without abnormal uterine bleeding: results from the International Endometrial Tumor Analysis study (IETA3)

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KEYWORDS: asymptomatic disease; endometrial neoplasm; endometrium; incidental finding; ultrasonography; uterine disease

CONTRIBUTION

What are the novel findings of this work?
This is the first prospective multicenter study using the International Endometrial Tumor Analysis terminology to describe the sonographic features of intracavitary pathology in pre- and postmenopausal women without abnormal uterine bleeding. Endometrial cancers in asymptomatic women appeared less vascularized and were associated with thinner endometrium than expected based on published data in women with abnormal uterine bleeding.

What are the clinical implications of this work?
Our study provides information on the ultrasound appearance of endometrial malignancy, polyps and other intracavitary histologies in women without abnormal uterine bleeding. Our results should help clinicians discriminate between benign and malignant endometrial pathology in women without abnormal uterine bleeding.

ABSTRACT

Objectives *The primary aim of this study was to describe the ultrasound features of various endometrial and other intracavitary pathologies in women without abnormal uterine bleeding (AUB) using the International Endometrial Tumor Analysis (IETA) terminology. The secondary aim was to compare our findings with published data on women with AUB.*

Methods *This was a prospective observational study of women presenting at one of seven centers specialized in gynecological ultrasonography, from 2011 until 2018, for indications unrelated to AUB. All patients underwent transvaginal ultrasound using the IETA examination and measurement techniques. Ultrasonography was performed as part of routine gynecological examination or follow-up of non-endometrial pathology, or as part of the work-up before undergoing treatment for infertility, uterine prolapse or ovarian pathology. Ultrasound findings were described using the IETA terminology. Endometrial sampling was performed after the ultrasound scan. The histological endpoints were endometrial atrophy, proliferative or secretory endometrium, endometrial hyperplasia without atypia, endometrial polyp, intracavitary leiomyoma, endometrial intraepithelial neoplasia (EIN), endometrial cancer (EC) and insufficient tissue. The findings in our cohort of women without AUB were compared with those in a published cohort of women with AUB who were examined with transvaginal ultra-*

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sound between 2012 and 2015 using the same IETA examination technique and terminology.

Results *In this study (IETA3), we included 1745 women without AUB who underwent a standardized transvaginal ultrasound examination followed by either endometrial sampling with histological diagnosis (*n = *1537) or at least 1 year of clinical and ultrasound follow-up (*n = *208). Of these, 858 (49.2%) women were premenopausal and 887 (50.8%) were postmenopausal. Histology showed the presence of EC and/or EIN in 29 (1.7%) women, endometrial polyps in 1028 (58.9%), intracavitary myomas in 66 (3.8%), proliferative or secretory changes or hyperplasia without atypia in 144 (8.3%), endometrial atrophy in 265 (15.2%) and insufficient tissue in five (0.3%). Most cases of EC or EIN (25/29 (86.2%)) were diagnosed after menopause. The mean endometrial thickness in women with EC or EIN was 11.2 mm (95% CI, 8.9–13.6 mm), being on average 2.4 mm (95% CI, 0.3–4.6 mm) thicker than their benign counterparts. Women with malignant endometrial pathology manifested more frequently non-uniform echogenicity (22/29 (75.9%)) than did those with benign endometrial pathology (929/1716 (54.1%)) (difference, +21.8% (95% CI, +4.2% to +39.2%)). Moderate to abundant vascularization (color score 3–4) was seen in 31.0% (9/29) of cases with EC or EIN compared with 12.8% (220/1716) of those with a benign outcome (difference, +18.2% (95% CI, −0.5% to +36.9%)). Multiple multifocal vessels were recorded in 24.1% (7/29) women with EC or EIN* vs *4.0% (68/1716) of those with a benign outcome (difference, +20.2% (95% CI, +4.6% to +35.7%)). A regular endometrial–myometrial junction was seen less frequently in women with EC or EIN (19/29 (65.5%))* vs *those with a benign outcome (1412/1716 (82.3%)) (difference, −16.8% (95% CI, −34.2% to +0.6%)). In women with endometrial polyps without AUB, a single dominant vessel was the most frequent vascular pattern (666/1028 (64.8%)). In women with EC, both in those with and those without AUB, the endometrium usually manifested heterogeneous echogenicity, but the endometrium was on average 8.6 mm (95% CI, 5.2–12.0 mm) thinner and less intensely vascularized (color score 3–4: difference, −26.8% (95% CI, −52.2% to −1.3%)) in women without compared to those with AUB. In both pre- and postmenopausal women, asymptomatic endometrial polyps were associated with a thinner endometrium, and they manifested more frequently a bright edge, a regular endometrial–myometrial junction and a single dominant vessel than did polyps in symptomatic women, and they were less intensely vascularized.*

Conclusions *We describe the typical ultrasound features of EC, polyps and other intracavitary histologies using IETA terminology in women without AUB. Our findings suggest that the presence of asymptomatic polyps or endometrial malignancy may be accompanied by thinner and less intensely vascularized endometria than their symptomatic counterparts. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Less is known about endometrial pathology in women presenting without abnormal uterine bleeding than in women with abnormal uterine bleeding[1]. Women with abnormal uterine bleeding are urged to seek medical advice[2–5]. Most studies on women with abnormal uterine bleeding have focused on reliably diagnosing or excluding malignancy. Histological confirmation is obtained by dilatation and curettage, hysteroscopy or outpatient sampling devices[6–9]. Transvaginal ultrasonography is the first-line diagnostic tool to triage which postmenopausal patients with abnormal uterine bleeding should undergo endometrial sampling[10,11]. Many studies have focused on endometrial thickness[12,13], but other ultrasound features are also important for distinguishing between benign and malignant endometrial pathology[14]. A combination of grayscale and Doppler ultrasound features of the endometrium (endometrial uniformity, echogenicity and midline, endometrial–myometrial junction, color score and vascular pattern) have been linked with various endometrial pathologies in women with abnormal uterine bleeding[14]. The risk of malignancy in asymptomatic women with an incidentally detected endometrial polyp remains an unsettled issue[15,16].

The primary aim of this study was to describe the ultrasound features of various endometrial and other intracavitary pathologies in women without abnormal uterine bleeding using the International Endometrial Tumor Analysis (IETA) terminology[17]. A secondary aim was to compare these findings with published data on women with abnormal uterine bleeding. For both aims, we focused on endometrial cancer (EC) and endometrial intraepithelial neoplasia (EIN), which necessitate medical or surgical treatment, and on endometrial polyps.

METHODS

This was a prospective observational multicenter study conducted between 1 January 2011 and 31 December 2018 by the IETA consortium in seven secondary and tertiary centers specialized in gynecological ultrasonography. The study was approved by the Leuven ethics committee EC Research (S52897/ML7087) and by the ethics committees of all participating centers. All patients provided oral informed consent.

Pre- and postmenopausal women without abnormal uterine bleeding were recruited consecutively. Abnormal uterine bleeding was defined as postmenopausal bleeding or non-gestational abnormal uterine bleeding in the reproductive years. The former was defined as any bleeding after menopause in women without hormonal therapy or unscheduled or heavy bleeding in women on hormonal therapy. Heavy bleeding was defined as vaginal bleeding that was deemed to be abnormal in duration, volume, frequency and/or regularity by the patient. The reasons for ultrasound assessment comprised routine gynecological examination, follow-up of non-endometrial pathology or work-up before fertility treatment or treatment for uterine

prolapse or ovarian pathology. Patients who denied abnormal uterine bleeding during the year preceding presentation were included in the study. After history taking, patients underwent physical examination followed by standardized transvaginal unenhanced ultrasonography with color or power Doppler assessment according to the IETA guidelines[17]. The findings were recorded in a dedicated web-based datasheet (Clinical Data Miner (CDM), ESAT-STADIUS, KU Leuven)[18]. CDM performed automated, integrated checks of the quality of the data and generated warnings in cases of incomplete or inconsistent input. To ensure stringent data management, data curation was supplemented with central manual and automatic data cleaning, as well as obtaining focused feedback from the contributing centers for any remaining unresolved issues.

Endometrial assessment

The uterine cavity and endometrium were examined using the IETA examination technique, and results are described using the IETA terminology[17]. Endometrial thickness was measured in the sagittal plane including both endometrial layers. In the presence of intracavitary fluid, both single layers were measured, and the sum was recorded. If the endometrium was not clearly visible, it was recorded as 'not visible'. Endometrial echogenicity was recorded as uniform or non-uniform. A uniform endometrium may have a three-layer pattern or be homogeneously hyper-, iso- or hypoechogenic (compared with myometrial echogenicity) with symmetric anterior/posterior endometrial thickness. A non-uniform endometrium may be a homogeneous background endometrium with regular or irregular cysts or a heterogeneous background endometrium with or without cysts. The endometrial midline may be linear, non-linear, irregular or not defined. A bright edge is the echo formed by the interface between an intracavitary lesion and the endometrium. The endometrial–myometrial junction was recorded as regular, irregular, interrupted or not defined. The IETA color score is a subjective assessment of the color content of the endometrium when using color or power Doppler, reflecting the amount of blood flow present; it is recorded as score 1 (no color), 2 (minimal color), 3 (moderate color) or 4 (abundant color)[17]. The vascular pattern within the endometrium may be a single dominant vessel with or without branching (the pedicle artery sign[19]), multiple vessels of focal or multifocal origin, scattered flow, or circular flow. If there was pre-existing intracavitary fluid, the features assessed were: endometrial thickness and outline of both endometrial layers, the presence of an intracavitary lesion including endometrial lesions and lesions arising from the myometrium and the ultrasonographic features (echogenicity, outline, color score and vascular pattern) of the intracavitary lesion(s) and of the endometrium itself. The statistical analysis plan (SAP) regarding cases with pre-existing intracavitary fluid is described in Table S1. In the presence of one or more lesions of suggested endometrial origin, to allow consistent recording, the predefined SAP stipulated that if the originally entered total thickness was less than the minimal diameter of the largest lesion, total endometrial thickness would be the sum of the two layers of the endometrium and the anteroposterior diameter of the largest lesion.

Outcome assessment

The histological examinations were performed by each center's pathologist dedicated to gynecological pathology. The pathologist was not blinded to clinical or ultrasound information. Endometrial sampling was performed after the ultrasound scan. The interval between the ultrasound examination and the procedure yielding the final histological examination should not exceed 120 days. Endometrial tissue was obtained by outpatient endometrial sampling devices, dilatation and curettage, hysteroscopic resection or hysterectomy. When multiple sampling methods were used in the same patient (e.g. office sampling, operative hysteroscopy with biopsy and hysterectomy), the most clinically relevant histological result was recorded according to the hierarchical order described below. The histological endpoints were endometrial atrophy, proliferative or secretory endometrium, endometrial hyperplasia without atypia, endometrial polyp, intracavitary leiomyoma, EIN, EC and insufficient tissue. In the presence of multiple histological diagnoses, a single outcome was allocated to each woman using the following hierarchy: EC, EIN, endometrial polyp, leiomyoma, hyperplasia without atypia, proliferative or secretory changes, endometrial atrophy, insufficient tissue. Patients without histological outcome were included if they were followed up for more than 1 year, and if there were no signs of endometrial malignancy at clinical and ultrasound follow-up, the outcome was classified as benign.

Exclusion criteria

We observed skewness in the recruitment across different centers, and acknowledge that we could not guarantee that women had been consecutively included in those centers that contributed the lowest number of cases. Aiming for consecutive inclusions and in order to avoid selection bias, patients from centers that contributed fewer than 50 women to the study were excluded. Other exclusion criteria were: double entries and women that were found in retrospect to have had abnormal bleeding, women with missing endometrial assessment, inconsistent or irretrievable data, pregnancy-related histology and missing histology if followed up for less than 1 year and those lost to follow-up.

Statistical analysis

Statistical analysis was performed using R statistical package version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical analysis includes descriptive statistics of sonographic features at ultrasonography of each individual histological endpoint. We

present the percentage of occurrence of the different sonographic features for each histological endpoint (equal to sensitivity). The mean endometrial thickness with 95% CI and point estimates of percentages with 95% CI are shown. Differences between groups are shown as mean difference with 95% CI or as difference in percentage with 95% CI of the difference. For each ultrasound feature, the area under the receiver-operating-characteristics curve (AUC) with 95% CI is shown, reflecting discrimination between EC or EIN and benign histology. All subgroup analyses (premenopausal *vs* postmenopausal) are exploratory but were specified *a priori*. No formal sample-size calculation was performed.

In addition to the above analyses, we compared the ultrasound findings in the current asymptomatic cohort with those in the published IETA1 cohort of women with abnormal uterine bleeding ($n = 2856$)[14]. The symptomatic cohort was comparable with the current cohort in that: (1) the IETA examination technique, measurement technique and terminology were used; (2) a large portion of participating centers contributed patients to both studies (i.e. Barcelona, Milan, Monza, Rome and Leuven); and (3) recruitment periods overlapped (IETA3 from 2011 until 2018; IETA1 from 2012 until 2015).

RESULTS

Women without abnormal uterine bleeding

We recruited 2206 women with both clinical and ultrasound entries. Of these, 421 patients were excluded because of double entry ($n = 24$), abnormal uterine bleeding ($n = 47$), pregnancy related outcomes ($n = 13$), missing endometrial assessment ($n = 20$), inconsistent data ($n = 1$) or follow-up of less than 1 year in the absence of histological confirmation ($n = 316$). In addition, we excluded 40 patients from centers ($n = 6$) that had recruited fewer than 50 women over the entire study period (number of

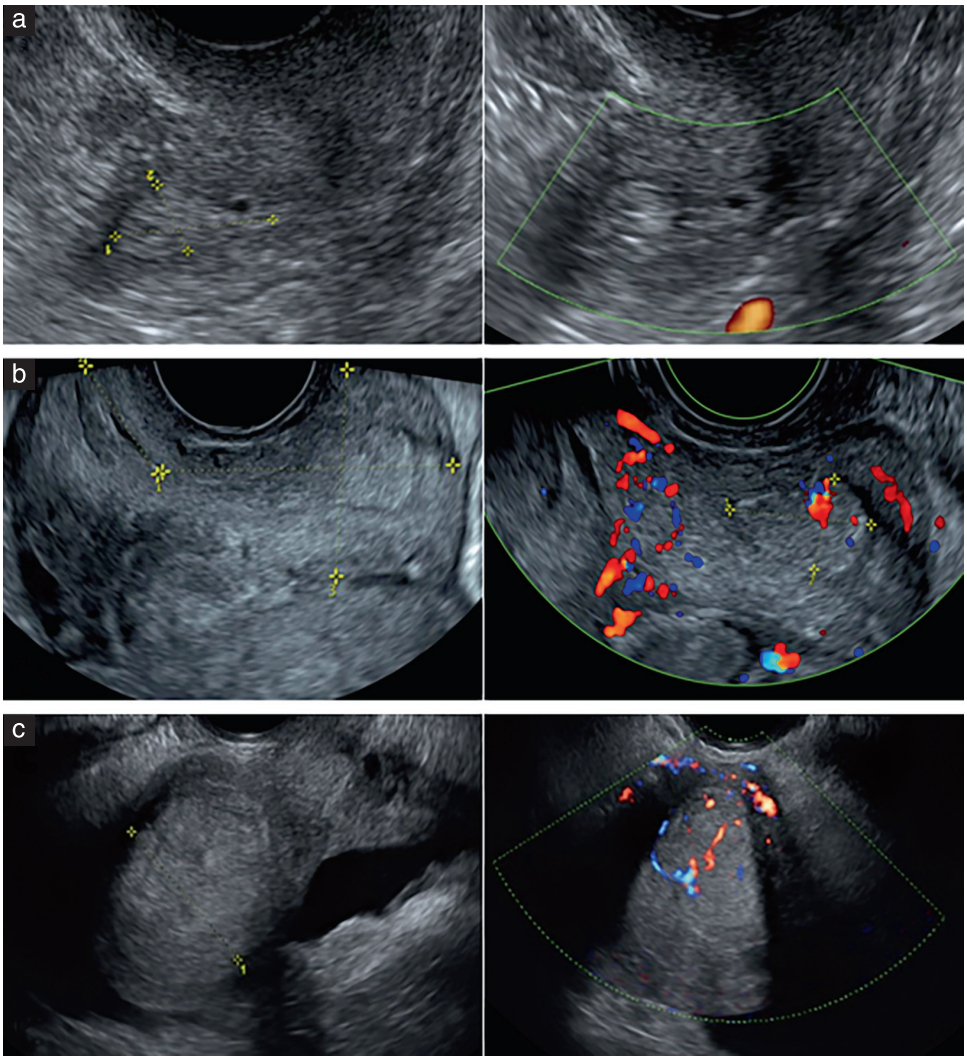

Figure 1 (a) Grayscale and corresponding power Doppler images of a Grade-1 endometrioid cancer, Stage IA, at a pulse repetition frequency (PRF) of 0.6 kHz. (b) Grayscale and corresponding color Doppler images showing a single dominant vessel and bright edge sign in a Grade-1 endometrioid cancer, Stage IA, possibly reflecting cancer in a polyp, at a PRF of 0.9 kHz. (c) Grayscale and corresponding bidirectional power Doppler images at a PRF of 0.3 kHz, in a patient with a serous endometrial cancer, Stage IVB, presenting with ascites, diffuse peritoneal carcinomatosis, omental and infiltrative mesenteric deposits and bilateral pleural effusion.

cases ranging from two to 24 per center). This resulted in a final study population of 1745 patients, scanned in seven centers. Of these, 88.1% (1537/1745) had a histological diagnosis. In the absence of histology, at least 1 year of clinical and ultrasound follow-up without signs of malignancy provided a proxy for benign outcome in the remaining 11.9% (208/1745). Histology confirmed the presence of EC ($n = 23$) or EIN ($n = 6$) in 29 (1.7%) women (Figure 1), endometrial polyps in 1028 (58.9%), intracavitary myomas in 66 (3.8%), proliferative or secretory changes or hyperplasia without atypia in 144 (8.3%) and endometrial atrophy in 265 (15.2%) (Table 1). The distribution of pathology according to sampling method and center is shown in Tables S2 and S3, respectively. The ECs were predominantly well-differentiated (13/23 (56.5%)), of endometrioid histology (20/23 (87.0%)) and International Federation of Gynecology and Obstetrics (FIGO)[20] Stage I (21/23 (91.3%)) (Table 2). Indications for surgery according to participating center and according to pathology are

Table 1 Histological diagnoses in 1745 women without abnormal uterine bleeding, overall and according to menopausal status

Outcome	*Total* (n = *1745*)	*Premenopausal* (n = *858*)	*Postmenopausal* (n = *887*)
Endometrial cancer	23 (1.3)	1 (0.1)	22 (2.5)
Endometrial intraepithelial neoplasia	6 (0.3)	3 (0.3)	3 (0.3)
Endometrial polyp	1028 (58.9)	567 (66.1)	461 (52.0)
Hyperplasia without atypia	23 (1.3)	6 (0.7)	17 (1.9)
Endometrial atrophy	265 (15.2)	9 (1.0)	256 (28.9)
Proliferative or secretory changes	121 (6.9)	105 (12.2)	16 (1.8)
Intracavitary myoma	66 (3.8)	56 (6.5)	10 (1.1)
Insufficient tissue	5 (0.3)	2 (0.2)	3 (0.3)
No histology available*	208 (11.9)	109 (12.7)	99 (11.2)

Data are presented as *n* (%). *Patients had clinical and sonographic follow-up for more than 1 year with no signs of malignancy, therefore, outcome was considered benign.

Table 2 Demographic characteristics of women with endometrial cancer (EC) and description of EC, in 23 women without abnormal uterine bleeding (AUB) analyzed in the present study and 137 women with AUB included in IETA1 cohort[14]

Variable	*Without AUB* (n = *23*)	*With AUB*[14] (n = *137*)	*Difference (95% CI)*
Age (years)	64.7 (59.7–69.7)	67.3 (65.3–69.3)	−2.6 (−4.5 to −0.7)
Postmenopausal	22 (95.7)	121 (88.3)	+7.4 (−5.1 to +19.8)
Age at menopause (years)*	48.6 (46.8–50.5)	50.9 (50.2–51.6)	−2.3 (−7.0 to +2.5)
Interval from menopause (years)*	16.9 (12.3–21.5)	19.3 (17.5–21.0)	−2.4 (−4.3 to −0.4)
Nulliparous	3 (13.0)	19 (13.9)	−0.9 (−16.6 to +14.9)
Body mass index (kg/m^2)	28.8 (25.9–31.7)	28.3 (26.8–29.8)	+0.5 (−0.1 to +1.0)
Hormonal therapy	5 (21.7)	14 (10.2)	+11.5 (−8.6 to +31.7)
EC grade			
0	0 (0)	3 (2.2)	−2.2 (−6.8 to +2.5)
I	13 (56.5)	63 (46.0)	+10.5 (−13.9 to +35)
II	7 (30.4)	36 (26.3)	+4.1 (−18.6 to +26.9)
III†	3 (13.0)	35 (25.5)	−12.5 (−30.6 to +5.6)
EC FIGO stage[20]			
IA	19 (82.6)	73 (53.3)	+29.3 (+9.2 to +49.5)
IB	2 (8.7)	21 (15.3)	−6.6 (−22.2 to +8.9)
II	0 (0)	6 (4.4)	−4.4 (−10.3 to +1.6)
IIIA	0 (0)	2 (1.5)	−1.5 (−4.9 to +2.0)
IIIB	1 (4.3)	4 (2.9)	+1.4 (−8.8 to +11.7)
IIIC	0 (0)	11 (8.0)	−8.0 (−15.1 to −0.9)
IVA	0 (0)	0 (0)	—
IVB	1 (4.3)	3 (2.2)	+2.1 (−8.7 to +13)
Not available	0 (0)	17 (12.4)	−12.4 (−20.5 to −4.3)
EC histotype			
Adenocarcinoma with squamous differentiation	0 (0)	6 (4.4)	−4.4 (−10.3 to +1.6)
Endometrioid	20 (87.0)	101 (73.7)	+13.3 (−4.9 to +31.4)
Serous	2 (8.7)	17 (12.4)	−3.7 (−19 to +11.6)
Clear cell	0 (0)	2 (1.5)	−1.5 (−4.9 to +2.0)
Mixed‡	1 (4.3)	5 (3.6)	+0.7 (−8.9 to +10.3)
Other	0 (0)	6 (4.4)§	−4.4 (−10.3 to +1.6)

Data are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). *Only for postmenopausal women. †Including endometrioid Grade 3, serous, clear cell, giant cell, carcinosarcoma, undifferentiated and mixed ECs. ‡Comprising carcinosarcomas and tumors with combinations of various EC histologies. §Including 1 giant cell carcinoma, 1 leiomyosarcoma, 1 adenosarcoma, 1 not otherwise specified sarcomatous tumor, 1 endometrial stromal sarcoma and 1 undifferentiated carcinoma. FIGO, International Federation of Gynecology and Obstetrics.

provided in Tables S4 and S5, respectively. Of the 23 women with EC, 16 (69.6%) had surgery owing to suspected intracavitary pathology, four (17.4%) were planned for urogynecological surgery, two (8.7%) had other gynecological indications for surgery and one woman (4.3%) had opportunistic sampling of a moderately vascularized thickened endometrium of 11 mm with an irregular midline. Women with EC or EIN were older, had a higher body mass index and were more frequently postmenopausal than women with benign outcomes (Table 3). Of the women with EC or EIN, 86.2% (25/29) were postmenopausal. Demographic characteristics according to pathology are presented in Table S6.

Sonographic characteristics of malignant and premalignant endometrial conditions and benign outcomes are listed in Tables 4 and 5 and of specific pathologies in Tables S7–S9. The mean endometrial thickness in patients with EC or EIN was 11.2 mm (95% CI, 8.9–13.6 mm) compared with 8.8 mm (95% CI, 8.5–9.0 mm) in patients with a benign outcome, endometria with malignant/premalignant pathology being, on average, 2.4 mm (95% CI, 0.3–4.6 mm) thicker than endometria with benign pathology. A non-uniform echogenicity of the endometrium was noted in 75.9% patients with EC or EIN compared with 54.1% of those with a benign outcome (difference, +21.8% (95% CI, +4.2% to +39.2%)). Endometrial cysts were seen in 34.5% (10/29) of patients with EC or EIN *vs* in 21.8% (374/1716) of those with a benign outcome (difference, +12.7% (95% CI, −6.5% to +31.9%)). Moderate to abundant vascularization (color score 3–4) was seen in 31.0% (9/29) of cases with EC or EIN compared with 12.8% (220/1716) of those with a benign outcome (difference, +18.2% (95% CI, −0.5% to +36.9%)). A single dominant vessel was seen in 37.9% (11/29) of cases with EC or EIN *vs* in 48.1% (826/1716) of benign cases (difference, −10.2% (95% CI, −29.8% to +9.4%)), while multiple multifocal vessels were recorded in 24.1% (7/29) women with EC or EIN *vs* 4.0% (68/1716) of those with a benign outcome (difference, +20.2% (95% CI, +4.6% to +35.7%)).

Table 3 Demographics characteristics of 1745 women without abnormal uterine bleeding, overall and according to whether they had malignant or benign outcome

		Outcome		
Variable	*Overall* (n = *1745*)	*EC or EIN* (n = *29*)	*Benign* (n = *1716*)	*Difference (95% CI)*
Age (years)	52.8 (52.2–53.4)	62.4 (57.7–67.1)	52.7 (52.1–53.3)	+9.7 (+5.0 to +14.5)
Postmenopausal	887 (50.8)	25 (86.2)	862 (50.2)	+36.0 (+21.4 to +50.5)
Age at menopause (years)*	50.1 (49.9–50.4)	48.8 (47.2–50.5)	50.2 (49.9–50.4)	−1.4 (−3.0 to +0.3)
Interval from menopause (years)*	12.7 (12.1–13.3)	16.4 (12.4–20.5)	12.6 (12.0–13.2)	+3.8 (−0.2 to +7.9)
Nulliparous	526 (30.1)	4 (13.8)	522 (30.4)	−16.6 (−31.1 to −2.1)
Body mass index (kg/m^2)	24.8 (24.6–25.0)	29.6 (26.8–32.3)	24.7 (24.5–24.9)	+4.9 (+2.2 to +7.5)
Hormonal therapy†	154 (8.8)	5 (17.2)	149 (8.7)	+8.5 (−7 to +24.1)
Intrauterine contraceptive device	10 (0.6)	0 (0)	10 (0.6)	−0.6 (−1.5 to +0.4)
Anticoagulant therapy‡	29 (1.7)	0 (0)	29 (1.7)	−1.7 (−4 to +0.6)

Data are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). *Only for postmenopausal women. †Estrogen-only, gestagen-only, combined estrogen–gestagen, selective estrogen or progesterone receptor modulators, aromatase inhibitors or gonadotropin-releasing hormone (ant)agonists. ‡Vitamin-K antagonists, (low molecular weight) heparins or antiaggregants (e.g. aspirin, clopidogrel, ticagrelor, dipyridamole). EC, endometrial cancer; EIN, endometrial intraepithelial neoplasia.

Table 4 Sonographic features of malignant and benign intracavitary pathology in 1745 women without abnormal uterine bleeding

Variable	*EC or EIN* (n = *29*)	*Benign outcome* (n = *1716*)	*Difference (95% CI)*	*AUC (95% CI) (%)*
Endometrial thickness (mm)	11.2 (8.9–13.6)	8.8 (8.5–9.0)	+2.4 (+0.3 to +4.6)	62.4 (51.7–73.2)
Intracavitary fluid	6 (20.7)	97 (5.7)	+15 (−1.5 to +31.6)	57.5 (50.0–65.0)
Endometrium not visible	2 (6.9)	54 (3.1)	+3.8 (−7.3 to +14.8)	51.9 (47.2–56.6)
Non-uniform echogenicity	22 (75.9)	929 (54.1)	+21.8 (+4.2 to +39.2)	60.9 (52.9–68.9)
Endometrial cysts	10 (34.5)	374 (21.8)	+12.7 (−6.5 to +31.9)	56.3 (47.5–65.2)
Color score 1–2	18 (62.1)	1442 (84.0)	−21.9 (−41.5 to −2.5)	39.0 (30.0–48.0)
Color score 3–4	9 (31.0)	220 (12.8)	+18.2 (−0.5 to +36.9)	59.1 (50.5–67.7)
Single dominant vessel +/− branching	11 (37.9)	826 (48.1)	−10.2 (−29.8 to +9.4)	44.9 (35.8–54.0)
Multiple, multifocal vessels	7 (24.1)	68 (4.0)	+20.2 (+4.6 to +35.7)	60.1 (52.2–68.0)
Bright edge	10 (34.5)	851 (49.6)	−15.1 (−34.3 to +4.1)	42.5 (33.6–51.3)
Regular EMJ	19 (65.5)	1412 (82.3)	−16.8 (−34.2 to +0.6)	41.6 (32.8–50.5)

Results are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). For each ultrasound feature, the area under the receiver-operating-characteristics curve (AUC) and 95% CI for discrimination between endometrial cancer (EC) or endometrial intraepithelial neoplasia (EIN) and benign outcome is also shown. +/−, with or without; EMJ, endometrial–myometrial junction.

Table 5 Sonographic features of benign and malignant intracavitary pathology in 1745 women without abnormal uterine bleeding, according to menopausal status

	Premenopausal				*Postmenopausal*			
Variable	*EC or EIN (n = 4)**	*Benign outcome (n = 854)*	*Difference (95% CI)*	*AUC (95% CI) (%)*	*EC or EIN (n = 25)†*	*Benign outcome (n = 862)*	*Difference (95% CI)*	*AUC (95% CI) (%)*
Endometrial thickness (mm)	12.5 (10.4–14.6)	10.5 (10.2–10.8)	+2.0 (+0.7 to +3.3)	72.9 (62.1–83.7)	11.0 (8.2–13.8)	7.0 (6.7–7.4)	+4.0 (+1.5 to +6.5)	70.4 (60.4–80.5)
Intracavitary fluid	0 (0)	20 (2.3)	−2.3 (−5.7 to +1.0)	48.8 (48.3–49.3)	6 (24.0)	77 (8.9)	+15.1 (−3.8 to +34)	57.5 (48.9–66.1)
Endometrium not visible	0 (0)	17 (2.0)	−2.0 (−4.9 to +0.9)	49.0 (48.5–49.5)	2 (8.0)	37 (4.3)	+3.7 (−9.1 to +16.5)	51.9 (46.4–57.3)
Non-uniform echogenicity	3 (75.0)	510 (59.7)	+15.3 (−39.8 to +70.4)	57.6 (33.1–82.2)	19 (76.0)	419 (48.6)	+27.4 (+8.3 to +46.5)	63.7 (55.0–72.4)
Endometrial cysts	0 (0)	55 (6.4)	−6.4 (−14.5 to +1.6)	46.8 (46.0–47.6)	10 (40.0)	319 (37.0)	+3.0 (−18.5 to +24.5)	51.5 (41.6–61.4)
Color score 1–2	2 (50.0)	676 (79.2)	−29.2 (−90.8 to +32.5)	64.6 (36.3–92.9)	16 (64.0)	766 (88.9)	−24.9 (−45.9 to −3.9)	37.6 (27.9–47.2)
Color score 3–4	2 (50.0)	161 (18.9)	+31.1 (−30.5 to +92.8)	65.6 (37.3–93.9)	7 (28.0)	59 (6.8)	+21.2 (+1.4 to +40.9)	60.6 (51.6–69.6)
Single dominant vessel +/− branching	3 (75.0)	572 (67.0)	+8 (−42.6 to +58.6)	54.0 (29.5–78.6)	8 (32.0)	254 (29.5)	+2.5 (−18.1 to +23.1)	51.3 (41.8–60.7)
Multiple, multifocal vessels	1 (25.0)	47 (5.5)	+19.5 (−35.6 to +74.5)	59.8 (35.2–84.3)	6 (24.0)	21 (2.4)	+21.6 (+4.8 to +38.4)	60.8 (52.2–69.3)
Bright edge	4 (100)	560 (65.6)	+34.4 (+18.7 to +50.2)	67.2 (65.6–68.8)	6 (24.0)	291 (33.8)	−9.8 (−28.9 to +9.3)	45.1 (36.4–53.8)
Regular EMJ	4 (100)	747 (87.5)	+12.5 (+10.1 to +14.9)	56.3 (55.2–57.4)	15 (60.0)	665 (77.1)	−17.1 (−36.5 to +2.3)	41.3 (31.5–51.3)

Data are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). *Comprising one woman with endometrial cancer (EC) and three with endometrial intraepithelial neoplasia (EIN). †Comprising 22 women with EC and three with EIN. Area under the receiver-operating-characteristics curve (AUC) and 95% CI for discrimination between EC or EIN and benign outcome are also shown. +/−, with or without; EMJ, endometrial–myometrial junction.

The majority of endometrial polyps were characterized by a single dominant vessel with or without branching, a bright edge and a regular endometrial–myometrial junction. In postmenopausal women, compared with premenopausal women, the presence of endometrial polyps was associated more frequently with intracavitary fluid (6.7% *vs* 1.8%; difference, +4.9% (95% CI, +2.2% to +7.7%)), endometrial cysts (53.6% *vs* 5.5%; difference, +48.1% (95% CI, +43.0% to +53.2%)) and undefined midline (85.0% *vs* 29.0%; difference, +56.0% (95% CI, +50.8% to +61.3%)), and lower color scores (color score 1: 44.4% *vs* 7.3%; difference, +37.1% (95% CI, +31.8% to +42.4%)) (Table 6). The mean endometrial thickness in postmenopausal women with endometrial polyps was 9.0 mm (95% CI, 8.6–9.3 mm) (Table 6) *vs* 11.0 mm (95% CI, 8.2–13.8 mm) in those with EIN or EC (Table 5). In postmenopausal women with polyps, compared with postmenopausal women with EC or EIN, the endometrium was on average 2 mm (95% CI, 0.3–3.8 mm) thinner, less frequently exhibited multifocal vascularization (3.5% *vs* 24.0%; difference, −20.5% (95% CI, −39.5% to −1.6%)) and more frequently showed a bright edge (51.4% *vs* 24.0%; difference, +27.4% (95% CI, +7.9% to +46.9%)). Women with hyperplasia without atypia frequently manifested non-uniform echogenicity (16/23 (69.6%)) without detectable vascularization (color score 1, 12/23 (52.2%)), but when there was vascularization, a single vessel with or without branching was the most common vascular pattern (5/11 (45.5%)) followed by scattered vessels (4/11 (36.4%)) (Table S7). The endometrium in women with atrophy, proliferative or secretory changes or intracavitary myomas was usually uniform (232/265 (87.5%), 68/121 (56.2%) and 48/66 (72.7%), respectively). When vascularized, intracavitary myomas most frequently exhibited circular flow (31/44 (70.5%)) (Table S7).

Comparison to women with abnormal uterine bleeding

Compared with a published cohort of women with abnormal uterine bleeding[14], endometrial cancers in women presenting without abnormal uterine bleeding tended to have a more favorable grade of differentiation, to present at lower stages of disease and to be more frequently of endometrioid histology (Table 2). Both in women with and those without abnormal uterine bleeding, endometria with malignant or premalignant pathology most often manifested non-uniform echogenicity (Table 7). Endometrial cancer in women without abnormal uterine bleeding was associated with a thinner endometrium than that in women with abnormal uterine bleeding, more often had a regular endometrial–myometrial junction, were less vascularized (color score 1–2) and were more frequently recorded as having a single dominant vessel

Table 6 Sonographic features of endometrial polyps in women without abnormal uterine bleeding, according to menopausal status

Variable	*Premenopausal* (n = *567*)	*Postmenopausal* (n = *461*)	*Difference (95% CI)*
Endometrial thickness (mm)	10.5 (10.2–10.8)	9.0 (8.6–9.3)	+1.5 (+1.1 to +2.0)
Intracavitary fluid	10 (1.8)	31 (6.7)	−4.9 (−7.7 to −2.2)
Endometrium not visible	8 (1.4)	20 (4.3)	−2.9 (−5.2 to −0.6)
Uniform echogenicity	173 (30.5)	123 (26.7)	+3.8 (−1.9 to +9.6)
Three-layer	35/173 (20.2)	0/123 (0)	+20.2 (+13.5 to +26.9)
Hyperechogenic	114/173 (65.9)	112/123 (91.1)	−25.2 (−34.5 to −15.8)
Isoechogenic	18/173 (10.4)	9/123 (7.3)	+3.1 (−4.1 to +10.3)
Hypoechogenic	6/173 (3.5)	2/123 (1.6)	+1.9 (−2.4 to +6.1)
Non-uniform echogenicity	386 (68.1)	318 (69.0)	−0.9 (−6.8 to +5.0)
Endometrial cysts	31 (5.5)	247 (53.6)	−48.1 (−53.2 to −43.0)
Homogeneous	20 (3.5)	198 (43.0)	−39.5 (−44.4 to −34.5)
Heterogeneous	366 (64.6)	120 (26.0)	+38.6 (+32.7 to +44.3)
Color score recorded	559 (98.6)	441 (95.7)	
1*	41/559 (7.3)	196/441 (44.4)	−37.1 (−42.4 to −31.8)
2*	402/559 (71.9)	194/441 (44.0)	+27.9 (+21.8 to +34.1)
3†	112/559 (20.0)	49/441 (11.1)	+8.9 (+4.3 to +13.6)
4†	4/559 (0.7)	2/441 (0.5)	+0.2 (−0.9 to +1.4)
Color score > 1	518 (91.4)	245 (53.1)	
Vascular pattern if color score > 1‡			
Single, no branching§	406/518 (78.4)	177/245 (72.2)	+6.2 (−0.8 to +13.1)
Single, with branching§	62/518 (12.0)	21/245 (8.6)	+3.4 (−1.4 to +8.2)
Multiple, focal	16/518 (3.1)	9/245 (3.7)	−0.6 (−3.7 to +2.5)
Multiple, multifocal	24/518 (4.6)	16/245 (6.5)	−1.9 (−5.8 to +2.0)
Scattered	9/518 (1.7)	22/245 (9.0)	−7.3 (−11.3 to −3.2)
Circular	1/518 (0.2)	0/245 (0)	+0.2 (−0.4 to +0.8)
Midline assessed	559 (98.6)	441 (95.7)	
Irregular	26/559 (4.7)	25/441 (5.7)	−1.0 (−4.0 to +2.0)
Linear	227/559 (40.6)	30/441 (6.8)	+33.8 (+28.9 to +38.7)
Not linear	144/559 (25.8)	11/441 (2.5)	+23.3 (+19.2 to 27.4)
Not defined	162/559 (29.0)	375/441 (85.0)	−56.0 (−61.3 to −50.8)
Bright edge assessed	555 (97.9)	421 (91.3)	
Present	451/555 (81.3)	237/421 (56.3)	+25.0 (+21.6 to +33.4)
Absent	104/555 (18.7)	184/421 (43.7)	−25.0 (−28.8 to −17.1)
Endometrial–myometrial junction assessed	555 (97.9)	421 (91.3)	
Interrupted	7/555 (1.3)	11/421 (2.6)	−1.3 (−3.3 to +0.6)
Irregular	8/555 (1.4)	33/421 (7.8)	−6.4 (−9.4 to −3.4)
Regular	537/555 (96.8)	365/421 (86.7)	+10.1 (+6.3 to +13.8)
Not defined	3/555 (0.5)	12/421 (2.9)	−2.4 (−4.2 to −0.4)

Data are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) or *n*/*N* (%) and difference in percentages (95% CI). *Difference in percentages for color score 1–2: −9.2 (95% CI, −13.9 to −4.5). †Difference in percentages for color score 3–4: +9.2 (95% CI, +4.5 to +13.9). ‡IETA vascular pattern[17]: 'Single, no branching', single dominant vessel without branching; 'Single, with branching', single dominant vessel with branching; 'Multiple, focal', multiple dominant vessels with focal origin; 'Multiple, multifocal', multiple dominant vessels with multifocal origin; 'Scattered', scattered vessels; 'Circular', circular flow. §Difference in percentages for single dominant vessel with or without branching: +9.6 (95% CI, +3.7 to +15.4).

with or without branching. The same differences were observed when evaluating only cases with endometrial cancer FIGO Stage IA (Table S10). Endometrial polyps in women without abnormal uterine bleeding, compared with those in women with abnormal uterine bleeding, more often manifested non-uniform echogenicity, a bright edge, a regular endometrial–myometrial border and a single dominant vessel, but had lower color score (Table 7). The differences in bright edge, regular endometrial–myometrial border, single dominant vessel and color score between polyps in women with *vs* without abnormal uterine bleeding were seen in both pre- and postmenopausal women (Table 8). Cystic endometrium was more common in postmenopausal women who had polyps without abnormal uterine bleeding than in those who had polyps with abnormal uterine bleeding.

DISCUSSION

We have described the sonographic appearance of various endometrial pathologies, including polyps, hyperplasia without atypia, EC and EIN, in women without abnormal uterine bleeding. The endometrial cancers in women without abnormal uterine bleeding were more frequently endometrioid, were diagnosed at earlier stages of disease and had a more favorable grade than cancers in women with abnormal uterine bleeding. On ultrasound, endometrial cancers appeared less vascularized and were associated with a thinner endometrium in women without abnormal uterine bleeding compared with those in patients with abnormal uterine bleeding. This was also true when considering only FIGO Stage IA cancers. Polyps in women without abnormal uterine

Table 7 Sonographic features of endometrial cancer, endometrial intraepithelial neoplasia and endometrial polyps in women without abnormal uterine bleeding (AUB) analyzed in the present study (IETA3) and women with AUB included in the IETA1 cohort[14]

	Endometrial cancer			*Endometrial intraepithelial neoplasia*			*Endometrial polyps*		
Variable	*Without AUB (n = 23)*	*With AUB[14] (n = 121)**	*Difference (95% CI)*	*Without AUB (n = 6)*	*With AUB[14] (n = 17)†*	*Difference (95% CI)*	*Without AUB (n = 1028)*	*With AUB[14] (n = 718)‡*	*Difference (95% CI)*
Endometrial thickness (mm)	11.3 (8.4–14.2)	19.9 (17.7–22.1)	−8.6 (−12.0 to −5.2)	11.0 (6.3–15.7)	13.4 (9.6–17.3)	−2.4 (−7.5 to +2.6)	9.8 (9.6–10.1)	11.2 (10.8–11.6)	−1.4 (−1.9 to −1.0)
Endometrium not visible	2 (8.7)	10 (8.3)	+0.4 (−12.5 to +13.4)	0 (0)	0 (0)	—	28 (2.7)	14 (1.9)	+0.8 (−0.8 to +2.3)
Uniform echogenicity	4 (17.4)	15 (12.4)	+5.0 (−14.2 to +24.1)	1 (16.7)	6 (35.3)	−18.6 (−67.4 to +30.1)	296 (28.8)	344 (47.9)	−19.1 (−23.8 to −14.4)
Three-layer	1 (25.0)	1 (6.7)	+18.3 (−41.8 to +78.4)	0 (0)	2 (33.3)	−33.3 (−100 to +37.7)	35 (11.8)	133 (38.7)	−26.9 (−33.5 to +20.2)
Hyperechogenic	1 (25.0)	11 (73.3)	−48.3 (−100 to +15.5)	1 (100)	3 (50.0)	+50.0 (−40.0 to +100)	226 (76.4)	188 (54.7)	+21.7 (+14.3 to +29.0)
Isoechogenic	0 (0)	2 (13.3)	−13.3 (−43.9 to +17.2)	0 (0)	1 (16.7)	−16.7 (−63.2 to +29.8)	27 (9.1)	20 (5.8)	+3.3 (−1.1 to +7.7)
Hypoechogenic	2 (50.0)	1 (6.7)	+43.3 (−23.1 to +100)	0 (0)	0 (0)	—	8 (2.7)	3 (0.9)	+1.8 (−0.5 to +4.2)
Non-uniform echogenicity	17 (73.9)	96 (79.3)	−5.4 (−27.4 to +16.5)	5 (83.3)	11 (64.7)	+18.6 (−30.1 to +67.4)	704 (68.5)	360 (50.1)	+18.4 (+13.6 to +23.1)
With cysts	8 (47.1)	35 (36.5)	—	2 (40.0)	6 (54.5)	—	278 (39.5)	178 (49.4)	—
Without cysts	9 (52.9)	61 (63.5)		3 (60.0)	5 (45.5)		426 (60.5)	182 (50.6)	
Endometrial cysts	8 (34.8)	35 (28.9)	+5.9 (−17.8 to +29.5)	2 (33.3)	6 (35.3)	−2.0 (−48.0 to +44.0)	278 (27.0)	178 (24.8)	+2.2 (−2.0 to +6.5)
Homogeneous	2 (8.7)	5 (4.1)	+4.6 (−10.1 to +19.2)	1 (16.7)	4 (23.5)	−6.8 (−49.7 to +36.0)	218 (21.2)	126 (17.5)	+3.7 (−0.2 to +7.5)
With irregular cysts	0 (0)	2 (40.0)	—	0 (0)	1 (25.0)	—	32 (14.7)	21 (16.7)	—
With regular cysts	2 (100)	3 (60.0)		1 (100)	3 (75.0)		186 (85.3)	105 (83.3)	
Heterogeneous	15 (65.2)	91 (75.2)	−10.0 (−33.5 to +13.5)	4 (66.7)	7 (41.2)	+25.5 (−30.2 to +81.2)	486 (47.3)	234 (32.6)	+14.7 (+10.0 to +19.4)
With irregular cysts	3 (20.0)	20 (22.0)	—	1 (25.0)	1 (14.3)	—	8 (1.6)	4 (1.7)	—
With regular cysts	3 (20.0)	10 (11.0)		0 (0)	1 (14.3)		52 (10.7)	48 (20.5)	
Without cysts	9 (60.0)	61 (67.0)		3 (75.0)	5 (71.4)		426 (87.7)	182 (77.8)	
Color score recorded	21 (91.3)	111 (91.7)	−0.4 (−13.4 to +12.5)	6 (100)	17 (100)	+0 (−0 to +0)	1000 (97.3)	704 (98.1)	−0.8 (−2.3 to +0.8)
1	3 (14.3)	13 (11.7)	+26.8	1 (16.7)	7 (41.2)	+30.4	237 (23.7)	204 (29.0)	+10.0
2	10 (47.6)	26 (23.4)	(+1.3 to +52.2)¶	4 (66.7)	2 (11.8)	(−19.0 to +79.8)¶	596 (59.6)	312 (44.3)	(+5.9 to +14.1)¶
3	7 (33.3)	35 (31.5)	−26.8	1 (16.7)	7 (41.2)	−30.4	161 (16.1)	171 (24.3)	−10.0
4	1 (4.8)	37 (33.3)	(−52.2 to −1.3)**	0 (0)	1 (5.9)	(−79.8 to +19.0)**	6 (0.6)	17 (2.4)	(−14.1 to −5.9)**
Color score > 1	18 (78.3)	98 (81.0)	−2.7 (−23.6 to +18.1)	5 (83.3)	10 (58.8)	+24.5 (−24.7 to +73.7)	763 (74.2)	500 (69.6)	+4.6 (+0.2 to +9.0)
Vascular pattern if color score > 1§			—			—			—
Single, no branching	5 (27.8)	4 (4.1)		4 (80.0)	1 (10.0)		583 (76.4)	262 (52.4)	
Single, with branching	2 (11.1)	6 (6.1)		0 (0)	1 (10.0)		83 (10.9)	83 (16.6)	

Continued over.

Table 7 *Continued*

Variable	*Endometrial cancer*			*Endometrial intraepithelial neoplasia*			*Endometrial polyps*		
	Without AUB (n = 23)	*With AUB[14] (n = 121)**	*Difference (95% CI)*	*Without AUB (n = 6)*	*With AUB[14] (n = 17)†*	*Difference (95% CI)*	*Without AUB (n = 1028)*	*With AUB[14] (n = 718)‡*	*Difference (95% CI)*
Multiple, focal	0 (0)	20 (20.4)	—	0 (0)	2 (20.0)	—	25 (3.3)	33 (6.6)	—
Multiple, multifocal	7 (38.9)	54 (55.1)	—	0 (0)	2 (20.0)	—	40 (5.2)	45 (9.0)	—
Scattered	4 (22.2)	13 (13.3)	—	1 (20.0)	4 (40.0)	—	31 (4.1)	73 (14.6)	—
Circular	0 (0)	1 (1.0)	—	0 (0)	0 (0)	—	1 (0.1)	4 (0.8)	—
Single vessel	7 (30.4)	10 (8.3)	+22.1 (+0.1 to +44.2)	4 (66.7)	2 (11.8)	+54.9 (+2.9 to +100)	666 (64.8)	345 (48.1)	+16.7 (+11.9 to +21.5)
Multiple, multifocal vessels	7 (30.4)	54 (44.6)	−14.2 (−37.6 to +9.2)	0 (0)	2 (11.8)	−11.8 (−38.4 to +14.8)	40 (3.9)	45 (6.3)	−2.4 (−4.6 to −0.1)
Midline assessed	21 (91.3)	111 (91.7)	−0.4 (−13.4 to +12.5)	6 (100)	17 (100)	—	1000 (97.3)	694 (96.7)	+0.6 (−1.1 to +2.4)
Irregular	6 (28.6)	8 (7.2)	+21.4 (−1.5 to +44.1)	0 (0)	0 (0)	—	51 (5.1)	19 (2.7)	+2.4 (+0.4 to +4.3)
Linear	1 (4.8)	1 (0.9)	+3.9 (−8.3 to +16.0)	0 (0)	2 (11.8)	−11.8 (−38.4 to +14.8)	257 (25.7)	172 (24.8)	+0.9 (−3.4 to +5.2)
Not linear	0 (0)	2 (1.8)	−1.8 (−6.1 to +2.5)	2 (33.3)	1 (5.9)	+27.4 (−23.2 to +78.1)	155 (15.5)	57 (8.2)	+7.3 (+4.1 to +10.4)
Not defined	14 (66.7)	100 (90.1)	−23.4 (−47.2 to +0.3)	4 (66.7)	14 (82.4)	−15.7 (−68.8 to +37.4)	537 (53.7)	446 (64.3)	−10.6 (−15.4 to −5.7)
Bright edge assessed	18 (78.3)	111 (91.7)	−13.4 (−33.6 to +6.7)	6 (100)	17 (100)	+0 (−0 to +0)	976 (94.9)	704 (98.1)	−3.2 (−4.9 to −1.3)
Present	6 (33.3)	15 (13.5)	+19.8 (−6.1 to +45.7)	4 (66.7)	4 (23.5)	+43.2 (−10.9 to +97.2)	688 (70.5)	338 (48.0)	+22.5 (+17.7 to +27.3)
Absent	12 (66.7)	96 (86.5)	−19.8 (−45.7 to +6.1)	2 (33.3)	13 (76.5)	−43.2 (−97.2 to +10.9)	288 (29.5)	366 (52.0)	−22.5 (−27.3 to +17.7)
Endometrial–myometrial junction assessed	18 (78.3)	111 (91.7)	−13.4 (−33.6 to +6.7)	6 (100)	17 (100)	+0 (−0 to +0)	976 (94.9)	704 (98.1)	−3.2 (−4.9 to −1.3)
Interrupted	3 (16.7)	47 (42.3)	−25.7 (−48.4 to −2.9)	0 (0)	3 (17.6)	−17.6 (−47.0 to +11.7)	18 (1.8)	41 (5.8)	−4.0 (−6.0 to −1.9)
Irregular	2 (11.1)	21 (18.9)	−7.8 (−27.3 to +11.7)	0 (0)	2 (11.8)	−11.8 (−38.4 to +14.8)	41 (4.2)	67 (9.5)	−5.3 (−7.9 to −2.7)
Regular	13 (72.2)	29 (26.1)	+46.1 (+20.6 to +71.6)	6 (100)	11 (64.7)	+35.3 (+1.3 to +69.3)	902 (92.4)	542 (77.0)	+15.4 (+11.8 to +19.1)
Not defined	0 (0)	14 (12.6)	−12.6 (−22.0 to +3.2)	0 (0)	1 (5.9)	−5.9 (−22.9 to +11.1)	15 (1.5)	54 (7.7)	−6.2 (−8.4 to −3.9)

Results are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). Percentages are given as fraction of total number of women or per subgroup. *IETA1[14] reports on unenhanced ultrasound features of 121 out of 137 histologically confirmed endometrial cancers. †IETA1[14] reports on unenhanced ultrasound features of 17 out of 18 histologically confirmed endometrial intraepithelial neoplasias. ‡IETA1[14] reports on unenhanced ultrasound features of 718 out of 751 histologically confirmed endometrial polyps. §IETA vascular pattern[17]: 'Single, no branching', single dominant vessel without branching; 'Single, with branching', single dominant vessel with branching; 'Multiple, focal', multiple dominant vessels with focal origin; 'Multiple, multifocal', multiple dominant vessels with multifocal origin; 'Scattered', scattered vessels; 'Circular', circular flow. ¶Difference for color score 1–2. **Difference for color score 3–4.

Table 8 Comparison of sonographic features of endometrial polyps in women without abnormal uterine bleeding (AUB) analyzed in the present study (IETA3) and women with AUB included in the IETA1 cohort[14]

	Premenopausal			*Postmenopausal*		
Variable	*Without AUB (n = 567)*	*With AUB[14] (n = 428)**	*Difference (95% CI)*	*Without AUB (n = 461)*	*With AUB[14] (n = 290)**	*Difference (95% CI)*
Endometrial thickness (mm)	10.5 (10.2–10.8)	11.5 (11.0–11.9)	−1.0 (−1.6 to −0.3)	9.0 (8.6–9.3)	10.7 (10.0–11.4)	−1.7 (−2.5 to −0.9)
Endometrium not visible	8 (1.4)	8 (1.9)	−0.5 (−2.3 to +1.4)	20 (4.3)	6 (2.1)	+2.2 (−0.5 to +5.0)
Uniform echogenicity	173 (30.5)	261 (61)	−30.5 (−36.7 to −24.3)	123 (26.7)	83 (28.6)	−1.9 (−8.8 to +4.9)
Uniform, three-layer	35 (6.2)	127 (29.7)	−23.5 (−28.5 to −18.5)	0 (0)	6 (2.1)	−2.1 (−4.0 to −0.1)
Uniform, hyperechogenic	114 (20.1)	122 (28.5)	−8.4 (−14.0 to −2.8)	112 (24.3)	66 (22.8)	+1.5 (−5.0 to +8.0)
Uniform, isoechogenic	18 (3.2)	11 (2.6)	+0.6 (−1.7 to +2.9)	9 (2.0)	9 (3.1)	−1.1 (−3.8 to +1.5)
Uniform, hypoechogenic	6 (1.1)	1 (0.2)	+0.9 (−0.3 to +2.0)	2 (0.4)	2 (0.7)	−0.3 (−1.6 to +1.1)
Non-uniform echogenicity	386 (68.1)	159 (37.1)	+31.0 (+24.7 to +37.1)	318 (69.0)	201 (69.3)	−0.3 (−7.4 to +6.7)
Non-uniform, homogeneous with cysts	20 (3.5)	29 (6.8)	−3.3 (−6.3 to −0.2)	198 (43.0)	97 (33.4)	+9.6 (+2.2 to +16.8)
Non-uniform, heterogeneous with cysts	11 (1.9)	12 (2.8)	−0.9 (−3.0 to +1.3)	49 (10.6)	40 (13.8)	−3.2 (−8.3 to +2.0)
Non-uniform, heterogeneous without cysts	355 (62.6)	118 (27.6)	+35.0 (+29.0 to +41.1)	71 (15.4)	64 (22.1)	−6.7 (−12.7 to −0.6)
Endometrial cysts	31 (5.5)	41 (9.6)	−4.1 (−7.7 to −0.5)	247 (53.6)	137 (47.2)	+6.4 (−1.3 to +13.9)
Color score 1–2	443 (78.1)	295 (68.9)	+9.2 (+3.5 to +15.0)	390 (84.6)	221 (76.2)	+8.4 (+2.2 to +14.6)
Color score 3–4	116 (20.5)	125 (29.2)	−8.7 (−14.4 to −3.1)	51 (11.1)	63 (21.7)	−10.6 (−16.5 to −4.8)
Single dominant vessel with/without branching	468 (82.5)	246 (57.5)	+25.0 (+19.2 to +30.9)	198 (43.0)	99 (34.1)	+8.9 (+1.4 to +16.2)
Multiple, multifocal vessels	24 (4.2)	31 (7.2)	−3.0 (−6.2 to +0.2)	16 (3.5)	14 (4.8)	−1.3 (−4.6 to +1.9)
Bright edge	451 (79.5)	232 (54.2)	+25.3 (+19.4 to +31.3)	237 (51.4)	106 (36.6)	+14.8 (+7.4 to +22.3)
Regular endometrial–myometrial junction	537 (94.7)	348 (81.3)	+13.4 (+9.1 to +17.7)	365 (79.2)	194 (66.9)	+12.3 (+5.4 to +19.1)

Results are presented as mean (95% CI) and mean difference (95% CI), or as *n* (%) and difference in percentages (95% CI). *IETA1[14] reports on unenhanced ultrasound features of 428 out of 434 histologically confirmed premenopausal and 290 out of 317 histologically confirmed postmenopausal endometrial polyps.

bleeding more often manifested a bright edge and a single dominant vessel and were less vascularized on color or power Doppler than polyps in women with abnormal uterine bleeding, and these differences were seen in both pre- and postmenopausal women.

To our knowledge, this is the first study providing a detailed overview of the grayscale and Doppler ultrasound features of different endometrial histological outcomes in women without abnormal uterine bleeding. Other strengths of the study are its multicenter design and the use of a standardized examination and standardized measurement techniques and terminology. In clinical practice, the exact time of menopause is often difficult to determine, and the variable 'menopausal status' contains a level of uncertainty. We have therefore deliberately presented data of pre- and postmenopausal patients both separately and together. We acknowledge that by relying on patients' recollection of abnormal bleeding, our study may be prone to some degree of recall bias. We have accounted for this by meticulous data curation and retrospective case exclusion. It is a limitation of the study that blind endometrial sampling was used in a small proportion (100/1745 (6%)) of cases. This may have resulted in some focal pathology, e.g. polyps, being missed. Another limitation is that for the 103 patients (6% of all patients) with pre-existing intracavitary fluid, we derived the ultrasound findings corresponding to unenhanced ultrasound from the ultrasound features of the endometrium and any lesions in the fluid-filled cavity. This may have introduced some bias.

It is important to emphasize that our study was not designed to provide information on the prevalence of uterine intracavitary pathology in women without abnormal uterine bleeding. The prevalence of pathologies is likely to be much higher in our study cohort (malignancy or premalignancy in 1.7%, polyps in 59%, hyperplasia without atypia in 1.3%) than in the general population of women without abnormal uterine bleeding, since suspicion of intracavitary pathology was the indication for surgery in 65% of cases. To the best of our knowledge, there are no studies describing the prevalence of uterine intracavitary pathology in a general population of women without abnormal uterine bleeding. In a cohort of 375 asymptomatic Danish women, invited from the general population, Dreisler *et al.*[21] found endometrial polyps in 9%, submucous myomas in 1% and polypoidal growing cancer in one (0.27%). In a systematic review investigating the ability of sonographic endometrial thickness to diagnose endometrial carcinoma in asymptomatic postmenopausal women not using hormone replacement therapy, the pooled prevalences of endometrial carcinoma and atypical endometrial hyperplasia were 0.62% and 0.59%, respectively[22]. However, both studies[21,22] suffer from selection bias, and their results cannot be extrapolated to a general population of women without abnormal uterine bleeding.

Screening for EC is not recommended[23]. However, even though there are data supporting the notion that diagnosing endometrial cancer at an asymptomatic stage does not improve the prognosis[24,25], most treating physicians would opt for further investigation in an asymptomatic woman with ultrasound findings suggestive of endometrial cancer, such as thickened, abundantly vascularized, heterogeneous lesions[26–28]. It is worth mentioning that the indication for sampling or hysteroscopic surgery in this study was at the clinician's discretion and also included suspicion of various benign pathologies. Previous studies have described the typical grayscale and color Doppler ultrasound findings in malignant endometrial pathology in women with abnormal uterine bleeding and showed differences in the ultrasound features between benign and malignant endometria[26–29]. Our results show that benign and malignant endometrial pathology also manifest different grayscale and color Doppler ultrasound features in women without abnormal uterine bleeding, supporting that, in most cases, it should be possible to recognize an EC in an asymptomatic woman based on its ultrasound appearance.

Even though there were some differences in the ultrasound appearance of polyps between women with and those without abnormal uterine bleeding, a polyp should also be recognizable on ultrasound in women without abnormal uterine bleeding, the typical features being a bright edge and the presence of a 'feeding vessel' (a single vessel with or without branching). However, whether a lesion manifesting the typical ultrasound features of a polyp should be surgically removed in an asymptomatic woman is controversial, and should be discussed with the patient. The risk of malignancy in polyps in women without abnormal uterine bleeding is low[30,31], some lesions thought to be polyps based on ultrasound may spontaneously regress in premenopausal women[32] and hysteroscopic surgery to remove a polyp is not without risks[6,33–36]. The findings of studies on risk factors for a polyp's being malignant in asymptomatic women are equivocal[30,31,37–39]. Further studies to elucidate this issue are needed. The IETA consortium aims to simplify the terms and definitions of endometrial pathologies to optimize applicability in non-expert hands.

In conclusion, our findings should help clinicians to discriminate between benign and malignant endometrial conditions in women without abnormal vaginal bleeding.

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REFERENCES

1. Wolfman W. No. 249 – Asymptomatic Endometrial Thickening. *J Obstet Gynaecol Can* 2018; **40**: e367–e377.
2. Allen DG, Correy JF, Marsden DE. Abnormal uterine bleeding and cancer of the genital tract. *Aust N Z J Obstet Gynaecol* 1990; **30**: 81–83.
3. Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C, Gallos I, Ganesan R, Gupta J, Johnson N, Kitson S, Mackintosh M, Martin-Hirsch P, Miles T, Rafii S, Reed N, Rolland P, Singh K, Sivalingam, Walther A. BGCS uterine cancer guidelines: Recommendations for practice. *Eur J Obstet Gynecol Reprod Biol* 2017; **213**: 71–97.
4. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. *JAMA Intern Med* 2018; **178**: 1210–1222.
5. National Institute for Health and Care Excellence (2018). Heavy menstrual bleeding: assessment and management (NICE Guideline 88). https://www.nice.org.uk/guidance/ng88/resources/heavy-menstrual-bleeding-assessment-and-management-pdf-1837701412549. / [accessed 23 October 2021].
6. Word B, Gravlee LC, Wideman GL. The fallacy of simple uterine curettage. *Obstet Gynecol* 1958; **12**: 642–648.
7. 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**: 1131–1136.
8. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. *BJOG* 2002; **109**: 313–321.
9. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. *JAMA* 2002; **288**: 1610–1621.
10. Karlsson B, Granberg S, Wikland M, Ylöstalo P, Torvid K, Marsal K, Valentin L. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding – a Nordic multicenter study. *Am J Obstet Gynecol* 1995; **172**: 1488–1494.
11. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, Brand R, Grady D. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. *JAMA* 1998; **280**: 1510–1517.
12. 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; **37**: 232–240.
13. Giannella L, Mfuta K, Setti T, Boselli F, Bergamini E, Cerami LB. Diagnostic accuracy of endometrial thickness for the detection of intra-uterine pathologies and appropriateness of performed hysteroscopies among asymptomatic postmenopausal women. *Eur J Obstet Gynecol Reprod Biol* 2014; **177**: 29–33.
14. Van Den Bosch T, Verbakel JY, Valentin L, Wynants L, De Cock B, Pascual MA, Leone FPG, Sladkevicius P, Alcazar JL, Votino A, Fruscio R, Lanzani C, Van Holsbeke C, Rossi A, Jokubkiene L, Kudla M, Jakab A, Domali E, Epstein E, Van Pachterbeke C, Bourne T, Van Calster B, Timmerman D. 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; **57**: 164–172.
15. Vuento MH, Pirhonen JP, Mäkinen JI, Tyrkkö JE, Laippala PJ, Grönroos M, Salmi TA. Screening for endometrial cancer in asymptomatic postmenopausal women with conventional and colour Doppler sonography. *BJOG* 1999; **106**: 14–20.
16. Goldstein SR. Postmenopausal endometrial fluid collections revisited: look at the doughnut rather than the hole. *Obstet Gynecol* 1994; **83**: 738–740.
17. Leone FP, Timmerman D, Bourne T, Valentin L, Epstein E, Goldstein SR, Marret H, Parsons AK, Gull B, Istre O, Sepulveda W, Ferrazzi E, Van den Bosch T. 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; **35**: 103–112.
18. Installé 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; **2**: e28.
19. Timmerman D, Verguts J, Konstantinovic ML, Moerman P, Van Schoubroeck D, Deprest J, Van Huffel S. 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; **22**: 166–171.
20. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *Int J Gynecol Obstet* 2014; **125**: 97–98.
21. Dreisler E, Sorensen SS, Ibsen PH, Lose G. Value of endometrial thickness measurement for diagnosing focal intrauterine pathology in women without abnormal uterine bleeding. *Ultrasound Obstet Gynecol* 2009; **33**: 344–348.
22. Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW, Timmermans A. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2012; **40**: 621–629.
23. National Institutes of Health (NIH). Endometrial Cancer Screening (PDQ®)–Health Professional Version. https://www.cancer.gov/types/uterine/hp/endometrial-screening-pdq. [Accessed 10 January 2022].
24. Gerber B, Krause A, Müller H, Reimer T, Külz T, Kundt G, Friese K. Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding. *Eur J Cancer* 2001; **37**: 64–71.
25. Gemer O, Segev Y, Helpman L, Hag-Yahia N, Eitan R, Raban O, Vaknin Z, Leytes S, Ben Arie A, Amit A, Levy T, Namazov A, Volodarsky M, Ben Shachar I, Atlas I,

Bruchim I, Lavie O. 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.e1–181.e6.
26. 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 > or = 4.5 mm. *Ultrasound Obstet Gynecol* 2007; **30**: 332–340.
27. Sladkevicius P, Opolskiene G, Valentin L. Prospective temporal validation of mathematical models to calculate risk of endometrial malignancy in patients with postmenopausal bleeding. *Ultrasound Obstet Gynecol* 2017; **49**: 649–656.
28. Epstein E, Skoog L, Isberg PE, De Smet F, De Moor B, Olofsson PA, Gudmundsson S, Valentin L. 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; **20**: 370–376.
29. Van den Bosch T, Ameye L, Van Schoubroeck D, Bourne T, Timmerman D. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. *Facts Views Vis Obgyn* 2015; **7**: 17–24.
30. Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, Barbieri M, Cammareri G, Capobianco G, Cicinelli E, Coccia ME, Donarini G, Fiore S, Litta P, Sideri M, Solima E, Spazzini D, Testa AC, Vignali M. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. *Am J Obstet Gynecol* 2009; **200**: 235.e1–6.
31. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. *Obstet Gynecol* 2010; **116**: 1197–1205.
32. Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. *J Minim Invasive Gynecol* 2009; **16**: 465–471.
33. Jansen FW, Vredevoogd CB, van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. *Obstet Gynecol* 2000; **96**: 266–270.
34. Kayatas S, Meseci E, Tosun OA, Arinkan SA, Uygur L, Api M. Experience of hysteroscopy indications and complications in 5,474 cases. *Clin Exp Obstet Gynecol* 2014; **41**: 451–454.
35. Aston B, Weaver E. Risks and benefits of hysteroscopy and endometrial sampling as a standard procedure for assessing serendipitous findings of endometrial thickening in postmenopausal women. *Aust N Z J Obstet Gynaecol* 2014; **54**: 597–599.
36. Lev-Sagie A, Hamani Y, Imbar T, Hurwitz A, Lavy Y. The significance of intrauterine lesions detected by ultrasound in asymptomatic postmenopausal patients. *BJOG* 2005; **112**: 379–381.
37. Baiocchi G, Manci N, Pazzaglia M, Giannone L, Burnelli L, Giannone E, Fratini D, Di Renzo GC. Malignancy in endometrial polyps: a 12-year experience. *Am J Obstet Gynecol* 2009; **201**: 462.e1–4.
38. Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, Dgani R, Hagay Z. The malignant potential of endometrial polyps. *Eur J Obstet Gynecol Reprod Biol* 2004; **115**: 206–210.
39. Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, Bovicelli L. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. *Am J Obstet Gynecol* 2003; **188**: 927–931.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Statistical analysis plan (SAP) for cases of pre-existing intracavitary fluid

Table S2 Distribution of sampling methods for each histological diagnosis

Table S3 Final diagnosis per participating center

Table S4 Indication for surgery per participating center

Table S5 Indication for surgery per pathology

Table S6 Demographic characteristics per pathology

Table S7 Ultrasound features per pathology, in both pre- and postmenopausal women

Table S8 Ultrasound features per pathology in only postmenopausal women

Table S9 Ultrasound features per pathology in only premenopausal women

Table S10 Comparison of ultrasound features of endometrial cancers FIGO[20] Stage IA between ultrasound studies featuring women with (IETA1)[14] and without (IETA3) abnormal uterine bleeding

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Características ecográficas de la patología endometrial en mujeres sin hemorragia uterina anómala: resultados del estudio internacional de análisis de tumores endometriales (IETA3)

RESUMEN

Objetivos. El objetivo principal de este estudio fue describir las características ecográficas de varias patologías endometriales y otras patologías intracavitarias en mujeres sin hemorragia uterina anómala (HUA) utilizando la terminología del Análisis Internacional de Tumores Endometriales (IETA, por sus siglas en inglés).

El objetivo secundario fue comparar los resultados con los datos publicados sobre las mujeres con HUA.

Métodos. Este fue un estudio observacional prospectivo de mujeres que se presentaron en uno de los siete centros especializados en ecografía ginecológica, desde 2011 hasta 2018 por indicios no relacionados con la HUA. Todas las pacientes fueron sometidas a una ecografía transvaginal utilizando las técnicas de examen y medición de la IETA. La ecografía se realizó como parte del examen ginecológico rutinario o del seguimiento de una patología no endometrial, o como parte de una exploración antes de someterse a un tratamiento por infertilidad, prolapso uterino o patología ovárica. Los hallazgos ecográficos se describieron utilizando la terminología de la IETA. El muestreo endometrial se realizó después de la ecografía. Los criterios de valoración histológicos fueron la atrofia endometrial, el endometrio proliferativo o secretor, la hiperplasia endometrial sin atipia, el pólipo endometrial, el leiomioma intracavitario, la neoplasia intraepitelial endometrial (NIE), el cáncer de endometrio (CE) y el tejido insuficiente. Los hallazgos en la cohorte de mujeres sin HUA se compararon con los de una cohorte publicada de mujeres con HUA que fueron examinadas con ecografía transvaginal entre 2012 y 2015 utilizando la misma técnica de examen y terminología de la IETA.

Resultados. En este estudio (IETA3), se incluyeron 1.745 mujeres sin HUA que se sometieron a una ecografía transvaginal estandarizada seguida de una toma de muestras endometriales con diagnóstico histológico (n=1537) o al menos 1 año de seguimiento clínico y ecográfico (n=208). De ellas, 858 (49,2%) eran premenopáusicas y 887 (50,8%) eran posmenopáusicas. La histología mostró la presencia de CE y/o NIE en 29 (1,7%) mujeres, pólipos endometriales en 1028 (58,9%), miomas intracavitarios en 66 (3,8%), cambios proliferativos o secretores o hiperplasia sin atipia en 144 (8,3%), atrofia endometrial en 265 (15,2%) y tejido insuficiente en cinco (0,3%). La mayoría de los casos de CE o NIE (25/29 (86,2%)) se diagnosticaron después de la menopausia. El grosor medio del endometrio en las mujeres con CE o NIE fue de 11,2 mm (IC 95%, 8,9–13,6 mm), siendo de media 2,4 mm (IC 95%, 0,3–4,6 mm) más grueso que el de sus homólogas benignas. Las mujeres con patología endometrial maligna manifestaron con mayor frecuencia una ecogenicidad no uniforme (22/29 (75,9%)) que las que tenían patología endometrial benigna (929/1716 (54,1%)) (diferencia, +21.8% (IC 95%, +4.2% a +39.2%)). Se observó una vascularización de moderada a abundante (puntuación de color 3–4) en el 31,0% (9/29) de los casos con CE o NIE, en comparación con el 12,8% (220/1716) de los que tuvieron un resultado benigno (diferencia, +18.2% (IC 95%, -0,5% a +36.9%)). Se registraron múltiples vasos multifocales en el 24,1% (7/29) de las mujeres con CE o NIE frente a 4.0% (68/1716) de las que tenían un resultado benigno (diferencia, +20.2% (IC 95%, +4.6% a +35.7%)). Se observó una unión endometrio-miometrio regular con menor frecuencia en las mujeres con CE o NIE (19/29 (65,5%)) frente a aquellas con un resultado benigno (1412/1716 (82,3%)) (diferencia, −16,8% (IC 95%, −34,2% a +0.6%)). En las mujeres con pólipos endometriales sin HUA, el patrón vascular más frecuente fue un único vaso dominante (666/1028 (64,8%)). En las mujeres con CE, tanto en las que tenían como en las que no tenían HUA, el endometrio solía manifestar una ecogenicidad heterogénea, pero el endometrio era, por término medio, 8,6 mm (IC 95%, 5,2–12,0 mm) más delgado y menos intensamente vascularizado (puntuación de color 3–4: diferencia, −26,8% (IC del 95%, −52,2% a −1,3%)) en las mujeres sin HUA, en comparación con las que la tenían. Tanto en las mujeres pre- como en las posmenopáusicas, los pólipos endometriales asintomáticos se asociaron a un endometrio más fino, y manifestaron con más frecuencia un borde brillante, una unión endometrio-miometrio regular y un único vaso dominante que los pólipos de las mujeres sintomáticas, y estuvieron menos intensamente vascularizados.

Conclusiones. Se describen las características ecográficas típicas del CE, los pólipos y otras histologías intracavitarias utilizando la terminología de la IETA en mujeres sin HUA. Estos hallazgos sugieren que la presencia de pólipos asintomáticos o de malignidad endometrial puede ir acompañada de endometrios más finos y menos intensamente vascularizados que sus homólogos sintomáticos.

无异常子宫出血女性子宫内膜病理超声特征：

国际子宫内膜肿瘤分析研究 (IETA3) 的结果

摘要

目的： 本研究的主要目的是使用国际子宫内膜肿瘤分析 (IETA) 术语描述无异常子宫出血 (AUB) 的女性的各种子宫内膜和其他腔内病变的超声特征。次要目的是将我们的研究结果与已发表的关于 女性无异常子宫出血（AUB）数据进行比较。

方法： 这是一项前瞻性观察研究，研究对象为从 2011 年到 2018 年在七个妇科超声检查专业中心之一就诊的女性，纳入范围为与 AUB 无关的适应症。所有患者均使用 IETA 检查和测量技术进行了经阴道超声检查。超声检查作为常规妇科检查或非子宫内膜病变随访的一部分，或作为不孕症、子宫脱垂或卵巢病变治疗前检查的一部分。使用 IETA 术语描述超声检查结果。超声扫描后进行子宫内膜取样。组织学检查终点为子宫内膜萎缩、增生或分泌性子宫内膜、无异型性的子宫内膜增生、子宫内膜息肉、腔内平滑肌瘤、子宫内膜上皮内瘤变（EIN）、子宫内膜癌（EC）和组织不足。我们将没有 AUB 的女性队列中的结果与已发表的 AUB 女性队列中的结果进行了比较，这些女性在 2012 年至 2015 年间使用相同的 IETA 检查技术和术语进行了经阴道超声检查。

结果：在这项研究 (IETA3) 中，我们纳入了 1745 名无 AUB 的女性，她们接受了标准化的经阴道超声检查，随后进行了子宫内膜取样并进行组织学诊断 (n=1537) 或进行至少 1 年的临床和超声随访 (n=208)。其中，858 名（49.2%）女性处于绝经前状态，887 名（50.8%）处于绝经后状态。组织学显示 29 例 (1.7%) 女性存在子宫内膜癌（ EC ）和/或 子宫内膜上皮内瘤变（EIN），1028 例 (58.9%) 存在子宫内膜息肉，66 例 (3.8%) 存在腔内肌瘤，144 例 (8.3%) 存在增殖性或分泌性改变或无异型性增生，265 例（(15.2%)子宫内膜萎缩 和 5 例 (0.3%) 组织不足。大多数子宫内膜癌（ EC） 或子宫内膜上皮内瘤变（ EIN ）病例 (25/29 (86.2%)) 是在绝经后诊断出来的。子宫内膜癌（EC） 或子宫内膜上皮内瘤变（ EIN） 女性的平均子宫内膜厚度为 11.2 毫米（95% CI，8.9-13.6 毫米），比其良性对照患者平均厚 2.4 毫米（95% 可信区间，0.3-4.6 毫米）。患有恶性子宫内膜病变的女性比患有良性子宫内膜病变的女性（929/1716（54.1%））更频繁地表现出不均匀回声（22/29（75.9%））（差异，+21.8%（95% CI，+4.2 % 至 +39.2%））。31.0% (9/29) 的 子宫内膜病变（EC） 或子宫内膜上皮内瘤变（ EIN ）病例出现中度至丰富的血管形成（颜色评分 3-4），而良性结果病例中的这一比例为 12.8% (220/1716)（差异，+18.2% (95 % CI，−0.5% 至 +36.9%)）。24.1% (7/29) 的 EC 或 EIN 女性与 4.0% (68/1716) 的良性结果女性（差异，+20.2%（95% CI，+4.6% 至 +35.7% ））。子宫内膜病变（EC）或子宫内膜上皮内瘤变 EIN 女性 (19/29 (65.5%)) 与良性结局女性 (1412/1716 (82.3%)) 相比，正常子宫内膜 - 肌层交界的频率较低（差异，−16.8% (95% CI , −34.2% 至 +0.6%)）。在没有 AUB 的子宫内膜息肉女性中，单一优势血管是最常见的血管模式 (666/1028 (64.8%))。在有 EC 的女性中，无论有和没有 AUB，子宫内膜通常表现出不均匀的回声，但子宫内膜平均变薄 8.6 毫米（95% CI，5.2-12.0 毫米）且血管化程度较低（颜色评分 3-4 ）与有 AUB 的女性相比，无 AUB 女性的差异为 −26.8%（95% CI，−52.2% 至 −1.3%））。在绝经前和绝经后的女性中，无症状的子宫内膜息肉与较薄的子宫内膜有关，与有症状的女性息肉患者相比，它们更多时候表现出明亮的边缘、子宫内膜-肌层交界处规则和单一的优势血管，而且它们的血管化程度不强。

结论： 我们使用 IETA 术语描述了没有 AUB 的女性的子宫内膜癌（ EC）、息肉和其他腔内组织学的典型超声特征。我们的研究结果表明，与有症状的对照患者相比，无症状息肉或子宫内膜恶性肿瘤患者可能伴有子宫内膜更薄且血管化程度较低的特征。