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REVIEW

Contrast-enhanced ultrasound in pregnancy

Stephanie A. Nguyen[1] · **David P. Burrowes**[1] · **Christina Merrill**[1] · **Stephanie R. Wilson**[1]

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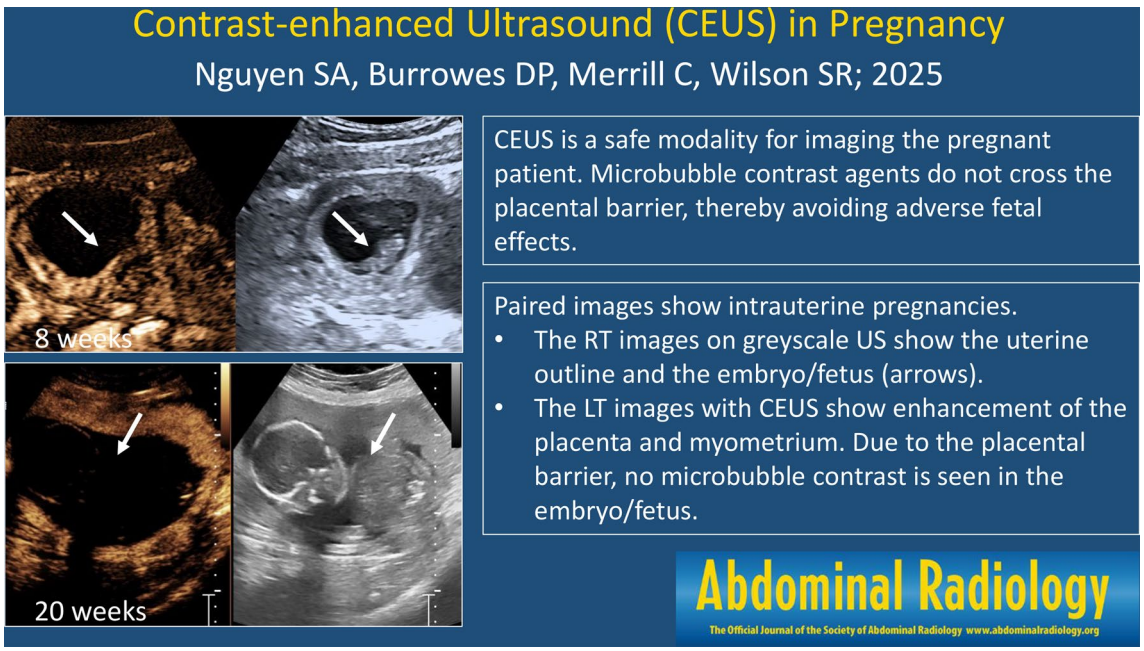
Abstract

There are complex problems related to diagnostic imaging of the pregnant patient Cross sectional imaging with computed tomography (CT) tends to be avoided to due to the risk radiation poses to the fetus and magnetic resonance imaging (MRI) may be limited due to avoidance of gadolinium contrast.

While ultrasound (US) is the primary test for imaging in pregnancy, there is limited awareness of contrast-enhanced US (CEUS) as a safe and accurate option for providing similar vascular information to that which is usually provided with contrast-enhanced CT and MRI. Microbubble contrast agents do not cross the placental barrier and have been shown in animal studies to pose no harm to the fetus at doses far above the human dose.

The literature on CEUS in pregnancy will be reviewed and the utility and diagnostic accuracy of CEUS for the assessment of acute and chronic maternal conditions and evaluation of neoplastic masses will be demonstrated with case examples.

Graphical abstract



Keywords Contrast-enhanced ultrasound (CEUS) · Microbubble contrast agent (MBCA) · Ultrasound contrast agent (UCA) · Pregnancy

Extended author information available on the last page of the article

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Introduction

Diagnostic ultrasound (US), including greyscale and Doppler, plays an integral role in the standard care of pregnant patients with examinations performed for pregnancy confirmation, dating, and fetal assessment. Additionally, US imaging may be utilized for complications occurring during pregnancy, whether they be of an obstetric nature or reflective of an acute condition generally affecting the gastrointestinal tract, examples include: acute appendicitis, acute cholecystitis, or complication of inflammatory bowel disease (IBD); or the genitourinary tract, i.e. obstructive ureteric stone or pyelonephritis. Routine maternal US exams may also be recommended during pregnancy for pre-existing chronic maternal conditions of IBD and confirmed chronic liver disease, both of which generally undergo routine US surveillance even for asymptomatic patients.

Although most pregnancies go to delivery without significant problem, in the minority of pregnancies, there may be observations that warrant and may even expedite further medical investigation. These include major trauma, an unexplained acute abdomen, and unexplained sepsis, to name only some of the many possibilities. Additionally, identification of a suspicious abdominal or pelvic mass with uncertain malignant potential is a cause of great concern and patient anxiety. Can these masses be safely confirmed and characterized during pregnancy? Waiting until the end of pregnancy to resolve any of the above often seems unreasonable and these occurrences may suggest consideration of performance of a contrast enhanced imaging examination during pregnancy to enable early and accurate diagnosis, guiding management and any possible treatment that might be required to preserve maternal and/or fetal health.

In any patient, the decision to image is influenced by weighing the potential risks against the anticipated benefit of imaging. In general, the benefits of imaging greatly outweigh the small or theoretical risks. In the pregnant patient, one must consider risks and benefits for both the patient and the fetus, sometimes resulting in more complex decision making. Anxiety around imaging in pregnancy is compounded by the fact that it is not practical or ethical to directly study many of the theoretical risks of imaging in pregnancy and therefore data is limited and often extrapolated from small case series or animal studies.

The American College of Obstetricians and Gynecologists (ACOG) states that US and non-contrast MRI are not associated with risk and are the preferred imaging modalities in pregnancy [1]. The ACOG also states that the radiation dose associated with most imaging with CT is much lower than the threshold associated with fetal harm, and that CT should not be withheld when deemed necessary, either as an adjunct to US or MRI, or, when CT is more readily available than US or MRI [1]. Regarding contrast agents, the ACOG states that the use of gadolinium-based contrast agents (GBCAs) should be limited and used only if it significantly improves the diagnostic performance of MRI in a way expected to improve maternal or fetal outcome [1]. The statements from the ACOG are in parallel with recommendations from the American College of Radiology (ACR) manual on contrast material which states "because it is unclear how GBCAs will affect the fetus, these agents should be administered with caution to pregnant or potentially pregnant patients. Each case should be reviewed carefully by members of the clinical and radiology service groups, and a GBCA should be administered only when there is a potential significant benefit to the patient or fetus that outweighs the possible but unknown risk of fetal exposure to free gadolinium ions" [2]. The ACR does not recommend withholding the use of iodinated CT contrast agents in pregnant or potentially pregnant patients when they are needed for diagnostic purposes [2].

Outside of CT and MRI contrast agents, vascular imaging is also possible with colour and power Doppler US and developments in microvascular flow imaging techniques have made US even more sensitive for detection of slow flow in small vessels. While US is the mainstay modality for imaging obstetric and non-obstetric pathology in pregnancy, it is not without its limitations. Even with microvascular flow imaging, US remains limited in scenarios in which arterial and venous/delayed phase wash-in and washout characteristics are important diagnostic features.

Contrast-enhanced US (CEUS) is a valuable adjunct to standard greyscale and Doppler US with a long history of use in cardiology and radiology settings, with a recent multi-societal expert consensus statement released on the safe administration of US contrast agents [3]. CEUS was first introduced around 2000 and shortly thereafter, approvals for microbubble contrast agents (MBCAs) were obtained in Asia, Europe, and Canada, with initial studies focused heavily on characterization of focal liver masses. Since that time there has been progressive increase in off-label uses of MBCAs to now include in addition to the liver, the kidney and all of the solid abdominal organs, as well as the ovaries, thyroid, testicles, and even the bowel. Performed with the intravenous injection of tiny bubbles of a low solubility gas within a thin lipid shell, the bubbles oscillate when exposed to an US field producing a substantial enhancement of the Doppler signal from blood. At approval, CEUS allowed the first opportunity for US to stand alongside CT and MRI in showing perfusion-level hemodynamics – a role from which it was previously excluded. CEUS in the United States occurred much later than elsewhere and an approved MBCA has only been present since April 1, 2016, making the American population less familiar with CEUS than elsewhere.

CEUS has an excellent safety profile and takes advantage of the high spatial resolution and dynamic real-time imaging capabilities of regular US. The software specific for performance of CEUS includes a highly effective subtraction technique allowing for creation of a microbubble/contrast only image with superb detection of blood flow even within thin septations and tiny nodules. MBCAs comprise purely intravascular contrast agents making them unique for blood flow quantification compared to CT and MRI agents which diffuse into the soft tissue interstitium. Today, geographic differences exist in the utilization of CEUS. Nonetheless, liver and kidney imaging have flourished, and pediatric imaging is comprehensive, taking advantage of the safety profile and ease of exam performance in children. Unlike CT and MRI contrast, MBCAs are not associated with renal toxicity, making CEUS safe for use in patients with impaired renal function. MBCAs are also an alternative for those who have an allergy to CT or MRI contrast.

Contrast-enhanced US (CEUS) in pregnancy

CEUS shares the same benefits of ultrasound in that it is a well-tolerated, repeatable exam capable of assessing multiple organs/areas. Easily performed at the bedside, CEUS examinations are not associated with the same challenges limited mobility and claustrophobia can pose when positioning patients for CT and MRI. This may be especially relevant to pregnant patients at advanced gestational ages.

As highlighted above, MBCAs used for CEUS provide similar vascular information gained from contrast-enhanced CT and MRI, though a unique characteristic of MBCAs is that they are purely intravascular, whereas CT and MRI contrast enters the interstitial space. When injected intravenously, the microbubbles circulate within the vasculature for a few minutes before they go into solution. The small volume of inert gas within the bubbles is exhaled and the lipid shell is metabolized by the liver. There is no urinary excretion or secretion of microbubbles. After approximately 15 min, nearly all of the contrast has been eliminated from the circulation [4].

Safety and evidence

CEUS studies in pregnant rats have shown that MBCAs do not cross the placenta and do not impact placental permeability [5,6]. In a study with 60 animals, researchers intravenously administered Evans blue dye to pregnant rats and assessed for the presence of dye in the placentae and fetuses. There were four groups: a control group, a group exposed to MBCA (SonoVue, Bracco), an US only group, and a group with US and MBCA. In circulation, Evans blue dye binds to albumin, the smallest macromolecule, hence its common use as a tracer to assess permeability. The researchers imaged at different mechanical indices, including at settings above those routinely used and recommended for human imaging. In the group exposed to ultrasound with MBCA, ultrasound at the time of contrast administration showed enhancement of the uterus and placenta with no enhancement/MBCA seen in the fetus, supporting MBCAs do not cross the placenta. Animals were sacrificed 30 min following testing and presence of dye was assessed for with fluoroscopy and microscopy. Dye was not observed in the fetuses in any of the groups, leading the researchers to conclude that US with MBCAs does not impact placental permeability and molecules the same size or larger than albumin, which the dye binds to, do not pass through the placental barrier [7]. In another study using pregnant rats at different gestational ages (14, 17 and 20 weeks), researchers monitored and quantified uteroplacental perfusion by Doppler US and CEUS (Vevo MicroMarker contrast, Visualsonics Inc.) [8]. During US assessment, they observed no contrast within the umbilical vein or fetal tissues. Pups were delivered at 20 days by cesearean section. Histological studies of the placenta in the control group versus the group exposed to MBCA showed no differential tissue damage. Pups in both groups were all grossly normal at the newborn stage [8]. In other studies, using rat and rabbit models, researchers have administered sulfur hexafluoride microbubble contrast at doses far above recommended human doses during organogenesis with no significant observed fetal findings, suggesting MBCAs are not associated with adverse fetal developmental outcomes [9]. While these studies provide valuable insights, translation of small animal model-based research to a human population may be limited by inherent differences in physiology and placental structure.

Larger pregnant mammals show greater similarities in gestational period and placentation to humans, making them a more clinically relevant translational model in studies using CEUS.

Interested in how the purely intravascular nature of MBCAs could be useful to diagnosing placental abnormalities, Schmiedl et al. aimed to assess the effects of MBCA (Levovist, Schering AG, Berlin) on placental circulation and whether there were hemodynamic effects on the fetus in late gestation Rhesus macaques [10]. They performed 10 studies in five pregnant macaques whereby CEUS was performed on two occasions during the pregnancy with a diagnostic dose and a high dose of MBCA (based on doses ranges from human studies). They assessed fetal heart rate, resistive index, and systolic-diastolic ratios in the fetal middle cerebral artery, aorta, umbilical artery, and uterine artery before and after administration of contrast and found no significant difference between baseline and the different

MBCA doses leading them to conclude MBCA administration did not have an adverse effect on fetal hemodynamics [10]. In a study using a sheep model to assess the impact of Levovist on small vessel imaging, researchers also noted no adverse effect of MBCA on fetal heart rate or fetal blood flow velocities during examinations [11].

In a very small study of only four pregnant rhesus macaques, CEUS was performed in early gestation to assess changes in uterine microvascular perfusion during early implantation. At birth, infant weights were all in the normal range [12]. In a study of uteroplacental vascular supply in mid second and early third trimester Japanese macaques using 12 animals (6 assessed with CEUS using the MBCA Definity; Lantheus Medical Imaging), researchers found no evidence of microvascular hemorrhage or acute inflammation in placental tissues [13]. Placentae were collected after caesarean section and underwent histologic testing, including molecular staining for markers of cellular stress and apoptosis. No adverse pregnancy events were noted between the time of imaging and time of delivery. Additionally, no significant differences were observed in placental or fetal weights in animals with and without CEUS exposure [13]. The same group also used CEUS to assess the impacts of gestational protein restriction on placental perfusion and pregnancy outcomes in Rhesus macaques. CEUS was performed twice during the pregnancies of animals in a control group (9) and a protein restricted group (10) at mid and late gestation with Definity [6]. The rate of pregnancy loss in their control group was 22% (2/9), which is higher than reported rates of pregnancy loss in rhesus macaques (5–17%); however, they attributed this to instability within the newly established animal group induced by male aggression that occurred after pregnancies were identified. Pregnancy loss in the protein restricted group was 50% (5/10) and attributed to the state of malnourishment. Pregnancies otherwise proceeded to term in both groups with normal healthy infants in the control group, suggesting CEUS in pregnancy does not impact early fetal outcomes [6].

In human patients, CEUS has a long history of safe use in both pediatric and adult settings for a wide range of on and off-label uses, reassuring for maternal safety. Small studies in noncontinuing pregnancies in the settings of feticide, cesearean ectopic pregnancy and characterization of invasive placentation have shown no adverse maternal events related to CEUS performance [14–18]. Of note, the study characterizing invasive placentation showed real-time visualization of abnormal placental blood flow in association with myometrial invasion, compelling for another potential indication for CEUS in pregnancy. Importantly, they also showed absence of microbubbles within the fetal circulation, suggesting that these do not cross the placenta. The other referenced studies did not comment on imaging the fetus/embryo at the time of CEUS examination; however, on review of figures in the publication by H. Li et al. on cesearean ectopic pregnancies, no microbubble contrast is seen within embryos on provided images [16].

Regarding potential effects of CEUS on the placenta and fetus, the small number of existing human studies align with results from animal studies. In a study of 69 patients with third trimester pregnancies, 25 were examined by CEUS with the first generation MBCA Levovist (Schering AG, Berlin), with others in a saline injection group or a control group. They assessed umbilical artery blood flow velocity, fetal cardiotocographic parameters, and obstetric outcomes including birthweight, placental weight, fetal and neonatal distress, prenatal hemorrhage, cord blood gas, and macroscopic placental examination. They observed no significant changes in umbilical artery blood flow velocity and no adverse fetal or maternal effects [19]. In a study with 34 patients undergoing elective first trimester pregnancy termination, researchers performed CEUS and tissue histopathology to study maternal flow to the placental intervillous space and vascular remodelling. They found no adverse effects of MBCA (Definity) on placental vasculature [20].

With 14 patients, one of the largest studies evaluating CEUS in pregnancy with a second generation MBCA, was published by Chen et al. in 2022 using sulfur hexafluoride microbubbles (SonoVue, Bracco) [21]. This group investigated the protective effects of the placental barrier by analyzing CEUS images and comparing the morphology of placentae from pregnant women requiring pregnancy termination (7 to 37 gestational weeks) who underwent CEUS examination and 6 healthy pregnant women who did not. No microbubble contrast was seen in the fetal umbilical circulation at any trimester. The structure of placentas with and without contrast exposure was compared by light microscopy and there were no obvious morphologic changes. The authors concluded that due to the protective effects of the placental barrier, CEUS during pregnancy may be a safe imaging technique. Notable limitations of this study are the small sample size and as all of the pregnancies which underwent CEUS underwent termination, it was impossible to assess for any long-term adverse effects on fetuses exposed to CEUS *in utero*.

Within the last five years, several small studies have been published specifically focused on CEUS for the assessment of maternal conditions during pregnancy. In 2020, Geyer et al. published their experience performing CEUS for assessing abdominal conditions in pregnancy [22]. They assessed five patients (14 to 27 gestational weeks) and observed no immediate adverse maternal, nor fetal adverse effects related to CEUS performance using sulfur hexafluoride microbubbles (SonoVue, Bracco). They also reported the absence of microbubble contrast within imaged fetuses. In

their population, CEUS helped in the diagnosis of a renal angiomyolipoma, pyelonephritis without abscess formation, a necrotic uterine fibroid, gallbladder polyp, and superior mesenteric vein thrombosis.

In 2020, Schwarze et al. published a retrospective single-center study examining the performance and safety of CEUS for the assessment of liver lesions in pregnant patients [23]. The study used sulfur hexafluoride microbubbles (SonoVue, Bracco) and included six patients (mean 28 weeks gestation). No adverse maternal or fetal events occurred during the evaluation and no microbubble contrast was seen within the fetuses. CEUS aided the diagnosis of hepatic metastases in patients with rectal cancer and pancreatic acinus cell carcinoma, focal nodular hyperplasia, atypical hemangioma, an arteriovenous malformation, and cystic echinococcus. Notably, results prompted immediate therapy in the cases of the patients with metastatic disease and echinococcal infection.

In 2021, the same group published a second retrospective single-center study sharing their experience performing CEUS with sulfur hexafluoride microbubbles (SonoVue, Bracco) for the work-up of non-obstetric conditions during pregnancy [24]. Their study included five pregnant patients (5–33 gestational weeks) who all underwent uncomplicated CEUS exams with neither adverse maternal nor fetal effects identified. No microbubble contrast was seen in the imaged fetuses. In one patient, CEUS contributed to the diagnostic workup of an abdominal wall desmoid tumour and was then used again to guide biopsy away from intratumoral vasculature to decrease the risk of significant bleeding. In another patient, CEUS helped diagnose amoebic hepatic abscesses, which directly contributed to initiation of appropriate therapy. In a third patient, CEUS excluded active bleeding in a post-traumatic hematoma, sparing the patient from repeat CT. In the last two patients, CEUS diagnosed a benign hepatic hemangioma and benign cystic renal mass. These patients could thus be confidently returned to regular obstetric care. In their group of five patients, two were reported to have gone on to normal term deliveries, with no specific comment on the other pregnancies.

These animal studies and small single-center studies support the safety of microbubble contrast as an intravascular agent which does not pass through the placental barrier. They also show the safe performance of CEUS at different stages of pregnancy, including in the first trimester. The most critical limitations however are the small number of pregnancies and the brief interval during which potential adverse effects were assessed. Short of observing normal term deliveries, there is no data on the potential long-term effects of CEUS in pregnancy. Ideally, multi-center prospective trials with large patient cohorts and long-term follow-up would be performed. However, as is also the case with CT and MRI, it is neither practical nor feasible to perform such a study on pregnant patients. Although the cumulative number of patients in these studies may be small, the findings remain consistent. CEUS is being safely employed during pregnancy to improve diagnostic clarification and guide management. To date, there has been no evidence of adverse maternal events, and no US detected evidence of contrast in the fetal circulation due to the placental barrier.

The manufacturer of sulfur hexafluoride microbubbles indicates there is no available clinical data on use during pregnancies, though animal studies do not suggest harm to the pregnancy or fetus [25]. The United States Food and Drug Administration (FDA) echoes the sentiment of a lack of data in pregnant women to inform drug associated risk. There are no explicit stated contraindications to the use of this type of contrast by the manufacturer or regulatory authorities in the pregnant population [25].

Applications of CEUS in pregnancy

The application of CEUS during pregnancy is uncommon. At our institution, between 2019 and 2023, we assessed 15 patients between the ages of 27 and 43 (mean age 35) with pregnancies ranging from as early as 8 weeks to 32 weeks gestational age. Before proceeding with a CEUS examination, a thorough discussion is held between the radiologist and the patient +/- their partner with the opportunity to include other parties such as the patient's referring physician. It is always clearly stated that there is limited evidence on CEUS in pregnancy, but existing studies suggest it to be safe, and a risk/benefit discussion is always had with the patient given ample opportunity to ask questions.

All exams include standard greyscale US, Doppler evaluation and CEUS performed with perflutren lipid microsphere contrast (Definity, Lantheus Medical Imaging). MBCA is administered intravenously with each injection 0.2 mL (150 µl/mL) followed by a 5–10 mL sterile 0.9% saline flush. In our patient population, number of injections per exam ranged from 1 to 4, with number of injections reflecting the minimum required to address the clinical question in keeping with principles of "as low as reasonably achievable (ALARA)". The pregnancy is always imaged before and after CEUS examination, and when feasible, the embryo/fetus was also imaged after MBCA injection. No MBCA injections are performed singly focused on the fetus. CEUS was successful and of diagnostic quality for each exam with no adverse maternal or fetal events observed during any of the exams.

Performance and interpretation of CEUS in pregnancy generally follows the same principles as in the non-pregnant patient. Previous publications have demonstrated excellent performance of CEUS in the assessment of a wide variety

of abdominal and pelvic pathologies. CEUS performs excellently in the evaluation of focal liver lesions in both the general population and in patients at risk for hepatocellular carcinoma (HCC), the ACR Liver Imaging Reporting and Data System (LI-RADS) can be applied [26,27]. CEUS can be used for evaluation of renal masses [28], bowel abnormalities [29] and various female pelvic conditions [30]. Although there is no official role at present, it is easy to envision how the vascular information from CEUS could be used to supplement the ACR Ovarian-Adnexal Reporting and Data System (O-RADS). Additionally, CEUS has been successfully utilized for assessment of traumatic [31] and non-traumatic [32] abdominal emergencies.

In our experience, one of the primary indications for CEUS is work-up of acute presentations in pregnancy. Acute abdominal pain in pregnancy may originate from complications of uterine fibroids, including degeneration (Fig. 1, Supplementary Movie 1) and infarction (Fig. 2). Torsion of ovarian masses, either pre-existing or discovered during pregnancy, may also benefit from assessment with CEUS which may be useful in characterizing the ovarian mass or confirming ovarian devitalization which would necessitate surgery.

As the ovaries are assessed during a full pelvic US exam, ovarian/adnexal pathology is not uncommonly incidentally encountered during routine pregnancy imaging. In this setting, the vascular information CEUS provides is helpful in lending diagnostic confidence to distinguishing benign avascular masses, such as hemorrhagic cysts (Fig. 3) from multilocular cystic neoplasms with vascular septations (Fig. 4, Supplementary Movie 2; Fig. 5, Supplementary movie 3). CEUS can also clearly demonstrate blood flow in

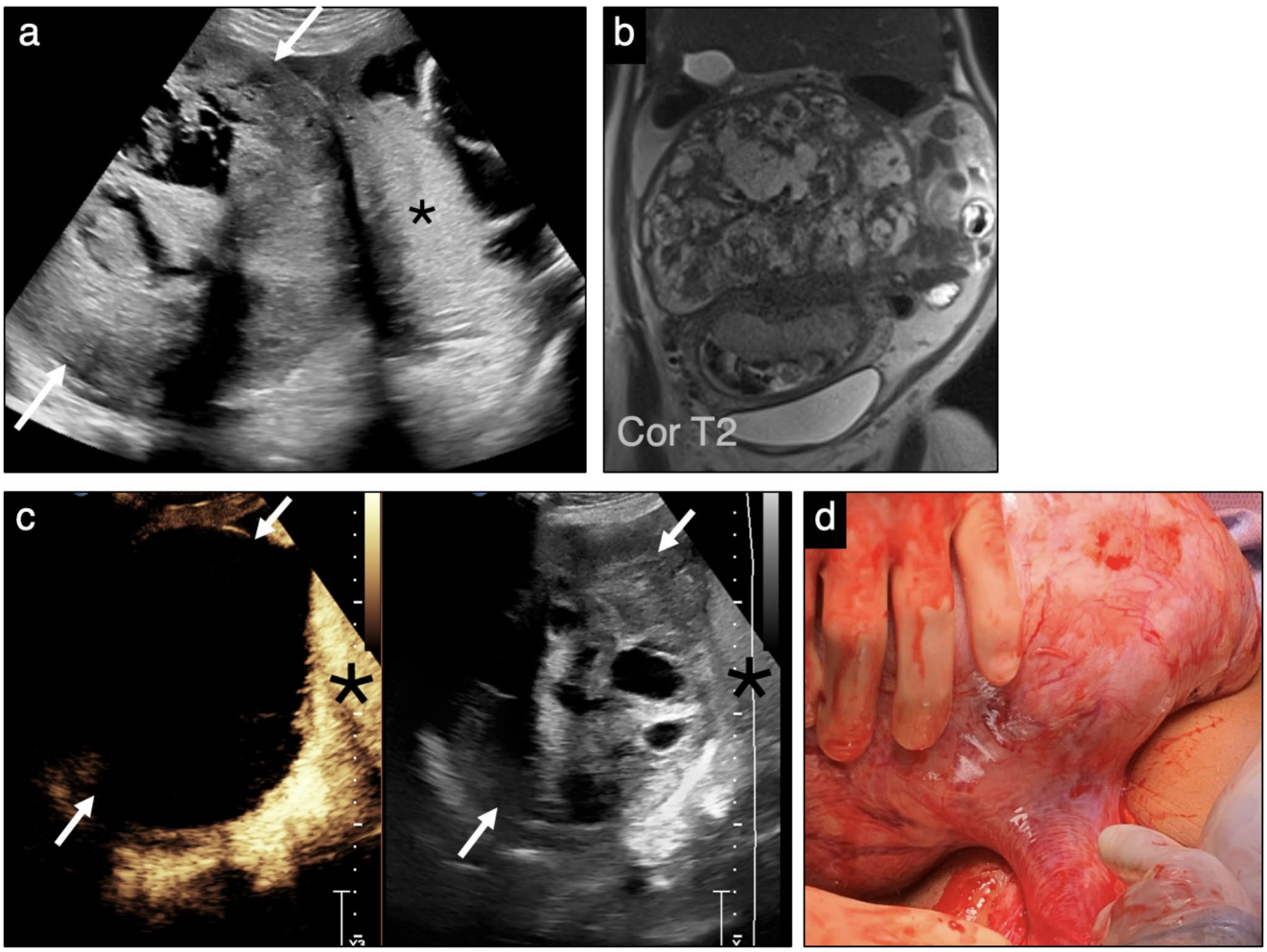

Fig. 1 Degenerating (apoplectic) fibroid. 31-year-old at 21 weeks with acute pain and a palpable mass. (**a**) Greyscale US shows a heterogeneous cystic and solid mass (arrows) superior to the gravid uterus with fundal placenta (*). (**b**) Coronal T2-weighted sequence from non-contrast MRI redemonstrates a cystic and solid mass. (**c**) Split screen display with CEUS image on the left and low mechanical index greyscale US image on the right shows the mass (arrows) is completely avascular, suggesting the diagnosis of a degenerated/infarcted fibroid. The normally enhancing placenta can also be seen (*). (**d**) Intraoperative photo at time of intrapartum myomectomy at 21 weeks shows the pedicle of the large pedunculated fibroid. Subsequently, the patient went on to a normal term delivery

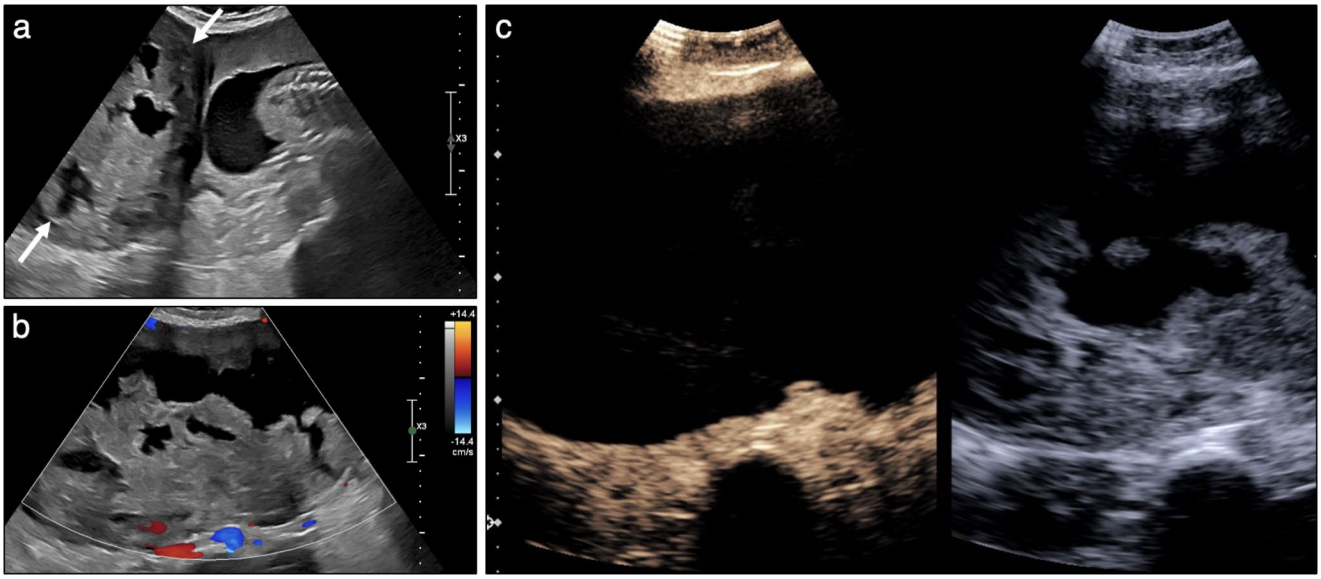

Fig. 2 Infarcted fibroid. 26-year-old at 25 weeks with severe pain and known large fundal fibroid. (**a**) US demonstrates a large (~30 cm) mixed cystic and solid fibroid (arrows) broadly abutting the fundal aspect of the gravid uterus. (**b**) Fibroid shows no internal vascularity on colour Doppler evaluation. (**c**) Split screen display with CEUS image on the left and low mechanical index greyscale US image on the right demonstrates the fibroid is completely avascular consistent with an infarcted fibroid. The patient's symptoms improved with conservative management, and she ultimately underwent a planned induction of labour at 37 weeks and 5 days given the known large fibroid

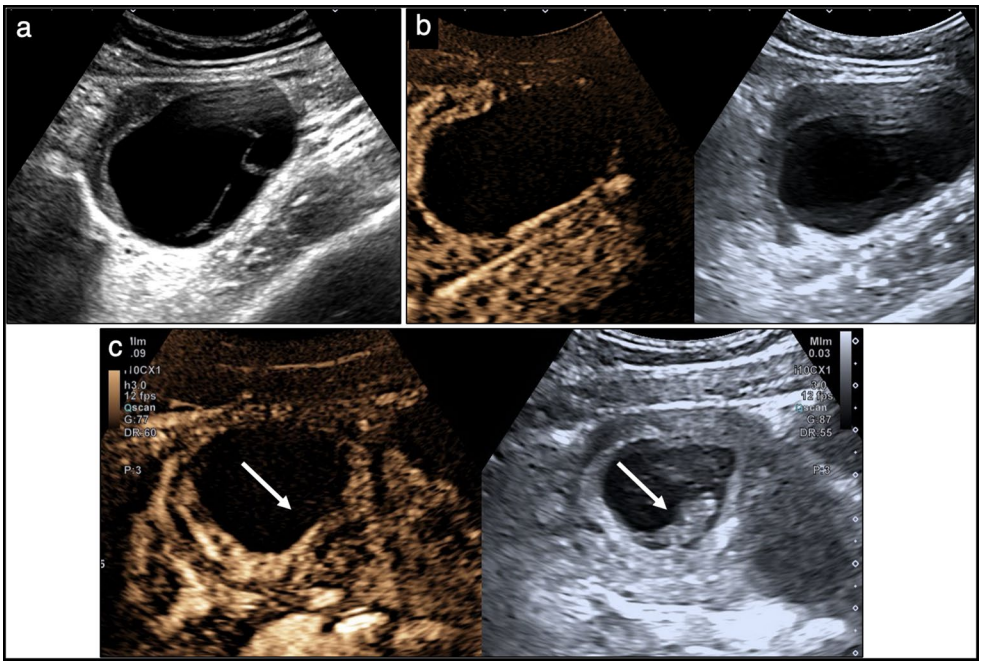

Fig. 3 Hemorrhagic ovarian cyst. 30-year-old at 8 weeks referred for evaluation of a reported 5 cm multilocular ovarian cyst detected at dating ultrasound at an outside institution (**a**) Greyscale US shows a 5 cm cystic ovarian lesion with several thin, smooth septations vs. reticular echoes. (**b**) On CEUS, all the septations are avascular with overall appearance consistent with a benign hemorrhagic cyst containing fibrin strands. (**c**) Split screen display with CEUS microbubble-only image on the left and low mechanical index greyscale US image on the right of the uterus shows an intrauterine pregnancy. As there are no microbubbles within the embryo (arrow), it does not show on the CEUS image. The patient and her care provider were reassured regarding the benign nature of the ovarian cyst, and she continued her pregnancy to term

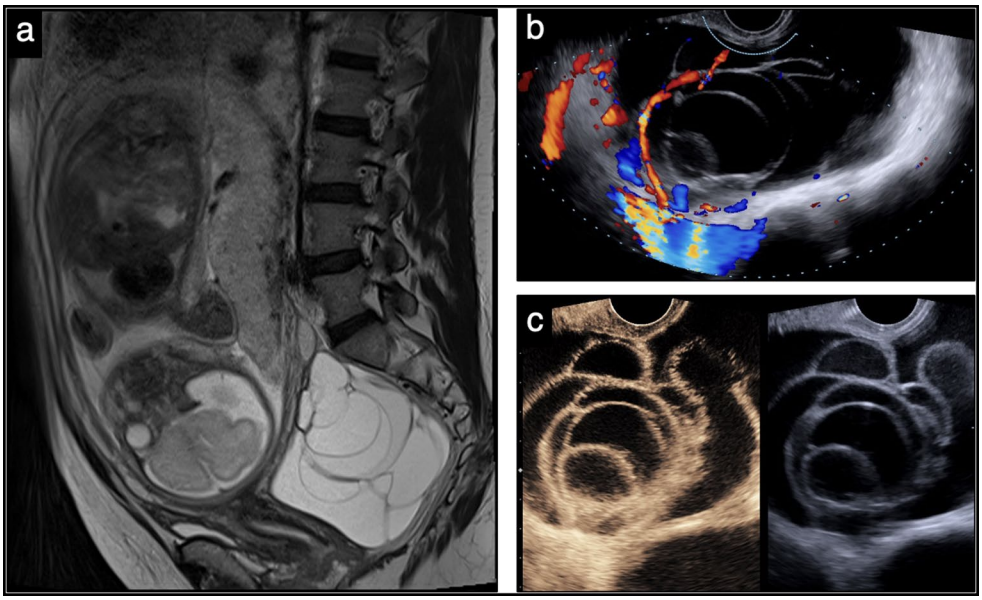

Fig. 4 Ovarian mucinous cystadenoma. 36-year-old at 30 weeks presenting for characterization of an 8 cm cystic right ovarian mass first identified on dating ultrasound and growing during pregnancy. (**a**) Sagittal T2-weighted sequence from unenhanced MRI shows a multilocular cystic mass with mild heterogeneity in cyst fluid and no solid component, favoured to arise from the right ovary, centered in the posterior cul-de-sac. (**b**) Colour Doppler US shows flow within at least one septation. (**c**) CEUS readily and much more sensitively shows flow within all of the septations. By the ACR US Ovarian-Adnexal Reporting and Data System (O-RADS), this is an O-RADS category 3 lesion. With CEUS, all the septations were clearly shown to be strongly enhancing with no solid nodular components and concern was raised for a mucinous neoplasm. The patient continued her pregnancy to 37 weeks at which time an elective caesarean section with salpingo-oophorectomy and surgical staging was arranged with Gyne-Oncology. Final histopathology showed a mucinous cystadenoma of the ovary

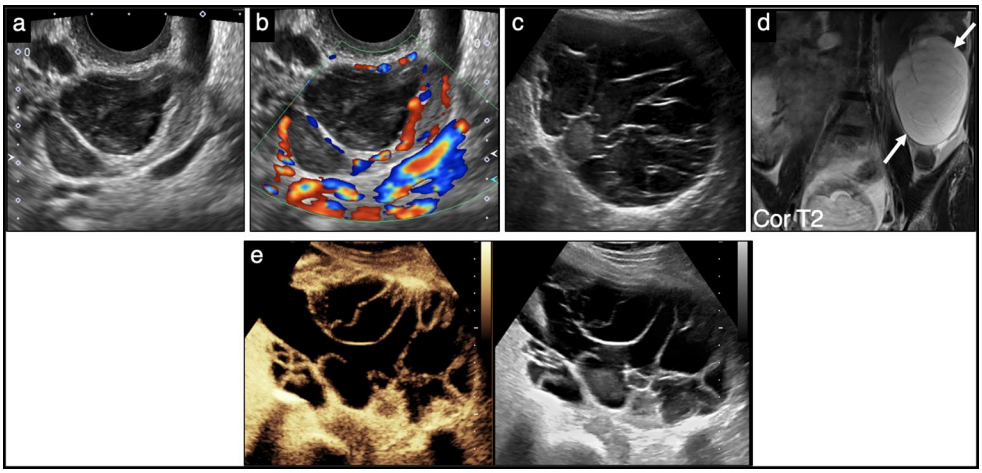

Fig. 5 Mucinous borderline ovarian tumour. 38-year-old referred for evaluation of a growing left ovarian lesion. (**a, b**) At time of a dating ultrasound, the patient was found to have a cystic left ovarian mass containing low level and reticular echoes without internal Doppler flow measuring up to 5.2 cm for which the possibility of a hemorrhagic cyst or endometrioma was raised (**c**) The lesion persisted and increased in size to 9.0 cm over a 10 week interval when reassessed at the time of a detailed anatomy US, now with numerous septations and mixed echogenicity cyst contents. (**d**) Non-contrast MRI shows a multilocular ovarian mass with multiple thin, smooth septations and homogeneous T2 hyperintense fluid. (**e**) CEUS best characterizes this mass, showing the multiplicity of septations and solid tissue with enhancement of these components, and raising concern for an epithelial malignancy The patient went on to a planned caesarean section and left salpingo-oophorectomy with Gyne-Oncology. Final pathology showed a mucinous borderline ovarian tumour

the pedicle of a pedunculated fibroid (Fig. 6, Supplementary Movie 4), distinguishing it from a solid ovarian mass.

The discovery of a focal mass within any abdominal or pelvic organ during pregnancy is challenging to establish diagnosis, significance and management. At 20 weeks and 6 days gestational age, a 31-year-old presenting to the Emergency Department with right flank pain was found to have a large solid renal mass (Fig. 7, Supplementary Movie 5).

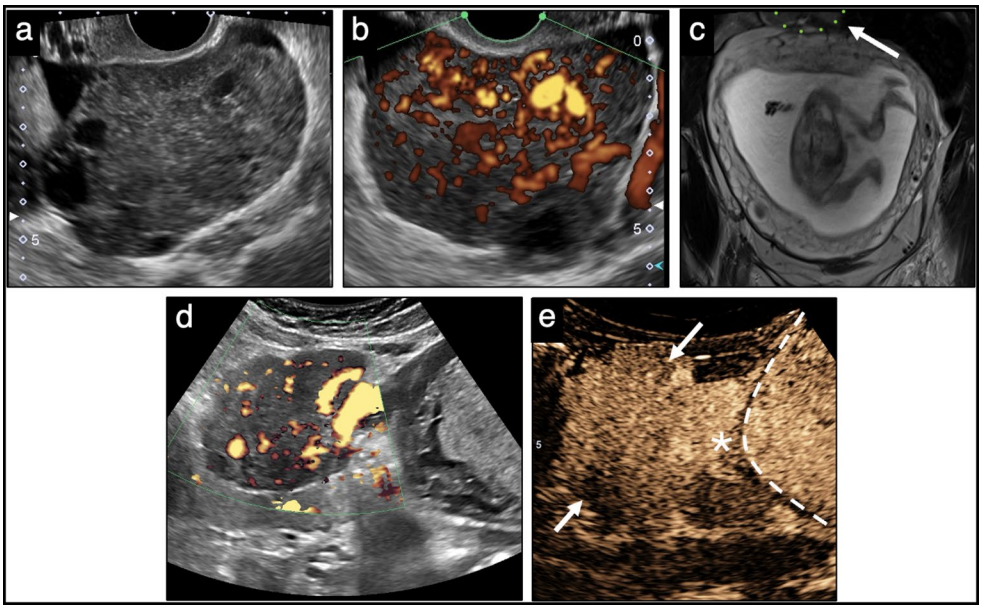

Fig. 6 Contribution of CEUS to problem clarification: Pedunculated (FIGO 7) fibroid. 39-year-old at 24 weeks referred for evaluation of a solid pelvic mass. (**a**, **b**) A dating ultrasound shows an 8 cm vascularized solid left adnexal mass presumed to arise from the ovary which was not identified separately. (**c**) Unenhanced MRI at an outside institution reported a normal left ovary. As no mass was noted, the report stated there was resolution of the solid adnexal mass. The patient was referred to our institution for diagnostic clarification. On our review of the outside MRI, we noted the mass had changed in location, present along the cephalad aspect of the uterus at the edge of the field of view (arrow). (**d**) Our US identified the mass cephalad to the uterine fundus with large vessels along the margins of the mass on Doppler imaging suspected to relate to a vascular pedicle. (**e**) CEUS readily confirms the vascular pedicle connecting the mass to the uterine fundus consistent with a pedunculated (FIGO 7) fibroid. The patient was reassured and continued with an uneventful pregnancy, undergoing elective caesarean section around 38 weeks for persistent breech presentation with intraoperative confirmation of a FIGO 7 fibroid and myomectomy

Maternal conditions of chronic liver disease (Fig. 8, Supplementary Movie 6; Fig. 9) and inflammatory bowel disease (Figs. 10 and 11) may involve patients in surveillance programs which are ideally continued throughout pregnancy. Screen detected abnormalities can provoke anxiety in any patient. During pregnancy, the ability to perform CEUS enables expedited diagnosis and management planning. In other circumstances, patients may have pre-existing pathology under follow-up with changes during pregnancy that require further evaluation (Fig. 12, Supplementary Movie 7).

Discussion

Until recently, major US and radiologic societies have had no official recommendation regarding the performance of CEUS during pregnancy. In 2023, the ACR, American Institute of Ultrasound in Medicine (AIUM), Society for Pediatric Radiology (SPR), and Society of Radiologists in Ultrasound (SRU) released revised practice parameters for the performance of CEUS including a section regarding use in pregnancy. As we have highlighted here, these societies reiterate that although limited, the literature suggests CEUS in pregnancy is safe and following a risk/benefit assessment, CEUS may be offered as a very valuable and frequently diagnostic supplementary test [33].

Leading obstetric/gynecologic societies currently have no official recommendation regarding the use of CEUS during pregnancy. The ACOG committee opinion on guidelines for diagnostic imaging during pregnancy states that "imaging tests should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient" [1].

Our brief description of a few cases supports the safety and efficacy of CEUS. We contribute to a growing body of evidence endorsing the use of CEUS in pregnancy. The state of pregnancy should not interrupt patient care and while uncommon, malignancy can occur and may be first detected during pregnancy [23]. Delaying diagnosis can create patient anxiety and runs the risk of poor outcomes for maternal and/or fetal health.

Imaging in pregnancy is an important subject which does not have a large body of research and therefore limited published reviews. Additionally, performance of prospective studies on pregnant patients has been and will continue to be limited. Nonetheless, animal studies and existing clinical experiences are reassuring for the safe use of CEUS in pregnancy. While the lack of long-term fetal outcome studies is a limitation, this information is unlikely to ever become

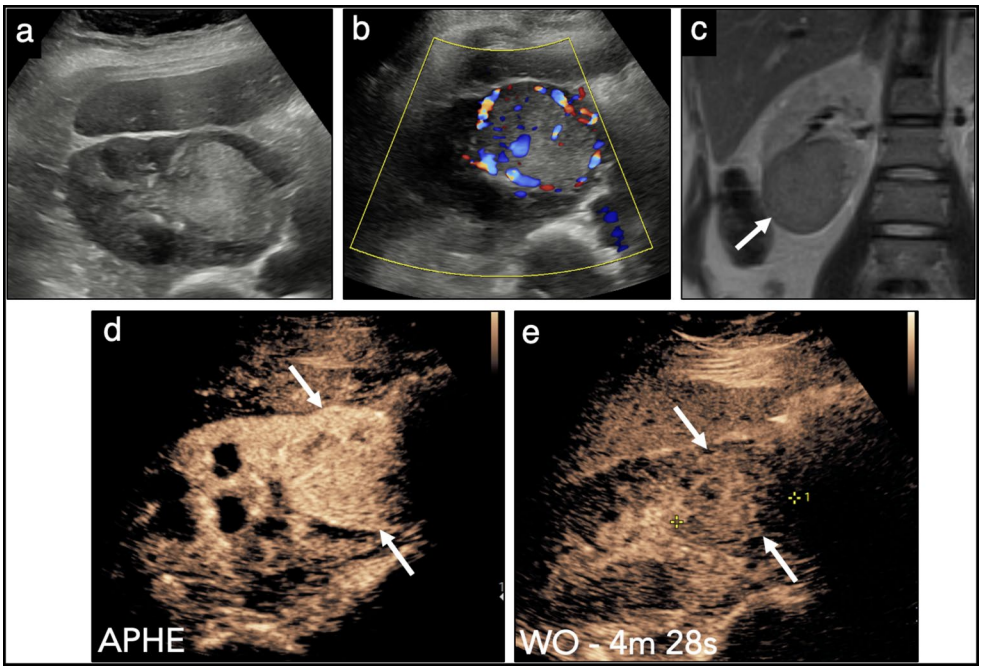

Fig. 7 Chromophobe Renal Cell Carcinoma (RCC). 31-year-old at 21 weeks with right flank pain. (**a**) Long axis greyscale image of the right kidney shows a large solid echogenic lower pole mass. (**b**) Colour Doppler imaging shows peripheral and internal vascularity. (**c**) Coronal image from T2-weighted MRI sequence shows the mass (arrow) is hypointense relative to renal cortex. Other sequences showed the mass to be isointense to cortex on T1 weighted sequence with no microscopic or macroscopic fat content (not shown). The MRI features are not consistent with a classic clear cell subtype RCC nor a benign lesion such as an angiomyolipoma. (**d**,**e**) On CEUS, the mass (arrows) demonstrates diffuse arterial phase hyperenhancement (APHE) and washout (WO) suggestive of a malignant tumour. In consultation with Urology, the patient proceeded with laparoscopic radical nephrectomy around 22 weeks gestational age with final pathology chromophobe subtype RCC. The patient recovered from her surgery and went on to a term pregnancy

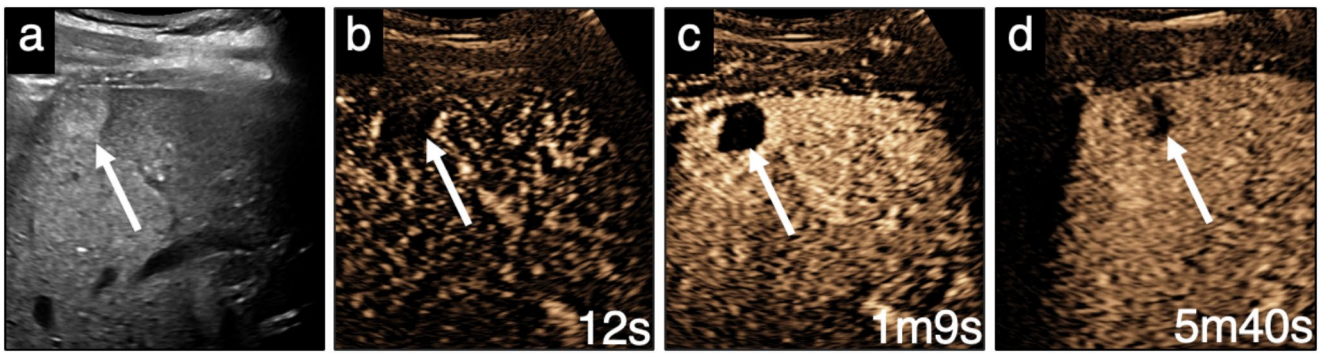

Fig. 8 Benign liver hemangioma. 43-year-old with chronic hepatitis B found to have a 1.7 cm nodule on hepatocellular carcinoma (HCC) screening US while in the first trimester of pregnancy. (**a**) Echogenic nodule on greyscale ultrasound in hepatic segment VIII (arrow). (**b**-**d**) Post microbubble contrast administration, nodule shows peripheral discontinuous nodular enhancement without washout on images taken from 12s to 5m40s consistent with a benign hemangioma. American College of Radiology (ACR) Liver Imaging Reporting and Data System (LI-RADS) can be applied in this patient with an at-risk liver. This is a LI-RADS 1 (definitely benign) observation, and the patient was reassured

available given obvious issues with feasibility and the ethics of performing appropriately controlled prospective studies.

For us and our patients, CEUS is an invaluable adjunct to standard greyscale and Doppler US. The vascular information CEUS provides has permitted us and others to make specific diagnoses which in turn has led to patient reassurance and/or direct management, including medical and surgical intervention, at times during pregnancy. US has been the longstanding test of choice during pregnancy and as evidence for the safe use of microbubble contrast agents continues to grow, CEUS should be considered as part of a new paradigm for diagnostic imaging for this population.

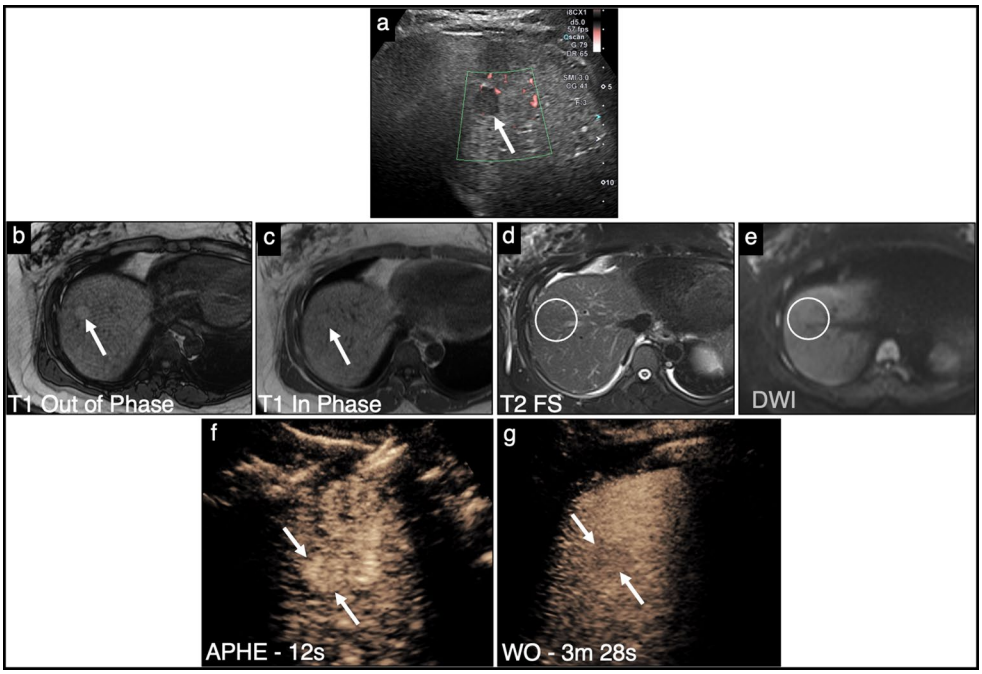

Fig. 9 ACR CEUS LI-RADS 5 liver nodule. 43-year-old at 28 weeks with chronic hepatitis B infection and cirrhosis with screen detected nodule. (**a**) Greyscale US shows a 1.7 cm hypoechoic nodule in a mildly echogenic liver in segment VII/VIII. (**b**, **c**) MRI shows the observation is mildly T1 hyperintense with no internal fat content on a background of mild hepatic steatosis. No corresponding abnormality is seen on T2 (**d**) or DWI (**e**). (**f**, **g**) On CEUS, the nodule shows arterial phase hyperenhancement (APHE) and late/mild washout (WO), consistent with a CEUS LR-5 nodule. The patient was referred to multidisciplinary tumour board and subsequently underwent ablation post-partum

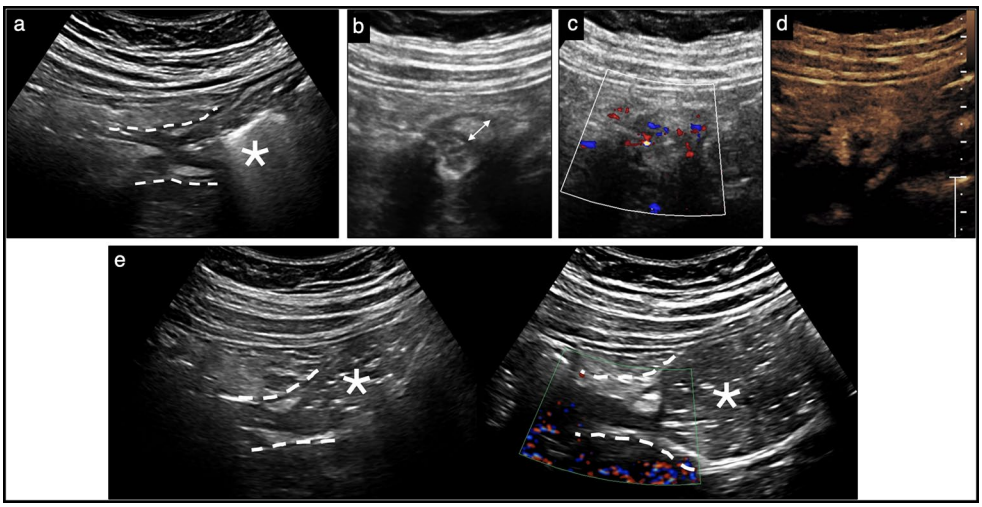

Fig. 10 Acute on chronic Crohn's disease with terminal ileal stricture. 27-year-old with Crohn's disease presenting at 24 weeks with bloating and episodic vomiting, abdominal pain and increased CRP. (**a**) Greyscale image of the terminal ileum in long axis shows a 2 cm stricture with luminal apposition (dashed lines) at the ileocecal valve. The upstream terminal ileum is dilated with excess content (*). (**b**) Short axis greyscale image of the stricture shows wall thickening up to 8 mm (arrows) with (**c**) moderate mural hyperemia on colour Doppler imaging. (**d**) On CEUS, there is transmural enhancement with peak enhancement 20 dB consistent with moderate active inflammation. Elastography median value of 1.6 m/s on this segment (not shown), suggests moderate increased bowel wall stiffness. The patient was started on a course of prednisone. (**e**) At follow-up six weeks later, there is clinical and sonographic improvement with decreased mural hyperemia and mild perienteric inflammatory fat. A stricture (dashed lines) with upstream bowel dilatation (*) persists. She proceeded uneventfully to a term pregnancy. Following delivery, the patient's symptoms continued corroborating the suspected chronic element of the stricture. She has since undergone surgical consultation and is awaiting an elective ileocolic resection

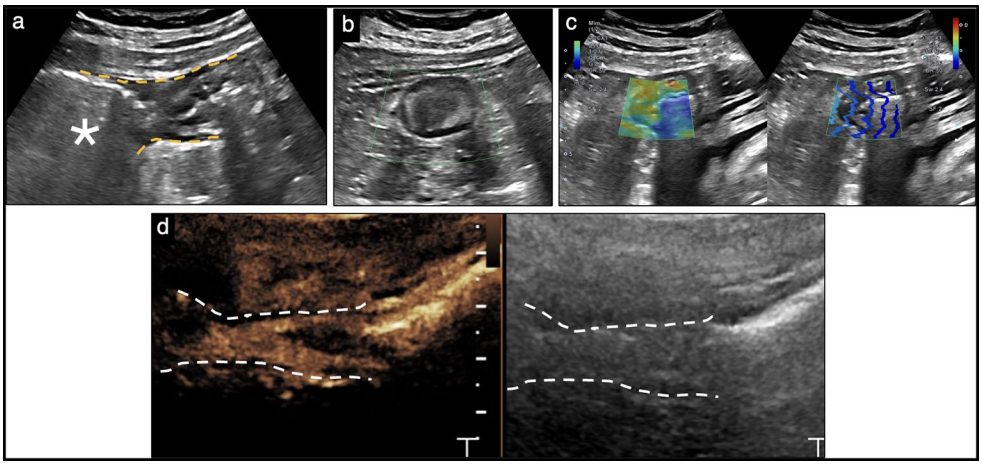

Fig. 11 Chronic Crohn's disease terminal ileum (TI) stricture. 40-year-old with Crohn's disease at 32 weeks reporting severe post-prandial bloating. (**a**) US of the TI in long axis (dashed lines) shows severe thickening over a 5 cm length. Stricture is suggested by fixed luminal apposition and prestenotic dilatation with increased fluid content (*). (**b**) Short axis image of the thickened TI shows no mural hyperemia on colour Doppler imaging. (**c**) Elastography shows a median value of 3.91 m/s suggesting severe increased bowel wall stiffness. (**d**) CEUS (left) and low mechanical index greyscale US (right) image of the thickened TI in long axis (dashed lines). There is transmural enhancement with CEUS peak enhancement measuring 15 dB indicating only mild active inflammation. Mild inflammatory activity and marked increased stiffness of the bowel suggest a chronic fibrostenotic stricture. The patient remained on adalimumab therapy during pregnancy and was referred for post-partum surgical opinion

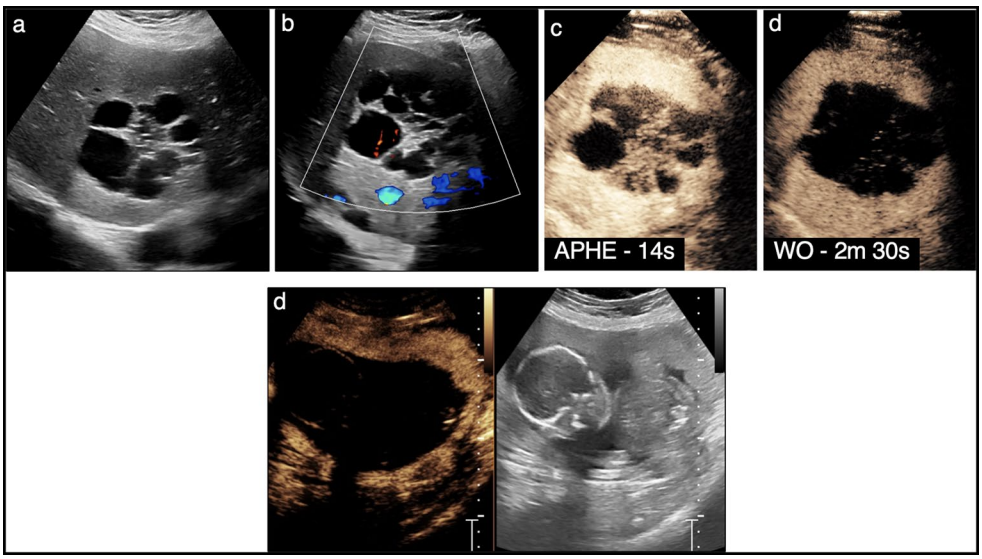

Fig. 12 Presumed mucinous cystic neoplasm of the liver. 32-year-old at 20 weeks with a known slowly enlarging cystic liver lesion. (**a**) Greyscale US shows an 8 cm multicystic liver mass with numerous septations of varying thickness. (**b**) On colour Doppler imaging, there is no detectable flow within the septations. (**c**,**d**) CEUS shows septal arterial phase hyperenhancement (APHE) with rapid washout (WO) that began before 1 min. Appearance is suggestive of a mucinous cystic neoplasm (**e**) Split screen display with CEUS image on the left and low mechanical index greyscale US image on the right show the gravid uterus with normal homogeneous enhancement of the anterior placenta and no microbubble contrast present within the fetus due to the placental barrier. The patient was referred to Hepatobiliary surgery and in consultation planned for continuation of pregnancy and a period of breast-feeding before elective mesoaxial liver resection

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Stephanie A. Nguyen[1] · David P. Burrowes[1] · Christina Merrill[1] · Stephanie R. Wilson[1]

✉ Stephanie R. Wilson
srwilson@ucalgary.ca

Stephanie A. Nguyen
Stephanie.Nguyen@albertahealthservices.ca

David P. Burrowes
David.Burrowes@albertahealthservices.ca

Christina Merrill
Christine.Merrill@albertahealthservices.ca

[1] University of Calgary, Calgary, Canada