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Endometriomas: their ultrasound characteristics

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KEYWORDS: endometrioma; endometriosis; ovarian neoplasms; ultrasonography

ABSTRACT

Objectives To describe the ultrasound characteristics of endometriomas in pre- and postmenopausal patients and to develop rules that characterize endometriomas.

Methods All patients included in the International Ovarian Tumor Analysis (IOTA) studies were used in our analysis. Patients with an adnexal mass were scanned by experienced sonologists using a standardized research protocol. The gold standard was the histology of the surgically removed adnexal mass. The gray-scale and Doppler ultrasound characteristics of the endometriomas were compared with those of other benign and malignant masses. Based on decision-tree analysis, the existing literature and clinical experience, ultrasound rules for the detection of endometriomas were created and evaluated.

Results Of all 3511 patients included in the IOTA studies, 713 (20%) had endometriomas. Fifty-one per cent of the endometriomas were unilocular cysts with ground glass echogenicity of the cyst fluid. These characteristics were found less often among other benign tumors or malignancies, or among the small set of endometriomas (4%) that were found in postmenopausal patients. Based on the decision-tree analysis, the optimal rule to detect endometriomas was 'an adnexal mass in a premenopausal patient with ground glass echogenicity of the cyst fluid, one to four locules and no papillations with detectable blood flow'. Based on clinical considerations, the following rule: 'premenopausal status, ground glass echogenicity of the cyst fluid, one to four locules and no solid parts' seems preferable.

Conclusions Several rules had a good ability to characterize endometriomas. The ultrasound characteristics of endometriomas differ between pre- and postmenopausal patients. Masses in postmenopausal women whose cystic contents have a ground glass appearance have a high risk of malignancy. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

During the sonographic assessment of an adnexal mass, the most important objective is to assess the likelihood of malignancy, because the treatment of benign and malignant adnexal masses is fundamentally different. However, further characterization of adnexal pathology is also desirable, for example with respect to endometrioma. An endometrioma is a soft marker for detecting the presence of deep endometriosis[1,2]. Patients with severe deep endometriosis, in particular those with a frozen pelvis or rectovaginal or bladder nodules, should be managed by a specialized multidisciplinary team[3–6]. The correct diagnosis of an endometrioma is also important with regard to fertility, because there is an association between endometrioma/endometriosis and subfertility[7,8]. Moreover, an endometrioid adenocarcinoma or clear cell carcinoma may develop in endometriomas[9–13].

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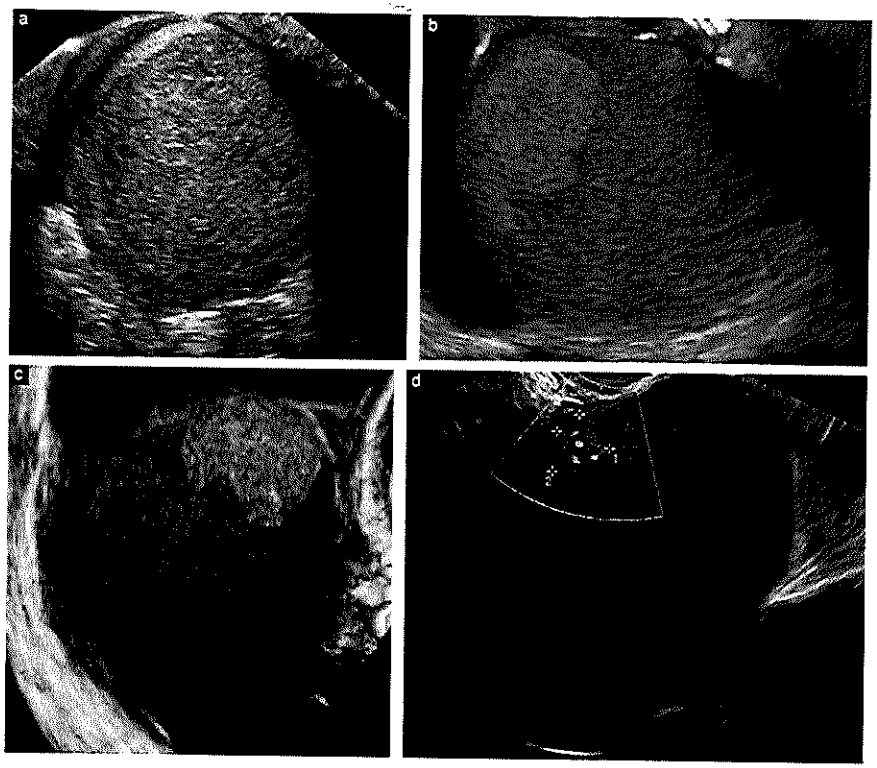


Figure 1 (a) A unilocular endometrioma with homogeneous ground glass echogenicity of the cyst fluid in a 28-year-old patient. The cyst wall is regular and thick (the largest diameter of the mass is 63 mm). This is the 'typical' ultrasound image of an endometrioma. (b) Endometrioma in a 27-year-old patient that presents as a unilocular cyst with heterogeneous ground glass echogenicity of the cyst content and minimal flow in the cyst wall (largest diameter 31 mm). (c) Unilocular-solid endometrioma (46 × 51 × 50 mm), in a 27-year-old-patient, with a thick cyst wall and one papillary projection (9 × 9 × 10 mm). The color score is 2 (minimal) but there is no flow inside the papillary projection. (d) Unilocular-solid endometrioma (88 × 62 × 71 mm) in a 54-year-old patient. The solid papillary projection (12 × 14 × 31 mm) contains internal flow.

Several studies have described the ultrasound characteristics of endometriomas and attempted to define their typical ultrasound features[14–22]. The 'typical' endometrioma is a unilocular cyst with homogeneous low-level echogenicity (ground glass echogenicity) of the cyst fluid (Figure 1a) but other morphological features have also been described[14,15,18–26]. Guerriero and Dogan were the first to perform studies to characterize atypical endometriomas[16,25].

The primary aim of this study was to describe the ultrasound characteristics of endometriomas in pre- and postmenopausal patients. The secondary aim was to develop rules to characterize endometriomas whilst avoiding the inclusion of malignancies and to compare them with a subjective impression by an experienced sonologist.

METHODS

The patients included in this study were all the 3511 patients with validated data in the International Ovarian Tumor Analysis (IOTA) studies[27,28]. The IOTA studies (IOTA Phase 1[27], IOTA Phase 1b[28] and IOTA Phase 2 (unpublished)) are large multicenter studies that prospectively collected patients with an adnexal mass. The patients were recruited in 21 ultrasound centers in nine countries. They were all scanned transvaginally by an experienced sonologist following a strict research

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protocol and using the IOTA terms and definitions to describe the ultrasound findings[29]. In addition to collecting information on more than 40 ultrasound variables and a few clinical variables, at the end of the ultrasound examination the sonologist classified the adnexal mass as benign or malignant using subjective evaluation of ultrasound findings. Moreover, he/she reported the level of diagnostic confidence with which the prediction of benignity/malignancy was made and suggested a specific histological diagnosis. The gold standard was the histological diagnosis of the surgically removed adnexal mass. Only patients who had the adnexal mass surgically removed within 120 days after the ultrasound examination were included. More information on the IOTA studies and on the ultrasound protocol can be found in the literature[27–29].

In this study, we define endometrioma as 'an endometrioma with or without ipsilateral extraovarian endometriosis and with or without concomitant ipsilateral other adnexal pathology'. The clinical characteristics and the gray-scale and Doppler ultrasound features of histologically confirmed endometriomas – as defined above – were compared with those of other benign and malignant adnexal masses. Ultrasound rules for the discrimination between an endometrioma and other benign and malignant adnexal pathology were created and their diagnostic performance was tested as described below. The rules were developed using decision-tree analysis, literature search and clinical experience. We also determined the diagnostic performance of subjective impression when assessed by an experienced sonologist. One literature-based rule was the diagnostic algorithm published by Guerriero *et al.*[16]. The algorithm of Guerriero *et al.* defines an endometrioma as either a unilocular mass with ground glass echogenicity and a color score between 1 and 3 (i.e. no vascularization to moderate vascularization) (Figure 1a and b) or a unilocular-solid mass with ground glass echogenicity with a papillary projection, a color score of 1 or 2 and no flow inside the papillary projection (Figure 1c). According to the algorithm of Guerriero *et al.*, a unilocular cyst with ground glass echogenicity and strong vascularization (color score 4) or a unilocular-solid cyst with ground glass echogenicity and a papillary projection with detectable flow or a color score of 3 or 4 (Figure 1d) are classified as non-endometriomas.

Statistical analysis

Descriptive statistics were computed for endometriomas, benign tumors other than endometriomas, and malignant tumors. For categorical variables, the endometriomas were compared with the two other groups by computing differences in percentages. For numerical variables, the theta (θ) measure of effect size was used[30]. A θ value of 1 means no overlap between groups and a θ value of 0.5 means maximal overlap. Theta is mathematically identical to the area under a receiver–operating characteristics curve[31]. Decision-tree analysis[32] was used for the derivation of ultrasound rules to detect endometriomas.

The decision tree split the data into two subgroups based on the commonly used Gini-index, a splitting criterion that aims to maximize predictive accuracy[32]. The subgroups were further split into smaller subgroups, and 10-fold cross-validation was used to determine when to stop splitting. The rules were compared with the subjective evaluation of the expert sonologist.

The diagnostic performance of the rules was expressed by their applicability (percentage of patients to which the rule applied), positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−), sensitivity and specificity, and the number of malignancies that were misclassified as endometriomas. The most important criteria were deemed to be PPV and LR+. PPV reflects the level of certainty when confronted with a mass for which the rule applies but is prevalence-dependent. LR+ presents the increase in the odds of endometrioma if the rule applies; it is not prevalence-dependent but is less straightforward to interpret. Because all analyses were based on the same data (i.e. fixed prevalence), PPV and LR+ values are directly related. Other important criteria were sensitivity and the number of malignancies wrongly picked up by the rule. For the purpose of this study we defined the optimal rule constructed by the decision-tree analysis (hereafter called 'the optimal decision-tree rule') as the rule with a combination of a high PPV, LR+ and sensitivity, but with as few malignancies as possible being misclassified as endometriomas.

RESULTS

Among the 3511 adnexal masses included, there were 2560 benign masses and 951 (27%) malignant masses (Table 1). Of the benign masses, 713 (28%) were endometriomas. The ultrasound findings, clinical and demographic characteristics for women with endometriomas, other benign tumors and malignancies are shown in Table 2. Patients with an endometrioma were younger than those with other benign (median age 34 vs. 45 years; $\theta = 0.71$, 95% CI 0.69–0.73) or malignant (median age 34 vs. 56 years; $\theta = 0.87$, 95% CI 0.86–0.89) tumors, and fewer were postmenopausal (4% vs. 39% vs. 66%). Thirty-five per cent of the endometrioma patients experienced pain during the ultrasound examination vs. 19% of the patients with other benign masses (difference = 16.5, 95% CI 12.6–20.5) and 15% of those with malignant masses (difference = 20.1, 95% CI 15.9–24.3). The median CA-125 level in women with endometriomas, other benign tumors and malignancies was 44 U/mL vs. 15 U/mL vs. 168 U/mL. The CA-125 values overlapped more between endometriomas and malignant tumors ($\theta = 0.71$, 95% CI 0.68–0.74) than between endometriomas and other benign tumors ($\theta = 0.79$, 95% CI 0.77–0.82).

The most prominent differences in the ultrasound features of endometriomas and other tumors were in the tumor type and the echogenicity of cyst fluid: 65% of the endometriomas were unilocular cysts vs. 37% of the other benign tumors (difference = 28.3, 95% CI 24.1–32.4) and 1% of the malignant tumors (difference = 63.7, 95% CI 60.0–67) (Figure 2); 17% of the endometriomas had solid parts vs. 40% of the other benign tumors and 93% of the malignant tumors; and 73% of the endometriomas had cyst fluid with ground glass echogenicity vs. 6% of the other benign tumors (difference = 67.0, 95% CI 63.5–70.3) (Figure 3a) and 6% of the malignancies (difference = 66.9, 95% CI 63.2–70.3) (Figure 3b and c). Most multilocular and multilocular-solid endometriomas contained no more than four locules (83%, 149/180) (Figure 2a and b). Ten per cent of the endometriomas had papillary projection(s), and 2.5% had papillary projections with blood flow detectable by color Doppler (Figure 1d).

The ultrasound findings and clinical characteristics of pre- and postmenopausal patients with endometriomas are shown in Table 3. Of all premenopausal patients, 32% (683/2134) had an endometrioma vs. only 2.2% (30/1377) of the postmenopausal patients. Endometriomas in postmenopausal patients were less often unilocular cysts than in premenopausal patients (40% vs. 66%; difference = −26.2, 95% CI −8.1 to −42.0) and they less often exhibited ground glass echogenicity (40% vs. 74%; difference = −34.4, 95% CI −16.4 to −50.1). Instead, they were more often multilocular-solid tumors and they more often exhibited anechoic cyst fluid or cyst fluid with mixed echogenicity. Of 77 masses with ground glass echogenicity in postmenopausal patients, 12/77 (15.6%) were endometriomas and 34 (44%) were malignant. The corresponding figures for premenopausal patients were 508/610 (83.3%) and 23/610 (3.8%) and,

Table 1 Demographic background data and histological diagnoses of all patients ($n = 3511$)

Variable	*Statistics*
Age in years (median (range))	45 (9–94)
Postmenopausal (n (%))	1377 (39)
Histological diagnosis (n (%))	
All benign tumors	2560 (72.9)
Endometrioma	713 (20.3)
Dermoid/teratoma	402 (11.4)
Serous cystadenoma	420 (12.0)
Simple cyst/parasalpingeal cyst	281 (8.0)
Mucinous cystadenoma	270 (7.7)
Fibroma	152 (4.3)
Functional cyst	116 (3.3)
Hydrosalpinx/salpingitis	100 (2.8)
Abscess	42 (1.2)
Rare benign tumor*	43 (1.2)
Peritoneal pseudocyst	21 (0.6)
All malignant tumors	951 (27.1)
Common primary invasive	575 (16.4)
Stage I	136 (3.9)
Stage II	47 (1.3)
Stage III	334 (9.5)
Stage IV	58 (1.7)
Rare primary invasive†	70 (2.0)
Borderline	186 (5.3)
Stage I	164 (4.7)
Stage II–IV	22 (0.6)
Metastatic	120 (3.4)

*For example: Brenner tumor, struma ovarii, Leydig cell tumor.
†For example: granulosa cell tumors, dysgerminoma, immature teratoma.

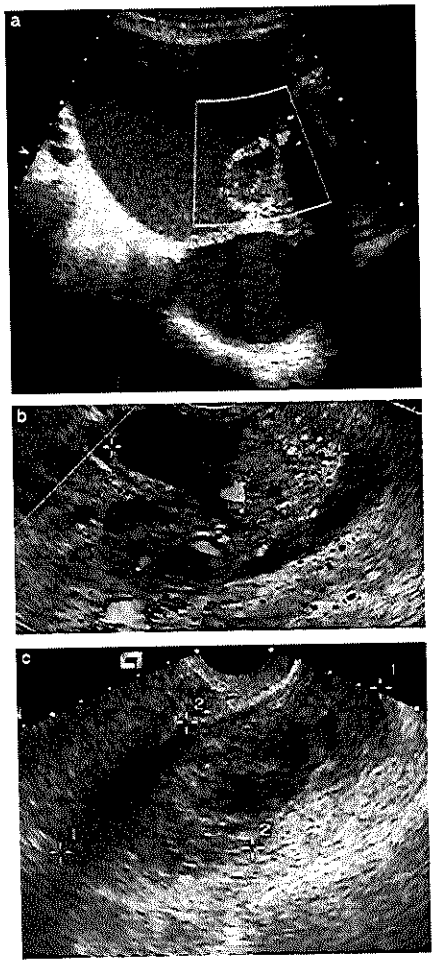


Figure 2 (a) Multilocular endometrioma (79 × 57 × 36 mm) with three locules in a 44-year-old patient. (b) Multilocular-solid endometrioma (45 × 26 × 45 mm) with a solid component (35 × 33 × 21 mm) and a color score of 4 in a 40-year-old patient. (c) Solid mass in a 47-year-old patient with poor vascularization and necrotic aspect that proved to be an endometrioma.

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Table 2 Clinical, demographic and ultrasound features of endometriomas, other benign tumors and malignant tumors

Demographic, clinical, or ultrasound variable	*Endometriomas (n = 713)*	*Benign tumors, other than endometrioma (n = 1847)*	*Malignant tumors (n = 951)*	*Endometriomas vs. other benign tumors: difference in % or θ values* as appropriate (95% CI)*	*Endometriomas vs. malignant tumors: difference in % or θ values* as appropriate (95% CI)*
Age (years, median (p_{25}–p_{75}))	34 (29–42)	45 (34–58)	56 (47–66)	0.71* (0.69; 0.73)	0.87* (0.86; 0.89)
Postmenopausal (*n* (%))	30 (4)	721 (39)	626 (66)	−34.8 (−37.4; −32.0)	−61.6 (−64.8; −58.1)
Personal history of ovarian cancer (*n* (%))	5 (0.7)	15 (0.8)	34 (3.6)	−0.1 (−0.8; 0.9)	−2.9 (−4.3; −1.5)
CA-125 (U/mL, median (p_{25}–p_{75}))†	44 (24–85)	15 (10–24)	168 (35–636)	0.79* (0.77; 0.82)	0.71* (0.68; 0.74)
Pain during ultrasound examination (*n* (%))	253 (35)	350 (19)	146 (15)	16.5 (12.6; 20.5)	20.1 (15.9; 24.3)
Type of tumor (*n* (%))					
Unilocular	463 (65)	673 (37)**	12 (1)	28.3 (24.1; 32.4)	63.7 (60.0; 67.1)
Unilocular-solid	60 (8)	215 (12)**	157 (17)	−3.3 (−5.7; −0.6)	−8.1 (−11.2; −4.9)
Multilocular	130 (18)	436 (24)**	57 (6)	−5.5 (−8.8; −1.9)	12.2 (9.1; 15.5)
Multilocular-solid	50 (7)	314 (17)**	384 (40)	−10.1 (−12.5; −7.4)	−33.4 (−36.9; −29.6)
Solid	10 (1)	200 (11)**	341 (36)	−9.5 (−11.1; −7.7)	−34.5 (−37.6; −31.3)
Echogenicity of cyst fluid (*n* (%))					
Anechoic	34 (5)	782 (42)	225 (24)	−37.6 (−40.2; −34.7)	−18.9 (−22.0; −15.7)
Ground glass	520 (73)	109 (6)	57 (6)	67.0 (63.5; 70.3)	66.9 (63.2; 70.3)
Low level	95 (13)	334 (18)	215 (23)	−4.8 (−7.7; −1.6)	−9.3 (−12.9; −5.6)
Hemorrhagic	13 (2)	32 (2)	7 (1)	0.1 (−0.9; 1.5)	1.1 (0.0; 2.4)
Mixed	41 (6)	390 (21)	106 (11)	−15.4 (−17.8; −12.7)	−5.4 (−8.0; −2.7)
No cyst fluid	10 (1)	200 (11)	341 (36)	−9.4 (−11.1; −7.7)	−34.5 (−37.6; −31.3)
Irregular cyst wall (*n* (%))	188 (26)	558 (30)	674 (71)	−3.8 (−7.6; 0.1)	−44.5 (−48.7; −40.0)
Presence of papillary projection (*n* (%))	73 (10)	304 (16)	379 (40)	−6.2 (−8.9; −3.3)	−29.6 (−33.4; −25.7)
Detectable blood flow within papillations (*n* (%))	18 (3)	76 (4)	287 (30)	−1.6 (−3.0; 0.1)	−27.7 (−30.8; −24.5)
Papillations with irregular surface (*n* (%))	31 (4)	166 (9)	314 (33)	−4.6 (−6.5; −2.5)	−28.7 (−32.0; −25.3)
Number of papillations (*n* (%))‡					
1	51 (70)	187 (62)	110 (29)		
2	8 (11)	41 (13)	37 (10)	0.54* (0.47; 0.61)	0.74* (0.68; 0.80)
3	6 (8)	34 (11)	42 (11)		
> 3	8 (11)	42 (14)	190 (50)		
Number of locules (*n* (%))§					
2	83 (46)	204 (27)	52 (12)		
3	40 (22)	137 (18)	50 (11)	0.66* (0.61; 0.70)	0.80* (0.75; 0.83)
4	26 (14)	84 (11)	58 (13)		
5–10	29 (16)	235 (31)	147 (33)		
> 10	2 (1)	90 (12)	134 (30)		
Color score (*n* (%))					
1	243 (34)	748 (41)	40 (4)		
2	317 (44)	615 (33)	212 (22)	0.51* (0.48; 0.53)	0.81* (0.79; 0.83)
3	134 (19)	416 (23)	407 (43)		
4	19 (3)	68 (4)	292 (31)		
Largest lesion diameter (mm, median (p_{25}–p_{75}))	53 (38–73)	65 (46–91)	93 (59–138)	0.62* (0.60; 0.64)	0.76* (0.74; 0.79)
Presence of solid parts (*n* (%))	120 (17)	730 (40)	882 (93)	−22.7 (−26.1; −19.0)	−75.8 (−78.8; −72.4)
Largest solid component diameter (mm, median (p_{25}–p_{75}))¶	19 (10–30)	25 (12–46)	54 (35–83)	0.60* (0.54; 0.65)	0.84* (0.79; 0.87)

*θ-value measuring the degree of overlap of a variable between groups (0.5 means maximal overlap, 1 means no overlap); 95% CIs for differences in percentage are based on a method using Wilson's score interval without continuity correction[29], for θ they are based on a previous report[30]. †Analysis of patients with available CA-125 level (456 endometriomas, 1340 other benign masses and 862 malignant masses). ‡Analysis of masses with a papillary projection (73 endometriomas, 304 other benign masses and 379 malignant masses). §Analysis of multilocular or multilocular-solid masses (180 endometriomas, 750 other benign masses and 441 malignant masses). ¶Analysis of masses with solid components (120 endometriomas, 730 other benign masses and 882 malignant masses). **In nine cases tumor type was noted to be not classifiable and therefore these numbers do not add up to 1847 but rather to 1838. p_{25}–p_{75}: 25th and 75th percentiles.

on the basis of subjective impression, five of the 26 (19%) postmenopausal patients presumed to have an endometrioma had a malignant tumor.

The single ultrasound variable that best discriminated between endometriomas and other adnexal pathology was ground glass echogenicity of cyst fluid (sensitivity 73%

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Table 3 Clinical, demographic and ultrasound features of histologically proven endometriomas in pre- and postmenopausal patients

Variable	*Endometriomas in premenopausal patients (n = 683)*	*Endometriomas in postmenopausal patients (n = 30)*	*Difference in % between pre-and postmenopausal women or θ values* where appropriate (95% CI)*
CA-125 (U/mL, median (p_{25}–p_{75}))†	46 (24–86)	33 (12–50)	0.61* (0.49; 0.72)
Pain during ultrasound examination (*n* (%))	247 (36)	6 (20)	16.2 (−1.5; 27.3)
Locularity (*n* (%))			
Unilocular	451 (66)	12 (40)	26.2 (8.1; 42.0)
Unilocular-solid	55 (8)	5 (17)	−8.6 (−25.6; 1.0)
Multilocular	124 (18)	6 (20)	−1.8 (−19.4; 9.1)
Multilocular-solid	43 (6)	7 (23)	−17.0 (−34.7; −5.3)
Solid	10 (1)	0 (0)	1.5 (−9.9; 2.7)
Echogenicity of cyst fluid (*n* (%))			
Anechoic	29 (4)	5 (17)	−12.4 (−29.4; −2.9)
Low level	88 (13)	7 (23)	−10.4 (−28.2; 1.4)
Ground glass	508 (74)	12 (40)	34.4 (16.4; 50.1)
Hemorrhagic	13 (2)	0 (0)	1.9 (−9.5; 3.2)
Mixed	36 (5)	6 (20)	−14.7 (−32.1; −4.1)
No cyst fluid	9 (1)	0 (0)	1.3 (−10.1; 2.5)
Irregular cyst wall (*n* (%))	178 (26)	10 (33)	−7.3 (−25.4; 7.2)
Presence of papillary projection (*n* (%))	67 (10)	6 (20)	−10.2 (−27.6; 0.6)
Detectable blood flow within papillations (*n* (%))	18 (3)	0 (0)	2.6 (−8.8; 4.1)
Number of locules (*n* (%))‡			
2	77 (46)	6 (46)	
3	38 (23)	2 (15)	0.52* (0.37; 0.67)
4	24 (14)	2 (15)	
5–10	26 (16)	3 (23)	
> 10	2 (1)	0 (0)	
Color score (*n* (%))			
1	232 (34)	11 (37)	
2	303 (44)	14 (47)	0.53* (0.42; 0.63)
3	130 (19)	4 (13)	
4	18 (3)	1 (3)	
Largest lesion diameter (mm, median (p_{25}–p_{75}))	53 (38–71)	59 (32–81)	0.53* (0.43; 0.63)
Largest solid component diameter (mm, median (p_{25}–p_{75}))§	19 (10–30)	18 (9–29)	0.53* (0.36; 0.68)

*θ-value measuring the degree of overlap of a variable between groups (0.5 means maximal overlap, 1 means no overlap); 95% CIs for differences in percentage are based on a method using Wilson's score interval without continuity correction[29], for θ they are based on a previous report[30]. p_{25}–p_{75}: 25th and 75th percentiles. †Analysis of patients with available CA-125 level (432 premenopausal endometriomas and 24 postmenopausal endometriomas). ‡Analysis of multilocular or multilocular-solid masses (167 premenopausal patients and 13 postmenopausal patients). §Analysis of masses with a solid component (108 premenopausal patients and 12 postmenopausal patients).

(520/713), specificity 94% (2632/2798), LR+ 12.3, LR− 0.29 and PPV 75.8% (520/686)) (Table 4). Ground glass appearance of cyst fluid was present in 6% of the benign masses that were not endometriomas (Figure 4a) and in 6% of the malignant masses (Figure 4b and c). Of the 57 malignant masses with ground glass echogenicity of the cyst fluid, 35 were primary invasive tumors (13 of the endometrioid type), 21 were borderline tumors and four were ovarian metastases. Thirty-seven of these malignant masses occurred in postmenopausal patients and 28 were multilocular-solid tumors.

The decision tree identified, in this order, ground glass appearance of the cyst fluid, premenopausal status, a tumor with one to four locules and the absence of papillations with detectable blood flow (i.e. tumors without papillations or tumors with papillations but without flow) as the important conditions to construct a rule to detect endometriomas. The tree is presented in Figure 4. The performance of all rules is presented in Table 4. The optimal decision-tree rule (i.e. rule 4 in Table 4) was applicable to 15.6% of tumors (95% CI 14.4–16.8), with PPV 88.6% (95% CI 85.7–91.0), LR+ 30.6 (95% CI 23.9–39.4), sensitivity 67.9% (95% CI 64.4–71.2), and specificity 97.8% (95% CI 97.2–98.3), and detected four (0.4%) malignancies (95% CI 0.2–1.1). A clinically interesting simplification is to replace the condition 'absence of papillations with detectable flow' with 'absence of solid parts' (i.e. rule A in Table 4). The performance of this rule was as follows: applicability 13.8% (95% CI 12.7–15.0), PPV 90.1% (95% CI 87.1–92.5), LR+ 35.8 (95% CI 26.9–47.7), sensitivity 61.4% (95% CI 57.8–64.9) and specificity 98.3% (95% CI 97.7–98.7). The rule detected two malignancies (0.2%, 95% CI 0.1–0.8) and 46 benign masses that were

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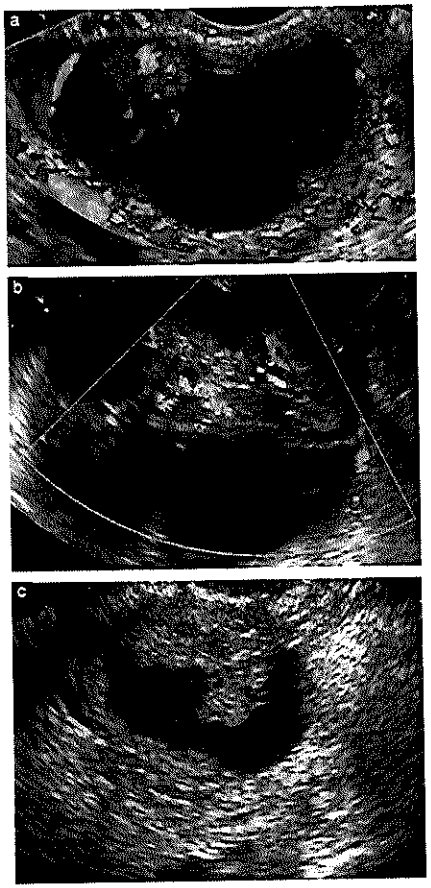


Figure 3 (a) Unilocular-solid mass (47 × 34 × 34 mm) with a vascularized papillary projection and ground glass appearance of the cyst fluid in a 27-year-old patient. The histological diagnosis was mucinous cystadenoma. (b) Multilocular-solid mass with ground glass echogenicity in a 68-year-old patient. The histological diagnosis was anaplastic tumor of the ovary (Stage IV). (c) Unilocular-solid mass with ground glass echogenicity in a 49-year-old patient. The histological diagnosis was serous borderline tumor.

not endometriomas (mostly cystadenomas[10], functional cysts[12] and simple cysts[7]).

No decision tree to predict endometrioma could be constructed for masses in postmenopausal patients because only 30 (2.2%) out of 1377 masses in postmenopausal patients were endometriomas and the ultrasound characteristics of endometriomas in postmenopausal patients were very heterogeneous.

The widely accepted ultrasound criterion of endometrioma, namely 'unilocular cyst with ground glass echogenicity of the cyst fluid' (i.e. rule B in Table 4), and its restriction to premenopausal patients (i.e. rule C in Table 4), were less applicable (11.8% and 11.3%) and had strongly reduced sensitivity (51.3% and 50.5%, respectively). Of the masses detected using rules B and C, malignancy was found in five and two cases, respectively. The diagnostic algorithm of Guerriero *et al.*[16] (rule G in Table 4) had an applicability of 12.5%, a PPV of 86.6%, an LR+ of 25.3, a sensitivity of 53.3% and a specificity of 98%. The Guerriero criteria identified seven malignant and 52 benign masses that were not endometriomas.

Subjective impression by an experienced sonologist (rule S in Table 4) had an applicability of 18.6%, a PPV of 88.5%, an LR+ of 30.2, a sensitivity of 81% and a specificity of 97%. Of the masses classified as endometriomas by subjective impression 1.4% (9/652) were malignancies and 10.1% (66/652) were benign masses that were not endometriomas.

To illustrate the diagnostic performance of the rules and of subjective impression, their PPV and 1 minus sensitivity were plotted on a graph (Figure 5). The key mentions the number of malignant cases for which the rule was applicable. The figure shows that subjective impression performed best despite nine malignancies included. The rule 'a premenopausal patient with a mass with ground glass echogenicity, one to four cyst locules, but without papillations with detectable blood flow' (i.e. rule 4) resulted in the best overall statistical performance.

DISCUSSION

We found that almost 50% of the endometriomas in this study had ultrasound characteristics other than the typical 'unilocular cyst with ground glass echogenicity of the cyst fluid', and that the ultrasound appearance of endometriomas differed between pre- and postmenopausal patients. The endometriomas in the postmenopausal patients were less often unilocular cysts and they were less likely to exhibit ground glass echogenicity. It was not possible to develop a rule to distinguish endometriomas from other types of adnexal masses specifically for postmenopausal patients, because of the heterogeneity of the ultrasound appearance of endometriomas in postmenopausal patients and because only 30 postmenopausal patients had endometriomas. On the basis of the decision-tree analysis and the predefined criteria of the optimal rule, the following rule was found to be the optimal decision-tree rule: 'premenopausal status, ground glass echogenicity, one to four locules and no papillations with detectable blood flow'. Although it characterized endometriomas reasonably well, it did not characterize them as well as subjective impression. Our results also showed that serum CA-125 levels cannot be

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Table 4 Diagnostic performance of single variables and combination of variables with regard to discriminating between endometriomas and other types of adnexal masses

Rule	*Applicability**	*PPV*	*Sensitivity†*	*Specificity†*	*LR+ (95% CI)‡*	*LR− (95% CI)‡*	*FPR-M*
Rules based on decision tree							
Ground glass echogenicity (rule 1)	19.5% (686/3511)	75.8% (520/686)	72.9% (520/713)	94.1% (2632/2798)	12.3 (10.5–14.3)	0.29 (0.25–0.32)	6.0% (57/951)
Ground glass echogenicity + premenopausal (rule 2)	17.3% (609/3511)	83.4% (508/609)	71.2% (508/713)	96.4% (2697/2798)	19.7 (16.2–24.0)	0.30 (0.27–0.33)	2.4% (23/951)
Ground glass echogenicity + 1–4 locules + premenopausal (rule 3)	16.2% (568/3511)	86.8% (493/568)	69.1% (493/713)	97.3% (2723/2798)	25.8 (20.5–32.4)	0.32 (0.28–0.35)	1.5% (14/951)
Ground glass echogenicity + 1–4 locules but without papillary flow + premenopausal (rule 4)	15.6% (546/3511)	88.6% (484/546)	67.9% (484/713)	97.8% (2736/2798)	30.6 (23.9–39.4)	0.33 (0.29–0.36)	0.4% (4/951)
Other rules							
Ground glass echogenicity + 1–4 locules, no solid parts + premenopausal (rule A)	13.8% (486/3511)	90.1% (438/486)	61.4% (438/713)	98.3% (2750/2798)	35.8 (26.9–47.7)	0.39 (0.36–0.43)	0.2% (2/951)
Ground glass echogenicity + unilocular cyst (rule B)	11.8% (416/3511)	88.0% (366/416)	51.3% (366/713)	98.2% (2748/2798)	28.7 (21.7–38.1)	0.50 (0.46–0.53)	0.5% (5/951)
Ground glass echogenicity + unilocular cyst + premenopausal (rule C)	11.3% (398/3511)	90.5% (360/398)	50.5% (360/713)	98.6% (2760/2798)	37.2 (26.9–51.4)	0.50 (0.46–0.54)	0.2% (2/951)
Diagnostic algorithm of Guerriero *et al.*[16] (rule G)	12.5% (439/3511)	86.6% (380/439)	53.3% (380/713)	97.9% (2739/2798)	25.3 (19.5–32.8)	0.48 (0.44–0.51)	0.7% (7/951)
Subjective impression (rule S)	18.6% (652/3511)	88.5% (577/652)	80.9% (577/713)	97.3% (2723/2798)	30.2 (24.1–37.9)	0.20 (0.17–0.23)	0.9% (9/951)

*Number and percentage of all tumors in which the variable/combination of variables was present. †Sensitivity and specificity with regard to endometrioma. ‡95% CIs were based on the Cox–Hinkley–Miettinen–Nurminen method[19]. §The algorithm is described in the methods section. FPR-M, number and percentage of malignant tumors with the feature present (false-positive malignant); LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value with regard to endometrioma.

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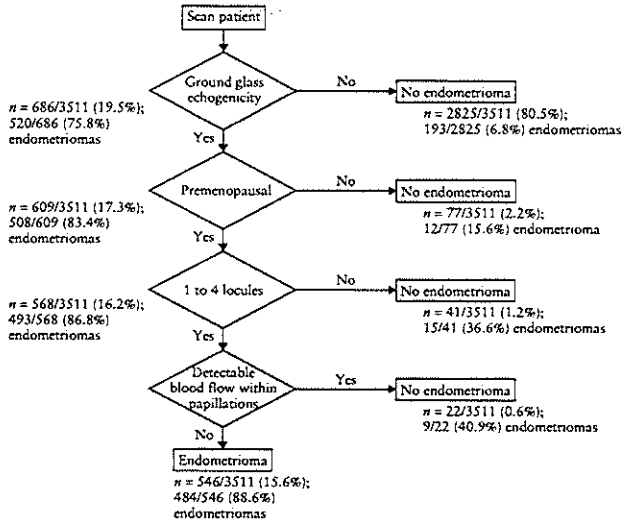
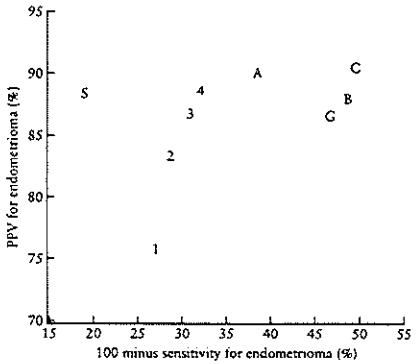


Figure 4 Decision tree with consecutive conditions for predicting an endometrioma. Diamonds are decision nodes. Rectangles are prediction nodes.



Rule:		
	1	Ground glass (57)
	2	Ground glass + Premenopausal (23)
	3	Ground + Premenopausal + 1–4 locules (14)
	4	Gr. glass + Pre. + 1–4 locules + no pap. flow (4)
	A	Gr. glass + Pre. + 1–4 locules + no solid parts (2)
	B	Ground glass + Unilocular cyst (5)
	C	Ground glass + Unilocular cyst + Pre. (2)
	G	Diagnostic algorithm of Guerriero (7)
	S	Subjective impression (9)

Figure 5 Plot presenting performance of different rules and subjective impression to predict an endometrioma. Between brackets in the box are the numbers of malignant masses classified as endometrioma by the different rules. Gr., ground; Pre., premenopausal; PPV, positive predictive value.

used to distinguish endometriomas from other benign tumors and malignancies.

To the best of our knowledge, this is the largest study to describe the ultrasound characteristics of endometriomas, and the first to describe the ultrasound appearance of endometriomas separately for pre- and postmenopausal patients. Because our data were collected prospectively in several centers and all patients were scanned following the same research protocol, our results are likely to be generalizable. However, our study suffers from selection bias: patients were included only if they underwent surgery within 4 months after the ultrasound examination. This may have resulted in 'atypical' endometriomas being over-represented, because patients with a 'typical' endometrioma are likely to remain longer on the waiting list for surgery than those with an 'atypical' endometrioma. It is also likely that a number of asymptomatic patients with an incidentally detected 'typical' endometrioma were managed conservatively and did not undergo surgery at all. Moreover, some of the centers that provided patients for the IOTA studies are referral centers or oncological centers. This may also have contributed to 'atypical' endometriomas being over-represented in our series. Some bias may also have been introduced by the fact that most acute hemorrhagic cysts, some of which have the same ultrasound morphology as an endometrioma, were probably identified as such by the expert sonologists, managed expectantly and not included in the study. Another weakness of our study was that the rule we suggest for distinguishing

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endometriomas from other adnexal masses has not been tested prospectively.

The proportion of 'atypical' endometriomas is higher in our study than in any other in the literature[16,17,20,23–25]. For example, in two studies by Guerriero *et al.*, 83% of endometriomas in premenopausal patients demonstrated the typical appearance of a unilocular cyst with ground glass echogenicity of cyst fluid[17,20] vs. only 53% (360/683) in our study. The discrepancy may be explained by selection bias, as discussed above, and by differences in study design with the studies by Guerriero *et al.* as they examined the patients immediately before surgery. In agreement with others we found CA-125 not to be helpful for distinguishing endometriomas from other tumors[17,18]. The role of color Doppler as an aid to the identification of endometriomas is controversial[16,33,34]. We found that using color Doppler to look for the presence or absence of flow in papillations helped to avoid classifying malignancies as endometriomas. Unfortunately, color Doppler variables used in rules or mathematical models will require optimal color Doppler settings, a high quality of the color Doppler function of the ultrasound equipment used and some special experience of the ultrasound examiner. Moreover, any rule based on ultrasound findings should be kept as simple and clinically practical as possible. Therefore, from a clinical perspective, we considered the rule 'ground glass echogenicity + 1–4 locules + no solid parts + premenopausal' to be very useful in most clinical settings because it allows the examiner to skip the color Doppler assessment of the mass. This clinical rule had almost as good discriminatory power as the statistically optimal rule, but its sensitivity was lower.

In our hands, the algorithm proposed by Guerriero *et al.*[16] did not perform any better than the criterion 'unilocular cyst with ground glass echogenicity' for discriminating between endometriomas and other pathology, and our own rule was an improvement on that of Guerriero *et al.* However, in our study, the rule of Guerriero *et al.* underwent external prospective validation, whilst our rule has not yet undergone any external validation. The Guerriero algorithm was originally also only tested in a group of premenopausal patients, and therefore a comparison between the two is inappropriate.

We were able neither to identify any ultrasound features typical of endometrioma in postmenopausal patients nor to construct a rule that is strongly suggestive of an endometrioma in a postmenopausal patient. However, it is clinically much less important to be able to recognize an endometrioma in postmenopausal patients compared with premenopausal patients. In postmenopausal patients the focus is on identifying malignancy[35,36]. It is unclear whether the risk of malignant transformation in endometriosis is higher in postmenopausal women than in premenopausal women[9–13]. Postmenopausal status substantially decreases the likelihood of an endometrioma. It seems wise to hesitate to suggest a diagnosis of endometrioma in a postmenopausal patient, even if the mass has ground glass echogenicity. Not only is it very unlikely that the final histology will be an endometrioma but our results suggest that a large proportion of masses with ground glass echogenicity in postmenopausal patients will be malignant (34/77, 44.2%).

The rule 'unilocular cyst with ground glass echogenicity in a premenopausal patient' misclassified only 0.2% of the malignancies as endometriomas but was a poorer discriminator between endometriomas and non-endometriomas (Table 4).

Nevertheless, no rule was as good as subjective impression by an experienced sonologist for identifying endometriomas. This is probably because the ultrasound examiner uses other available clinical information when suggesting a diagnosis and in addition takes subtle ultrasound findings into account. However, subjective impression misclassified 0.9% of the malignancies as endometriomas.

Our next step will be to prospectively test our proposed ultrasound rules to discriminate between endometriomas and other tumors in different centers. Although our rules did not achieve the same performance as subjective impression in the hands of an expert sonologist, we believe that for less experienced sonologists, our clinical rule might be useful in daily clinical practice.

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