Ultrasound Obstet Gynecol 2010; 35: 228–232
Published online 22 December 2009 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.7535

Assessment of cyst content using mean gray value for discriminating endometrioma from other unilocular cysts in premenopausal women

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KEYWORDS: diagnosis; endometrioma; ultrasound

ABSTRACT

Objective *To assess whether the analysis of cyst content using mean gray value (MGV) can discriminate ovarian endometriomas from other unilocular ovarian cysts in premenopausal women.*

Methods *Stored three-dimensional (3D) volumes from 54 unilocular ovarian cysts diagnosed in 50 premenopausal women (mean age, 37 (range, 22–50) years) were analyzed to calculate the MGV from cyst content. Cysts with solid components or septations were excluded. MGV was calculated in all cases with the Virtual Organ Computer-aided AnaLysis™ technique. The B-mode presumptive diagnosis based on the examiner's subjective impression was also recorded.*

Results *Sixteen of the cysts resolved spontaneously and were given a final clinical diagnosis of hemorrhagic functional cyst, while 38 cysts were removed surgically (diagnosed histologically as seven simple cysts, three hemorrhagic cysts, 20 endometriomas, five mucinous cysts and three paraovarian cysts). B-mode diagnoses were as follows: seven simple cysts, 18 hemorrhagic cysts, 24 endometriomas, three mucinous cysts and two paraovarian cysts. MGV was significantly higher in ovarian endometrioma when compared with all other kinds of cyst. The receiver–operating characteristics curve showed that using an MGV cut-off ≥ 15.560 had a sensitivity of 85% and a specificity of 76.5% for diagnosing ovarian endometrioma (area under the curve, 0.831; 95% CI, 0.718–0.944). These figures were similar to those for B-mode diagnosis (sensitivity, 90%; specificity, 82%) (McNemar test, P = 1.000). Combining B-mode and MGV gave a sensitivity of 80% and a specificity of 91%.*

Conclusion *Cyst content MGV is higher in ovarian endometrioma than it is in other unilocular ovarian cysts. The diagnostic performance of MGV is similar to that of the examiner's subjective impression. The combination of both criteria achieves the highest specificity.*

INTRODUCTION

Endometriosis is a common disease causing sterility and pelvic pain[1]. The exact prevalence is difficult to ascertain and varies depending on the population studied and the diagnostic criteria used[2]. The ovary is one of the sites most affected[3], but the pathogenesis of ovarian endometriotic cysts is not well known. Current knowledge suggests that these cysts may arise from progressive invagination of endometriotic implants on the ovarian surface[4], from metaplasia of epithelial inclusions in the ovary[5] or from functional ovarian cysts[6,7].

Two-dimensional (2D) ultrasound has been used widely for diagnosing ovarian endometrioma. The characteristic appearance of an endometrioma on sonography is that of a hypoechoic cyst containing diffuse low-level internal echoes[8–11]. However, the spectrum of findings is wide, from an anechoic cyst to an entirely solid mass[12]. Furthermore, this appearance may change over time[13]. Three-dimensional (3D) ultrasound is being used increasingly in clinical practice. This technique allows what could be regarded as sonographic tissue characterization by calculating the mean gray value (MGV) using Virtual Organ Computer-aided AnaLysis (VOCAL™) software[14]. This parameter represents the mean intensity of gray-scale voxels (the smallest unit of volume) within a region of interest.

The aim of this study was to evaluate whether the assessment of cyst content by MGV could be helpful for discriminating endometrioma from other unilocular ovarian cysts in premenopausal women.

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Accepted: 29 June 2009

METHODS

This was a retrospective study including 54 ovarian unilocular cysts < 6 cm in diameter diagnosed in 50 consecutive premenopausal women managed at the Department of Obstetrics and Gynecology at the University of Navarra (Pamplona, Spain) between January 2007 and October 2008. Their mean age was 37 (range, 22–50) years. Reasons for referral to our center were pelvic pain ($n = 14$), sterility ($n = 8$) or a second opinion because of diagnosis of an asymptomatic ovarian cyst ($n = 32$).

All women underwent 3D transvaginal ultrasound examination performed by one of the authors (J.L.A.) using a Voluson 730 Expert (GE Healthcare, Milwaukee, WI, USA) machine according to a predefined scanning protocol[15]. Briefly, B-mode ultrasonography was performed to characterize morphologically the adnexal mass as simple cyst, ovarian endometrioma (Figure 1), hemorrhagic cyst or mucinous cyst. A simple cyst was defined as a sonolucent thin-walled (< 3 mm thick) cyst larger than 30 mm in diameter, without septations or papillary projections[16]. Ovarian endometrioma was suspected on visualizing a hypoechoic cyst containing diffuse low-level internal echoes[9]. Hemorraghic cyst was considered in the presence of a cyst containing fibrin strands crossing the cyst and/or a retracting clot[17]. A mucinous cyst was defined as a cyst with variable echogenic content[18]. Although septations are a common finding in mucinous cysts, we excluded these; any cyst containing any kind of papillary projection, solid area or septation was excluded, because we wanted to exclude from within the MGV analysis area any source of 'tissue' content. We also excluded those cysts with typical findings of dermoid cyst[19]. The 3D volume box was then activated to obtain a 3D volume from the whole cyst. Only cysts < 6 cm in diameter were included because it is our experience that larger cysts cannot be included within one single volume using the maximum 3D angle sweep (90°). Once a 3D volume was obtained, it was stored on a hard disk (SonoView™, Kretztechnik-Medison, Zipf, Austria).

Stored volumes were analyzed using VOCAL software by a second observer (M.L.) with 1 month's experience of using 3D ultrasound. This observer had completed a specific 2-week training course on the use of VOCAL software. Calculations were performed offline on a personal computer using 4D View software version 7.0 (GE Healthcare). Measurements were undertaken using the VOCAL software's 'manual' mode, manually outlining the internal contour of the cyst's wall. We chose plane A and a rotation step of 15°, giving a total of 12 outlines per cyst (Figure 2a). The mean signal intensity of the gray voxels within the traced contour was calculated automatically using the software's histogram facility (Figure 2b) and presented as the MGV according to a scale ranging from 0 to 100. Using the 'outside shell' facility set at 1-mm thickness we also calculated the MGV of the cyst wall (Figure 3).

Statistical analysis was performed using the SPSS 15.0 statistical package (SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to check normal distribution of raw data. One-way ANOVA with Bonferroni post-hoc test for multiple comparisons was used to compare

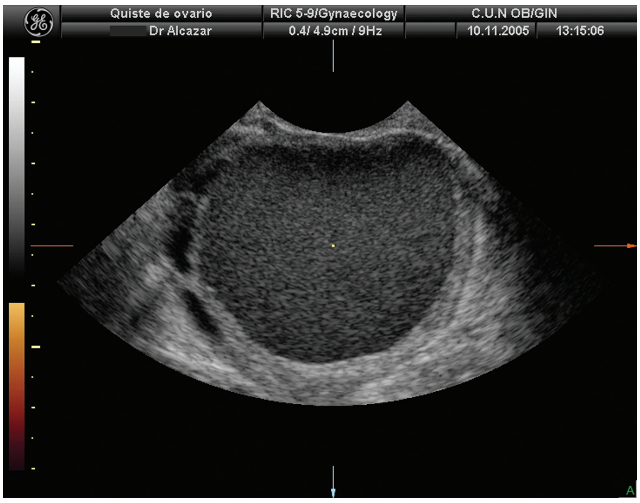

Figure 1 Transvaginal B-mode ultrasound image showing typical appearance of an ovarian endometrioma: a cyst containing diffuse low-level echoes.

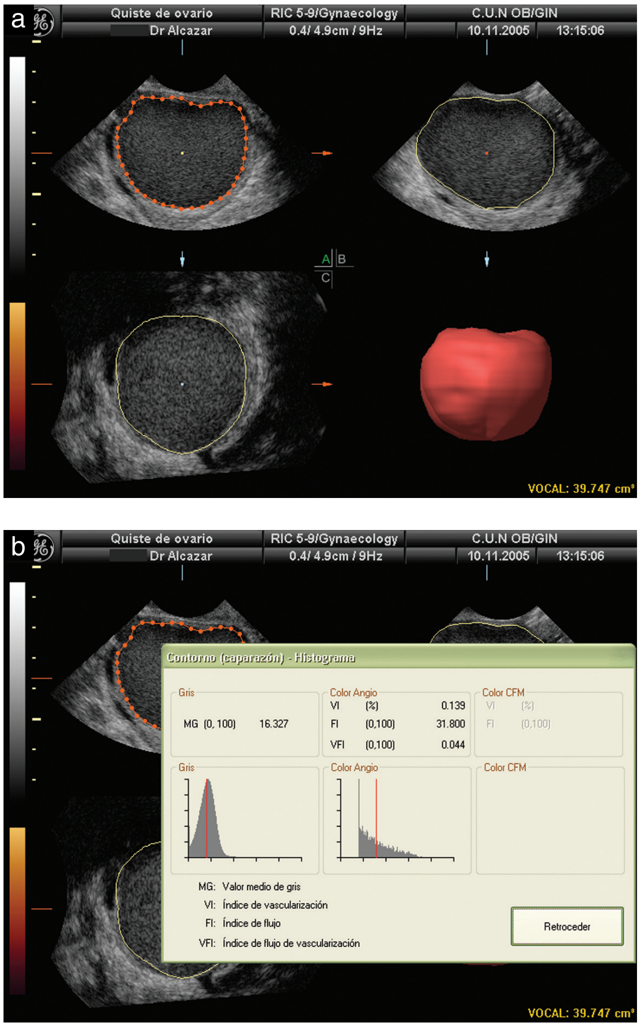

Figure 2 Three-dimensional multiplanar ultrasound image depicting the outlining of cyst content (a) for histogram calculation of the mean gray (MG) value (b).

continuous variables. Receiver–operating characteristics (ROC) curves were plotted for MGV in order to assess its diagnostic performance. The best cut-off value was selected according to the highest sensitivity achieved with the lowest false-positive rate. Sensitivity, specificity and positive and negative likelihood ratios were calculated for B-mode diagnosis and for MGV. Sensitivity and specificity were compared using the McNemar test. Likelihood ratios were compared using Biggerstaff's graphic method[20]. Intraobserver reproducibility for MGV measurement was estimated by calculating the intraclass correlation coefficient with 95% CIs from two different measurements in 10 cases performed by the same examiner[21]. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty-eight of the 54 cysts (in 34 women) were surgically removed. Definitive histological diagnosis was obtained in all of these cases: seven of the 54 (13%) were simple cysts, three (6%) were hemorrhagic luteal cysts, five (9%) were mucinous cysts, three (6%) were paraovarian cysts and 20 (37%) were endometriomas. The other 16 (29%) were diagnosed clinically as hemorrhagic functional cysts and patients were managed conservatively with a follow-up scan in the early follicular phase after two menstrual periods and, if the cyst persisted, a second scan 3 months later. In all of these cases the cyst resolved spontaneously and was considered to have a final diagnosis of hemorrhagic cyst for analytical purposes.

Agreement between B-mode and final diagnoses is shown in Table 1. The MGV of cyst contents was significantly higher for endometriomas compared with the other cysts (Table 2). There were no significant differences for MGVs of cyst walls. The intraclass correlation coefficient for MGV measurement was 0.989 (95% CI, 0.999–0.978).

ROC curve analysis revealed the best MGV cut-off to be 15.560 (Figure 4). Among the 24 cases diagnosed as endometrioma based on B-mode findings, the MGV was above the 15.560 cut-off in 19 cases, 16 of which were ultimately diagnosed as endometriomas at histology (Table 3).

The sensitivity, specificity and positive and negative likelihood ratios for B-mode ultrasound, MGV and the combination of B-mode ultrasound and MGV in the diagnosis of endometrioma are presented in Table 4 and the case distribution for B-mode, MGV and combination of both is shown in Table 5. There were no significant differences in terms of sensitivity and specificity between B-mode and MGV (McNemar test: $P = 1.000$). However, when considering both B-mode and MGV as criteria for diagnosing endometrioma, the positive likelihood ratio increased to 9.1 (95% CI, 3.0 to 27.3) (Table 4). According to Biggerstaff's method, the positive likelihood ratios indicate that combining B-mode and MGV as diagnostic criteria was significantly better than using B-mode or MGV alone.

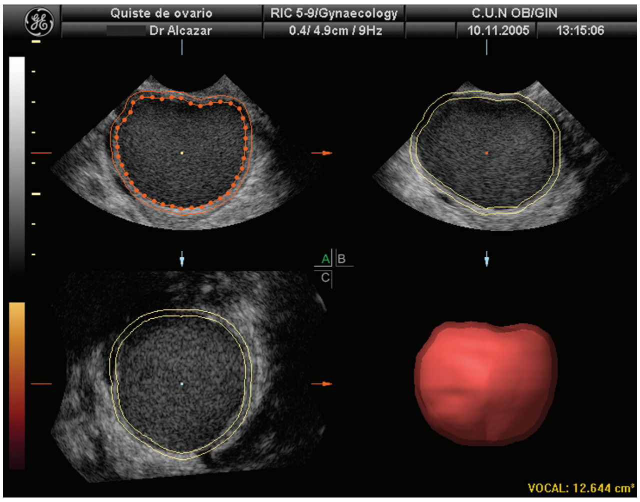

Figure 3 Three-dimensional multiplanar ultrasound image depicting the 1-mm shell for cyst wall histogram calculation.

DISCUSSION

The accurate diagnosis of ovarian endometrioma is important for avoiding unnecessary surgical procedures. Ultrasound has become the first line imaging technique for its diagnosis. On 2D real-time B-mode ultrasonography the typical sonographic appearance of endometrioma is that of a unilocular thin-walled cyst containing diffuse low-level internal echoes[9]. The performance of 2D ultrasound for diagnosing ovarian endometrioma using this criterion

Table 1 Agreement between B-mode ultrasound diagnosis and final diagnosis ($n = 54$)

	Final diagnosis (n)					
B-mode ultrasound diagnosis	*Simple cyst*	*Hemorrhagic cyst*	*Mucinous cyst*	*Paraovarian cyst*	*Endometrioma*	*Total*
Simple cyst	5	2	0	0	0	7
Hemorrhagic cyst	1	14	0	1	2	18
Mucinous cyst	1	0	2	0	0	3
Paraovarian cyst	0	0	0	2	0	2
Endometrioma	0	3	3	0	18	24
Total	7	19	5	3	20	54

Final diagnosis based on histology in 38 cases and clinical diagnosis in 16.

Table 2 Mean gray value (MGV) of cyst contents and cyst wall according to type of cyst

	Cyst contents		*Cyst wall*	
Type of cyst (final diagnosis)	*MGV*	P	*MGV*	P
Simple cyst	8.649 (4.9)	< 0.001	38.291 (8.9)	NS
Hemorrhagic cyst	12.896 (7.6)	0.003	36.834 (10.7)	NS
Mucinous cyst	12.354 (9.0)	0.036	35.724 (11.6)	NS
Paraovarian cyst	8.495 (3.9)	< 0.001	36.391 (9.6)	NS
Endometrioma	21.127 (6.2)		32.484 (7.4)	

Data expressed as mean (SD). *P*-values are for comparison with endometrioma.

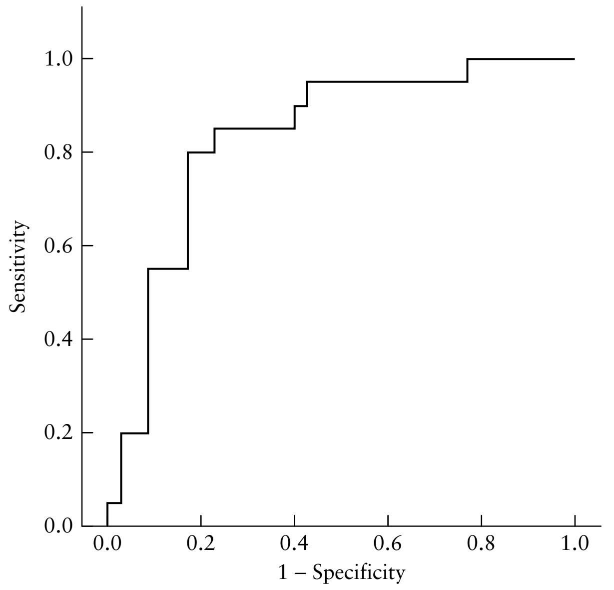

Figure 4 Receiver–operating characteristics curve for cyst contents mean gray value in the prediction of ovarian endometrioma. Area under the curve = 0.831 (95% CI, 0.718–0.944).

Table 3 Distribution of the 24 lesions that were considered to be endometriomas on B-mode ultrasound, according to mean gray value (MGV) cut-off derived from receiver–operating characteristics curve analysis

Type of cyst (final diagnosis)	*Cyst content MGV < 15.560*	*Cyst content MGV ≥ 15.560*
Hemorrhagic cyst (*n* = 3)	2	1
Mucinous cyst (*n* = 3)	1	2
Endometrioma (*n* = 18)	2	16

Data are given as *n*.

is well established, with several studies reporting sensitivities ranging from 82 to 89%[8–11]. However, a recent review[22] reported that published positive likelihood ratios vary from 7.6 to 29.8. This variation could be explained by several facts, such as different study populations, different prevalence of endometrioma within the studied population and the diagnosis by 2D real-time ultrasound being based on an examiner's subjective impression[23].

The role of color Doppler in diagnosing the nature of adnexal masses is controversial[9–11], but 3D ultrasound offers new and unique ways for their assessment[14]. A recent pictorial essay by Raine-Fenning *et al.*[24] showed some of the possibilities of this technique in the assessment of ovarian endometrioma, such as with 3D surface rendering, tomographic ultrasound imaging and speckle reduction imaging. Yet 3D ultrasound offers additional possibilities, one being the virtual analysis of gray-scale and power Doppler data using VOCAL software. The MGV, a parameter calculated using this software, might be regarded as providing 'tissular ultrasound characterization' as it represents the mean intensity of gray-scale voxels contained within a region of interest in a 3D volume. The parameter is unit-less and is represented by a single numeric value ranging from 0 to 100, with 0 representing all voxels being black (minimum echogenicity, e.g. pure water without particles) and 100 representing all voxels white (maximum echogenicity, e.g. bones). In other words, MGV is an objective quantification of the grayness of the tissue on 3D ultrasound.

We speculated that different cysts, with differing contents, such as recent blood clots, fat, mucus or serum, could be discriminated objectively using MGV. Our results confirm the utility of this parameter for the discrimination of ovarian endometrioma from other cysts: the MGV was significantly higher in ovarian endometriomas compared with serous, hemorrhagic and mucinous cysts. The parameter is easy to calculate, reproducible and represents an objective measurement of the sonographic characteristics of cyst contents. Its performance for diagnosing ovarian endometrioma was similar to that achievable by an experienced examiner using B-mode; it could be used for reinforcing the examiner's subjective impression. However, our positive likelihood ratios for B-mode, MGV, and B-mode combined with MGV were lower than those reported in previous studies using B-mode criteria alone[8–12].

An interesting finding was that the addition of MGV to B-mode ultrasound increased the test's positive likelihood ratio from 5.1 to 9.1, while the negative likelihood ratios were similar (0.12 vs. 0.2). This may be relevant for clinical decision-making because the combination of both criteria increased the post-test probability of endometrioma. However, it should be borne in mind that this method is not perfect, since there were four false-negative cases and three false-positive cases. A false-negative case might be less clinically relevant if the patient is asymptomatic and fertility is not a problem (all our

Table 4 Sensitivity, specificity and positive (LR+) and negative (LR−) likelihood ratios for B-mode ultrasound, mean gray value (MGV) and their combination in the diagnosis of endometrioma

Method	*Sensitivity (% (95% CI))*	*Specificity (% (95% CI))*	*LR+ (95% CI)*	*LR− (95% CI)*
B-mode ultrasound	90 (70–97)	82 (66–92)	5.1 (2.4–10.7)	0.12 (0.03–0.46)
MGV*	85 (64–95)	76.5 (60–87)	3.6 (1.9–6.8)	0.2 (0.1–0.6)
B-mode ultrasound + MGV*	80 (58–92)	91 (77–97)	9.1 (3.0–27.3)	0.2 (0.1–0.5)

*Using cut-off derived from receiver–operating characteristics curve analysis of 15.560.

Table 5 Comparison of B-mode and MGV diagnosis of endometrioma with final diagnosis

	Final diagnosis	
	Endometrioma	*Non-endometrioma*
B-Mode + and MGV +	16	3
B-Mode + and MGV −	2	3
B-Mode − and MGV +	1	5
B-Mode − and MGV −	1	23
Total	20	34

Data are given as *n*.

false-negative cases were asymptomatic fertile patients); to the best of our knowledge, there is no evidence that endometriosis should be treated in asymptomatic women[25]. However, false-positive diagnoses may affect clinical decisions. Our three false-positive cases were two mucinous cysts and one hemorrhagic cyst. One mucinous cyst was a 5-cm lesion in a woman presenting with pelvic pain who underwent surgery because of her complaints. The other was a 6-cm lesion in an asymptomatic woman who underwent surgery because of the lesion's size. The third case was a 4-cm functional hemorrhagic cyst in an asymptomatic woman that resolved spontaneously after a follow-up scan. These functional cysts are usually diagnosed after follow-up scans rather than after surgical removal, so false-positive diagnoses may lead to a decision to perform surgery unnecessarily.

In conclusion, we believe that calculating the MGV of cyst contents may contribute to the diagnosis of ovarian endometrioma.

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