



## Application of contrast-enhanced ultrasound for scar pregnancy cases misdiagnosed as other diseases



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### ABSTRACT

**Objective:** To demonstrate the feasibility of utilizing contrast-enhanced ultrasound (CEUS) in scar pregnancies misdiagnosed by transvaginal ultrasound (TVS).

**Methods:** CEUS was performed in three patients with clinically suspected abnormal pregnancy, and the diagnosis were inconclusive by TVS. Clinical manifestations and features of TVS and CEUS in these cases were analyzed. **Results:** Three cases included an intramural pregnancy (IMP) after hysteromyomectomy, and two mass-based cesarean scar pregnancy (CSP), the mass was caused by curettage and spontaneous abortion, respectively. In all these cases, early enhancement with high intensity was observed by CEUS at the site of implantation. Moreover, prominently enhanced signal was detected inside the mass, with or without peritrophoblastic ring. No enhancement was detected in clots or masses after effective treatment.

**Conclusion:** CEUS can be used as a supplementary method to diagnose scar pregnancy and evaluate the treatment efficacy, especially in cases with ambiguous results by TVS.

### 1. Introduction

Scar pregnancy is a rare form of ectopic pregnancy with embryo implanted at the site of scar caused by previous cesarean section, hysteromyomectomy, or uterine curettage. It can lead to life-threatening complications such as massive hemorrhage and uterine rupture [1]. With an increased cesarean section rate in recent years, cesarean scar pregnancy (CSP) became a common type of scar pregnancy [2]. Intramural pregnancy (IMP), often related to hysteromyomectomy or uterine curettage, is a rare form of scar pregnancy. IMP could be misdiagnosed as cornual pregnancy or trophoblastic tumor by transvaginal ultrasound (TVS), and it has a high risk of uterine rupture and hysterectomy [3,4]. An accurate and early diagnosis of scar pregnancy is the key for applying proper therapeutic measures to protect patients' health and preserve their fertility [5].

TVS is the preferred method of imaging to diagnose scar pregnancy. It can locate the gestational sac, and provide internal ultrasonographic features and blood flow information [6]. However, TVS has limitations in assessing blood perfusion in small vessels, and it may lead to misdiagnosis, which adversely affects optimal treatment [7]. Contrast-enhanced ultrasound (CEUS) is known as a revolutionary non-invasive ultrasonic technique, which utilizes contrast agent to make a dynamic detection of blood flow and microvascular perfusion. The contrast agent

has advantages in considering safety, no nephrotoxicity, and no need for hypersensitivity testing [8]. CEUS has already been used widely in clinical practice, including applications for liver examination and non-hepatic examination (e.g. breast, kidney, carotid, endometrial carcinoma, cervical lesions) [9–14]. Ordén MR et al. applied contrast agent on thirty patients with ectopic pregnancy, and described a visible effect on pelvic blood flow in early pregnancy [15].

In this study, CEUS was performed in three patients who were clinically suspected of abnormal pregnancy, and whose pre-diagnosis using TVS were inconclusive, but nevertheless termination of pregnancy was requested. We analyzed and compared the features of TVS and CEUS images as well as the clinical courses of three patients, and discussed the applicability of CEUS in scar pregnancy that are potentially misdiagnosed by TVS.

### 2. Case series

#### 2.1. Materials and methods

This study is a retrospective case series of three patients with clinically-suspected scar pregnancies who decided to terminate the pregnancy, and received treatment in the Obstetrics and Gynecology Clinic at Beijing Shijitan Hospital, Capital Medical University. The

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**Table 1**  
Clinical data of three patients with scar pregnancies.

Case	Age	Last menstruation	History of gestation	Operation history	HCG level (mIU/ml)	Indication
A	34	17 December 2016	gravida 2 para 1	A cesarean section and myomectomy in 2011	113,068	Amenorrhea 48 days
B	30	11 July 2017	gravida 2 para 2	Two cesarean sections, performed in 2012 and 2017, respectively	12,287	Continuous bleeding for 17 days and 1 day of massive bleeding
C	35	05 May 2016	gravida 2 para 1	A curettage on 21 June 2016, A cesarean section in 2011	94.77	Continuous bleeding for 2 months after curettage

HCG: human chorionic gonadotropin.

clinical data of the patients was summarized in Table 1. Careful imaging of the uterus and adnexa was initially constructed with TVS, and the finding was ambiguous. Therefore, CEUS was recommended for further clarification. The study was approved by the Ethical Committee of Beijing Shijitan Hospital, Capital Medical University, and was carried out after receiving informed consent from the patients. Histories of severe allergies and cardio-cerebrovascular diseases were excluded.

The observation equipment was LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA), with a transvaginal probe (frequency, 4–9 MHz; mechanical index [MI], 0.06). SonoVue (Bracco Imaging Company, Milan, Italy), an intravascular contrast agent consisting of phospholipid-stabilized shell microbubbles filled with sulfur hexafluoride gas, was used in this study. The diameter of the microbubbles was similar to that of blood cells (2–6  $\mu\text{m}$ ). The agent was diluted with 5 ml of 0.9% saline. After thorough re-suspension by vigorous shaking, 2.4 ml of the contrast agent was injected in the antecubital vein in bolus fashion (within 1–2 s), followed by a flush of 5 ml of 0.9% normal saline. The dynamic image from the beginning to the fade stage was saved. The features of enhancement and the perfusion patterns were analyzed, and the clinical course and outcome were recorded and discussed.

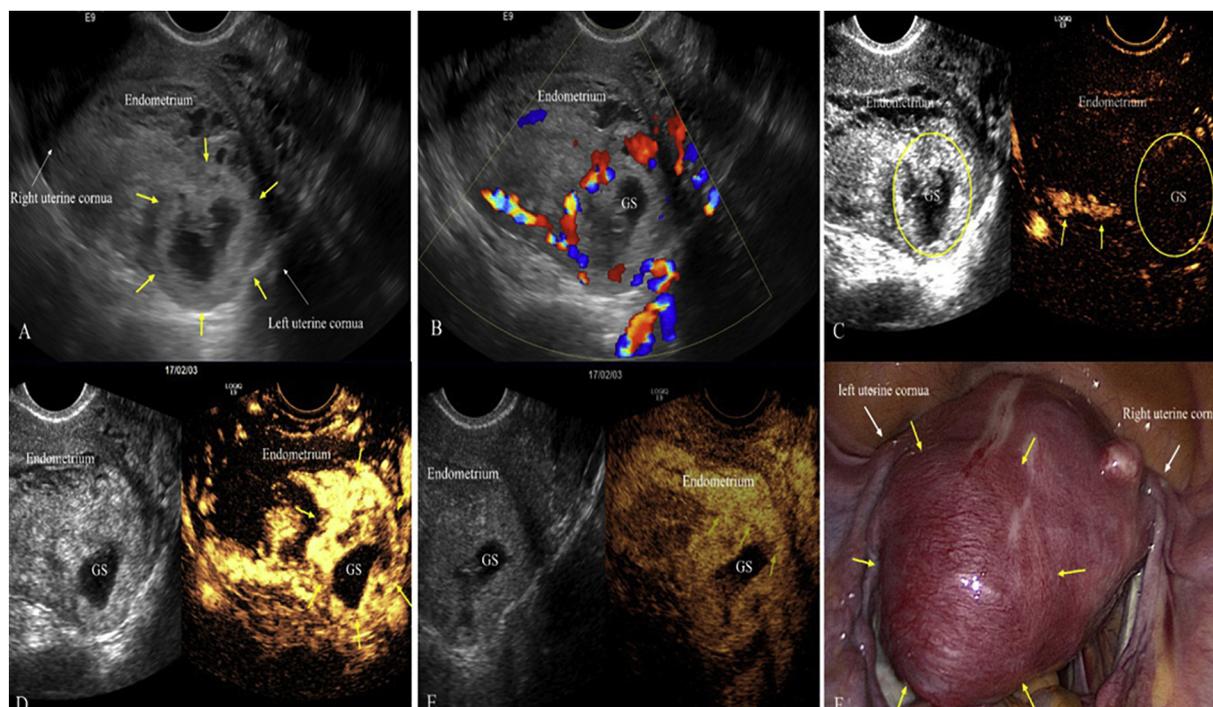
### 2.2. Case A

Patient A was a 34-year-old female presented for a routine prenatal examination with no abdominal pain or vaginal bleeding. TVS revealed a bulging gestational sac (GS) located in the left cornual area. Color Doppler flow imaging (CDFI) showed abundant blood flow between the GS and left cornual area. The result of diagnosis was a cornual pregnancy by TVS. On further inquiry of her medical history, a cesarean section and myomectomy for a hysteromyoma (5.4 cm  $\times$  3.9 cm) in left fundus of the uterus had been performed simultaneously in 2011. CEUS showed an obvious vessel-like intensification in the posterior wall of the left uterine fundus at the 9th second after agent injection, extending rapidly to the edge of the GS. After the 10th second, the proximal myometrium was intensified subsequently. The distance from the highly intensified GS with a circular outline to the uterine serous layer was 0.12 cm. The myometrium in other parts of the uterus and the endometrium were enhanced gradually from the 11th second. After the 29th second, the high intensification around GS faded away slowly, and a low-enhanced myometrium was noted between the pregnant mass and endometrium. CEUS showed that the GS was located in the posterior myometrium of the uterine fundus nearby the left cornua (Fig. 1).

The patient underwent a hysteroscopy and laparoscopy. GS was not found in uterine cavity by hysteroscopy, and the fallopian tube ostium were visible bilaterally. However, the endometrium was violet-blue in the area about 1.5 cm inferior to the left fallopian tube ostium. The GS location was in the subserosal myometrium at the posterior wall of the uterine fundus near the left cornua according to the postoperative section of specimen. The pathologic report of the remaining tissues in the surrounding myometrium was smooth muscle with hemorrhage, necrotic tissue, villous tissue, and few trophoblastic cells.

### 2.3. Case B

Patient B was a 30-year-old female admitted to the Emergency Department of Beijing Shijitan Hospital, presented with complaints of continuous bleeding for 17 days and 1 day of massive bleeding 7 months after delivery. She lost consciousness with blood pressure of 90/54 mmHg during the physical examination. An emergency TVS examination showed a heterogeneous mass (3.8 cm  $\times$  2.3 cm) at the right anterior wall of the lower uterine segment. The mass was located next to the serous layer and bulged outwards with an irregular anechoic area. The surrounding blood flow signal was detected, and the resistance index (RI) was 0.41. The diagnosis of a mass-based CSP was considered based on a history of cesarean section. However, a hysteromyoma was not excluded according to TVS imaging. Another



**Fig. 1.** (A) Transverse section of the uterus, showing both sides of the uterine cornua (white arrow) and the gestational sac (GS) in the left cornual area (yellow arrow). (B) Color Doppler image showing abundant blood flow surrounding the gestational sac. (C) CEUS demonstrating an obvious early enhanced vessel-like area (arrow) in the posterior wall of the uterine fundus at the 9th second after agent injection. (D) CEUS demonstrating an enhanced ring (arrow) around the GS at the 13th second after agent injection. (E) CEUS demonstrating area with low enhancement (arrow) between the GS and endometrium during the fade stage. (F) Laparoscopy showing both sides of the uterine cornua (white arrow) and revealing a bulging lesion (yellow arrow) in the posterior wall of the fundus near the left uterine cornua, confirmed the location of trophoblast within the myometrium.

hyperechoic mass (7.2 cm × 1.3 cm) with no blood signal was detected from the uterine cavity to the cervical canal by TVS.

CEUS was performed to verify ultrasound diagnosis. At the 9th second after agent injection, fast accumulation of contrast agents with high intensity was observed in the mass at the right anterior wall of the lower uterine segment, and the myometrium was enhanced at the 11th second subsequently. There was a continuously enhanced area around the mass connected with the cesarean section scar. There was a 0.15 cm distance from the edge of mass to the uterine serous layer. However, no enhancement was detected in the hyperechoic mass from the uterine cavity to cervical canal. CEUS confirmed that the case was a mass-based CSP with clots and decidua tissue in the cavity (Fig. 2).

The patient underwent emergency uterine artery embolization (UAE). The human chorionic gonadotropin (HCG) level increased to 16,063 mIU/ml after UAE. As a consequence, another CEUS were performed, which showed a circularly enhanced mass at the right anterior wall of the lower uterine segment. CEUS suggested that villous tissue still existed in the mass. The patient underwent an ultrasound-guided hysteroscopy combined with curettage three days later. Hysteroscopy showed pregnancy tissue protruding inwards from the right anterior wall of the lower uterine segment.

#### 2.4. Case C

Patient C was a 35-year-old female, presented with continuous bleeding for 2 months with a 94.77 mIU/ml HCG level after curettage. A TVS examination revealed a heterogeneous mass at the lower segment of the uterus with unclear boundaries, which located closely with a cesarean section scar and partially reached the serous layer. The size was 5.2 cm × 5.2 cm. CDFI showed abundant blood flow signals with dilated blood vessels inside and surrounding the mass, and the RI was 0.27.

CEUS showed that only several dilated vessels in the mass was

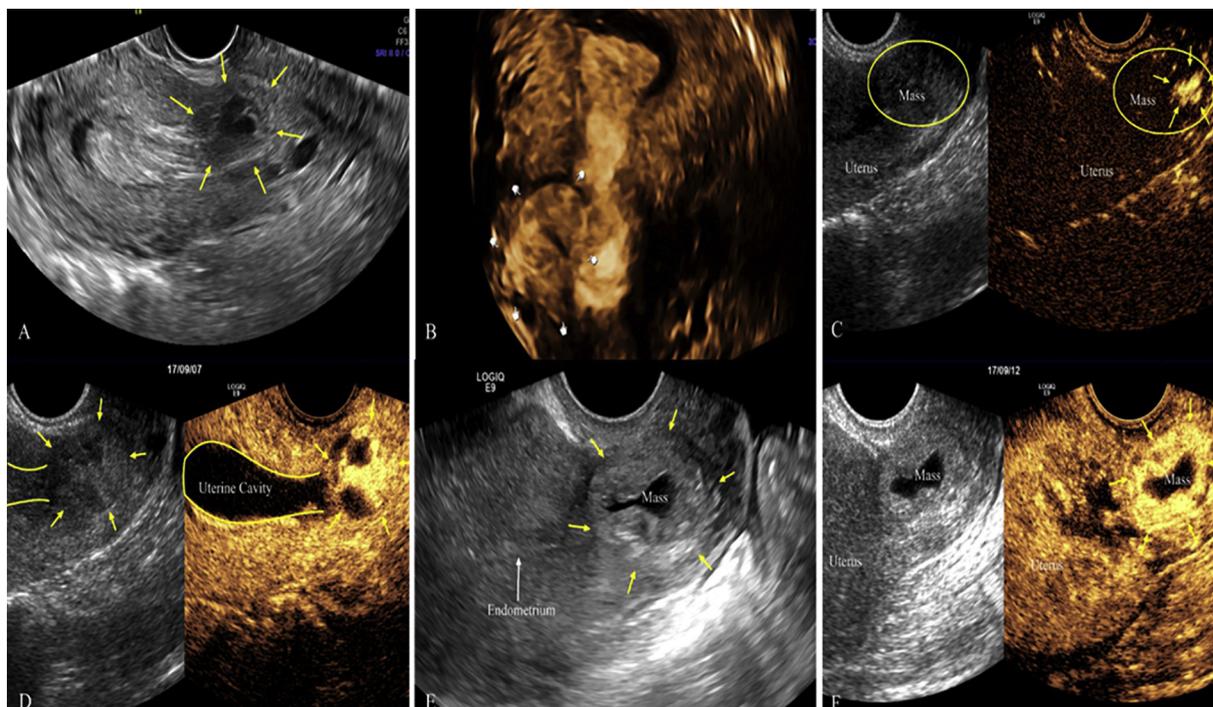
highly intensified at the 12th second after contrast agent injection, most part of the mass was with no enhancement. The contrast agent accumulated faster and faded later in the lesion than the myometrium. It was considered that some villous tissue invaded into the cesarean section scar after curettage. The result of diagnosis was a mass-based CSP after curettage (Fig. 3).

The patient was treated with UAE, and the level of HCG decreased to 2.5 mIU/ml. TVS and CEUS were performed again one month later during the follow-up evaluation. TVS showed a decreased-size mass (3.1 cm × 3.0 cm) with no blood flow. Meanwhile, CEUS demonstrated no enhancement inside the mass. It indicated that the UAE was effective. Three months later, TVS revealed a cesarean scar defect at the lower section of the uterus without the mass.

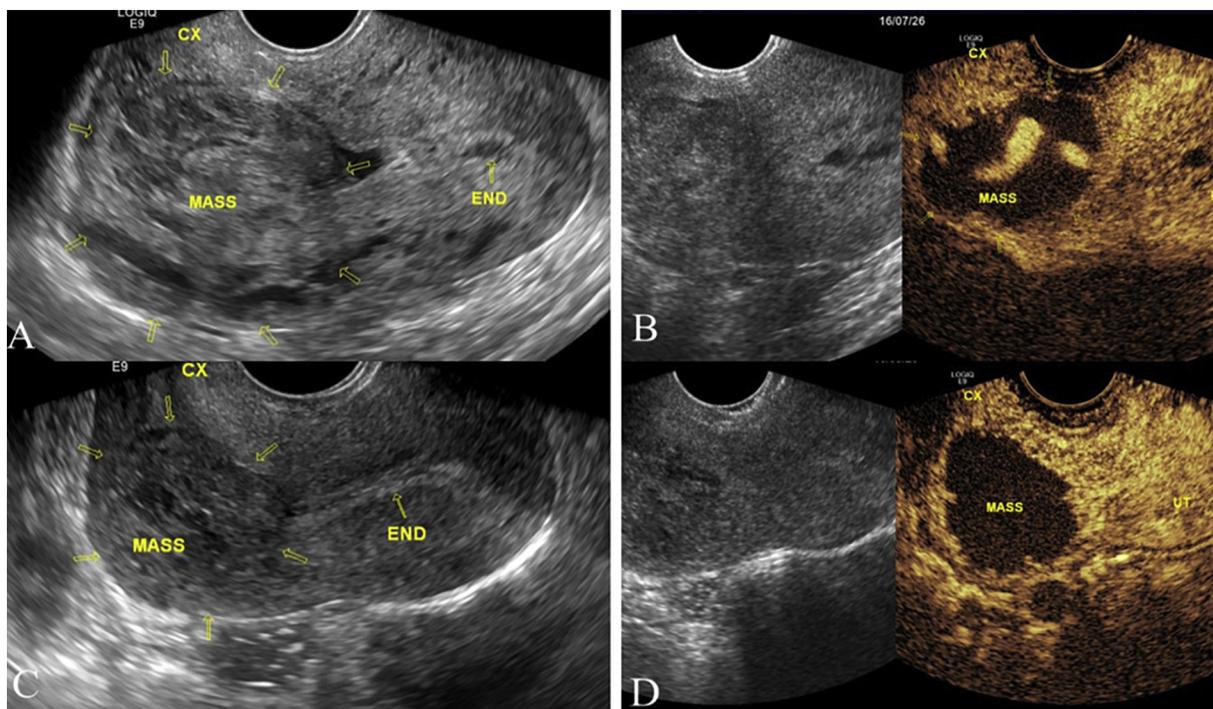
### 3. Discussion

In recent years, the incidence of scar pregnancies is on the rise [16]. The main cause is that the rate of cesarean section, abortion, curettage, and hysteromyomectomy has increased in China and other countries. Other reasons include the advancement of diagnostic technology and increased physician awareness [2,16]. For some cases, TVS is not efficient for diagnosis due to its limited image resolution and capabilities in detecting low velocity perfusion in small vessels. Scar pregnancy cases should be differentiated from abnormal pregnancy and other diseases such as intrauterine pregnancies, ectopic pregnancies (including cornual pregnancy, tubal interstitial pregnancy, and cervix pregnancy), trophoblastic disease, and hysteromyoma/adenomyoma in the lower segment of the uterus [17–19] (Fig. 4). It has been reported that the accuracy of TVS on CSP is 84.6% [20]. However, because of the extremely low incidence of Intramural pregnancy (IMP), the diagnosis rate is much lower [4,17].

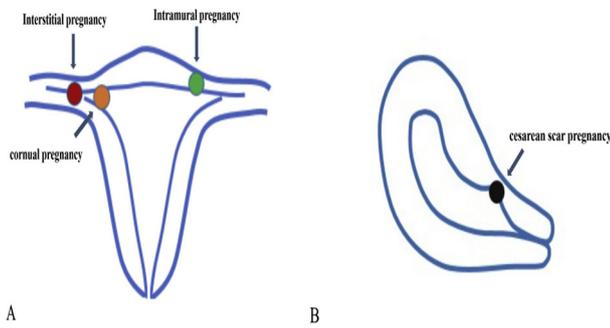
Of the three cases in this study, Case A should be differentiated from cornual and interstitial pregnancy. The embryo of a cornual pregnancy



**Fig. 2.** (A) Longitudinal section through the uterus, showing a heterogeneous mass at the anterior wall of the lower uterine segment (arrow). (B) Three-dimensional ultrasound showing a bulging mass at the right anterior wall of the lower uterine segment. (C) CEUS showing an early high intensity (arrow) in the mass at the 9th second after agent injection. (D) CEUS demonstrating a continuously enhanced area (arrow) around the mass connected with the cesarean section scar, but no enhancement in the uterine cavity. (E) After uterine artery embolization treatment, longitudinal section of the uterus showing thin endometrium (white arrow) and a decreased-size mass (yellow arrow). (F) After uterine artery embolization treatment, CEUS showing a circularly enhanced mass at the anterior wall of the lower uterine segment (arrow), which suggested that villous tissue still existed.



**Fig. 3.** (A) Longitudinal section through the uterus, showing a heterogeneous mass at the lower segment of the uterus with unclear boundaries (yellow arrow) and thin endometrium (END). (B) CEUS demonstrating dilated vessels with persistently high intensity inside and surrounding the mass (yellow arrow). (C) After uterine artery embolization treatment, longitudinal section of the uterus showing a decreased size of the mass (yellow arrow) and a thin endometrium (END). (D) After uterine artery embolization treatment, CEUS demonstrating no enhancement inside the mass, which indicated that the treatment was effective.



**Fig. 4.** Schematic illustration of various types of intrauterine ectopic pregnancy. (A) Coronal section through the uterus showing interstitial pregnancy, cornual pregnancy and intramural pregnancy. (B) Longitudinal section through the uterus showing cesarean scar pregnancy.

is implanted in the endometrium of the uterine cornua [21]. Interstitial pregnancy is embedding of embryo in the interstitium of the fallopian tube, often at a position connected to the uterine cornua [22]. In some cases it is difficult to distinguish cornual from interstitial pregnancies by TVS [23]. Case A was misdiagnosed as a cornual pregnancy by two-dimensional and three-dimensional TVS. The challenging features in this case were as follows: a) The location of the GS was in the area of left uterine cornua. Two-dimensional ultrasound did not identify the relationship between the GS and the endometrium. b) Three-dimensional ultrasound showed that the GS was connected with the left uterine cornua, whereas the GS was completely encircled by the adjacent myometrium. However, CEUS provided reliable information for diagnosis. The features of CEUS in IMP is summarized as follows: a) The implantation site in the myometrium was intensified early. A vessel-like area in the myometrium was enhanced early, indicating that the GS blood supply arose from the myometrium. b) The agent was persistently highly accumulated around the GS, and faded away later than the myometrium. c) During later enhancement stage and the fade stage, the myometrium boundary between the GS and endometrium was clearly shown with low enhancement, so that the relationship between the GS and uterine cornua was clarified.

Case B and Case C were diagnosed as mass-based CSP by CEUS. A mass-based CSP is the consequence of continued growth of residual villous tissue after an incomplete abortion or blind curettage with a falsely diagnosed CSP. A uterine arteriovenous malformation (AVM) forms when arteries and veins connect abnormally [24]. Typically GS could not be visualized by TVS in mass-based CSP. In addition, the heterogeneous mass in mass-based CSP is difficult to be distinguished from trophoblastic disease, hystero myoma and adenomyoma [25].

CEUS can provide evidence of real-time blood perfusion in organs, with obvious advantages in blood flow imaging to identify the implantation site of the embryo [26,27]. It may reveal the trophoblastic area and the shape of trophoblastic tissue in a heterogeneous mass. It was reported that prominent vascularity or enhanced ring detected inside the mass could be regarded as trophoblastic flow [15,16]. In Case B, the enhanced peritrophoblastic ring is a characteristic imaging feature for scar pregnancy by CEUS, because the trophoblastic villi invades the scar and periphery myometrium to form the intervillous space around GS. But in some cases, the intervillous architecture may be destructed due to ruptures and bleeding, so a peritrophoblastic ring could not be found. The imaging of branches were observed in Case C by CEUS, which was considered to be the sign of villous tissue in the residual placenta. The features of CEUS in mass-based CSP is summarized as follows: a) The mass was early enhanced, the contrast agent accumulated faster and faded later in the mass than the myometrium. b) There was a continuously enhanced area around the mass connected with the cesarean section scar.

CEUS may also be an effective monitoring method for evaluating conservative treatment of scar pregnancy. Traditionally, trophoblastic

activity are determined by monitoring serum HCG level and ultrasound images. Decreased size and blood supply with higher resistance index observed by color/power Doppler ultrasound suggests an effective treatment [28,29]. Nevertheless, limited by resolution, Color/power Doppler ultrasound is difficult to display tiny vessels and low velocity flow [30]. CEUS can be used as a supplementary method to partially correct this deficiency. By CEUS, apparent enhancement in the mass indicated that there were still viable villous tissue. On the other hand, absence of enhancement is indicative of effective treatment.

#### 4. Conclusion

We reported and discussed three cases of scar pregnancy diagnosed by CEUS. Villus tissue has the feature of early and persistently enhanced signals compared with myometrium in CEUS. CEUS can be used as a supplementary method to diagnose scar pregnancy, especially in cases that diagnostic result are ambiguous by TVS. CEUS can also be an effective method for evaluation of clinical treatment.

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