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Original Article

Mean grey value is lower in endometriomas: Differentiating a hypoechogenic adnexal cyst by 3-dimensional power Doppler ultrasound—A preliminary study

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Abstract

Background: To assess parameters of 3-dimensional power Doppler ultrasound in differentiating an endometrioma from other hypoechogenic adnexal cysts.
Methods: We collected 58 patients with classic-appearing endometriomas (homogeneous hypoechogenic adnexal cysts with round shapes) on a 2-dimensional conventional sonography. The serum level of CA-125, parameters of 3-dimensional pelvic ultrasound including the volume of the cyst, the mean grey value (MGV), and three vascular indices: vascularization index, flow index, and vascularization flow index, were measured and then, after surgical intervention, were compared between the group with histologically proven endometriomas and the group with other histological diagnoses.
Results: In the chocolate cyst group, the parity was significantly lower (0.68 ± 0.17, $p = 0.012$). The MGV and lesion volume of histologically proven endometriomas were significantly lower (14.78 ± 0.7; 118.34 ± 15.5) than those of other hypoechogenic benign adnexal cysts (17.17 ± 0.74; 227.18 ± 47.46), and the p values were 0.038 and 0.041, respectively. No differences in vascularization index (VI), flow index (FI), and vascularization flow index (VFI) were found between the two groups. No relationship between lesion volume and MGV in the two groups, either ($p = 0.127$ and 0.353). We also found little correlation between CA-125 and the volume of a histologically proven endometrioma as well as between CA-125 and its MGV.
Conclusion: MGV might be useful to differentiate an endometrioma from other homogeneous hypoechogenic adnexal cysts.

Keywords: Chocolate cyst; Endometrioma; Flow index (FI); Mean grey value (MGV); Power Doppler ultrasound; 3-Dimensional ultrasound; Vascularization index (VI); Vascularization flow index (VFI)

1. Introduction

An adnexal cyst is common in various gynecologic conditions with or without discomforts, and a 2-dimensional (2D) pelvic ultrasound is the primary diagnostic modality for evaluation. Endometriosis is pathologically defined by the presence of viable endometrial tissue outside the uterine cavity. The ectopic endometrial tissue undergoes cyclical changes and bleeds during the menstrual cycle. Therefore, one of the most commonly occurring appearances of endometriomas is that of an adnexal cyst with diffuse low-level internal echoes, which is seen in 95% of endometriomas.[1] However, the sonographic characteristics of endometriomas

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are diverse and may overlap with those of other adnexal lesions. For example, hemorrhagic cysts also arise from the clotted blood showing diffuse low-level echoes and, occasionally, cannot be confidently distinguished from endometriomas. Moreover, pus in a tubo-ovarian abscess, mucous in a mucinous cystadenoma, and sebaceous material in a dermoid cyst can be hypoechogenic[2] (Fig. 1A and B). With 2D pelvic ultrasound, it can thus sometimes be difficult to differentiate an endometrioma from other various adnexal cysts, with hemorrhagic cysts and dermoids being the two most commonly misdiagnosed conditions.[3] With current clinically available equipment, 3-dimensional (3D) sonographic reconstruction is fast and has high resolution, giving ultrasound the ability not only to image in real time but also to display much other information. The purpose of this study was to evaluate parameters of 3-dimensional power Doppler (3DPD) ultrasound in differentiating of an endometrioma from other hypoechogenic adnexal cysts.

2. Methods

This was a single-center, prospective study. Patients who demonstrated an adnexal cyst with classic appearance of endometrioma (round shape, homogeneous, and hypoechogenic) on 2D pelvic ultrasound were eligible for this study. The inclusion of the cases was agreed on by two experienced sonologists without any other clinical information. From March through December 2006, 58 patients were included in the study. The study was approved by the institution's ethics committee, and all patients gave oral consent.

The serum level of CA-125 was checked around 1 month before the surgery. An additional 3D ultrasound evaluation was preoperatively performed for the adnexal cyst. It was carried out by one experienced gynecologist with the same instrument and transvaginal probe (Voluson™ 730; GE Healthcare, Milwaukee, WI, USA). The power Doppler characteristics applied were: normal color quality, Doppler gain −5.0, low wall motion filter of 1 and pulse repetition frequency of 0.6 kHz, grey scale gain 0, normal frequency and OTI level, and focal zone 2. All women were examined with the same sonographic presets. If the tumor's diameter was greater than 8 cm or the patient was a virgin, we performed transabdominal ultrasound. The attenuation effect was avoided by the appropriate ultrasound settings mentioned above. Volume acquisition lasted less than 30 seconds. To avoid breathing-related artifacts, the woman was asked to hold her breath during volume acquisition. Cyst volumes were estimated by manually tracing the surface geometry with the procedure of virtual organ computer-aided analysis (VOCAL) imaging technique (GE Healthcare). The volume of interest was based on a semiautomated algorithm that defined geometric surfaces using six rotational steps of 30° each. Rotational cyst contours were manually traced at 30° intervals until completion of a 180° sweeps (Fig. 2).

Automatic acquisition of the volume, mean grey value (MGV), and 3DPD indices for the adnexal cyst were obtained. The MGV represents quantification of the echogenicity of the adnexal cyst. It is expressed as a percentage, with a minimum value being 0 (least echogenic, darkest) and maximum value being 100 (most echogenic, brightest). 3DPD indices included the vascularization index (VI), the flow index (FI), and the vascularization flow index (VFI), and was used as originally described by Pairleitner et al.[4] VI (0−100) represented the amount of blood vessels shown as color areas in the adnexal lesion. FI (0−100) measured the intensity of blood flow within and near the lesion, indicating velocity of blood flow (a brighter color reflecting a higher blood flow velocity). VFI (0−100) represented the combination of the amount of blood vessels and blood flow intensity.

After the surgery, the pathologic diagnoses were analyzed with values of these parameters.

2.1. Statistical analysis

SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA) was used for data entry and analysis. The means of the parameters (serum level of CA-125, volume, MGV, VI, FI, VFI) were compared between the group with histologically proven endometriomas and the group with other histological diagnoses. All differences between means were computed using *t* test. Statistical analysis was also done using correlation coefficients to evaluate the linear relationship between the CA-125 and the volume of histologically proven endometriomas, between the

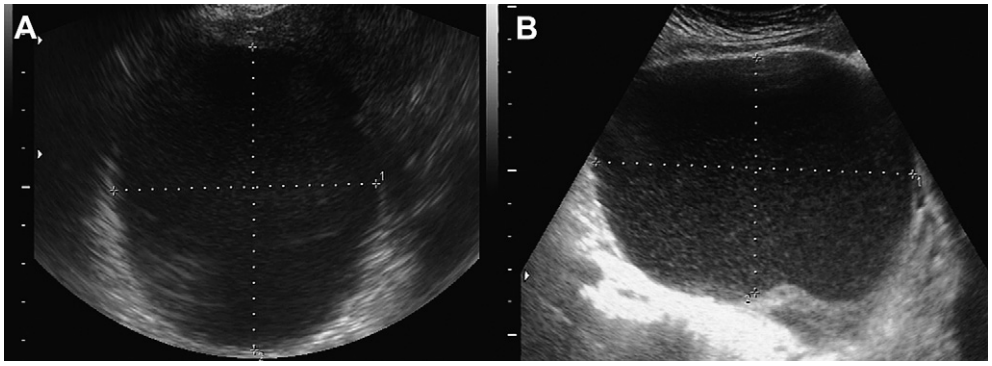

Fig. 1. It is difficult to differentiate these two adnexal cysts under conventional 2D ultrasound. (A) Histologically proven endometrioma; (B) histologically proven serous cystadenoma. 2D = 2-dimensional.

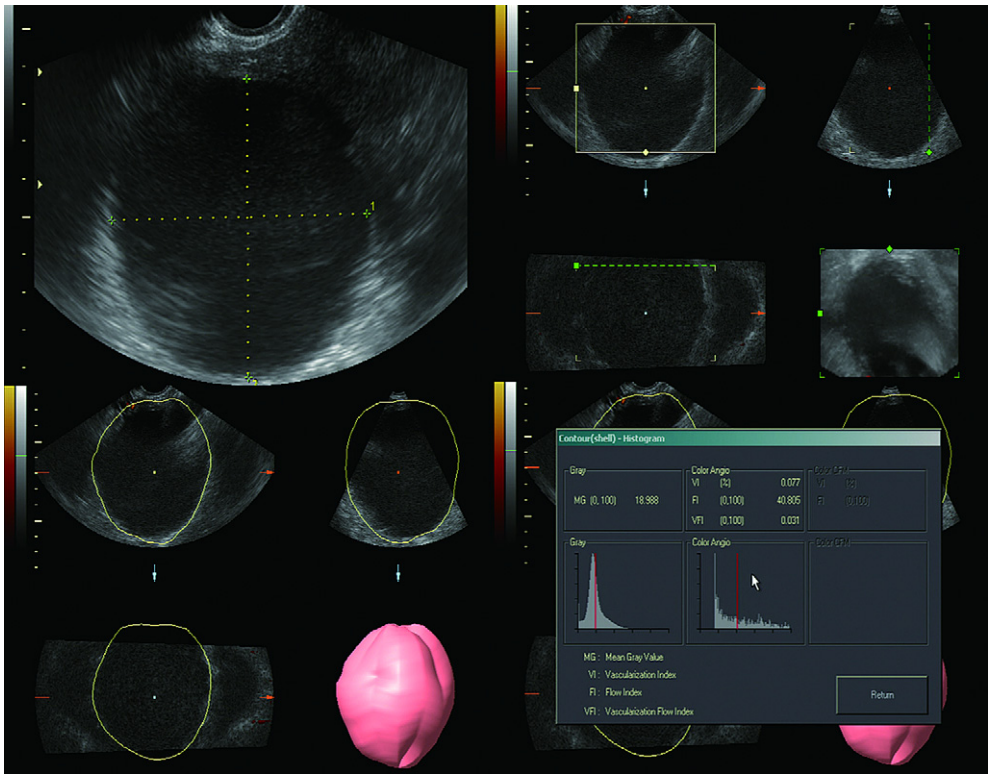

Fig. 2. The image taken from the 2D pelvic ultrasound shows, on the upper-left column, a classic-appearing endometrioma with diffuse low-level echoes. The remaining three columns exhibit the procedures of automatic acquisition. Order: right-upper → left-lower → right-lower. 2D = 2-dimensional.

CA-125 and the MGV, respectively. Two-sided significance was set at the 0.05 level.

3. Results

We collected data from 58 patients (mean age, 37 years old; ranging from 20 to 62 years of age) with adnexal cysts impressed as endometriomas *via* sonography. All the cysts displayed similar appearances with diffuse low-level internal echoes in the visualization of 2D sonographic morphology. The range of tumors' diameters was between 32 mm and 108 mm. After the surgery and pathologic diagnosis, there were 37 patients with endometriotic ovarian cysts and 21 patients with other benign adnexal cysts (Table 2). No malignancy was noted. There was no significant difference of mean age between the two groups (Table 1). We might reveal a wider range of ages in the group with other benign adnexal cysts, and most of reproductive age in the group with endometriotic ovarian cysts. Comparing the two groups (endometriotic ovarian cysts *vs.* other benign adnexal cysts), there were significant differences in parity (Table 1), CA-125, and MGV (Table 3).Patients with histologically proven endometriomas revealed significantly lower MGV (14.8 ± 0.7) than those with other benign adnexal cysts (17.17 ± 0.74, $p = 0.038$). As to VI, FI, VFI, there were no differences between the two groups (Table 3). The lesion volumes were 118.34 ± 15.50 mL and 227.18 ± 47.46 mL in the endometrioma group and other benign adnexal cyst group, respectively. The p value was 0.041. We also analyzed the relationship between the lesion volume and MGV, and the p values were 0.127 and 0.353 in the endometrioma group and other benign adnexal cyst group, respectively.

Table 1
General characteristics of patients

Characteristics	Group 1 ($n = 37$)	Group 2 ($n = 21$)	p
Mean age, yr	35.97 ± 1.20	40.65 ± 2.51	0.142
Age range, yr	20–48	26–62	
Mean parity	0.68 ± 0.17	1.35 ± 0.28	0.012

Data are presented as n or mean ± stand error.
Group 1 = histologically proven endometriotic ovarian cysts.
Group 2 = other benign adnexal cysts.

Table 2
Histological types among Group 2

Histologic type	Case number
Mucinous	5
Serous	3
Dermoid	4
Follicular	1
Corpus luteum	1
Tubo-ovarian cyst	1
Para-tubal cyst	1
Hydrosalpinx	5
Total	21

Group 2 = other benign adnexal cysts.

Table 3
Comparison of parameters in 3DPD ultrasound and serum level of CA-125 between Group 1 (37 cases with histologically proven endometrioma) and Group 2 (21 cases with other benign adnexal cysts)

Parameter	Group 1 ($n = 37$)		Group 2 ($n = 21$)		p
	Mean	SE	Mean	SE	
VI[a]	0.128	0.043	0.796	0.666	0.338
FI[b]	25.018	1.440	25.144	1.972	0.959
VFI[c]	0.034	0.011	0.209	0.171	0.330
MGV[d]	14.78	0.70	17.17	0.74	0.038
CA-125, U/mL	88.25	20.05	17.38	2.78	0.0001
Lesion volume, mL	118.34	15.50	227.18	47.46	0.041

[a] VI = vascularization index.
[b] FI = flow index.
[c] VFI = vascularization flow index.
[d] MGV = mean grey value.
SE = standard error; 3DPD = 3-dimensional power Doppler.
Group 1 = histologically proven endometriotic ovarian cysts.
Group 2 = other benign adnexal cysts.

In the group with histologically proven endometriotic cysts, there was little correlation between CA-125 and the volume of the cyst ($r = 0.23$, Fig. 3), nor between CA-125 and MGV ($r = 0.129$, data not shown).

4. Discussion

The prevalence of endometriosis among asymptomatic women ranges from 2% to 22%, whereas in women with dysmenorrhea, pelvic pain, or infertility, the incidence of endometriosis can go up to 90%.[5] In our study, the parity of the patients with histologically proven endometriomas was significantly lower than that of the patients with other benign adnexal cysts (Table 1). Also, they had higher probability of abortion. However, surgical removal of endometriomas may decrease the ovarian reserve and induce adhesion, which worsens infertility. Overall, laparoscopic cystectomy for endometriomas before *in vitro* fertilization (IVF) does not offer any additional benefit in terms of fertility outcomes.[6] For infertile women before IVF, therefore, Garcia-Velasco and Somigliana recommended that an endometrioma over 4 or even 5 cm does not require surgery in asymptomatic patients if all healthy growing follicles may be reached without damaging the endometrioma.[6] In addition, prolonged treatment with a GnRH agonist before IVF should be considered in patients with moderate–severe endometriosis to improve pregnancy rates.[7] It is thus important to accurately diagnose endometriomas without using surgery.

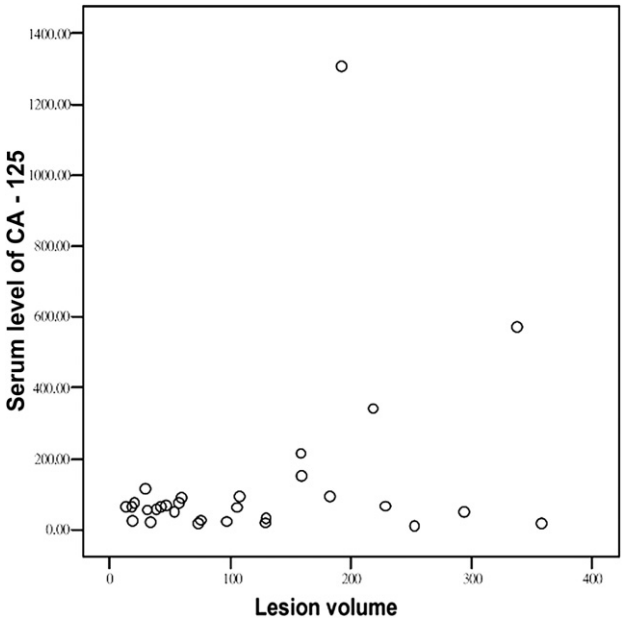

Fig. 3. The graph shows little correlation between the volume of the endometrioma and the serum level of CA-125 ($r = 0.23$).

Guerriero et al. reported the sensitivity and specificity of endovaginal ultrasound in differentiating endometriomas from other ovarian cysts to be 83% and 89%, respectively.[8] Patel et al. showed sonographic appearances with diffuse low-level echoes in 95% of endometriomas in a retrospective review.[1] A prospective study by Dogan et al. determined the positive predictive value of sonography in the diagnosis of surgically proven endometriomas to be 91.5% overall and 97% for classic-appearing endometriomas (round shape and homogeneous low-level internal echoes).[9] Various methods have been proposed to increase the accuracy in the sonographic diagnosis of endometriomas, such as hyperechoic foci,[1] and absent acoustic streaming[10]; however, there are still limitations despite the improved methods. Also, conventional 2D ultrasonography is well known to be operator-dependent. 3D ultrasonography, a relatively new imaging modality, permits improved quantification of sonographic features of the interest including its volume, echogenicity, and blood flow. Our study aimed to find a more objective method with quantitative measurements by 3D ultrasonography to diagnose endometriomas.

We found no differences in VI, FI, and VFI between the group with histologically proven endometriomas and the group with other adnexal cysts, which was compatible with the result of no malignant pathology that frequently manifests increased vasculature and blood flow. Previous studies of color flow Doppler ultrasound have also shown no improvement in the diagnosis of endometriomas.[11]

Via conventional 2D sonography, we usually identify an adnexal cyst with diffuse internal low-level echoes as an endometrioma. Depending on the amount and organization of an internal clot, however, endometriomas may have a spectrum of sonographic appearances.[2] In the group with other benign adnexal cysts, even with various histological types (Table 2), the MGV range of the group was not as wide as that of the group with histologically proven endometriomas. This phenomenon showed how great is the diversity of echogenicity that various degrees of coagulation and blood amount can make. Classically, fresh blood is anechoic. In subacute stages, when a clot forms, it becomes echogenic.[12] Directly perceived through the apparent nature of the clotted blood, we originally hypothesized the MGV to be higher in endometriomas than in other hypoechogenic benign adnexal cysts. The result,

however, conflicts with this stereotypical perception, but we will return to the possible causes of this conflict after a literature review regarding MGV.

In estimating the MGV, we assess the echogenicity of the structure objectively and quantitatively. The concept of quantitative evaluation of the echogenicity has actually been applied in many areas, such as thyroid glands,[13] carotid plaques,[14,15] and perianal Crohn's disease.[16] In an obstetric study in the evaluation of the placenta, MGV was similar in placentas of all women regardless of maternal age and parity.[17] In the field of reproductive endocrinology, the polycystic ovaries were of significantly lower MGV (less echogenic) in Chinese women compared with the polycystic ovaries of a Caucasian cohort, which was explained with the hypothesis that the thecal cells in the ovarian stroma of Caucasian patients with PCOS produce more excessive androgen, undergo hypertrophy, and therefore become more echogenic.[18]

In autoimmune thyroid diseases, lymphocytic infiltration and disruption of tissue architecture cause a reduction in thyroid echogenicity,[19,20] and a stronger inflammatory process is seen in higher grades of hypoechogenicity.[21] In regards to endometriosis, in spite of a common pathologic condition, an in-depth understanding of the pathophysiology of endometriosis is still elusive. Through decades of research, it has been suggested that there are multiple mechanisms, including an inflammatory process involving macrophages, several growth factors, cytokines,[22] thrombin,[23] and a circle of tissue injury and repair.[24] Despite not being a malignant disorder, endometriosis exhibits cellular proliferation, cellular invasion, and occasionally neoangiogenesis.[25] It may be the mechanisms listed above that contribute to lower MGV of an endometrioma. In our study, we noticed different MGV and lesion volume in the two groups which reminded us that the MGV might change with lesion volumes. In fact, the MGV values were constant regardless of lesion volume in both groups. We might conclude that MGV could faithfully present the cystic texture of both groups, no matter what the volume is. Unfortunately, we could not calculate the cut-off values of MGV because of the small sample size, and it seems that the most MGV in both groups were overlapping. Even so, it is still an innovative method to differentiate endometrioma and other benign adnexal cysts.

In our study, the serum level of CA-125 was significantly higher in the group with histologically proven endometriomas. However, the minimal serum CA-125 contained in this group was 11.68 U/mL (data not shown), which reminds us that a serum level of CA-125 within normal range doesn't exclude endometriosis. On the other hand, the maximal serum CA-125 contained in the group with other benign adnexal cysts was 53.06 (data not shown), which showed that a higher-than-normal serum level of CA-125 may still be correlated with a condition other than endometriosis and malignancy.

Our initial hypothesis was that CA-125 should be positively linearly correlated to the volume of the endometrioma. On the other hand, presuming that the lower MGV correlated with a stronger inflammatory process, we supposed that there would be a negative correlation between MGV and CA-125. However, there were no significant correlations noted in our study. CA-125 is mainly derived from the endometrium and the irritated peritoneum. It might be the area of the surface of the endometrioma in contact with the peritoneum (but not the volume or the inflamed contents) that accounts for the elevation of serum CA-125. Some other factors should also be taken into consideration, such as combination with adenomyosis, pelvic inflammatory disease or adhesion, the timing of testing (which phase of the menstrual cycle), etc.

MGV analysis allows an objective and quantitative evaluation for endometriomas' echogenicity to distinguish them from other benign adnexal cysts in an ambiguous condition. This method might exclude a subjective component of evaluation, thereby improving the diagnostic reliability of ultrasound examination. It is automatic and easily reproducible, and removes observer variability. Nevertheless, we must be aware that the reproducibility of data is dependent strictly on standardization of operating conditions, as the reference normal echogenicity could change in relation to different ultrasound equipment settings.

We consider our findings only preliminary in the sense that the results are evidence of the general feasibility of the method itself. Further studies are needed to demonstrate a range or the cut-off value of MGV to differentiate an endometrioma from other benign adnexal cysts.

In conclusion, for infertile patients before IVF and asymptomatic patients who hesitate to receive surgical intervention for pathological diagnosis, MGV might be useful in differential of homogeneous hypoechogenic adnexal cysts. This is a novel method to discriminate an endometrioma from other hypoechogenic adnexal cysts, and its application in different areas might be pursued *via* further studies.

References

1. Patel MD, Feldstein VA, Chen DC. Endometriomas: diagnostic performance of US. *Radiology* 1999;**210**:739−45.
2. Fleischer AC, Entman SS. Sonographic evaluation of pelvic masses with transabdominal and/or transvaginal sonography. In: Fleischer AC, Manning FA, Jeanty P, Romero R, editors. *Sonography in obstetrics & gynecology: principles and practice*. 6th ed. McGraw-Hill; 2001. p. 884−911.
3. Moore J, Copley S, Morris J, Lindsell D, Golding S, Kennedy S. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. *Ultrasound Obstet Gynecol* 2002;**20**:630−4.
4. Pairleitner H, Steiner H, Hasenoehrl G, Staudach A. Three-dimensional power Doppler sonography: imaging and quantifying blood flow and vascularization. *Ultrasound Obstet Gynecol* 1999;**14**:139−43.
5. D'Hooghe TM, Debrock S, Hill JA, Meuleman C. Endometriosis and subfertility: is the relationship resolved? *Semin Reprod Med* 2003;**21**: 243−54.
6. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. *Hum Reprod* 2009;**24**: 496−501.
7. Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002;**78**:699−704.
8. Guerriero S, Mais V, Ajossa S. The role of endovaginal ultrasound in differentiating endometriomas from other ovarian cysts. *Clin Exp Obstet Gynecol* 1995;**22**:20−2.

9. Dogan MM, Ugur M, Soysal SK, Soysal ME, Ekici E, Gokmen O. Transvaginal sonographic diagnosis of ovarian endometrioma. *Int J Gynaecol Obstet* 1996;**52**:145−9.
10. Clarke L, Edwards A, Pollard K. Acoustic streaming in ovarian cysts. *J Ultrasound Med* 2005;**24**:617−21.
11. Alcázar JL, Laparte C, Jurado M. The role of transvaginal ultrasonography combined with color velocity imaging and pulsed Doppler in the diagnosis of endometrioma. *Fertil Steril* 1997;**67**:487−91.
12. Coelho JC, Sigel B, Ryva JC. B-mode sonography of blood clots. *J Clin Ultrasound* 1982;**10**:323−7.
13. Vitti P. Grey scale thyroid ultrasonography in the evaluation of patients with Graves' disease. *Eur J Endocrinol* 2000;**142**:22−4.
14. Mayor I, Momjlan S, Lalive P, Sztajzel R. Carotid plaque: comparison between visual and grey-scale median analysis. *Ultrasound Med Biol* 2003;**29**:961−6.
15. Pedro LM, Fernandes JF, Pedro MM. Ultrasonographic risk score of carotid plaques. *Eur J Vasc Endovasc Surg* 2002;**24**:492−8.
16. Losco A, Vigano C, Conte D, Cesana BM, Basilisco G. Assessing the activity of perianal Crohn's disease: comparison of clinical indices and computer-assisted anal ultrasound. *Inflamm Bowel Dis* 2009;**15**: 742−9.
17. Zalud I, Shaha S. Three-dimensional sonography of the placental and uterine spiral vasculature: influence of maternal age and parity. *J Clin Ultrasound* 2008;**36**:391−6.
18. Lam P, Raine-Fenning N, Cheung L, Haines C. Three-dimensional ultrasound features of the polycystic ovary in Chinese women. *Ultrasound Obstet Gynecol* 2009;**34**:196−200.
19. Gutekunst R, Hafermann W, Mansky T, Scriba PC. Ultrasonography related to clinical and laboratory findings in lymphocytic thyroiditis. *Acta Endocrinol* 1989;**121**:129−35.
20. Mazziotti G, Sorvillo F, Iorio S. Grey-scale analysis allows a quantitative evaluation of thyroid echogenicity in the patients with Hashimoto's thyroiditis. *Clin Endocrinol* 2003;**59**:223−9.
21. Schiemann U, Avenhaus W, Konturek J. Relationship of clinical features and laboratory parameters to thyroid echogenicity measured by standardized grey scale ultrasonography in patients with Hashimoto's thyroiditis. *Med Sci Monit* 2003;**9**:MT49−53.
22. Kyama CM, Debrock S, Mwenda JM, D'Hooghe TM. Potential involvement of the immune system in the development of endometriosis. *Reprod Biol Endocrinol* 2003;**1**:123.
23. Osuga Y. Novel therapeutic strategies for endometriosis: a pathophysiological perspective. *Gynecol Obstet Invest* 2008;**66**:3−9.
24. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet* 2009;**280**: 529−38.
25. Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. *Reproduction* 2002;**123**: 217−26.