Complex Pelvic Mass as a Target of Evaluation of Vessel Distribution by Color Doppler Sonography for the Diagnosis of Adnexal Malignancies

Results of a Multicenter European Study

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Objective. To compare the diagnostic accuracy of gray scale sonography and color Doppler imaging in the differential diagnosis of adnexal malignancies from benign complex pelvic masses in a multicenter prospective study. ***Methods.*** The study was performed as a collaborative work at 3 European university departments of obstetrics and gynecology. A total of 826 complex pelvic masses on which transvaginal sonography and evaluation of cancer antigen 125 plasma concentrations were performed before surgical exploration were included in the study. The scanning procedure was the same in the 3 institutions. An adnexal mass was first studied in gray scale sonography, and a probable histologic type was predicted. Second, solid excrescences or solid portions of the tumor were evaluated for vascular flow with color Doppler sonography (conventional or power). A mass was graded malignant if flow was shown within the excrescences or solid areas and benign if there was no flow. The overall agreement between the test result and the actual outcome was calculated by κ statistics. ***Results.*** Color Doppler evaluation was more accurate in the diagnosis of adnexal malignancies in comparison with gray scale sonography ($\kappa = 0.82$ and 0.65, respectively) because of significantly higher specificity (0.94 versus 0.84; $P < .001$). The evaluation of the cancer antigen 125 plasma concentration did not seem to increase the accuracy of either method. ***Conclusions.*** The evaluation of vessel distribution by color Doppler sonography in complex adnexal cysts seems to increase the diagnostic accuracy of gray scale sonography in the detection of adnexal malignancies in a large study population. ***Key words:*** Color Doppler sonography; complex ovarian masses; ovarian cancer; sonography.

Abbreviations
CA-125, cancer antigen 125

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The main problem of gray scale morphologic sonography is the high false-positive rate in the differential diagnosis of adnexal malignancies, even with several scoring systems.[1] Nevertheless, gray scale sonography is precise enough in the diagnosis of several benign adnexal conditions[2–5]; therefore, the actual problem of false-positive results is reduced to complex or "indeterminate" masses. Conventional color and pulsed Doppler imaging has been introduced to improve the diagnostic accuracy of gray scale morphologic sonography. Initial reports were encouraging, but today's literature is full of conflicting results[6–9] about the use of pulsed Doppler sonography and quantitative parameters such as the pulsatility index, resistive index,

and peak systolic velocity, which make this approach unpractical from a clinical point of view and poorly reproducible, especially in multicenter studies. In previous studies,[10,11] we suggested that color Doppler imaging should be used only to grade masses with central vascular flow or vascular flow within excrescences previously identified on B-mode sonography as malignant. With the use of this approach, power Doppler imaging has been shown to have performance similar to conventional color Doppler imaging.[11] Our method is simple, and, as suggested by Schelling et al, "this purely qualitative measurement of vascularization avoids the generally recognized disadvantages of quantitative blood flow parameters."[12] These include angular dependence of blood flow measurement between different examiners and even by 1 examiner on different occasions. The main problem with reproducibility could remain sensitivity among different machines. In the case of a multicenter study performed to increase the number of cysts and the power of the study, this bias can be avoided if previously standardized protocols with updated sonographic machinery and the maximum sensitivity possible are used routinely in tertiary centers for presurgical evaluation, as suggested in several previously published articles by our groups.[10,11,13] A similar approach has been used in some multicentric studies involving the use of color Doppler equipment to evaluate the presence of flow with contrast agents.[14,15]

The purpose of this multicenter prospective study was to compare the diagnostic accuracy of gray scale sonography with color Doppler imaging in the differential diagnosis of ovarian malignancies from other complex pelvic masses in a large study population. The overall agreement between the test result and the actual outcome was calculated by κ statistics.[16]

Materials and Methods

The study was performed between April 1997 and July 2000 as a collaborative work among 3 departments of obstetrics and gynecology of University of Cagliari (center 1), University of Florence (center 2), and University of Navarra (center 3). The potential study population (N = 1020: center 1, 374; center 2, 319; and center 3, 327) included all women scheduled for surgery for the presence of a persistent adnexal mass. Women with an anechoic unilocular or bilocular cystic mass with a thin regular wall without endocystic vegetation were excluded from the study (N = 234).

A total of 826 complex pelvic masses in 789 women were included in the study. The average ± SD age of the study population was 40 ± 14 years (range, 14–81 years). Six hundred seventeen patients (78%) were premenopausal (average age, 34 ± 9 years), and 172 (22%) were postmenopausal (average age, 61 ± 9 years). Within 15 days before surgery, all patients underwent transvaginal sonography before surgical exploration. In addition, cancer antigen 125 (CA-125) plasma levels were determined by commercially available assays. State-of-the-art, commercially available sonographic equipment was used. The systems used were an SSA-370 A system (Toshiba Medical Systems Co, Ltd, Tokyo, Japan), a 128XP/10 system (Acuson, a Siemens Company, Mountain View, CA), and a Sonoline Elegra system (Siemens AG, Munich, Germany). All machines had transvaginal probes with a maximum frequency of 5 to 7 MHz.

The scanning procedure was the same in all 3 institutions. Any cystic mass containing excrescences, thick septations, or multiple septations was included within the complex category. Also, masses in which the echo features were highly characteristic of a given disease, such as endometrioma, cystic teratoma, hemorrhagic ovarian cyst, and hydrosalpinx, were categorized as benign but included within the complex category. With the use of B-mode sonography, a mass was thought to be benign when it had a typical benign pattern based on the following morphologic criteria: endometrioma, characterized by circular homogeneous, hypoechoic "tissue" without papillary proliferations and a clear demarcation from the ovarian parenchyma[3]; cystic teratoma, characterized by 1 of the following 3 echo patterns: (1) a densely echogenic mural tubercle with a posterior acoustic shadow associated with a cystic echo pattern, (2) echogenic, thin, bandlike echoes (hyperechoic sparkling lines and dots in a dark field), and (3) a dense echo pattern associated with posterior acoustic shadow with or without a cystic component[2]; and hydrosalpinx, characterized by an irregular, elongated mass filled with anechoic fluid.[5]

Any multiloculated, complex, or solid mass in which the echo architecture was not highly indicative of a benign histologic type was categorized as malignant. The maximum transverse,

anteroposterior, and longitudinal diameters of each mass were measured, and the volume was calculated according to the prolate ellipsoid formula (height × length × width × 0.5233) and expressed in milliliters.

The gray scale results were then supplemented by color Doppler sonography (evaluation of vessel distribution). In the 3 institutions, the color Doppler study was performed by looking for color signals along the wall and within the septa, if present, of all masses. When color was detected, the pulsed Doppler gate was superimposed, and the pulsatility index and resistive index were electronically computed. The data of spectral Doppler analysis were not used in this study so that its reproducibility would not be reduced and because of the limited diagnostic value shown in several previous studies.[6–9]

On color Doppler sonography (evaluation of vessel distribution), malignancy was suggested when arterial flow was visualized in an echogenic structure or in an irregular solid portion defined as malignant on B-mode imaging.[10] A mass was thought to be benign on transvaginal color Doppler imaging when flow was seen only in the wall of a mass defined as benign or malignant on B-mode imaging.[10]

Although the difference in sonographic systems and Doppler frequency can be considered a limitation of the study, in the 3 institutions Doppler settings were the most sensitive possible with the lowest risk of artifacts, and each setting was evaluated in several articles previously published by the 3 groups.[10,11,13] In addition, Doppler gain was increased routinely if no flow was detected. All scans were performed in the follicular phase by the same physicians (J.L.A., M.E.C., and S.G.). To increase the reproducibility of the study, the 3 examiners discussed and checked the different findings (B-mode and color Doppler) before the beginning of the study.

The risk of malignancy was based on an overall impression that included morphologic classification, histologic prediction, and color Doppler results. Malignant tumors were staged surgically according to the criteria established by the International Federation of Gynecology and Obstetrics. The sensitivity, specificity, and positive and negative predictive values of B-mode transvaginal sonography and other methods were calculated for each mass.[3] The z statistic for comparison of 2 proportions[17] was used to evaluate the results. In addition, to evaluate the overall agreement between a test result and the actual outcome with the use of the 2 different methods, the κ index was calculated according to the method of Fleiss.[16] The use of κ statistics allows comparison of different diagnostic tests in different populations. κ values ranging between 0.40 and 0.75 were assumed to indicate strong agreement.

Results

A total of 679 of the 826 complex pelvic masses were benign, and 147 were malignant (prevalence per mass, 18%); 53 of the malignant masses were in the premenopausal group, and 94 were in the postmenopausal group. Nineteen of the 132 ovarian carcinomas were low-malignancy potential tumors; 23 were stage I according to the International Federation of Gynecology and Obstetrics; 6 were stage II; 67 were stage III; and 17 were stage IV. Six masses were ovarian metastases, the primary tumor being a carcinoma of the colon in 3 cases, a carcinoma of the breast in 1 case, and a uterine sarcoma in 1 case. The remaining 9 malignant masses were 5 lymphomas, 2 granulosa cell tumors, a mesothelioma peritonei, and a fallopian tube carcinoma. The median CA-125 values were 240 U/mL (range, 6–21,811 U/mL) in the malignant masses and 26 U/mL (range, 0–2620 U/mL) in the benign masses.

Of the 254 masses thought to be malignant on gray scale sonography, 146 were confirmed by pathologic examination. The sonographic findings of the 108 cases with false-positive results resembled findings that are characteristic of malignant masses. The details of the cases with false-positive results are summarized in Table 1. The 146 masses thought to be malignant and confirmed by pathologic examination had a median sonographic volume of 168 mL (range, 5–6231 mL).

Of the 572 sonographic diagnoses of benign cysts (Fig. 1), 571 were confirmed by pathologic examination (endometrioma, n = 294; mature teratoma, n = 125; hemorrhagic cyst, n = 46; mucinous cystadenoma, n = 30; hydrosalpinx, n = 22; serous cystadenoma, n = 22; serous cyst, n = 11; tubo-ovarian complex, n = 11; cystadenofibroma, n = 4; leiomyoma, n = 3; ovarian fibroma, n = 2; and Brenner tumor, n = 1). The case with false-negative results on B-mode

Table 1. Description of 108 Cases With False-Positive Results on B-Mode Sonography

Histopathologic Diagnosis	No. of Masses	Volume of Adnexal Masses on Sonography, mL*
Endometrioma	19	34 (6–823)
Hemorrhagic cyst	14	103 (12–776)
Ovarian fibroma	13	77 (26–597)
Mucinous cystadenoma	10	567 (23–22,449)
Cystadenofibroma	10	87 (10–473)
Mature teratoma	9	147 (4–1,342)
Tubo-ovarian complex	8	86 (15–298)
Serous cystadenoma	6	262 (4–4,316)
Follicular cyst	5	30 (17–395)
Fibrothecoma	5	49 (8–263)
Peritoneal cyst	2	107 (79–135)
Leiomyoma	3	99 (8–3,454)
Paraovarian cyst	1	79
Hydrosalpinx	1	401
Brenner tumor	1	20
Pseudomixoma	1	131

*Values are median (range).

sonography was an adnexal mass with hypoechoic content without septa (sonographic volume, 79 mL; histopathologic diagnosis: mucinous low-malignancy potential tumor).

Sixty-seven of the 108 cases with false-positive results obtained on B-mode sonography were successfully diagnosed as benign on the basis of color Doppler sonography. In 51 cases, an echogenic structure was present inside the cyst, but the color Doppler signal was absent (endometrioma, n = 10; mature teratoma, n = 1; hemorrhagic cyst, n = 12; mucinous cystadenoma, n = 5; cystadenofibroma, n = 7; tubo-ovarian complex, n = 3; hydrosalpinx, n = 1; serous cystadenoma, n = 4; follicular cyst, n = 5; peritoneal cyst, n = 2; and paraovarian cyst, n = 1). In 16 cases, an irregular and prevalently solid portion was detected, but a color Doppler signal was absent (endometrioma, n = 4; ovarian fibroma, n = 3; mature teratoma, n = 6; tubo-ovarian complex, n = 1; and fibrothecoma, n = 2). With the use of color Doppler sonography, the 41 cases with false-positive results (Fig. 2) included the following histopathologic diagnoses: ovarian fibroma, n = 10; mucinous cystadenoma, n = 5; endometrioma, n = 5; tubo-ovarian complex, n = 4; leiomyoma, n = 3; cystadenofibroma, n = 3; fibrothecoma, n = 3; serous papillary cystadenoma, n = 2; mature teratoma, n = 2; hemorrhagic cyst, n = 2; Brenner tumor, n = 1; and pseudomyxoma, n = 1. In all these masses, a color signal was visualized in an echogenic structure or in an irregular solid portion.

With the use of color Doppler sonography, 6 cases with false-negative results were added; thus the cases with false-negative color Doppler results consisted of 7 adnexal masses (median sonographic volume, 73 mL; range, 10–6231 mL; Fig. 3) in which nonarterial flow was visualized in an echogenic portion (mucinous low-malignancy potential tumor, n = 2; serous low-malignancy potential tumor, n = 1; serous ovarian carcinoma, n = 1; and mucinous ovarian carcinoma, n = 1) or in a prevalently solid portion (endometrioid ovarian carcinoma, n = 1; and undifferentiated ovarian carcinoma, n = 1).

The sensitivity, specificity, positive and negative predictive values, and κ value of gray scale and color Doppler sonography are reported in Table 2. Color Doppler evaluation (Figs. 4 and 5) was more accurate than gray scale sonography in the diagnosis of adnexal malignancies ($\kappa = 0.82$ and 0.65, respectively), with significantly higher specificity (0.94 versus 0.84; $P < .001$) and similar sensitivity (0.95 versus 0.99, respectively). The false-positive rate significantly decreased (from 16% of gray scale sonography alone to 6% of color Doppler sonography; $P < .001$), but the false-negative rate increased (from 0.7% of gray scale sonography alone to 5% of color Doppler sonography; $P < .001$). The diagnostic accuracy of the tests in discriminating a benign from a malignant tumor was dependent on menopausal status. The positive predictive values of B-mode and color Doppler sonography were always lower in premenopausal women (44% and 69%, respectively) compared with the postmenopausal population (70% and 83%, respectively) because of

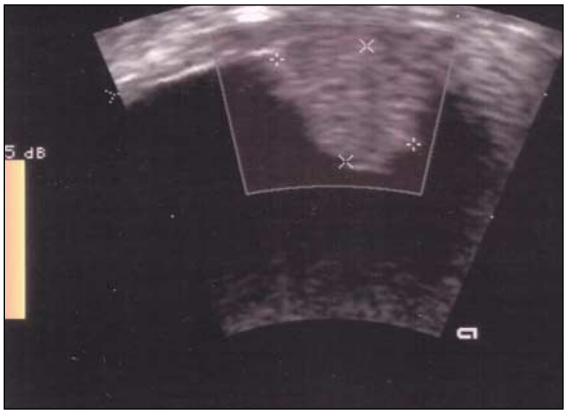


Figure 1. Case with true-negative results. No flow is shown in the echogenic structure on color Doppler sonography.

the lower prevalence of malignancies in the premenopausal population (8% versus 53%, respectively).

The association of CA-125 combined with B-mode sonography (Table 2) had lower sensitivity than B-mode sonography alone (0.99 versus 0.77; $P < .001$). Also, the association of CA-125 combined with color Doppler sonography (Table 2) had lower sensitivity than color Doppler sonography alone (0.95 versus 0.76; $P < .001$).

Discussion

The risk of malignancies associated with unilocular echo-free cysts is very low.[18,19] Unfortunately, in these masses, Doppler sonography does not improve diagnostic accuracy.[12] On the contrary, complex adnexal cysts shown on sonography have a higher risk of malignancy.[18] In this kind of mass, this study showed that qualitative color Doppler evaluation is a useful tool in the diagnosis of adnexal malignancies. The reduction of false-positive results by color Doppler sonography could increase the use of less invasive techniques such as laparoscopy instead of a conventional laparotomic approach with a low risk of missing ovarian cancer.

Only recently has the role of vascular distribution[12] received increasing attention, because it seems an easy method for investigating adnexal masses. Other authors have used a similar approach with a more complex technique such as three-dimensional power Doppler sonography. Cohen et al[20] correctly identified complex adnexal masses as the targets of color Doppler investigations, but the accuracy[21] was low, with a κ value of 0.55 calculated from the data published by Cohen et al.[20] The selection of only complex adnexal masses might only partially explain these results, which also could be due to the sonographic modality used. The present study confirms this suspicion. As a matter of fact, using a comparable approach, we have obtained higher overall accuracy with a κ value of 0.82. As also stated by Cohen et al,[20] a prospective randomized clinical trial is required before three-dimensional power Doppler sonography can be included among clinical diagnostic tools.

In addition, the use of a simple approach is the only way to increase the reproducibility of the study. Validation of complex formulas for detec-

Figure 2. Case with false-positive results. Vascular flow is shown in the echogenic structure on color Doppler sonography. The cyst was thought to be malignant, but surgery showed the presence of severe pelvic adhesion syndrome.

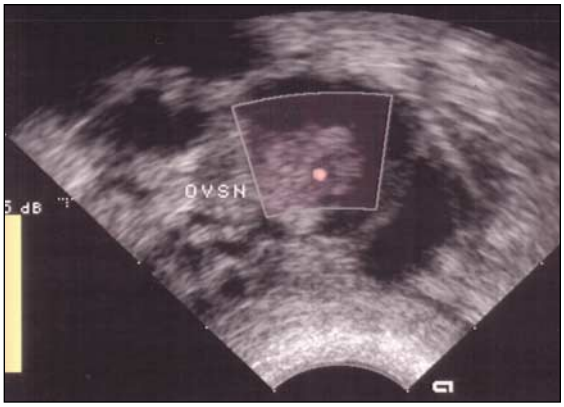


Figure 3. Case with false-negative results. No vascular flow is shown in the echogenic structure on color Doppler sonography. The cyst was thought to be benign, but surgery showed the presence of a mucinous cystadenocarcinoma.

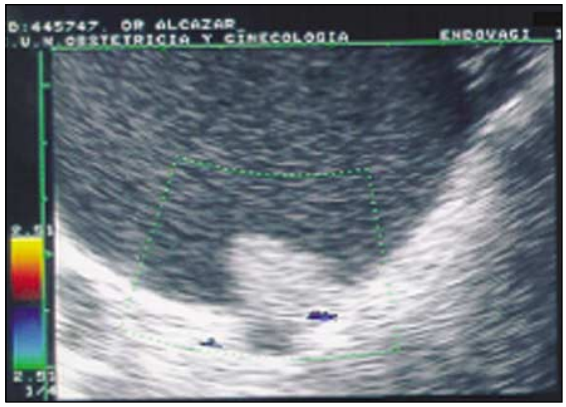


Table 2. Accuracy of Different Sonographic Methods With or Without Association With CA-125 Determination in the Diagnosis of Adnexal Malignancies

Modality	Specificity, %	Sensitivity, %	PPV, %	NPV, %	κ
B-mode					
Premenopause	89	98	44	100	0.55
Postmenopause	51	100	70	100	0.53
Total	84	99	57	100	0.65
Color Doppler					
Premenopause	96	94	69	99	0.78
Postmenopause	77	96	83	94	0.74
Total	94*	95	77	99	0.82
B-mode and CA-125 >35 U/mL†					
Premenopause	96	75	63	98	0.65
Postmenopause	93	78	92	79	0.70
Total	96	77	79	95	0.73
Color Doppler and CA-125 >35 U/mL†					
Premenopause	99	75	85	98	0.78
Postmenopause	96	76	96	78	0.71
Total	99	76	92	95	0.8

NPV indicates negative predictive value; and PPV, positive predictive value.
*Significantly different from B-mode imaging; $P < .05$.
†Positive results for both tests.

tion of ovarian cancer is lacking. Aslam et al[22] recently criticized this approach, evaluating 3 logistic regression models published in the English literature. All models performed less well than originally reported, and combining the models did not lead to a significant improvement in performance. In conclusion, despite the possible bias introduced in our study by the use of different sonographic equipment and operators, evaluation of vessel distribution by color Doppler sonography in complex adnexal cysts seems to be useful for increasing the diagnostic accuracy of gray scale sonography in the detection of adnexal malignancies in a large study population.

Figure 4. Case with true-positive results. Irregular small vessels are shown in the solid portion on color Doppler sonography. Histopathologic evaluation confirmed the presence of a mucinous cystadenocarcinoma.

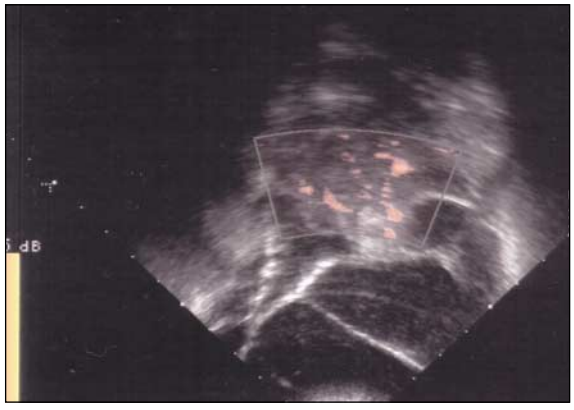
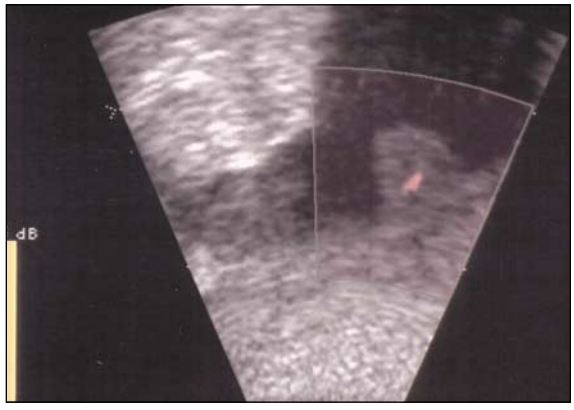


Figure 5. Case with true-positive results. Small vessels are shown in the echogenic structure on color Doppler sonography. Histopathologic evaluation confirmed the presence of a serous cystadenocarcinoma.



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