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Typical ultrasound features of various endometrial pathologies described using International Endometrial Tumor Analysis (IETA) terminology in women with abnormal uterine bleeding

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KEYWORDS: cancer; diagnosis; endometrium; hyperplasia; IETA; leiomyoma; polyp; sonohysterography; ultrasonography

CONTRIBUTION

What are the novel findings of this work?
This is the first prospective multicenter study evaluating the International Endometrium Tumor Analysis (IETA) terms and definitions in women with abnormal uterine bleeding, before and after menopause. Both unenhanced sonography and fluid-instillation sonography were evaluated and compared with histology.

What are the clinical implications of this work?
Our study provides didactic, evidence-based data on the sonographic findings of the normal and abnormal endometrium. This will help clinicians in the diagnosis of malignant as well as benign endometrial pathology. We also describe some easy-to-assess features which, when detected, make endometrial cancer very unlikely.

ABSTRACT

Objective *To describe the ultrasound features of different endometrial and other intracavitary pathologies in pre- and postmenopausal women presenting with abnormal uterine bleeding, using the International Endometrial Tumor Analysis (IETA) terminology.*

Methods *This was a prospective observational multicenter study of consecutive women presenting with abnormal uterine bleeding. Unenhanced sonography with color Doppler and fluid-instillation sonography were performed. Endometrial sampling was performed according to each center's local protocol. The histological endpoints were cancer, atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (EIN), endometrial atrophy, proliferative or secretory endometrium, endometrial hyperplasia without atypia, endometrial polyp, intracavitary leiomyoma and other. For fluid-instillation sonography, the histological endpoints were endometrial polyp, intracavitary leiomyoma and cancer. For each histological endpoint, we report typical ultrasound features using the IETA terminology.*

Results *The database consisted of 2856 consecutive women presenting with abnormal uterine bleeding.*

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Unenhanced sonography with color Doppler was performed in all cases and fluid-instillation sonography in 1857. In 2216 women, endometrial histology was available, and these comprised the study population. Median age was 49 years (range, 19–92 years), median parity was 2 (range, 0–10) and median body mass index was 24.9 kg/m^2 (range, 16.0–72.1 kg/m^2). Of the study population, 843 (38.0%) women were postmenopausal. Endometrial polyps were diagnosed in 751 (33.9%) women, intracavitary leiomyomas in 223 (10.1%) and endometrial cancer in 137 (6.2%). None (0% (95% CI, 0.0–5.5%)) of the 66 women with endometrial thickness < 3 mm had endometrial cancer or atypical hyperplasia/EIN. Endometrial cancer or atypical hyperplasia/EIN was found in three of 283 (1.1% (95% CI, 0.4–3.1%)) endometria with a three-layer pattern, in three of 459 (0.7% (95% CI, 0.2–1.9%)) endometria with a linear endometrial midline and in five of 337 (1.5% (95% CI, 0.6–3.4%)) cases with a single vessel without branching on unenhanced ultrasound.

Conclusions *The typical ultrasound features of endometrial cancer, polyps, hyperplasia and atrophy and intracavitary leiomyomas, are described using the IETA terminology. The detection of some easy-to-assess IETA features (i.e. endometrial thickness < 3 mm, three-layer pattern, linear midline and single vessel without branching) makes endometrial cancer unlikely. Copyright © 2020 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Abnormal uterine bleeding is one of the most common reasons for attending a gynecology outpatient clinic. Owing to the potential for a lethal outcome in endometrial cancer, most published studies focus on the diagnosis of malignancy[1–9]. However, both before and after menopause, abnormal uterine bleeding is caused mainly by benign conditions such as hormonal disturbances, endometrial polyps, intracavitary leiomyomas or endometrial hyperplasia[10,11].

Many ultrasonography studies in women with abnormal uterine bleeding have exclusively evaluated endometrial thickness measurements for the exclusion of endometrial cancer, a thin endometrium being associated with a low risk of malignancy and a thick endometrium increasing the risk[3,4,8,12]. However, the value of endometrial-thickness measurements is restricted mainly to postmenopausal women[13]. In women of reproductive age, the normal endometrium grows rapidly after menstruation, hence endometrial-thickness measurements are associated with a low specificity for endometrial pathology[14]. Moreover, irrespective of age, a thick endometrium is associated not only with cancer but also, and more frequently, with benign pathology such as endometrial polyps or hyperplasia without atypia[11].

In 2010, the International Endometrial Tumor Analysis (IETA) consortium published a consensus statement on how to examine and measure the endometrium and what terminology to use to describe the sonographic features of the endometrium and intracavitary lesions[15].

The aim of this study was to describe, using the IETA terminology, the ultrasound features of different endometrial and other intracavitary pathologies in pre- and postmenopausal women presenting with abnormal uterine bleeding.

METHODS

This was a prospective observational multicenter study of consecutive pre- and postmenopausal women presenting with abnormal uterine bleeding between 1st January 2012 and 31st December 2015 at 12 centers specializing in gynecological ultrasound in nine European countries. The study was approved by the Leuven ethics committee (S52897/ML7087), and all patients gave informed consent. The full protocol is available on request from the corresponding author.

Abnormal uterine bleeding included non-gestational abnormal uterine bleeding in women of reproductive age, defined as bleeding from the uterine corpus that is abnormal in duration, volume, frequency and/or regularity, as well as postmenopausal bleeding, defined as any bleeding after menopause in women not on hormonal therapy, and as unscheduled or heavy bleeding in women on hormonal therapy. Unenhanced transvaginal sonography with color Doppler and fluid-instillation sonography using saline[16,17] or gel[18,19] were performed using the IETA examination technique, and the ultrasound findings were described using the IETA terminology[15]. All ultrasound results were recorded in a specially designed web-based database (Clinical Data Miner (CDM), ESAT-STADIUS, KU Leuven, Belgium)[20]. Endometrial thickness was measured in the sagittal plane including both endometrial layers. In the presence of intracavitary fluid, the two layers were measured separately and the sum was recorded. If the entire endometrium was not clearly visible, it was recorded as 'not measurable'. Endometrial echogenicity was recorded as uniform or non-uniform. Uniform endometrium may be homogeneous without cysts and hyper-, iso- or hypoechogenic in comparison with the myometrial echogenicity, with symmetric anterior/posterior sides, and may have a three-layer or monolayer pattern. Non-uniform endometrium may be homogeneous with regular or irregular cysts, or heterogeneous 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 visible. The color-Doppler score is a subjective assessment of the amount of color, reflecting the vascularity, and is scored as 1 (no color), 2 (minimal color), 3 (moderate color) or 4 (abundant color). The vascular pattern may be a single dominant vessel with or without branching (formerly referred to as the pedicle artery sign)[21], multiple vessels of focal or multifocal origin, scattered flow or circular

flow. Fluid-instillation sonography features included endometrial thickness of both endometrial layers, the presence of an intracavitary lesion, including endometrial lesions and lesions arising from the myometrium and the ultrasonographic features of the intracavitary lesion(s) and background endometrium, i.e. echogenicity, outline, color score and vascular pattern. We recorded the largest of the three orthogonal diameters of the largest lesion. We did not register whether adverse events occurred during the ultrasound examination.

The study protocol encouraged liberal use of fluid-instillation sonography and histological confirmation, but it was left to the examiner's discretion to decide when to perform fluid-instillation sonography and endometrial sampling. The histological examination was performed by each center's dedicated gynecological pathologist. Endometrial sampling was performed after the ultrasound scan, and the interval between the ultrasound examination and the final histological examination could not exceed 120 days. The pathologist was not blinded to clinical and ultrasound information. The histological endpoints were endometrial atrophy, proliferative or secretory endometrium, endometrial hyperplasia without atypia, endometrial polyp, intracavitary leiomyoma, atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN), endometrial cancer and other (endometritis, retained products of conception, adenomyosis, intramural leiomyoma, synechiae, cervical cancer, gestational trophoblastic disease, tubal carcinoma, lymphoma, bladder carcinoma, urethral carcinoma, cervical tissue and no tissue). For fluid-instillation sonography, the histological endpoints were endometrial polyp, intracavitary leiomyoma and cancer. For each patient a single outcome was recorded. In the presence of multiple pathological entities, a single outcome was allocated to each woman using the following hierarchy: cancer, atypical hyperplasia/EIN, polyp, leiomyoma, hyperplasia without atypia.

Statistical analysis included descriptive statistics for the presence of sonographic features, using the IETA terminology, on unenhanced sonography and on fluid-instillation sonography, for each individual histological endpoint. Only complete cases, i.e. subjects with observed values for both the studied ultrasound feature and the histological outcome, were included. The cut-off value for endometrial thickness of less than 3 mm for excluding malignancy was based on analysis of the presented data.

We present the rate of occurrence of the different sonographic features for each histological endpoint (equal to sensitivity) with 95% CIs. For endometrial thickness, the interquartile range is given. Wilson 95% CIs were calculated using the binom package. Subgroup analysis of pre- *vs* postmenopausal women was exploratory and specified *a posteriori*. We planned to include a minimum of 30 cases per outcome category. We expected the prevalence of malignancy in women with abnormal vaginal bleeding to be 3%[11], hence we aimed for a minimum sample size of 1000 women, but would have preferred at least 2000. Statistical analysis was performed using R 3.4.3, (https://www.r-project.org/).

RESULTS

After data cleaning, the database consisted of 2856 consecutive women presenting with abnormal uterine bleeding. Unenhanced sonography with color Doppler was performed in all women and fluid-instillation sonography in 1857. In 640 women, no histological examination was performed, while in 2216 women endometrial histology was available; the latter group comprised the study population. Median age was 49 years (range, 19–92 years) and median parity was 2 (range, 0–10). Median patient height and weight were 164 cm (range, 143–188 cm) and 68 kg (range, 40–180 kg), respectively, and median body mass index was 24.9 kg/m^2 (range, 16.0–72.1 kg/m^2). Eight hundred and forty-three women (38.0%) were postmenopausal and 1373 (62.0%) were premenopausal. A quarter of patients ($n = 556$ (25.1%)) used hormonal therapy, including combined contraceptive pills, gestagen-only medication and postmenopausal hormone substitution therapy.

Histology was obtained by office endometrial sampling or dilatation and curettage (D&C) in 797 (36.0%) and 74 (3.3%) women, respectively, during hysteroscopy in 1080 (48.7%) women and after hysterectomy in 265 (12.0%) women. On histology (Table 1), endometrial atrophy was diagnosed in 224 (10.1%) cases, proliferative endometrium in 306 (13.8%), secretory endometrium in 309 (13.9%), endometrial hyperplasia without atypia in 148 (6.7%), endometrial polyp in 751 (33.9%), intracavitary leiomyoma in 223 (10.1%), atypical hyperplasia/EIN in 18 (0.8%), malignancy in 137 (6.2%) and other in 100 (4.5%). The malignant cases included endometrioid adenocarcinoma in 102 (74.5%) women, adenocarcinoma with squamous differentiation in six (4.4%), clear-cell carcinoma in two (1.5%), mixed carcinoma in four (2.9%), serous carcinoma in 16 (11.7%), undifferentiated carcinoma in one (0.7%) and other diagnoses in six (4.4%) (one low-grade endometrial stromal sarcoma, two sarcomatous tumors, one giant-cell carcinoma, one Müllerian adenosarcoma and one leiomyosarcoma). Table 2 shows endometrial thickness according to the different histological endpoints.

For each of the histological outcomes, the most common features of the endometrium on unenhanced sonography and fluid-instillation sonography, overall and according to menopausal status, are summarized in Tables 3 and 4, respectively. Detailed overviews of the features are shown in Tables S1 and S2, respectively. The incidence of primary intracavitary lesions on fluid-instillation sonography is summarized in Table S3, and Tables S4 and S5 provide a detailed overview of the ultrasound findings for those judged by the ultrasound examiner to be of endometrial origin and those judged to be of myometrial origin, respectively.

In atrophic endometria, on unenhanced sonography, the interquartile range for endometrial thickness was

3–7 mm. In 23.5% (50/213) of cases, the endometrium was not clearly visible. Endometrial echogenicity was generally uniform and hyperechogenic or non-uniform heterogeneous without cysts (67% (95% CI, 59–74%)). The endometrial midline was mostly undefined (75% (95% CI, 69–82%)). The endometrial–myometrial junction was regular in more than half (55% (95% CI, 48–63%)) of the cases, and color signals within the endometrium were absent (color score of 1) in 83% (95% CI, 78–89%).

In cases of proliferative or secretory endometrium, the interquartile range for endometrial thickness was 6–13 mm. In 12.8% (76/592) cases, the endometrium was not measurable or visible. Echogenicity was generally uniform hyperechogenic or non-uniform heterogeneous without cysts (65% (95% CI, 62–70%)), the endometrial–myometrial junction was mostly regular (53% (95% CI, 49–58%)) and the color score was often 1 (55% (95% CI, 51–59%)). Because the endometrium had not been sampled on the same day as the ultrasound examination in all patients, discrimination between proliferative and secretory-phase endometrium could not be reported.

In endometrial hyperplasia without atypia, the interquartile range for endometrial thickness was 9–17 mm, the endometrium was often uniform hyperechogenic or non-uniform heterogeneous without cysts (65% (95% CI, 57–73%)), the midline was usually undefined (73% (95% CI, 66–81%)), particularly after menopause, and the endometrial–myometrial junction was usually regular (63% (95% CI, 55–71%)). The color score was usually 1 or 2 (78% (95% CI, 72–85%)) and, when color-Doppler signals were present, the most common vessel morphology was multiple vessels with multifocal origin or a scattered pattern (78% (95% CI, 69–87%)).

In women with endometrial polyps, the interquartile range for endometrial thickness was 8–14 mm. Echogenicity was usually uniform hyperechogenic or non-uniform with no cysts or regular cysts (74% (95% CI, 71–78%)), the latter being more frequent in postmenopausal women. The endometrial midline was often undefined (64% (95% CI, 61–68%)), particularly after menopause. A bright edge was present in 48% (95% CI, 44–52%) of women, more often before than after menopause (55% *vs* 37%). The endometrial–myometrial junction was usually regular (77% (95% CI, 74–80%)). On color-Doppler imaging, there was a single vessel with or without branching in 69% (95% CI, 65–73%) of cases with detectable color-Doppler signals, and the most common color score was 2 or 3 (69% (95% CI, 65–72%)). The color score was higher and a single vessel was seen more often in pre- than in postmenopausal women.

In the presence of an intracavitary leiomyoma, the interquartile range for endometrial thickness was 5–13 mm, although the endometrium was not measurable or visible in 25.0% (54/216) of cases. The endometrium often appeared uniform hyperechogenic or non-uniform heterogeneous without cysts (61% (95% CI, 54–68%)), the endometrial midline undefined (53% (95% CI, 45–61%)) and the endometrial–myometrial junction interrupted (60% (95% CI, 53–68%)); an interrupted endometrial–myometrial junction was more common before than after menopause. On color Doppler, there was circular flow in 52% (95% CI, 41–62%) of cases

Table 2 Endometrial thickness in 2216 women with abnormal uterine bleeding, according to histological endpoint

Histological outcome	*Endometrial thickness (mm)*
Atrophy	5.0 (3.2–7.0)
Proliferative or secretory endometrium	9.2 (6.3–13.0)
Endometrial hyperplasia without atypia	12.1 (9.0–16.5)
Endometrial polyp	10.0 (7.5–14.0)
Intracavitary leiomyoma	9.0 (5.0–13.3)
Atypical hyperplasia/EIN	10.1 (8.0–18.0)
Endometrial cancer	16.0 (11.3–26.0)

Data are given as median (interquartile range). EIN, endometrioid intraepithelial neoplasia.

Table 1 Histological outcomes of 2856 women with abnormal uterine bleeding, overall and according to menopausal status

Outcome	*All patients (n = 2856)*	*Premenopausal patients (n = 1715)*	*Postmenopausal patients (n = 1141)*
Histology available	2216 (77.6)	1373 (80.1)	843 (73.9)
Atrophy	224/2216 (10.1)	42/1373 (3.1)	182/843 (21.6)
Proliferative endometrium	306/2216 (13.8)	235/1373 (17.1)	71/843 (8.4)
Secretory endometrium	309/2216 (13.9)	270/1373 (19.7)	39/843 (4.6)
Endometrial hyperplasia without atypia	148/2216 (6.7)	99/1373 (7.2)	49/843 (5.8)
Endometrial polyp	751/2216 (33.9)	434/1373 (31.6)	317/843 (37.6)
Intracavitary leiomyoma	223/2216 (10.1)	199/1373 (14.5)	24/843 (2.8)
Atypical hyperplasia/EIN	18/2216 (0.8)	10/1373 (0.7)	8/843 (0.9)
Endometrial cancer*	137/2216 (6.2)	16/1373 (1.2)	121/843 (14.4)
Other	100/2216 (4.5)	68/1373 (5.0)	32/843 (3.8)
No histology available	640 (22.4)	342 (19.9)	298 (26.1)

Data are given as *n* (%) or *n*/*N* (%). *Malignant cases included endometrioid adenocarcinoma in 102 women, serous carcinoma in 16, adenocarcinoma with squamous differentiation in six, mixed carcinoma in four, clear-cell carcinoma in two, sarcomatous tumors in two, undifferentiated carcinoma in one, low-grade endometrial stromal sarcoma in one, giant-cell carcinoma in one, Müllerian adenosarcoma in one and leiomyosarcoma in one. EIN, endometrioid intraepithelial neoplasia.

Table 3 Overview of most common morphological features of endometrium on unenhanced sonography in women with abnormal uterine bleeding, for different histological endpoints, overall and according to menopausal status

	Feature present		
Histological outcome	*All patients*	*Premenopausal patients*	*Postmenopausal patients*
Endometrial atrophy			
Endometrial thickness 3–7 mm	84/163 (52 (44–59))	15/30 (50 (32–68))	69/133 (52 (43–60))
Uniform hyperechogenic	68/167 (41 (33–48))	12/31 (39 (22–56))	56/136 (41 (33–49))
Non-uniform heterogeneous echogenicity without cysts	43/167 (26 (19–32))	8/31 (26 (10–41))	35/136 (26 (18–33))
Undefined midline	123/163 (75 (69–82))	23/30 (77 (62–92))	100/133 (75 (68–83))
Regular endometrial–myometrial junction	92/167 (55 (48–63))	13/31 (42 (25–59))	79/136 (58 (50–66))
Color score 1	139/167 (83 (78–89))	21/31 (68 (51–84))	118/136 (87 (81–92))
Proliferative or secretory endometrium			
Endometrial thickness 6–13 mm	264/516 (51 (47–55))	229/430 (53 (49–58))	35/86 (41 (30–51))
Uniform hyperechogenic	196/526 (37 (33–41))	164/436 (38 (33–42))	32/90 (36 (26–45))
Non-uniform heterogeneous echogenicity without cysts	149/526 (28 (24–32))	127/436 (29 (25–33))	22/90 (24 (16–33))
Linear midline	142/516 (28 (24–31))	132/430 (31 (26–35))	10/86 (12 (5–18))
Regular endometrial–myometrial junction	281/526 (53 (49–58))	238/436 (55 (50–59))	43/90 (48 (37–58))
Color score 1	290/526 (55 (51–59))	237/436 (54 (50–59))	53/90 (59 (49–69))
Endometrial hyperplasia without atypia			
Endometrial thickness 9–17 mm	72/138 (52 (44–61))	54/94 (57 (47–67))	18/44 (41 (26–55))
Uniform hyperechogenic	39/139 (28 (21–36))	25/94 (27 (18–36))	14/45 (31 (18–45))
Non-uniform heterogeneous echogenicity without cysts	51/139 (37 (29–45))	41/94 (44 (34–54))	10/45 (22 (10–34))
Undefined midline	101/138 (73 (66–81))	61/94 (65 (55–75))	40/44 (91 (82–99))
Regular endometrial–myometrial junction	87/139 (63 (55–71))	61/94 (65 (55–75))	26/45 (58 (43–72))
Multiple vessels of multifocal origin or scattered*	60/77 (78 (69–87))	45/57 (79 (68–90))	15/20 (75 (56–94))
Color score 1 or 2	109/139 (78 (72–85))	72/94 (77 (68–85))	37/45 (82 (71–93))
Endometrial polyp			
Endometrial thickness 8–14 mm	373/694 (54 (50–57))	246/417 (59 (54–64))	127/277 (46 (40–52))
Uniform hyperechogenic	188/704 (27 (23–30))	122/420 (29 (25–33))	66/284 (23 (18–28))
Non-uniform heterogeneous echogenicity without cysts	182/704 (26 (23–29))	118/420 (28 (24–32))	64/284 (23 (18–27))
Non-uniform echogenicity with regular cysts	153/704 (22 (19–25))	32/420 (8 (5–10))	121/284 (43 (37–48))
Bright edge	338/704 (48 (44–52))	232/420 (55 (50–60))	106/284 (37 (32–43))
Undefined midline	446/694 (64 (61–68))	205/417 (49 (44–54))	241/277 (87 (83–91))
Regular endometrial–myometrial junction	542/704 (77 (74–80))	348/420 (83 (79–86))	194/284 (68 (63–74))
Single vessel with or without branching*	345/500 (69 (65–73))	246/326 (75 (71–80))	99/174 (57 (50–64))
Color score 2 or 3	483/704 (69 (65–72))	314/420 (75 (71–79))	169/284 (60 (54–65))
Intracavitary leiomyoma			
Endometrial thickness 5–13 mm	80/162 (49 (42–57))	70/143 (49 (41–57))	10/19 (53 (30–75))
Uniform hyperechogenic	69/174 (40 (32–47))	62/154 (40 (33–48))	7/20 (35 (14–56))
Non-uniform heterogeneous echogenicity without cysts	37/174 (21 (15–27))	30/154 (19 (13–26))	7/20 (35 (14–56))
Undefined midline	86/162 (53 (45–61))	71/143 (50 (41–58))	15/19 (79 (60–97))
Interrupted endometrial–myometrial junction	105/174 (60 (53–68))	98/154 (64 (56–71))	7/20 (35 (14–56))
Circular flow*	47/91 (52 (41–62))	45/79 (57 (46–68))	2/12 (17 (5–45))
Color score 2–4	92/174 (53 (45–60))	80/154 (52 (44–60))	12/20 (60 (39–82))
Atypical hyperplasia/EIN			
Endometrial thickness 8–18 mm	10/17 (59 (35–82))	5/10 (50 (19–81))	5/7 (71 (36–92))
Non-uniform heterogeneous echogenicity without cysts	5/17 (29 (8–51))	4/10 (40 (10–70))	1/7 (14 (3–51))
Undefined midline	14/17 (82 (59–94))	8/10 (80 (49–94))	6/7 (86 (49–97))
Regular endometrial–myometrial junction	11/17 (65 (42–87))	6/10 (60 (30–90))	5/7 (71 (36–92))
Multiple vessels of multifocal origin or scattered*	6/10 (60 (30–90))	4/7 (57 (20–94))	2/3 (67 (21–94))
Color score 2 or 3	9/17 (53 (29–77))	7/10 (70 (42–98))	2/7 (29 (8–64))
Endometrial cancer			
Endometrial thickness 11–26 mm	55/110 (50 (41–59))	5/14 (36 (11–61))	50/96 (52 (42–62))
Non-uniform heterogeneous echogenicity without cysts or irregular cysts	81/111 (73 (65–81))	8/15 (53 (28–79))	73/96 (76 (67–85))
Undefined midline	99/110 (90 (84–96))	11/14 (79 (52–92))	88/96 (92 (86–97))
Interrupted endometrial–myometrial junction	47/111 (42 (33–52))	9/15 (60 (35–85))	38/96 (40 (30–49))
Multiple vessels of focal or multifocal origin*	74/98 (76 (67–84))	9/11 (82 (52–95))	65/87 (75 (66–84))
Color score 3–4	72/111 (65 (56–74))	10/15 (67 (43–91))	62/96 (65 (55–74))

Data are given as *n*/*N* (% (95% CI)). *For vascular pattern, denominator includes only cases with detectable color Doppler signals. EIN, endometrioid intraepithelial neoplasia.

with detectable color-Doppler signals. The most common color score was 2–4 (53% (95% CI, 45–60%)). Circular flow was seen more often in pre- than postmenopausal women.

Endometrial thickness in atypical hyperplasia/EIN had an interquartile range of 8–18 mm, the most common echogenicity being non-uniform heterogeneous without cysts (29% (95% CI, 8–51%)). The endometrial midline was very often undefined (82% (95% CI, 59–94%)). The endometrial–myometrial junction was regular in 65% (95% CI, 42–87%) of women. In most cases with detectable color-Doppler signals, multiple vessels of multifocal origin or scattered vessels were visible (60% (95% CI, 30–90%)), with a color score of 2 or 3 in 53% (95% CI, 29–77%) of women.

In endometrial cancer the endometrium was thickened, the interquartile range of endometrial thickness being 11–26 mm. However, in 9.1% (11/121) of women, endometrial thickness could not be measured reliably. Echogenicity was non-uniform heterogeneous without cysts or heterogeneous with irregular cysts in 73% (95% CI, 65–81%) of cases. In the vast majority (90% (95% CI, 84–96%)) of cases, the endometrial midline was undefined, particularly after menopause, and the endometrial–myometrial junction was interrupted in 42% (95% CI, 33–52%) of women. A high color score of 3 or 4 was common (65% (95% CI, 56–74%)) and, if color-Doppler signals were detectable, the most common vessel pattern was multiple vessels of focal or multifocal origin (76% (95% CI, 67–84%)).

On fluid-instillation sonography, endometrial polyps had a median maximum diameter of 16 mm. Other characteristics were assessed only for endometrial polyps judged by the examiner to be of endometrial origin. They

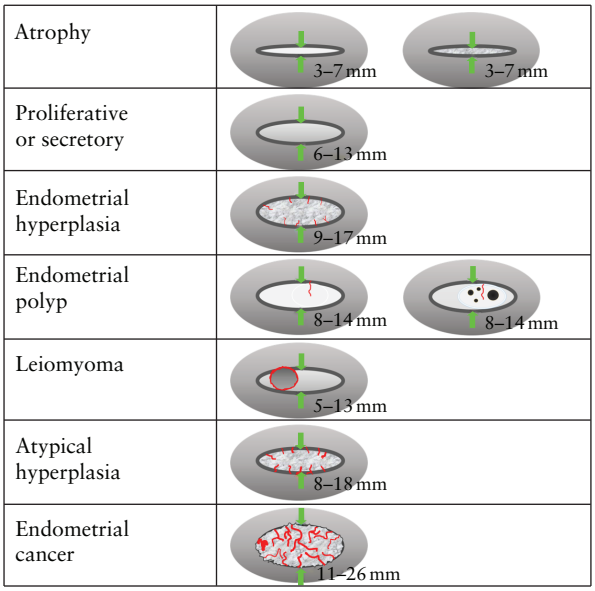

Figure 1 Schematic diagrams of common features of different endometrial pathologies on unenhanced sonography, based on univariable analysis. Circular flow in intracavitary leiomyomas applies to premenopausal women, and is rarely visible after menopause. For endometrial polyps, regular cysts were observed primarily in postmenopausal women.

Table 4 Overview of most common morphological features of primary intracavitary lesions on fluid-instillation sonography in women with abnormal uterine bleeding, for different histological endpoints, overall and according to menopausal status

	Feature present		
Histological outcome	*All patients*	*Premenopausal patients*	*Postmenopausal patients*
Endometrial polyp			
Localized	385/402 (96 (94–98))	176/181 (97 (95–100))	209/221 (95 (92–98))
Pedunculated	282/395 (71 (67–76))	128/180 (71 (64–78))	154/215 (72 (66–78))
Uniform hyperechogenic	176/403 (44 (39–49))	115/181 (64 (57–71))	61/222 (27 (22–33))
Non-uniform echogenicity with regular cysts	117/403 (29 (25– 33))	15/181 (8 (4–12))	102/222 (46 (39–53))
Regular outline	381/403 (95 (92–97))	176/181 (97 (95–100))	205/222 (92 (89–96))
Color score 2–4	280/403 (69 (65–74))	137/181 (76 (69–82))	143/222 (64 (58–71))
Single vessel with or without branching*	219/280 (78 (73–83))	117/137 (85 (79–91))	102/143 (71 (64–79))
Intracavitary leiomyoma			
Uniform echogenicity	102/140 (73 (65–80))	98/131 (75 (67–82))	4/9 (44 (12–77))
Grade 0 or 1	97/140 (69 (62–77))	88/131 (67 (59–75))	9/9 (100 (70–100))
Color score 1	62/140 (44 (36–53))	59/131 (45 (37–54))	3/9 (33 (3–64))
Circular flow*	53/78 (68 (58–78))	50/72 (69 (59–80))	3/6 (50 (19–81))
Endometrial cancer			
Extended	26/52 (50 (36–64))	1/4 (25 (4–67))	25/48 (52 (38–66))
Non-uniform heterogeneous echogenicity without cysts	19/52 (37 (23–50))	1/4 (25 (4–67))	18/48 (38 (24–51))
Uniform hyperechogenic	13/52 (25 (13–37))	1/4 (25 (5–70))	12/48 (25 (13–37))
Irregular outline	31/52 (60 (46–73))	2/4 (50 (1–99))	29/48 (60 (47–74))
Multiple vessels of focal or multifocal origin*	31/44 (70 (57–84))	2/3 (67 (21–94))	29/41 (71 (57–85))
Color score 3 or 4	33/52 (63 (50–77))	3/4 (75 (30–95))	30/48 (63 (49–76))

Data are given as *n*/*N* (% (95% CI)). Results presented for endometrial polyps and cancer are based only on those cases in which ultrasound examiner judged lesion to be of endometrial origin (Table S4), and those presented for intracavitary leiomyoma are based only on those cases in which ultrasound examiner judged lesion to be of myometrial origin (Table S5). *For vascular pattern, denominator includes only cases with detectable color Doppler signals.

were often pedunculated (71% (95% CI, 67–76%)), and the echogenicity of the polyp was usually either uniform hyperechogenic or non-uniform with regular cysts (73% (95% CI, 68–77%)). In premenopausal women, polyps were typically uniform hyperechogenic and less often non-uniform with regular cysts, while the opposite was true of postmenopausal women. The outline of polyps was almost always regular (95% (95% CI, 92–97%)). In most polyps, color-Doppler signals were detectable (69% (95% CI, 65–74%)), and a single vessel with or without branching was the most common vessel pattern (78% (95% CI, 73–83%)).

On fluid-instillation sonography, intracavitary leiomyomas had a median maximum diameter of 23 mm. Other characteristics were assessed only for intracavitary leiomyomas judged by the examiner to be of myometrial origin. Echogenicity was often uniform (73% (95% CI, 65–80%)). Most intracavitary leiomyomas were grade 0 or 1 (69% (95% CI, 62–77%))[15]. Vascularization was often not detectable (44% (95% CI, 36–53%)), but, when color-Doppler signals were present, the most typical vascular feature was circular flow.

On fluid-instillation sonography, endometrial cancer lesions had a median maximum diameter of 24 mm. Other characteristics were assessed only for endometrial cancer lesions judged by the examiner to be of endometrial origin. They were described as an extended lesion in half of the cases (50% (95% CI, 36–64%)), but less frequently in pre- than in postmenopausal women. Echogenicity was often non-uniform heterogeneous without cysts or uniform hyperechogenic (62% (95% CI, 48–75%)), and the outline of the lesion was typically irregular (60% (95% CI, 46–73%)). The color score was often 3 or 4 (63% (95% CI, 50–77%)) and, if color-Doppler signals were detectable, multiple vessels of focal or multifocal origin was the most common vessel pattern (70% (95% CI, 57–84%)).

The most common features on unenhanced sonography and fluid-instillation sonography for each pathology, based on univariable analysis, are presented in schematic diagrams in Figures 1 and 2, respectively.

On unenhanced sonography, none of the 66 women with endometrial thickness < 3 mm (0% (95% CI, 0.0–5.5%)) had endometrial cancer or atypical hyperplasia/EIN. Endometrial cancer or atypical hyperplasia/EIN was found in three of 283 (1.1% (95% CI, 0.4–3.1%)) endometria with a three-layer pattern, in three of 459 (0.7% (95% CI, 0.2–1.9%)) endometria with a linear endometrial midline and in five of 337 (1.5% (95% CI, 0.6–3.4%)) endometria with a single vessel without branching on unenhanced ultrasound (Figure 3). These calculations include the 100 cases with other histology.

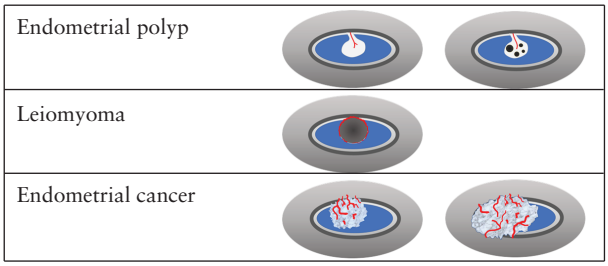

Figure 2 Schematic diagrams of common sonographic features of different endometrial pathologies on fluid-instillation sonography, based on univariable analysis.

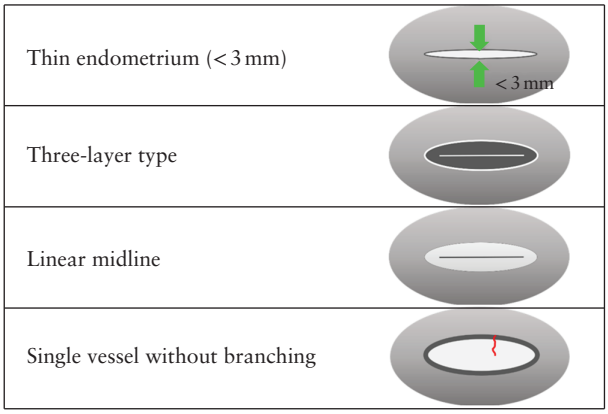

Figure 3 Schematic diagrams of reassuring features of endometrium on unenhanced sonography, the detection of which makes malignancy or atypical hyperplasia/endometrioid intraepithelial neoplasia highly unlikely.

DISCUSSION

In this study, we describe the most frequent ultrasound features of common endometrial and intracavitary lesions, based on prospectively collected data from 2856 women with abnormal vaginal bleeding.

The strengths of this study are its prospective design, the use of both unenhanced sonography and fluid-instillation sonography, the large number of patients included, the use of standardized examination and measurement techniques and terminology, and the outcome not being restricted to endometrial cancer.

Possible limitations are the exclusion of cases without histology, the timing of endometrial sampling in relation to the menstrual cycle and the use of blind endometrial sampling in some cases. Benign histology, for example in patients with a thin endometrium discharged without endometrial sampling, is probably under-represented. However, the study contained reasonably large numbers in all endometrial-thickness categories including thin endometria (Table 2). Second, because endometrial sampling was not always performed on the day of the ultrasound examination, we cannot comment on sonographic differences between proliferative and secretory endometria. Third, 871 out of 2216 (39.3%) women underwent office endometrial sampling or D&C. Blind endometrial sampling is associated with a risk of missing focal intracavitary lesions[22–24]. Because most women in the study underwent fluid-instillation sonography and hysteroscopy[25–27], and because according to the research protocol those with suspicion of an intracavitary lesion should undergo operative hysteroscopy, we assume that most blind sampling procedures (office endometrial

biopsy or D&C) were performed in women without intracavitary lesions.

The results broadly confirm our current knowledge on endometrial ultrasound[7,9,28–39]. Alcázar and Galvan[38] evaluated power-Doppler features in 91 postmenopausal women with abnormal bleeding. They reported that the large majority (81%) of cancer cases showed a multiple-vessel pattern. Moreover, all but one polyp case (97%) had a single-vessel pattern, whereas endometrial hyperplasia and cystic atrophy were associated mostly with a scattered-vessel pattern (73% and 67%, respectively). A prospective study in 95 women demonstrated that the presence of heterogeneous echogenicity, an irregular lesion surface, multiple vessels and vascular branching was associated with a higher risk for endometrial cancer[39]. Opolskiene *et al.*[9], in a series of 223 women with postmenopausal bleeding, confirmed the importance of heterogeneous endometrial echogenicity and irregular vascular branching in the prediction of malignancy.

However, our study also demonstrates some diagnostic pitfalls reflected by the occurrence of non-typical morphology. Moreover, the typical sonographic appearance of some endometrial lesions may vary according to menopausal status. In our study, only a minority of endometrial polyps in premenopausal women exhibited regular cysts, most being uniform hyperechogenic, whereas after menopause, many polyps contained cysts and were less vascularized than before menopause. Before menopause, intracavitary leiomyomas often manifested circular flow on unenhanced sonography, while after menopause this was rare.

Diagnostic evaluation of women with abnormal uterine bleeding comprises more than merely confirming or excluding endometrial cancer[28,29]. In our series, about 11% of postmenopausal women and a much lower percentage (1%) of women of reproductive age had endometrial malignancy. In most women presenting with abnormal uterine bleeding secondary to benign conditions, ultrasound examination is important to identify the cause of the bleeding and to tailor the management (e.g. hysteroscopic polypectomy).

Although the different histological endometrial and intracavitary entities showed predictable sonographic features, our data demonstrate that, for each histological entity, there are some cases that do not exhibit typical features; for example, absence of a dominant vessel (pedicle sign) in a polyp, a relatively thick atrophic endometrium or endometrial cancer in a thin endometrium. The appearance of non-typical morphology may be due to physical limitations (for example, absence of Doppler signals when the distance between the ultrasound probe and the endometrium is large, or when the uterus is in an upright position), histological characteristics (for example, presence of endometrial cysts in cystic atrophy) or true outliers (for example, endometrial cancer associated with an endometrial thickness of 5 mm or less). The issue of malignancy in thin endometria has been discussed previously. In a meta-analysis, Timmermans *et al.*[8] suggested the use of a cut-off value for endometrial thickness as low as 3 mm. This is in line with a previous prospective series reporting malignant cases with an endometrial thickness between 3 and 5 mm[11]. However, using a low threshold is associated with a high false-positive rate. This issue could be addressed by integrating other sonographic features when building new diagnostic algorithms.

The fact that the endometrium could not be delineated clearly and measured reliably in some cancer cases is also in line with previous reports[11]. In most of those cases, fluid-instillation sonography enables proper evaluation of the endometrium and uterine cavity.

In conclusion, our study provides didactic, clinically relevant, evidence-based data on sonographic findings of the endometrium and uterine cavity in women with abnormal uterine bleeding. Detection of some easy-to-assess sonographic features makes endometrial cancer unlikely.

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Detailed overview of features of endometrium on unenhanced sonography in women with abnormal uterine bleeding

Table S2 Detailed overview of features of endometrium on fluid-instillation sonography in women with abnormal uterine bleeding

Table S3 Incidence of primary intracavitary lesions on fluid-instillation sonography in women with abnormal uterine bleeding

Table S4 Detailed overview of ultrasound features of primary lesions judged by ultrasound examiner to be of endometrial origin on fluid-instillation sonography

Table S5 Detailed overview of ultrasound features of primary lesions judged by ultrasound examiner to be of myometrial origin on fluid-instillation sonography