The diagnostic value of washing curves obtained by dynamic contrast enhanced transvaginal ultrasonography in the diagnosis of ovarian tumors – preliminary study

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Abstract:
Objective: The main objective of this study was to evaluate the role of contrast-enhanced ultrasonography in the diagnosis of ovarian masses. Methods and Materials: Seventy-three patients with morphologically abnormal ovarian masses (cystic with focally thickened walls, with papillary excrescences or irregular solid areas, solid tumor) were investigated by contrast enhanced transvaginal ultrasound (SonoVue). The following parameters were assessed in all ovarian masses: peak contrast enhancement (dB), time to peak enhancement (s), half washout time and area under the enhancement curve. The histology diagnoses were performed for all lesions included in this study. Results: Twenty-three malignant masses and fifty benign tumors were studied. The statistical data analysis showed a difference between benign and malignant tumors, for the following parameters: peak contrast enhancement (mean ± SD, 4.82 ± 2.3 versus 34.09 ±7.8 dB), half washout time (23.26 ± 18 versus 41± 8.6 s) and the area under the enhancement curve (1.89± 0.7 versus 4.38± 2.5). There were no statistically significant differences for the time to peak enhancement (15 ±9.3 versus 19.17 ± 4.1). Conclusion: The quantification of ultrasonographic contrast media kinetics using pulse inversion harmonic sonography has potential to accurately differentiate between benign and malignant ovarian tumors.

Key words: ovarian cancer, ultrasonography, contrast agent

Rezumat:
Obiectiv: Principalul obiectiv al studiului a fost evaluarea rolului ecografiei cu substanţă de contrast în diagnosticul maselor tumorale ovariene. Material şi metoda: Şaptezece şi trei de pacienţei cu mase tumurale ovariene (tumori solide sau chistice cu îngroşări focale la peretii, excrescenţe papilare sau arii solide neregulate) au fost investigate prin ecografia transvagină cu substanţă de contrast (Sono Vue). S-au urmărit următorii parametrii: intensitatea semnalului maxim (dB), timpul de peak maxim (s), timpul de wash-out relativ şi aria de sub curbă. Rezultate: Au fost studiate 23 mase tumurale maligne şi 50 de mase tumurale binegrade. Analiza statistică a parametrilor a arătat diferenţe între tumorele binegrade şi maligne pentru următorii parametri: intensitatea semnalului maxim (medie ± SD, 4,82 ± 2,3 versus 34,09 ±7,8 dB), timpul de wash-out relativ (23,26 ± 18 versus 41± 8,6 s) şi aria de sub curbă (1,89± 0,7 versus 4,38± 2,5). Nu s-au obţinut diferenţe semnificative statistic pentru timpul de peak maxim (15 ±9,3 versus 19,17 ± 4,1). Concluzii: Cuantificarea cineticii agenţilor de contrast ecografic utilizând ecografia armonică de impulsie inversată are potenţial în diferenţierea cu acurateţe între tumorele ovariene binegrade şi maligne.

Cuvinte cheie: cancer ovarian, ecografia, agenţi de contrast

Pelvic transabdominal sonography and transvaginal sonography were until recently the standard exams in the diagnosis of ovarian tumor pathology. Both approaches have advantages, clear pathways through increased availability, relatively low cost etc, being for a long time the first-choice imaging methods, not only for diagnosis and
staging of ovarian tumors, but also for elucidating other diseases in the gynecologic field [1,2]. New ultrasound technologies had to be developed, in order to explore the morphologic features of malignant tumors, especially angiogenesis phenomena. Therefore a new ultrasound, peculiar technology was developed in order to detect intravascular contrast agents.

The objective

The main objective of this study is to evaluate the role of ultrasound contrast enhancement kinetics (using microbubble contrast agent in pulse inversion harmonic technology) in the diagnosis of adnexal masses.

Material and methods

The study was prospective. From May 2008 to October 1st 2009 (18 months) seventy-three patients were enrolled. Mean age: 53 years, range: 18 – 81 years.

All patients were referred because of uncertain adnexal masses discovered during a routine pelvic transabdominal sonography. This initial sonographic examination (following a gynecological exam or a suspicion of acute surgical abdomen) showed morphological anomalies like cystic or mixed ovarian masses with thickened walls, intracystic vegetation, etc. Fifty-three patients who presented anomalies of the CA 125 tumor marker were also included in this study. In all cases a final histology diagnosis was established.

All patients underwent the ultrasound exams using a TOSHIBA Aplio XG machine. An initial pelvic transabdominal sonography (mode B, color Doppler) was performed (2 – 6 MHz multi-frequency convex transducer) followed by an endovaginal ultrasound (5 – 8 MHz multi-frequency transducer). This “standard” ultrasound exploration was followed by a dynamic, contrast enhanced transvaginal ultrasonography using a Bracco’s contrast agents (SonoVue) [15]. All patients gave their informed consent. 2.4 ml SonoVue intravenous bolus injection was administered. 10 ml of 0.9% sodium chloride solution was given to flush the vessel in order to obtain an efficient enhancement.

The acquired 3 minutes cine-loops after bolus injection were stored. Every “video sequence” was centered and

Fig 1. a, b, c, d. Mixed ovarian lesion intense vascularization around peripheral areas and central areas (a, b) the contrast-enhancement (c); intensity-time wash-out curve (d) Ovarian adenocarcinoma.
fixed by a region of interest (ROI). The images acquisition was done using a special software, (called: Raw-Date), developed by TOSHIBA. All video sequences were stored on the internal memory to allow for further processing.

Stored as DICOM images, contrast enhancement kinetics, were analyzed with the CHI-Q software.

The parameters obtained were: the intensity value (maximum contrast volume enhanced by the lesion), the time to peak (the time from injection to the peak intensity), the half washout time (the time between the peak enhancement and the time when half of the enhancement had disappeared) and the area under the enhancement curve (calculated from the arrival of the contrast agent to the end of the washout period).

All data were synthesized and analyzed in an Excel base and underwent statistical analysis with the aid of the SPPS statistical program.

**Results**

Seventy-three patients with a total of 88 adnexal masses were examined. We found bilateral lesions in 15 patients (17.04%), (6 malignant lesions-6.81% and 9 benign masses-10.23%). The histopathological exam revealed tumors of malignant origin in 23 patients (31.05%).

Three metastatic ovarian lesions were found, two of them were bilateral metastasis from gastric cancer (solid bilateral Krukenberg tumor) and another one from a breast cancer (a small size lesion in right ovary).

About histology: 12 cases of epithelial ovarian cancers were found: 8 serum cystadenocarcinomas (3 of them with bilateral involvement), 4 mucinous cystadenocarcinomas (one case with bilateral involvement); one case of non-differentiated tumor, 1 ovarian sarcoma, 1 Sertoli-Leydig tumor, 3 borderline tumors, 1 malpighian origin ovarian tumor and 1 adult granulosa tumor. Only one patient with mucinous adenocarcinoma had associated a breast cancer (fig 1, fig 2).

In the 50 patients with benign lesions, 9 cases presented bilateral involvement (3 functional cysts, 3 endometriotic cysts, 3 organic cysts) and 41 cases unilateral involvement (functional, organic, dermoid cysts, serous and mucinous cystadenoma, ovarian fibroma, hydrosalpinx and endometriotic cysts) (fig 3, fig 4, fig 5).

The "standard" ultrasonographic exam showed morphological anomalies, such as cysts in only in 19 cases. In 54 cases we found mixed ovarian masses with thickened walls and intracystic vegetation. Only 19 cases had very suspicious ultrasound aspects (morphological and Doppler findings, i.e. thickened walls ≥ 3mm, size ≥ 5 cm, intracystic papillary, resistivity index – IR ≤ 0.4).

The dynamic contrast transvaginal ultrasonography did not reveal contrast enhancement in only 9 out of all explored cases (12,32%), while 64 of the patients presented enhancement after contrast media administration.

The following parameters were monitored: the intensity value, the time to peak, the half washout time and the area under the enhancement curve.

For malignant tumors the intensity value has an average value of 34.09 dB with a standard deviation (SD) of ±11.89, corresponding to a time to peak of 19.17 s and
a standard deviation of ±4.1. The average values of the half washout time were estimated at 41s with a standard deviation of 8.3. The area under the enhancement curve was estimated at an average of 4.38cm² ± 2.5 (tab I).

For benign ovarian tumors, the intensity value was approximated at 4.82 dB with a standard deviation of ± 3.9 and the time to peak was evaluated at 15s with a SD of ± 9.3. The half washout time for benign tumors was estimated around 23.26s with a standard deviation of ±1.1 (tab II).

Comparing the two types of ovarian tumors (malignant versus benign), we observed a major difference between the follow-up parameters. The average value and the maximum and minimum values of the intensity value are much higher in malignant tumors (34.09 dB ± 11.89 for malignant lesions versus 4.82 ± 3.9 for benign lesions) (fig 6).

There is also a significant difference for the half washout time (in malignant tumors: 41±8.6, in benign lesions: 23.26±18) and the area under the enhancement curve in the two types of lesions (in malignant tumors: 4.38±2.5, in benign lesions: 1.89±0.7). (fig 7, fig 8).

The statistical analyses indicated that the time to peak does not represent a significant parameter (p = 0.08) (fig 9).

Discussions

Contribution of “standard” pelvic sonography in the differential diagnosis of ovarian tumor pathology proved...
to be limited while requiring implementation of new methods of ultrasound imaging, based on Doppler, harmonics and 3D ultrasound techniques. Unfortunately, the implementation of these techniques did not lead to a significant improvement in the sensitivity and specificity of malignant ovarian tumors diagnosis by ultrasound exams, the quality of these explorations being highly dependent on the sonographer’s experience and skills [3-8].

If initially the Doppler technique was the only ultrasound method able to characterize ovarian vascularization, the implementation of contrast enhanced ultrasound techniques represents a significant improvement in the detection and assessment of angiogenesis [9]. It was postulated that the flow in the microvascular circulation would have unique enhancement parameters as depicted with contrast enhanced transvaginal sonography. The microvasculature associated with malignancies (tumor angiogenesis/ neovascularization) is characterized by irregular branching vessels, derived from pre-existing normal venules that contain numerous arteriolar-venous malformations without an intact basement membrane, allowing extravasations of erythrocytes into normal parenchyma [10].

The contrast enhanced ultrasound techniques is based on harmonic signals produced by microbubbles through the macro circulation and microcirculation. The broadband ultrasonic signals from surrounding tissue are filtered out completely differentiated, representing key points in the evaluation of the microvascular flow by means of contrast ultrasound [11,12,13,14]. A large variety of impulsion sequences were developed in order to detect contrast, harmonic imaging (HI) and pulse inversion harmonic imaging (PIHI). Whatever the ultrasound devices are used, the sonographer must adjust the equipment in order to optimize the microbubbles detection. This requires a low mechanical index with minimal destructive effect on the sonographic agents [9].

The transvaginal exams led to an improvement in the ability of the operator to distinguish benign from malignant lesions. The new software allows the qualitative and quantitative assessment of tumor enhancement by calculating various parameters resulting from washout curves.

Table II. Results of statistical analysis for benign tumors

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
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<td>41</td>
<td>15,00</td>
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<tr>
<td>Eco contrast T_{washout rel}</td>
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<td>90</td>
<td>23,26</td>
<td>11,234</td>
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<tr>
<td>Eco contrast S_{curve}</td>
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<td>0</td>
<td>7</td>
<td>1,89</td>
<td>1,12</td>
</tr>
<tr>
<td>Eco contrast I_{max} (x10^{-5}dB)</td>
<td>49</td>
<td>0</td>
<td>45</td>
<td>4,82</td>
<td>3,981</td>
</tr>
</tbody>
</table>

Fig 4. a, b, c. Ovarian cyst mass with papillary projection (a), contrast-enhancement in peripheral, the papillary not enhanced (b), intensity-time wash-out curve (c) Endometrioma.
In order to obtain an optimal exam, a good cooperation between the examiner physician and the radiology technician is needed.

The statistical analysis performed in our study, demonstrates differences in perfusion between malignant and benign tumors.

Several previous studies have addressed the use of contrast-enhanced sonography for benign and malignant tumors by showing the greater degree of enhancement of malignant tumor on Doppler sonography [6,15]. Only two studies have been published that used the kinetic parameters of the contrast agent to compare benign with malignant tumors in the power Doppler mode [17,18]. The first study published in literature debated the use of contrast media when using the Doppler technique in order to differentiate malignant ovarian tumors from benign ones and to increase the Doppler signal after injection [19]. This argument was not sufficient because there are benign tumors that enhance after contrast injection and consequently one can notice an increase of the signal. This problem was improved by evaluating the kinetics of the contrast agents. In this way, Orden et al. published in 2003 the first study, which analyzed the time intensity curve in the ovarian pathology for the differentiation of malignant and benign tumors and also described a numeric analysis of the Power Doppler intensity in ovarian tumors using a new informatics program [17]. In their study, the duration of the contrast effect (DCE) and the area under the enhancement curve are the best factors for discriminating benign and malignant tumors. Thus, the average values for DCE have been of 190.4 seconds for malignant tumors and 103.6 for benign tumors (p < 0.001). Another study, elaborated later by Marret et al, published in 2004 [20], revealed the significant role of the washout time analysis and of the area under the enhancement curve for the detection of malignant tumors, compared to the application of Doppler ultrasound. Their results suggest that the kinetic parameters resulted from the Power Doppler ultrasound with Levovist type contrast provides valid criteria for differentiating benign pelvic lesions from malignant epithelial ovarian tumors and can improve the pre-surgery diagnosis of ovarian cancer.

Fig 5. a, b, c, d. Transonic ovarian lesion with discrete vascularization around the peripheral area (a, b), contrast-enhancement around the peripheral area (c) in PIH mode; intensity-time wash-out curve (d). Ovarian cyst.
In this study, all patients were examined with two ultrasound modalities: standard exams (pelvic transabdominal sonography and transvaginal sonography) and dynamic contrast enhanced transvaginal sonography. In “standard” exams, differentiation of a solid benign lesion from a malignant tumor still remains difficult, even if the prevalence of the solid ovarian tumor is small. The “standard” ultrasound suggested malignant tumors in only 19 cases out of 73, while the contrast-enhanced ultrasound detected all 23 suspected cases. This is why using contrast substance ultrasound techniques seems a more adapted method for the characterization of ovarian tumor vascularization and detection of ovarian cancers in early stages.

Within our preliminary study, the contrast ultrasound was performed with the aid of modern ultrasonographic techniques, using harmonic ultrasound in the pulse inversion mode (PIH). In all cases we disposed of the histological results. A significant difference was noticed between the intensity value of the contrast medium uptake of benign ovarian tumors, which reached an average of 4.82 dB, and that of malignant tumors that measured 34.09 dB. Another significant parameter for the malignant versus benign differential diagnosis is the half washout time, with an average of 23 seconds for benign tumors and 41 seconds for malignant tumors. The area under the enhancement curve represents another important parameter (estimated at 4.38 for malignant tumors and 1.89 for benign tumors).
The time to peak does not show a great difference for the two types of ovarian lesions as it probably reflects the intrinsic circulation depending on cardiac contractions, blood pressure and the global vascular tonus.

The statistical analysis performed in this study led us to believe that the three parameters (intensity value, the half wash-out time, the area under the enhancement curve) are important elements in the study of contrast kinetics in ovarian pathology. It could represent a method of making differential diagnosis between benign and malignant ovarian tumors. The linear regression of these parameters compared to the histopathology result demonstrated statistical significance (p < 0.01).

Conclusions

The use of contrast agents allows the detection of small tumor angiogenesis foci undetectable in Doppler ultrasound and Power Doppler, representing a very promising method in the diagnosis of early ovarian malignant lesions.

Bibliography