ROLE OF CONTRAST-ENHANCED ULTRASOUND (CEUS) IN THE DIAGNOSIS OF ENDOMETRIAL PATHOLOGY

CIPRIAN MIHAITA POP[1], DAN MIHU[1], RADU BADEA[2]

[1]2nd Department of Obstetrics and Gynecology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Ultrasound Laboratory, Department of Imaging and Radiology, Octavian Fodor Regional Institute of Gastroenterology and Hepatology and Department of Medical Imaging, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Ultrasound is the reference imaging procedure used for the exploration of endometrial pathology. As medical procedures improve and the requirements of modern medicine become more demanding, gray-scale ultrasound is insufficient in establishing gynecological diagnosis. Thus, more complex examination techniques are required: Doppler ultrasound, contrast-enhanced ultrasound (CEUS), 3D ultrasound, etc. Contrast-enhanced ultrasound is a special examination technique that gains more and more ground. This allows a detailed real-time evaluation of microcirculation in a certain territory, which is impossible to perform by Doppler ultrasound. The aim of this review is to synthesize current knowledge regarding CEUS applications in endometrial pathology, to detail the technical aspects of endometrial CEUS and the physical properties of the equipment and contrast agents used, as well as to identify the limitations of the method.

Keywords: ultrasound, endometrium, contrast-enhanced ultrasound (CEUS), contrast agents, microcirculation

Introduction

Conventional ultrasound is the basic imaging procedure for endometrial examination, having definite advantages: obtaining real-time images, repeatability, low costs, etc. However, there are situations in which complex diagnosis requires the use of more sophisticated examination methods: Doppler ultrasound, 3D ultrasound, sonohysterography, etc. Over the past decade, contrast-enhanced ultrasound (CEUS) has gained increasing credibility [1,2]. The technique allows the real-time evaluation and quantification of microcirculation in a certain territory, having practical applications in various areas. It is relatively easy to use in clinical practice and, through the information provided, it improves the detection and characterization of various diseases, reducing the need for additional imaging examinations such as computed tomography (CT) or magnetic resonance imaging (MRI) [3]. Literature data on CEUS applications in endometrial pathology are relatively few. The EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guidelines on the non-hepatic clinical applications of CEUS evidence the need for prospective studies to confirm the effectiveness of CEUS in the diagnosis of uterine pathology [4].

The aim of this review is to synthesize current knowledge regarding CEUS applications in endometrial pathology, to detail the technical aspects of endometrial CEUS and the physical properties of the equipment and contrast agents used, as well as to identify the limitations of the method.

Contrast agents

Contrast agents (CA) used in ultrasound are lyophilized substances made up of gas microspheres enclosed in a rigid or elastic protein, lipid or polymeric membrane [5]. Solutions are prepared extemporaneously

and two types of contrast agents are found in their composition:

- first-generation contrast agents (Levovist, Schering, Germany): these have a low circulatory stability and are not useful for the evaluation of microcirculation;

- second-generation contrast agents (Sonovue, Braca, Italy – sulfur hexafluoride; Optisone, G.E. Healthcare USA – perflutren gas, etc.). These have a circulation lifespan of 5 to 7 minutes, which provides significant comfort for the examiner [6]. The diameter of these gas microspheres varies between 1-10 microns, which is practically similar to that of erythrocytes, allowing passage through pulmonary and peripheral capillaries. Microbubbles do not pass into the extravascular space, thus being an important serum marker in the evaluation of microcirculation both for normal and pathological tissues [7]. CEUS can be used for the evaluation of capillaries less than 40 microns in diameter, unlike power Doppler ultrasound, which visualizes capillaries with a minimum diameter of 100 microns [8].

Due to their gas composition and elastic membrane, these second-generation CA microspheres can change their size; when an ultrasound beam is focused on them, they contract in a first stage, after which they undergo expansion, doubling their size. Due to these oscillations, they send non-linear energy flows (harmonic echoes) to the transducer, a process that underlies the functioning principle of the method [9]. After repeated vascular passage, in about 4-5 minutes the microspheres dissolve, the contained gas is eliminated through the lungs, and the containing membrane is metabolized in the liver. Because of the non-involvement of the renal system in the excretion and metabolization of contrast agents, the technique can also be safely used in patients with renal failure [10].

Physical principles. Equipment. Examination technique

Performing this type of ultrasound examination requires equipment capable of detecting contrast agents, modulating at the same time the acoustic power (mechanical index – MI) of the ultrasound beam. The physical principle on which CEUS examination is based is the phase reversal principle: two ultrasound pulses, dephased by 180°, are consecutively emitted. The dimensional oscillations of the gas microspheres in the composition of contrast agents will generate non-linear echoes towards the transducer, and the machine software will overlap the two harmonic waves. While linear echoes from the surrounding tissues are mutually cancelled, harmonic echoes from contrast agents will generate a strong signal [11]. A 20-25 dB increase in the acoustic impedance of the blood column results, which allows the direct visualization of the circulatory torrent regardless of direction or speed.

Ultrasound equipment should be able to represent on the same screen both the gray-scale image and the dual-mode image. The gray-scale image facilitates the guidance of the examiner on the region of interest [12]. CEUS consists of the bolus injection of the contrast agent into the cubital vein, in a dose of 1.6-2.4 mL, depending on the equipment used and the weight of the patient. Dual-mode imaging is used, which allows the examiner to monitor the contrast agent over a period of 4-5 minutes in the region of interest (ROI).

The penetration of the contrast agent in the region of interest is followed by an increase of its echogenicity. Most of the organs examined using the CEUS technique, except for the liver, show two phases: arterial and venous [13]. The arterial phase usually starts 10-15 seconds after the injection of the contrast agent and lasts up to 40 seconds, being followed by the venous phase. Echogenicity during examination progressively increases and subsequently decreases (this phase is termed "wash-out"). In addition to this aspect, the distribution of the contrast agent in the tissue during examination is also important [14]. Image analysis is visual, qualitative, being performed both during exploration and subsequently, by the reevaluation of the AVI loops. Moreover, there is the possibility of studying time-intensity contrast curves, which represent in a quantitative and reproducible graphical manner the dynamics of the transition of the contrast agent through the region of interest in relation to a control region.

It is important to mention that for an effective ultrasound evaluation of the female genital system using both gray-scale ultrasound and the CEUS technique, the machine must be equipped with an endovaginal transducer (6-8 MHz).

Normal appearance. Endometrial evaluation always starts with gray-scale ultrasound, as it is known that normal endometrial appearance depends on the phases of the menstrual cycle. Thus, in the menstrual phase (days 1-5), the endometrium is thin (<4 mm) and slightly echogenic. During the proliferative (follicular) phase, corresponding to days 5-14, the endometrium progressively increases in size, reaching 10 mm around the 14th day of the menstrual cycle. In the secretory phase (days 14-28), under the influence of increased progesterone secretion, the amount of glycogen in the endometrial glands increases and spiral arteries become more tortuous, all these changes resulting in an increase of endometrial thickness (12-14 mm) and echogenicity. Normal sizes vary between 4-14 mm during a menstrual cycle. In postmenopausal patients, the normal appearance of the endometrium is homogeneous, slightly hyperechogenic compared to that of the myometrium, not exceeding 6 mm. For a correct measurement of the endometrium, a midsagittal section should be used [15]. For CEUS examination, the equipment must be adjusted to the specific software: the dual-view mode is selected, the focus is positioned below the level of the region of interest (ROI), acoustic power is set at 0.10, the contrast agent is injected into the cubital vein in a single bolus dose of about 2.4 mL, the image is continuously monitored over approximately 3

minutes. The order of appearance of the contrast substance in the uterus is as follows: uterine artery – myometrium – endometrium, with a clear demarcation between the endometrium and the myometrium. Endometrial examination includes the two phases: the arterial phase, with a maximum duration of 40 seconds (during which an increase of endometrial echogenicity is found), and the venous phase, up to 4 minutes, during which echogenicity progressively decreases [16]. Given the lack of toxicity of the substance, administration can be performed whenever necessary.

Pathology

Endometrial polyps

Endometrial polyps represent a frequently diagnosed pathology both in symptomatic patients and in patients without clinical symptomatology. The etiopathogenetic potential of polyps is not completely understood. For some authors, endometrial polyps are focal endometrial hyperplasia lesions, and the risk of malignant transformation varies in the literature between 0.5% and 4.8% [17]. The presence of endometrial polyps can be suspected by conventional endovaginal ultrasound. These appear as intracavitary formations or focal alterations of endometrial architecture. There are multiple ultrasound patterns, these lesions can be hyper-, iso- or hypoechogenic compared to the surrounding endometrium. Because their histological structure includes a vascular axis, the Doppler technique is also indicated for its identification. CEUS evaluation evidences a more rapid filling in the arterial phase and a slower release of the contrast medium during the venous phase compared to normal endometrium [18]. Certainty diagnosis is made after hysteroscopic resection and histopathological examination.

Endometrial hyperplasia

Endometrial hyperplasia is the only recognized precursor of endometrial carcinoma and is represented by changes in the architecture of endometrial glands under the influence of estrogen hormones, at the limit between normal endometrium and invasive carcinoma [19]. Consequently, it is a strictly histologically diagnosed lesion. Endometrial hyperplasia is divided into two classes: simple hyperplasia and complex hyperplasia, both of which can appear with or without cellular atypias. The risk of progression towards endometrial carcinoma increases from 1% in simple hyperplasia without atypias to 29% in complex hyperplasia with cellular atypias [20].

Paraclinical evaluation in endometrial hyperplasia is only suggestive of diagnosis. On conventional ultrasound examination, a significant thickening (>14 mm) of the endometrium is found, which becomes at the same time hyperechogenic, inhomogeneous in complex hyperplasia, without signs of myometrial invasion. Doppler ultrasound also evidences an increase of endometrial vascularization [21]. Contrast-enhanced ultrasound in endometrial hyperplasia provides information on the pattern, order and quantity of blood perfusion of the lesion. It shows whether the lesion violates the uterine wall and the extent of violation.

Endometrial cancer

Endometrial cancer ranks first in terms of frequency among gynecological cancers in developed countries; 142,000 new cancer cases are diagnosed every year worldwide, and 42,000 patients die every year of this disease [22,23]. In Romania, endometrial cancer is the second most frequent gynecological cancer after uterine cervical cancer. Risk factors for endometrial cancer include obesity (through an increase of endogenous estrogen production), hormone replacement therapy used for a long time period, polycystic ovary syndrome, late menopause, early menarche, family history, tamoxifen treatment; comorbidities (type 2 diabetes mellitus, arterial hypertension, gallbladder stones) are also associated with endometrial neoplasms [24,25].

The etiopathogenesis of endometrial cancer remains unknown, but like in the case of other malignant tumors, angiogenesis is an important factor in its development. Unlike benign lesions (endometrial polyps), which have a well individualized vascular axis, malignant lesions have anarchic vascularization, with several nutritive branches, without the presence of precapillary sphincters, ensuring a high amount of blood inside the tumor [26,27].

For the preoperative evaluation of patients with malignant endometrial tumors, conventional endovaginal ultrasound, magnetic resonance imaging (MRI), endometrial biopsy, and more recently, contrast-enhanced ultrasound are used.

Conventional endovaginal ultrasound evidences a thickening (>15 mm) of the endometrium, most frequently in a postmenopausal patient, which becomes inhomogeneous, unclearly demarcated from the surrounding myometrium. Doppler ultrasound shows a lesion with an intense vascular signal, having a low resistivity on spectral investigation, as an expression of the presence of tumor neoangiogenesis [28,29].

CEUS examination has been introduced over the past years in the study of endometrial carcinoma, although it is not yet used on a wide scale. Liung et al., in a study on patients with endometrial tumors, found the following aspects: in the arterial phase, 65.8% of the patients had an inhomogeneous uptake of the contrast medium, and 34.2% had a homogeneous uptake; 60.8% had contrast hyper-uptake, 27.8% contrast iso-uptake, and 11.4% contrast hypo-uptake. Also, it was found that malignant tumors had a more rapid wash-out phase (about 67.5 s) compared to normal endometrium (about 76.6 s) [30,31]. Other literature studies report similar results in this respect [32].

Endometritis

Endometritis (inflammation of the endometrial mucosa) is an anatomo-clinical form of pelvic inflammatory disease whose etiological agents are (in more than 95% of

the cases) gonococcus, chlamydia, as well as anaerobic germs in the vagina. Because it usually has a subclinical evolution, the imaging exploration of this disease does not provide useful information for diagnosis. Although characteristic changes in hepatic inflammatory lesions (abscesses) have been evidenced by using CEUS, the method is not currently used in the evaluation of this type of gynecological pathology[33].

Safety of the CEUS method. Advantages of the method

Contrast agents used in contrast-enhanced ultrasound have low risks, with a lower rate of anaphylactic reactions (1:7000 patients, 0.014%) compared to contrast agents used for CT or MRI (0.035%-0.095%) [34,35]. Cautious use is recommended in the case of the presence of certain associated cardio-respiratory diseases (myocardial infarction, recently diagnosed angina, heart failure, severe pulmonary disease, dyspnea, etc.) [36,37]. The advantage of contrast agents in CEUS is that since they are not renally excreted, they can be safely used in patients with renal failure. For the same reason, the testing of renal function before the procedure is not necessary. Therefore, CEUS is extremely useful in cases where, for objective reasons, CT or MRI cannot be performed, being the only modality for the dynamic evaluation of endometrial microperfusion.

Limitations of the method

The CEUS technique can provide useful information in the ultrasonographic examination of the endometrium. However, literature studies cite several limitations of the method. Contrast-enhanced ultrasound involves a higher level of training in ultrasound interpretation. In this sense, EFSUMB established 3 hierarchical levels, recommending the performance of CEUS by highly experienced operators [4,38]. Even under these conditions, the method remains operator-dependent.

The majority of the existing ultrasound equipment does not have the technical qualities required for CEUS. The unifocal nature of CEUS examination involves continuous examination, focused on a single lesion, in order to obtain the maximum of possible information; CEUS performance depends on a higher quality of the ultrasound image [39].

The time allocated to CEUS examination should be reconsidered because effective duration increases not so much due to examination itself, but rather due to the preparatory elements of the intervention (placement of the intravenous catheter, setting of the machine, etc.). Also, the costs of the procedure are higher because of the acquisition of contrast agents. However, contrast-enhanced ultrasound is currently used worldwide for various diseases (hepatic, renal, biliary, digestive, etc.) [40,41,42]. The role of CEUS in gynecological examination is not clearly established by current guidelines and clinical practice.

Conclusions

Contrast-enhanced ultrasound (CEUS) finds its place among the methods for the exploration of gynecological pathology as a complementary technique, which provides accurate qualitative and quantitative information about uterine (and implicitly endometrial) vascularization. Even if current recommendations and guidelines do not clearly identify CEUS indications in the gynecological area, possible practical applications in this area would include: a) evidence of the vascular axis of very small polyps; b) assessment of the degree of intramyometrial invasion in endometrial cancer; c) alteration of the circulatory pattern in inflammatory lesions. CEUS performance will be definitely improved considerably in the near future, with the introduction of three-dimensional transducers in current practice. All the more so, prospective studies on the concrete applications of CEUS in endometrial pathology, as well as on the effectiveness of the technique in the diagnosis of this pathology are required.

Acknowledgements

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