# IV.5

# Recent Advances in Contrast-Enhanced Ultrasound in Woman Pelvis Lesions

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## Introduction

Ultrasound (US) is the primary imaging modality for the detection and characterization of female pelvis lesions during screening, or for any pelvic symptom. It has been proven that the association of suprapelvic and transvaginal approaches gives a complete view of the female pelvis and provides some specific indicators for a high level confidence diagnosis. As it was demonstrated that Doppler US plays a role in such diagnoses, some research has been conducted to allow better detection of vessels within or surrounding a lesion. The sensitivity of Doppler methods remains limited because of either patient or technical limitations, allowing us to detect vessels larger than 80 μm; not enough for a correct assessment of neoangiogenesis. This has led physicians to propose the use of contrast agents for US in order to enhance contrast between the lesion and parenchyma and thus to improve the quality of information provided by US methods.

The recent introduction of US contrast agents has totally changed the depiction of specific vascular signs for a definite diagnosis by allowing a marked increase in signal from the vessels, especially with modern non-linear imaging techniques. Contrast-enhanced ultrasound (CEUS) allows an adequate depiction of vessels in relation to the pure intravascular characteristics of those agents, reinforced by the real-time assessment of the enhancement after contrast injection. The recent availability of this imaging technique for transvaginal applications has allowed physicians to use CEUS in gynecology, such as in ovarian or uterine lesions, for a better assessment of vascular patterns that could play a role in diagnosis management.

## Ovarian Lesions

Ovarian carcinoma represents the second most frequent gynecological cancer observed in women, with a poor long-term outcome largely related to late diagnosis and the frequency, around 15%, of malignant lesions. This is due to the absence of any alarm signal for initiating an US exam to detect any ovarian abnormalities. It has long been proven that US is the most powerful technique for detecting ovarian cancer, with a sensitivity of 80-85%. One of the most common suggestions for an early diagnosis of ovarian cancer is to detect the neovessels that allow the tumor to grow. Vessel changes within the ovary may be visualized before tumor detection itself. Color Doppler has been assessed as one of the US techniques that can be used to describe specific characteristics of ovarian vascularization [1-6]. Power Doppler is useful to map ovarian vessels, including those associated with malignancy (in septa, papillarities and tissular parts of the lesion) while pulsed Doppler is used to measure blood flow velocity [7-9]. Doppler imaging and the subjective evaluation of the gray-scale image improves our ability to make a correct diagnosis prior to surgery [10, 11], which improves patient outcome if a malignancy is present [12-15]. The need for a more powerful US technique is driven by the specific role of US in pelvic lesions and the need for the treatment planning, including chemotherapy and particularly, surgery. Recently, quantification of the vascularization of a tumor using power Doppler has been performed by analysis of images using special software [16-18], allowing us to calculate the number of colored pixels on a digitized image. Until now, subjective evaluation of the gray-scale and Doppler US in experienced hands has been considered the most powerful method for dis-

criminating between benign and malignant adnexal masses [11]. We have demonstrated that power Doppler index (colored pixel number inside the tumor/total pixel of the tumor) is a simple and accurate parameter to discriminate an ovarian malignancy from a benign ovarian mass [19].

## Prior Studies

The first-generation US contrast agent used was mainly Levovist (Schering, Germany) [20, 21]. Only a few small studies [22-24] have been published using this contrast agent for gynecological purposes. They validated the feasibility of the technique in ovaries. Orden in 2003 [25] and our team in 2004 [26] first described the kinetics of the agent within the ovary and ovarian tumors in order to define the parameters that can be useful for malignancy discrimination. Our prospective pilot study was conducted, with the following aims: (1) to evaluate the contribution of contrast-enhanced power Doppler and derive objective parameters for the diagnosis of malignancy in ovarian tumors; and (2) to compare these parameters to other variables that have been evaluated to differentiate malignant adnexal masses from benign ones.

The time intensity curves of Levovist can then be derived over 5 minutes for a region of interest (ROI) corresponding to solid tissue from each mass (Fig. 1). The software calculates the total power Doppler intensity, which is determined by the number and intensity of colored pixels inside the ROI for each image. The enhancement quickly achieves a maximum intensity and has a biphasic wash-out phase, with a decrease in intensity down to the baseline level at around 3 minutes. From the time-intensity curve, baseline intensity and peak intensity were noted and the percentage ratio of intensity enhancement (expressed as a fraction of enhancement) was calculated using the following formula: 100*(peak intensity-baseline intensity)/baseline intensity. The time-intensity curves were analyzed for the following indices: uptake time (in seconds), wash-out time, half-intensity wash-out time, and the area under the curve (AUC). Orden [25] and ourselves [26] describe almost the same differences between benign and malignant enhancement curves. After a quick rise to maximum enhancement, the wash-out phase differed between cancers and benign ovarian tumors. The duration of contrast-enhancement or wash-out period and the AUC appeared to have a very important power of discrimination. In our study, AUC and wash-out time were the two discriminate parameters with the highest sensitivity (96%). Only one cancer was missed using these two parameters with the threshold (derived from the received operating characteristic (ROC) curve) fixed at 88 seconds-1 and 175 seconds, respectively. Using the traditional criteria of resistance index (RI) and CA125, the sensitivity was lower, at 86% with four missed cancers (three of the missed cancers were borderline tumors and one was Stage I), but no false positives (specificity = 100%). Orden [25] found that the mean duration of contrast-enhancement was 190 seconds in malignant tumors and 104 seconds in benign tumors, whereas we found 221 seconds versus 114 seconds. These results suggest that kinetic parame-

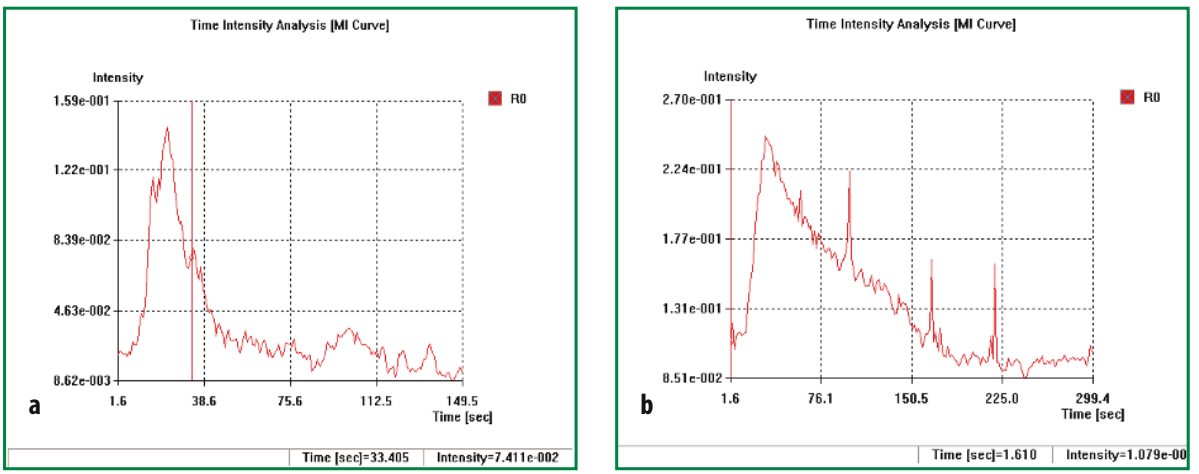


**Fig. 1a, b. a** Results of Levovist contrast-enhancement in ovarian tumors. Example of a benign tumor showing a short wash-out time. **b** Example of a malignant tumor showing a long wash-out time (peaks are related to movements artifacts)

ters derived from power Doppler enhanced using Levovist provide new valid criteria that appear accurate for the discrimination of benign pelvic masses from malignant primary epithelial ovarian tumors and could improve the pre-operative diagnosis of ovarian cancer.

## Second-Generation Agents: SonoVue, Definity

Second generation US contrast agents (SonoVue, Bracco SpA, Italy; Definity, Bristol Myers Squibb, USA) have previously demonstrated their value in the investigation of neovessels in organs other than ovaries with a high degree of safety [27]. In our case, the dose of SonoVue needs to be increased to 4.8 ml, as we use higher US frequencies for the transvaginal approach.

To date no study has been published in human ovaries using SonoVue, except a recent paper from Testa et al. [28], who described some vascular patterns in the female pelvis. We have recently conducted a study to determine whether second-generation contrast agents could characterize changes in ovarian vascularization during the ewe estrus cycle and to select parameters that remained stable with cyclic changes [29]. Following SonoVue injection, wash-out time and AUC were the most stable parameters derived from the time-intensity curve between ovaries and between the follicular and luteal phases. Uptake time and total time of enhancement were also constant. Enhancement ratio and wash-in period changed with corpus luteum formation. Our results reflect menstrual cycle changes and vascular physiology of the normal ovary. One of the limitations of this study is the heterogeneity of the ovarian vascular characteristics. The ovary of the ewe is smaller than that of a woman and the corpus luteum is proportionately larger, which could influence the results of this study; however, the same heterogeneity should be present in women, albeit in a smaller portion of the ovary. Further studies in women should be performed to characterize menstrual changes in enhancement in order to define stable and unstable parameters of enhancement.

We are currently conducting several ovarian studies to validate SonoVue in Europe, and Definity in the United States, for discrimination of human ovarian tumors. In our preliminary experience using both products, we were able to describe the microbubble distribution inside the tumor vessels with high accuracy, resulting in an improvement in the diagnostic confidence for the discrimination of benign from malignant ovarian tumors. For example, the absence of enhancement inside solid tissue or intracystic papillarities can confirm a diagnosis of clots or solid component included within a dermoid cyst. In the first cases, detection of enhancement within septa and/or papillarities is always the sign of malignancy confirmed by histology (Figs. 2, 3). Compared to Levovist, the results appear to be much more precise and accurate without artifacts such as blooming or movement. However, time-intensity curves appear quite similar, with a few differences in the wash-out period, such as a longer return to baseline and a less marked biphasic phase (distribution and elimination phase).

A single injection of SonoVue gives us access to a very precise map of the ovarian and tumor microcirculation in both the ewe and the woman. One of the challenges in detecting small vascular changes is the selection of the ROI. In all published studies, the ROI encompassed the entire ovary and the enhancement curve was based on pixel mapping extracted from this ROI.

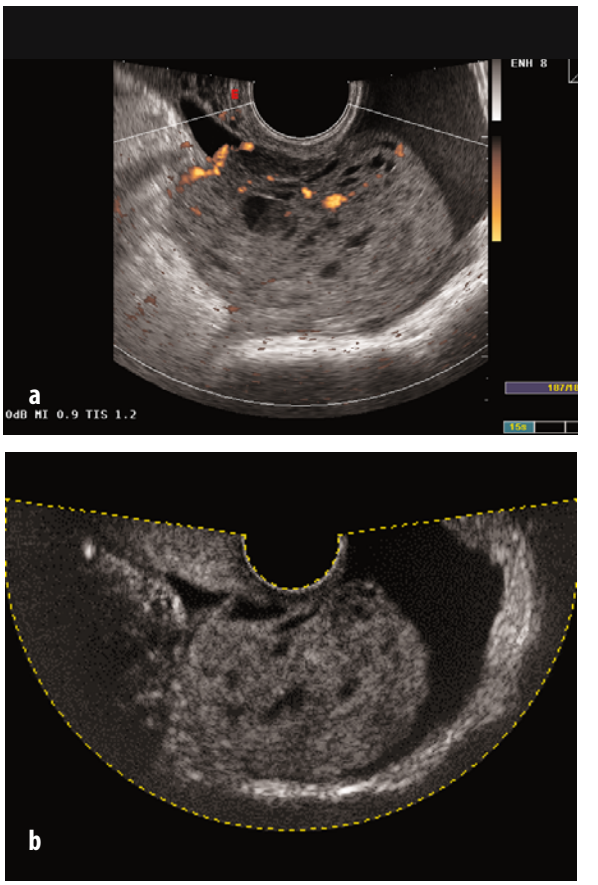


**Fig. 2a, b.** Arterial enhancement within an ovarian cancer (**a** power Doppler imaging) after SonoVue injection (Esaote system, transvaginal examination), demonstrating a heterogeneous global and intense enhancement from the tissular part (**b**), confirmed by surgery

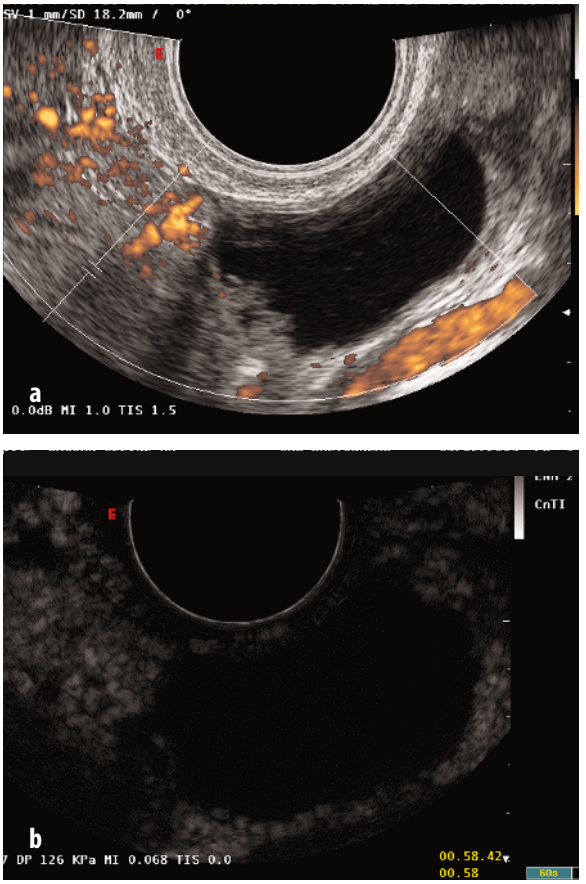


**Fig. 3a, b.** Absence of arterial enhancement within a wall abnormality in an ovarian cystic lesion (**a**) after SonoVue injection (**b** Esaote system, transvaginal examination) in favor of the diagnosis of a hemorrhagic cyst (confirmed by surgery)

Reproducibility of this procedure is very high and will be higher using CEUS, which allows the ovarian contours to be drawn more accurately. However, this method ignores heterogeneity of tissue components and enhancement. Therefore, selective sampling of regions within the ovary may be required to improve discrimination of lesions. Although visual appreciation of heterogeneity is improved by pixel mapping displays, selection of ROI is operator-dependent. Moreover, it is known that the baseline signal for any given tissue differs with the US machine, the probe used, the movements of the probe and the settings of the US machine, even if identical sequences are used. In addition, the calculation of the ratio of enhancement will differ with different conditions [30]. Consequently, the ratio of enhancement is probably not the best parameter to use, although gray-scale imaging reduces artifacts and improves the reproducibility compared to color Doppler. Wash-out parameters may be more adapted to discriminate regions inside the ovary with high enhancement. Improvement in microvessel detection and increased visibility of nodular areas of enhancement inside the ovary with different enhancement curves could be shown, as has been demonstrated in prostate cancer [31]. Moreover, one case of ovarian cancer with normal-sized ovaries was diagnosed only by CEUS [32], suggesting that contrast agents will improve the ability of US to detect small cancers that are not associated with ovarian enlargement or areas within a mass that have a focus of malignancy.

From an angiogenesis perspective, contrast agents markedly increase the number of visible vessels available for dynamic analysis, and allow us to identify the aberrant vascularity that pathologists visualize in early stage cancers. Any imaging assay of tumor microvascular characteristics must be validated against accepted surrogates of angiogenesis, including histological microvessel density (MVD), vascular endothelial growth factor (VEGF), and VEGF receptors. Correlation of these factors with Doppler US has been previously carried out in other organs, but not in the ovary, and not using CEUS [33]. In addition, CEUS should also be validated against other imaging techniques that measure vascular function, such as magnetic resonance imaging (MRI) [34].

In conclusion, results of all these preliminary studies are in favor of the use of CEUS being applied prospectively in non-invasive studies of ovarian angiogenic function, mainly for the diagnosis of malignancy, but also including response to drug treatment, fertility research, ovarian hyperstimulation syndrome, and early assessment of response to antiangiogenic chemotherapy.

## Uterine Lesions

Study of uterine vascularity using power Doppler is nowadays one of the most important tools to describe and discriminate uterine tumors. Macroscopic vascularization of myomas, polyps, endometrial cancer, adenomyosis, or cervical cancer is well known, but some limitations are encountered in therapeutic monitoring of these tumors. Microbubble enhancement affords the direct depiction of tumor neoangiogenesis and may help us to establish a more precise vascular map of the tumor and normal surrounding myometrium. By quantifying time-intensity curves after injection of microbubbles, tumors can be shown to exhibit significantly different enhancement kinetics from normal tissue.

## A Myoma Evaluation

Leiomyomas are the most common benign tumors of the uterus in women between 20 and 50 years old. A successful and safe alternative treatment to hysterectomy is uterine artery embolization (UAE) [35-38]. Symptoms are improved or resolved in 90% of women at one year [36, 39]. However, rare potential complications, such as uterine necrosis and premature menopause, have been reported [40, 41]. The polyvinyl alcohol particles, the Embospheres, or other embolic agents injected into each uterine artery tend to reach leiomyomas selectively, but may reduce blood supply to the uterus and induce ischemic uterine necrosis [42]. Moreover, because uterine and ovarian vessels communicate directly via the tubal arteries, once stasis has begun, they may also reach the ovaries, probably by a phenomenon of reflux, reducing ovarian perfusion and even causing infarction [40, 41]. The reported incidence of amenorrhea after UAE is 1-3%. However, these rare cases limited UAE to women with accomplished childbearing. Such complications might be prevented, or at least rapidly detected by comparison of pre- and post-operative assessment of leiomyoma vasculature occlusions.

We successfully used contrast-enhanced sonography with SonoVue during UAE procedures in a patient with multiple large leiomyomas to demonstrate that injected micro-particles were targeted uniquely to leiomyomas [43]. Contrast-enhanced sonography was performed just before UAE, immediately after left UAE, and after bilateral UAE. Pre-UAE images showed a completely perfused uterus with hyperenhanced areas corresponding to the leiomyomas. The next two acquisitions showed hypoperfused areas corresponding to the leiomyomas. The last acquisition, taken after complete bilateral uterine artery occlusion, showed persistent perfusion into normal myometrium but none in the leiomyomas.

Following this first publication, we tested the feasibility of contrast-enhanced US for the diagnosis of fibroids. It is remarkable that this indication could be reached by the use of transvaginal approach for tiny fibroids (with injection of 4.8 ml of SonoVue) but also by the use of the suprapubic approach for large fibroids (with injection of 2.4 ml of SonoVue only). Injection of SonoVue could provide a very precise description of the uterine vascularization more esaily than with angiography and cheaper than MRI. After contrast injection, macro- and microcirculation of the myoma first appeared, followed by the normal myometrial enhancement and finally within the endometrium (Fig. 4). Enhancement patterns vary markedly among the patients, from an absence of enhancement for the whole tumor, to a complete and rapid enhancement after injection. Wash-out was typically complete after 3 minutes, giving a black hole corresponding to the whole lesion. This wash-out helps us to iden-

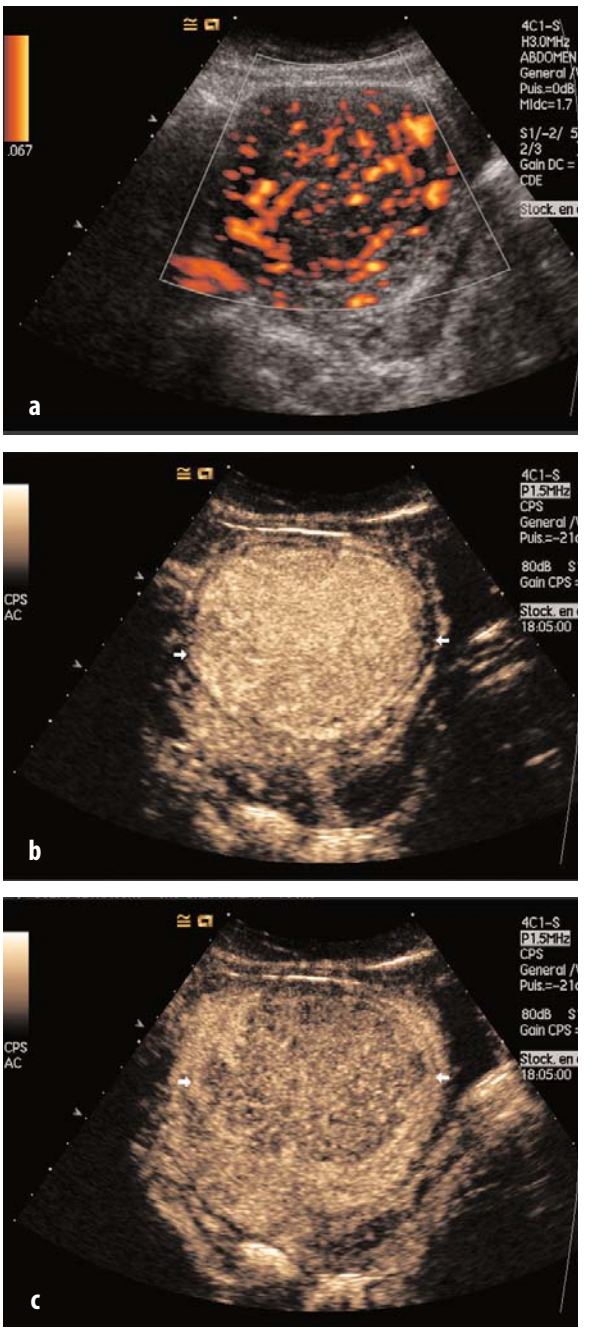


**Fig. 4a-c.** Arterial enhancement within a uterine fibroid (**a**) after SonoVue injection (Sequoia system, suprapubic examination) demonstrating a quite global and intense enhancement, higher than from normal myometrium (**b**), followed by a marked wash-out (**c**)

tify some tiny fibroids that are not visible on conventional sonography, for a perfect match with MRI detection. Secondly, it is remarkable that most of the endometrium clearly demonstrates an early wash-out after contrast injection, in some cases exceeding the size of endometrium. Third, it clearly shows that microbubbles first arrive in the myoma before the normal myometrium, except in some large myomas with marked necrobiosis. By showing SonoVue distribution within the uterus, we are able to better select fibroids with possible benefit of embolization and we were able to corroborate the approach used by the particles injected for embolization.

Using CEUS, we could quickly assess the efficacy of UAE as well as evaluate local consequences on normal myometrium and ovaries, whereas both uterine arteries were totally occluded. This US method could play a major role in the assessment of early technical failure rate and in the identification of vascular risk factors for clinical failure and late recurrences. Contrast-enhanced US can also be proposed to detect the persistence of vessels within a treated myoma with higher confidence, as it was reported that this precedes the late recurrence confirmed by an increased size of the myomas (Fig. 5). This will be a more sensitive method than color Doppler US for an assessment of induced vascularity changes [44].

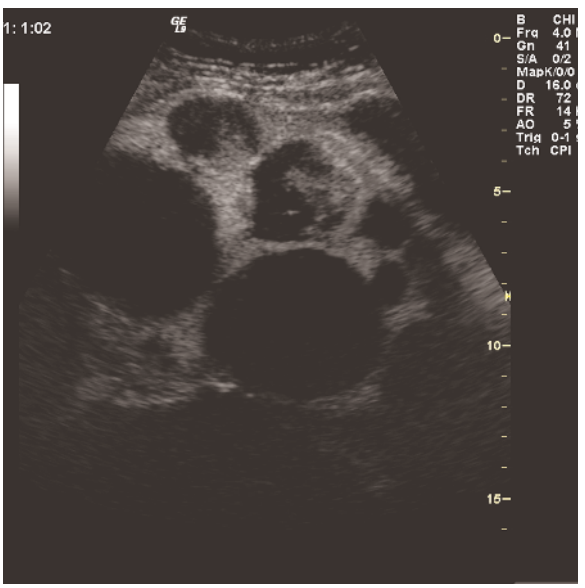


**Fig. 5.** Detection of a persistent enhancement (Logiq9, General Electric) within two fibroids (arrows) after uterine artery embolization, which corresponds to an incomplete embolization when the other fibroids were totally excluded. This was confirmed six months later by a size increase of these two fibroids, while the other fibroids decreased in size

In conclusion, we can state that contrast-enhanced sonography provides a means to assess tumor response to various therapeutic approaches. Thus, the potential for imaging uterine perfusion with microbubble-enhanced sonography is significant and warrants further investigation.

## Cancer of the Cervix

Cancer of the cervix is frequent and is accompanied by local extension or lymph node extension, which guides treatment planning, i.e., the choice between initial treatment by surgery or by radiochemotherapy. An intense enhancement is reported for these lesions before specific treatment, with an improvement in the definition of limits but with some limitations in the positive diagnosis (Fig. 6) as reported by Testa et al. [28]. Local assessment of angiogenesis will be of value to follow local changes under chemotherapy or radiotherapy and to better schedule surgery. This method could be used in place of MRI to assess treatment efficacy and in conjunction with positron emission tomography (PET) for treatment planning.

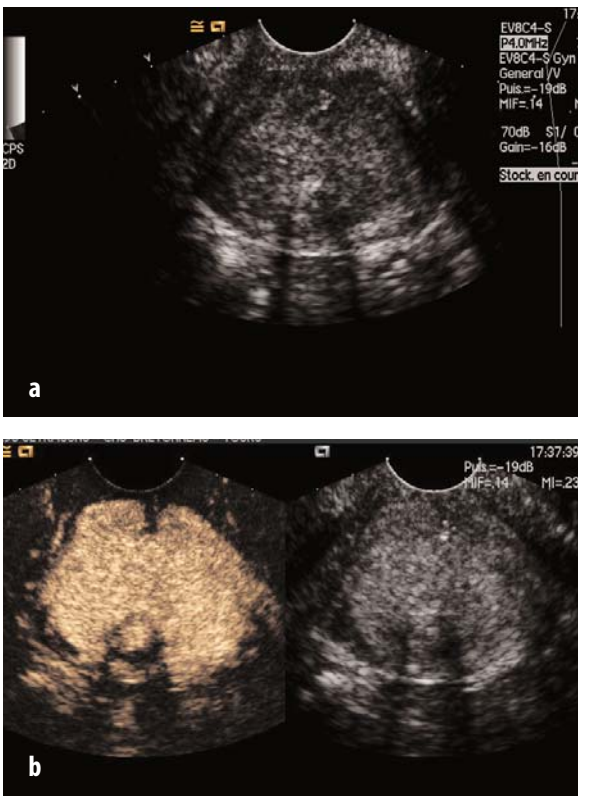


**Fig. 6a, b.** Typical strong and homogeneous enhancement from a cervical cancer (**a**) after SonoVue injection (**b**) (Sequoia system, transvaginal examination)

## Key Points

- Contrast-enhanced ultrasound is useful for the discrimination of malignancy in ovarian disease.
- In cases of myoma, contrast-enhancement is useful for uterine artery embolization monitoring by selecting patients with possible early recurrence.
- In cervical cancer, ultrasound enhancement using contrast agents is useful for monitoring radiochemotherapy, to select patients that present a good or a poor response to treatment.

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