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Safety of contrast-enhanced ultrasound using microbubbles in human pregnancy: A scoping review.

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Abstract:
Abstract
Introduction – Successful placentation is crucial for fetal development and maintaining a healthy pregnancy. Placental insufficiency can cause a variety of obstetric complications. Despite the many efforts to enhance diagnosing placental insufficiency, no imaging technique has proven satisfactory. A promising imaging technique is contrast-enhanced ultrasound (CEUS) using microbubbles which is proven capable of (micro)vascular imaging. Its use for placental vascularization assessment in human pregnancies remains constrained by limited evidence and safety concerns. This scoping review aims to demonstrate the safety of CEUS used in human pregnancy in the published literature to date.
Material and methods – a systematic search using PubMed, Medline, Embase, and Cochrane databases was performed. All studies where contrast-enhanced ultrasound was used in pregnant humans were included. Studies, where there was a planned termination of pregnancy, were excluded. To assess the safety of CEUS during pregnancy, relevant outcomes were divided into the following three categories; fetal outcome, maternal outcome, and pregnancy and neonatal outcomes.
Results – A total of 13 articles were included, in which 256 women received CEUS during pregnancy. No clinically significant maternal or fetal adverse events or negative pregnancy or neonatal outcomes associated with CEUS were described.
Conclusions - Based on our findings, we consider expanding the knowledge of this promising diagnostic technique in the future, larger clinical studies safe and relevant.

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Appendix I - search

Supplementary table 1.1. Search Medline (Ovid)

No.	Searches	Results December 2022	Results July 2023
6	5 not ((exp animals/ or exp models, animal/) not humans/)	969	**984**
5	1 and 4	1021	**1037**
4	2 or 3	32668	**33615**
3	**exp Microbubbles/ or microbubble*.ti,ab,kf.**	9123	**9483**
2	***Ultrasonography/mt or ("contrast-enhanced" and (ultrasound* or ultrasonograph*)).ti,ab,kf. or ceus.ti,ab,kf.**	25695	**26330**
1	**exp Pregnancy/ or ('child bearing' or childbearing or gestation or gravidity or pregnan* or 'labor presentation' or 'labour presentation').ti,ab,kf.**	1152456	**1178912**

Supplementary table 1.2. Search Embase

No.	**Query**	**Results December 2022**	**Results July 2023**
#6	**#5 NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)**	**149**	**171**
#5	**#1 AND #4**	**182**	**205**
#4	**#2 OR #3**	**23175**	**24496**
#3	**'microbubble'/exp OR 'microbubble*':ti,ab,kw**	**13018**	**13568**
#2	**'contrast-enhanced ultrasound'/exp OR 'ceus (echography)':ti,ab,kw OR 'contrast enhanced ultrasound':ti,ab,kw OR 'contrast-enhanced ultrasonograph*':ti,ab,kw OR 'contrast-enhanced ultrasound':ti,ab,kw**	**12092**	**12951**
#1	**'pregnancy'/exp OR 'child bearing':ti,ab,kw OR childbearing:ti,ab,kw OR gestation:ti,ab,kw OR gravidity:ti,ab,kw OR pregnan*:ti,ab,kw OR 'labor presentation':ti,ab,kw OR 'labour presentation':ti,ab,kw**	**1194430**	**1227559**

Supplementary table 1.3. Search Cochrane_

No.	Search	Results December 2023	Results July 2023
#8	#3 AND #7	15	18
#7	#4 OR #5 OR #6	855	895
#6	(microbubble*):ti,ab,kw	238	249
#5	**MeSH descriptor: [Microbubbles] explode all trees**	31	37
#4	**('contrast-enhanced ultrasound' OR ceus OR 'contrast enhanced ultrasound' OR 'contrast-enhanced ultrasonograph*' OR 'contrast-enhanced ultrasound'):ti,ab,kw**	672	701
#3	#1 OR #2	85676	91087
#2	**('child bearing' OR childbearing OR gestation OR gravidity OR pregnan* OR 'labor presentation' OR 'labour presentation'):ti,ab,kw**	85414	90675
#1	**MeSH descriptor: [Pregnancy] explode all trees**	25029	31229

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Appendix II critical appraisal

Supplementary table 2.1. Geyer et al. (2020). Contrast-Enhanced Ultrasound for Assessing Abdominal Conditions in Pregnancy

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?	+		
2. Was the study population clearly and fully described, including a case definition?		**-**	
3. Were the cases consecutive?	**+/-**		**Not clearly described**
4. Were the subjects comparable?		**- all pregnant, different pregnancy stages, different abdominal conditions**	
5. Was the intervention clearly described?	++		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		**-**	**Not clearly reported**
7. Was the length of follow-up adequate?		**- different per patient**	**Not clearly reported**
8. Were the statistical methods well-described?			**Not applicable**
9. Were the results well-described?	**+**		

Supplementary table 2.2. Orden et al. (1998). Intravascular Ultrasound Contrast Agent: An Aid in Imaging Intervillous Blood Flow?

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?	**+**		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		**-, no in-/ exclusion criteria described. Only characteristics**	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	**+**		
4. Were all eligible participants that met the prespecified entry criteria enrolled?			**Not reported**
5. Was the sample size sufficiently large to provide confidence in the findings?			**Not reported, no sample size calculation**
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	**+**		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	**+**		
8. Were the people assessing the outcomes blinded to the		**+**	**Not**

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participants' exposures/interventions?			applicable
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	+		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	+		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		-, measured once	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			Not applicable

Supplementary table 2.3. Orden et al. (2000). Contrast-enhanced ultrasonography of uteroplacental circulation does not evoke harmful CTG changes or perinatal events

Criteria	Yes	No	Other
1. Was the research question or objective in this paper clearly stated and appropriate?	+		
2. Was the study population clearly specified and defined?	+		
3. Did the authors include a sample size justification?		+	Not reported
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?		-, no seperate control selection, recieved from uncomplicated cases.	
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?		-, no clear in-/exclusion criteria stated, no definitions stated	
6. Were the cases clearly defined and differentiated from controls?		-, 69 cases of which 25 in group A (n=15 controls, came from?) and 15 in group B (controls?)	
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			Not applicable
8. Was there use of concurrent controls?	+, saline vs contrast		
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			Not reported
10. Were the measures of exposure/risk clearly defined,	+		

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valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?		-, not blinded	
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?		-	

Supplementary table 2.4. Schwarze et al. (2019). Single-Center Study: Evaluating the Diagnostic Performance and Safety of Contrast-Enhanced Ultrasound (CEUS) in Pregnant Women to Assess Hepatic Lesions

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?	+		
2. Was the study population clearly and fully described, including a case definition?	+		
3. Were the cases consecutive?	+		
4. Were the subjects comparable?	+/-, different pregnancy stages, all hepatic lesions (different types)		
5. Was the intervention clearly described?	++		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		-, different outcome measures per patient	
7. Was the length of follow-up adequate?		+	
8. Were the statistical methods well-described?			Not applicable
9. Were the results well-described?	+		

Supplementary table 2.5. Schwarze et al. (2021). Safe and pivotal approaches using contrast-enhanced ultrasound for the diagnostic workup of non-obstetric conditions during pregnancy, a single-center experience

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?	+		
2. Was the study population clearly and fully described, including a case definition?	+, no case definition		
3. Were the cases consecutive?	+		
4. Were the subjects comparable?		-, all pregnant, different pregnancy stages, different pathology	
5. Was the intervention clearly described?	++		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		-, all pregnant, different pregnancy stages, different pathology	
7. Was the length of follow-up adequate?		+	
8. Were the statistical methods well-described?			Not applicable
9. Were the results well-described?	+		

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Supplementary table 2.6. Kirkinen et al. (1997). Placenta accreta: imaging by gray-scale and contrast-enhanced color Doppler sonography and magnetic resonance imaging

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?		-, descriptive case report, no aim/ objective stated	
2. Was the study population clearly and fully described, including a case definition?		-, no case definition	
3. Were the cases consecutive?			Not reported
4. Were the subjects comparable?		- comparable patients, different pregnancy outcome, different imaging techniques	
5. Was the intervention clearly described?		-, unclear if patient 1 recieved CEUS, no dosage reported	
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		+	Not reported
7. Was the length of follow-up adequate?	+, no follow-up for patient 1, adequate follow-up for patient 2		
8. Were the statistical methods well-described?			Not applicable
9. Were the results well-described?	+		

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Introduction

The placenta is vital for fetal development, maintaining a healthy pregnancy, nutrient delivery, gas exchange, and immune regulation[1]. Successful placentation is crucial and achieved by trophoblast invasion. Defective placentation could ultimately lead to placental insufficiency, causing obstetric complications like fetal growth restriction (FGR) and pre-eclampsia (PE), impacting 3-5% and 2-8% of all pregnancies, respectively[2,3]. The FGR definition is consensus-based and ultrasound diagnosis is often inaccurate[4]. Furthermore, it is challenging to differentiate FGR from small-for-gestational-age (SGA) cases[4]. Roughly 70% of all small-for-date fetuses are healthy (SGA), while 30% are FGR and prone to complications[5]. Despite the many efforts to enhance diagnosing placental insufficiency, no imaging technique has proven satisfactory.

A promising imaging technique is contrast-enhanced ultrasound (CEUS), which employs ultrasound contrast agents (UCAs), microbubbles encapsulating a non-toxic gas in a (phospho)lipidic shell[6,7]. UCAs remain metabolically inert, immuno-neutral, and stay within the intravascular space rendering them suited for (micro)vascular imaging[8–10]. With a half-life averiging between 2 to 15 minutes, they are rapidly eliminated through renal or pulmonary clearance[11–13]. Contrast-specific imaging sequences, exploiting the highly nonlinear acoustic respone of UCAs compared to tissue, improve the visualization of the UCA-perfused (micro)vasculature[14]. CEUS has been widely used for various non-obstetric indications including cardiac diagnostic imaging[15]. Its safety profile for these indications is well-established, with minimal adverse events (AE) reported. In a cohort study of 49,100 patients, the incidence of AE was found to be merely 0.088%, with no fatalities[16]. Adverse events include anaphylactia, nausea, dizziness, headache, chest discomfort, back pain, and injection site reactions[17]. CEUS is more accessible when compared to other contrast-enhanced imaging techniques and enholds no radiation. Most importantly, it is proven capable of identifying intervillous space perfusion, suggesting its potential to identify compromised villous tree architecture leading to placental insufficiency[8,18,19]. Yet, its use for placental vascularization assessment in human pregnancies remains constrained by limited evidence and safety concerns. Safety encompasses maternal complications, placental tissue integrity, and fetal development interference[20].

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Though CEUS's safety is not firmly established, prior research has already explored its use during pregnancy. However, this mostly entails studies in animals or pregnancies with planned termination[8,9,21–28]. These studies yield reassuring findings regarding the effect of CEUS on maternal, and fetal safety, and perinatal outcomes[29]. For example, studies describe that microbubbles, used during CEUS, do not interfere with the permeability nor cross the placental barrier[9,30]. However, data on ongoing pregnancies and postnatal effects remain scarce. Consequently, it has not yet been approved for use in pregnancy by the FDA.

The objective of this scoping review is to comprehensively examine all studies utilizing CEUS during ongoing human pregnancies, for both obstetric and non-obstetric indications, to evaluate fetal and maternal safety.

Methods

We conducted this scoping review to identify and review all published literature to date on the safety of using microbubbles in human pregnancy, adhering to the PRISMA-ScR guidelines checklist.

The inclusion criteria involved original studies employing CEUS with microbubbles as UCAs on pregnant subjects with both obstetric and non-obstetric indications. Exclusions were made for studies involving planned termination of pregnancy, as well as review articles and study protocols. Language restrictions were not applied.

To identify relevant literature, a structured literature search was performed in December 2022 across databases including Medline, Embase, and Cochrane, with an update conducted on July 19, 2023. Additionally, we conducted a free text term search in PubMed and examined reference lists of both included and excluded publications to identify any additional relevant studies.

The search terms used were: Pregnancy, contrast-enhanced ultrasound, and microbubbles (and synonyms). Search terms were applied to all fields using MeSH and Emtree terms were used in the database searches (Appendix I, supplementary table 1.1-1.3).

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All papers generated by the searches were screened for titles, abstracts, and keywords by two independent reviewers (referred to as A and B) labeling them as “include”, “exclude”, or “maybe”. Reviewers were able to leave comments if needed. Articles were reviewed in full text by both reviewers in case of a disagreement or ambiguity, followed by discussion leading to inclusion or exclusion. All included studies were reviewed in full text.

The study quality assessment tools by the National Heart, Lung, and Blood Institute (NHLBI) were used to assess the quality of the case series, case-control studies, pre-post studies, and observational studies [31]. However, quality assessment was not performed for case reports, as is common in scoping reviews. The quality and risk of bias were assessed by the two researchers by answering the predefined quality checklist questions and stating the degree of quality as “high”, “moderate”, or “low’. Any discrepancies were resolved through discussion and, if necessary, consultation with a third expert (C) (Appendix II, supplementary table 2.1-2.6).

To assess the safety of CEUS during pregnancy, outcomes were categorized into fetal, maternal, and pregnancy/ neonatal outcomes. Relevant fetal effects seen during or shortly after the CEUS included microbubble uptake in fetal compartments or the umbilical cord, alteration in the fetal cardiovascular system (indicated by changes in cardiotocography (CTG), fetal heart rate, or umbilical cord blood flow), alterations in fetal movements, impairment of fetal growth and/ or development, and fetal death. Maternal adverse events considered relevant included nausea, abdominal/ flank pain, headache, pruritus, rash, allergic reactions, or anaphylaxis. Lastly, relevant pregnancy outcomes were; the mode of delivery (vaginal or cesarean section (CS)), gestational age at the time of delivery, the indication in case of termination of pregnancy, and subsequent neonatal outcomes (live birth, neonatal death, and neonatal condition postpartum). Study characteristics were noted before data extraction in a data extraction form in which the results from all included studies were systematically presented.

Results

The literature search was carried out in July 2023 and yielded 1166 results. After resolving duplicates, 1097 studies remained. Screening of titles and abstracts excluded 1066 studies primarily unrelated to the topic of interest, CEUS used in a non-ongoing

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pregnancy or involving animal subjects, or those concerning review articles or study protocols. Following full-text review and discussion, 22 articles were excluded for similar reasons. Thus, 9 studies were eligible for inclusion. The additional PubMed search and reference list review provided another 4 eligible studies. A total of 13 studies, comprising 256 women receiving CEUS during pregnancy, were included in the scoping review (Figure 1).

The studies, published between 1997 and 2022 were predominantly from northwestern European countries (10), with two from Asia, and one from North America. They all utilized quantitative methods, with various study designs: six case reports, three case series, two diagnostic studies, one observational study, and one experimental study. Sample sizes ranged from one to 137 women with both uncomplicated and complicated singleton or twin pregnancies. The contrast agents SonoVue,Levovist and Definity were used across all trimesters for both obstetric and non-obstetric indications (Table 1). The varied agents utilized, type of UCA, and the number of patients involved are illustrated in Table 2.

For all studies, except the case reports, a risk of bias assessment and critical appraisal of methodological quality was performed. After reviewer discussion, one study was rated as “high” quality, four as “moderate”, and one study as “low” (Appendix II). Two studies had only abstracts available but were included since a significant number of participants underwent CEUS for placental vascularization imaging and the information in the abstract was considered sufficient for inclusion [32,33].

Charted data

To determine the safety of CEUS in human pregnancy, the following outcome measures were charted; fetal and maternal outcome during or directly after the use of CEUS, pregnancy outcome, and neonatal outcome postpartum (Table 3).

Maternal outcomes

Seven studies addressed maternal adverse events post-CEUS, of which only one case report showed a transient mild lipase elevation after the CEUS-guided endoscopic retrograde cholangiopancreatography (ERCP) in a third-trimester pregnant woman. CEUS was used during the ERCP procedure to visualize the common bile duct during

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cannulation as an alternative to fluoroscopy[34]. This elevation, common after ERCP, was not clinically significant nor related to CEUS. Furthermore, six studies reported the absence of maternal adverse events without further elaboration [35–40]. The remaining six studies did not report on maternal outcomes after CEUS [32,33,41–44].

Fetal outcomes

Seven out of thirteen studies stated fetal outcomes during or directly after CEUS without any adverse events. A 1997 case study used CEUS to determine chorionicity in a twin pregnancy with discordant fetal growth at 30 weeks because chorionicity was not assessed accurately at 16 weeks gestation. The procedure was uncomplicated. Fetal heart rate and Doppler measurements of the umbilical artery remained unchanged post-CEUS [41].

Another case series described 11 CEUS examinations in 5 pregnant women evaluating non-obstetric intra-abdominal conditions including renal angiomyolipoma, pyelonephritis, and uterine fibroids. The absence of fetal adverse events and fetal contrast uptake is described in this article [35].

Furthermore, in a 1998 diagnostic study, 25 pregnant women (29-42 weeks gestation) underwent power Doppler ultrasound with and without contrast agent enhancement to evaluate uteroplacental circulation. Seventeen pregnancies were uncomplicated, while eight pregnancies were already complicated with FGR. No fetal adverse events occurred and acute fetal distress was excluded before, during, and after CEUS using computerized CTG analysis [36].

In a 2019 case-control study, 69 high-risk patients, based on their general or obstetric history or current obstetric problems, received CEUS in the third trimester. A subset received computerized CTG analysis shortly before and after CEUS (n=25). They were compared to a control group who received a physiological saline injection during the ultrasound examination (n=15). Both CEUS and control groups showed statistically significant increase in short-term variability, accelerations, and fetal movements after injection. There were no significant changes detected in the umbilical blood flow velocity waveform 5 minutes after UCA administration. This study stated that there

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were no signs of immediate deterioration of fetal well-being trelated to the CEUS examination [37].

Of the seven studies remaining, three reported the absence of fetal adverse events without elaborating on it [38–40] and four did not reportthe presence or absence of fetal adverse events [32–34,42–44].

Pregnancy and neonatal outcome

Nine out of thirteen studies assessing pregnancy and neonatal outcomes after CEUS found no direct negative effects.. In a recent case report, published as an abstract in 2023, CEUSwas employed during the 32nd week of gestation to diagnose liver lesions suspected of malignancy. The urgency to accurately confirm or rule out a malignancy during pregnancy was crucial due to potential consequences for the mother and child. CEUS confirmed liver metastasis derived from colon cancer. The pregnancy was terminated by a planned CS at 34 weeks gestation, after antenatal corticosteroids. Neonatal outcomes were not stated [33]. The remaining four studies did not explicitly report pregnancy or neonatal outcomes [32,34,36,40]

In a recent case series examining non-obstetric intra-abdominal conditions using CEUS, pregnancy and neonatal outcomes were reported for one of the five pregnant participants. This patient, diagnosed with renal angiolipoma, received five consecutive CEUS to monitor tumor growth and delivered a healthy neonate at 38 weeks. The outcomes for the remaining four participants were not stated [35].

In the 2019 case-control study with 69 high-risk pregnancies, as described above, CEUS was used. No immediate complications were seen post-procedure. Six patients delivered prematurely. Two of these were already known with FGR, two had placenta abruption and/or vaginal hemorrhage 5 and 9 days after CEUS, and one had an abnormal CTG 10 days after CEUS. The sixth pregnancy was not described specifically. The remaining 63 patients delivered at term. Seventeen patients delivered by CS, where the indication for the CS was not reported. A total of seventeen neonates were treated in the neonatal intensive care unit (NICU) for different indications.This study concluded no direct harmful effects, attributing infavorable outcomes more to high-risk aspects of the

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pregnancy. They also stated that UCAs for the examination of maternal circulation are safe in the third trimester [37].

In a case series with 6 participants, CEUS and MRI were compared for visualizing various liver abnormalities (i.e., hepatic metastases, atypical hemangiomaand arteriovenous malformation) during pregnancy. Two CEUS were performed: one confirmed hepatic metastases of rectal cancer at 24 weeks gestation, followed by delivery at 32 weeks gestation, and the other to diagnose an unknown hepatic mass at 19 weeks gestation. Four months later, progressive hemorrhages in the liver prompted an immediate CS at 35 weeks gestation. One vaginal delivery occurred spontaneously at 35 weeks. The mode of delivery was not described for the other participants [38].

In a German case series, 5 pregnant women underwent CEUS for different non-obstetric conditions. In one case, CEUS was used initially to diagnose rhabdomyosarcoma in the rectus abdominis muscle and secondly to perform a CEUS-guided biopsy of the lesion. Furthermore, CEUS was performed in a patient 33 weeks pregnant, for identification of a hepatic hemangioma. Both patients gave birth vaginally to a healthy term neonate. The other indications included diagnostics for liver abscess at 5 weeks gestation, diagnostics for intra-abdominal bleeding after a high-speed car accident at 21 weeks gestation, and analysis of a renal cyst in a pregnant woman with recurrent urinary tract infections at 12 weeks. Further pregnancy and neonatal outcomes were not described in these last 3 cases. Despite this, coupled with the absence of fetal and maternal adverse events, the researchers concluded that CEUS is safe for these indications during pregnancy [39].

In a case study, using CEUS to determine chorionicity in a twin pregnancy, monochorionicity was confirmed prompting delivery due to discordant fetal growth. Both infants required supportive neonatal care after CS at 30 weeks due to prematurity [41].

One case report used CEUS to visualize the invasion of the placenta into the cesarean scar tissue at nineteen weeks gestation after two previous CS. It showed an invasion of the placenta through the myometrium into the bladder wall. At 22 weeks of gestation, immature rupture of the membranes occurred simultaneously with vaginal bleeding. Labor was induced immaturely with oxytocin. The neonate passed away 14 minutes

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after vaginal delivery [42]. It is unlikely that CEUS was the luxating factor for this immature rupture of membranes. Placenta accreta together with vaginal bleeding is a more plausible explanation for this event and the subsequent pregnancy outcome.

In a case report, a patient with two prior term CS experienced an incomplete uterine rupture at 17 weeks gestation. After the rupture was repaired in the ongoing pregnancy, MRI and CEUS were used, which indicated placenta increta as the underlying cause for this complication. The pregnancy progressed without complications until the planned CS at 32 weeks, when the patient gave birth to a live-born neonate [43].

Lastly, a diagnostic study published in 2022 used CEUS to differentiate between benign or malignant ovarian tumors during pregnancy. The study involved 105 subjects in the live birth group. Among them, 52 cases were diagnosed with malignant tumors using CEUS in the 3rd trimester ,all of whom gave birth to a healthy baby. This article also reported that 72 women delivered at term, while 27 had preterm deliveries. However,the reason for preterm delivery was not specified, nor whether it was iatrogenic. In addition, therewas notelaborated on the neonatal outcome. Pregnant women who were diagnosed with an ovarian tumor early in pregnancy opted more often for elective abortion [44].

Discussion

Overall, the results of this scoping review provide reassurance regarding the safety of CEUS during human pregnancy. Safety was assessed based on maternal adverse effects, fetal outcomes impacted by CEUS, and interference with the pregnancy and neonatal outcome. Across all trimesters, a considerable number of pregnant individuals received CEUS for both obstetric and non-obstetric indications without any complications, regardless of the type of UCA used. The majority of the included articles described pregnancy and neonatal outcomes after using CEUS with no apparent negative outcomes directly attributed to CEUS. Similarly, no maternal adverse events linked to the CEUS procedure were observed. Moreover, research investigating the direct effect of CEUS on fetuses indicated that the UCAs do not enter the fetal circulation and therefore cannot adversely affect fetal health or development[8,30].

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These findings are consistent with prior research in animal models and human pregnancies where termination of pregnancy was planned. In recent years, CEUS has found application in pregnant animal models for several indications, consistently confirming that UCAs remain confined to the maternal circulation, preserving placental integrity and presenting no risk to the fetus[8,9,20,27,28,45]. In addition to these findings, a recent study in animal models featuring FGR demonstrated CEUS's potential in estimating and quantifying placental perfusion [18].

Comparable outcomes emerged from studies conducted in non-ongoing human pregnancies, which showed no detection of UCA's on the placenta's fetal side, umbilical vein, or fetal compartments during the CEUS procedure [25,30]. Moreover, one of these studies demonstrated the absence of maternal adverse events such as nausea, abdominal pain, headache, itching, rash, or allergic reactions [30]. Additionally, a subset of human cases subjected to CEUS in the first trimester right before TOP, placental tissue was obtained one hour after this procedure for histological examination of tissue integrity using electron microscopy, revealing no signs of microvascular hemorrhage, lodging of microbubbles in the intervillous space, nor damage to the syncytiotrophoblast microvilli [19].

Various microbubble types have been commercially available for years[46,47]. Sulfur hexafluoride microbubbles, also known as Lumason or SonoVue, and perflutren microbubbles like Definity are categorized as pregnancy category B by the Food and Drug Administration (FDA), meaning animal studies show no harm to the fetus, but no adequate studies have been done in pregnant women[48,49]. This suggest the use of this drug only if clearly needed. Other microbubble agents are FDA-approved for human use but not yet for use in pregnancy.

This scoping review is the first to structurally assess the maternal and fetal safety of CEUS during pregnancy. Combining all published reports results in a relatively large number of pregnant women who underwent CEUS. Overall, reassuring pregnancy, maternal, and fetal outcomes were reported. However, it is important to consider that the degree of evidence was notably variable, and the included studies were not all specifically designed to investigate the safety of CEUS during pregnancy. Therefore, no meta-analysis could be performed. In addition, different contrast agents were used by

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different research groups, at different moments in pregnancy for different indications, which makes it more difficult to compare the results. Finally, publication bias could be a limitation, although no specific signs of publication bias were identified after the quality assessment.

Conclusion

CEUS has demonstrated effectiveness in visualizing the placental microvasculature and assessing maternal blood flow in the placental intervillous space (IVS) [6,8,9,20,24,47]. It is a promising, relatively straightforward technique that can be used during pregnancy for a wide range of (non-) obstetric indications [50]. In the future, CEUS might be an imaging modality of great added value in diagnosing (non-)obstetric complications during pregnancy, for instance, the distinction between SGA and FGR fetuses based on the placental microvasculature.

So far, clinical data on CEUS using microbubbles in pregnancy is still limited. However, this scoping review suggests that there is evidence of CEUS being safe during pregnancy. Furthermore, theoretical knowledge and previous animal and human studies, show no harmful effects of CEUS during pregnancy. In conclusion, we recommend expanding the knowledge of this promising diagnostic technique in future, larger clinical studies to establish the additional value and safety of CEUS during ongoing human pregnancies further.

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Table 1. Study characteristics of studies using CEUS in pregnancy

Reference & country	Year of publication	Study type	Population	Total number of participants	Number of participants eligible	Number of CEUS	Contrast agent	Indication for use of CEUS	Expos period
Roberts et al. USA [32]	2017	Experimental study	Pregnant women, uncomplicated pregnancies	35	35	35	Definity	Assessment of placental perfusion	1st trimes
Mengjia et al. Japan [33]	2023	Case report	Pregnant woman, uncomplicated pregnancy	1	1	1	Perflubutane~~Not stated~~	Diagnosing liver metastasis during pregnancy	3rd trimes
Götzberger et al. Germany [34]	**2020**	**Case report**	**Pregnant woman,** uncomplicated **pregnancy**	**1**	**1**	**1**	**SonoVue**	**CEUS-guided ERCP for treatment of common bile duct stones**	**3rd trime**
Geyer et al. Germany [35]	**2020**	**Case series**	**Pregnant women,** uncomplicated **pregnanc**ies	**5**	**5**	**11**	**SonoVue**	**Assessment of various intra-abdominal conditions during pregnancy**	**2nd & trime**
Ordén et al. Finland & Sweden [36]	1998	Diagnostic study	Pregnant women. 16 uncomplicated pregnancies, 7 FGR, 1 PE & FGR, 1 gestational	25	25	25	Levovist	Examination of uteroplacental circulation	3rd trimes

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			diabetes (GDM)						
Ordén et al. Finland [37]	2000	Case-control	Pregnant women. 45 uncomplicated pregnancies, 8 FGR, 1 PE & FGR, 5 PE, 4 GDM, 4 vaginal bleeding, 1 fetal Down's syndrome, 1-hypothyreodism	69	69	69	Levovist	Examination of uteroplacental circulation and umbilical artery blood flow	3rd trimes
Schwarze et al. Germany [38]	**2019**	**Case series**	**Pregnant women,** uncomplicated **pregnancies**	**6**	**6**	**6**	**SonoVue**	**Assessment of hepatic lesions during pregnancy**	**2nd & trime**
Schwarze et al. Germany [39]	2021	Case series	Pregnant women, uncomplicated pregnancies	5	5	6	SonoVue	Evaluate safety and value of CEUS during pregnancy to investigate non-obstetric conditions	1st, 2nd 3rd trimes
Schwarze et al. Germany [40]	**2020**	**Case report**	**Pregnant woman,** uncomplicated **pregnancy**	**1**	**1**	**1**	**SonoVue**	**Diagnosing liver echinococcosis during pregnancy**	**1st trime**
Denbow et al. England	**1997**	**Case report**	**Pregnant woman, twin-pregnancy**. Uncertainty	**1**	**1**	**1**	**Levovist**	**Assess chorionicity**	**3rd trime**

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[41]			of chorionicity.					**and placental vascularization**	
Kirkinen et al. Finland [42]	1997	Case report	Pregnant woman with 2 previous cesarean sections	1	1	1	Levovist	Imaging of abnormal placental adherence	2nd trimes
Pintault et al. France [43]	2021	Case report	Pregnant woman with incomplete uterine rupture and repair in current pregnancy	1	1	1	Not stated	Imaging of the placenta adherence	2nd trimes
Yin et al. China [44]	2022	Diagnostic study	Pregnant women with an ovarian tumor	137	105	105	Not stated	Assessment of ovarian tumors in pregnancy	1st, 2nd 3rd trimes

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Table 2. Results of included studies on the safety of CEUS in pregnancy.

UCA*	Type of microbubble agent	Pharmacokinetics	
		$t_{1/2}$ #	Clearance
SonoVue	Sulphur hexafluoride microbubbles	12 minutes (range 2-33 minutes)	Pulmonary
Levovist	Galactose – Palmitic Acid microbubbles (No longer in use)	Galactose: 10-15 minutes Palmitic Acid: 1-4 minutes	Renal
Definity	Phospholipids-encapsulated perfluoropropane microspheres	1.68 minutes	Pulmonary

*: UCA: ultrasound contrast agent. #: half-time.

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Table 3. Results of included studies on the safety of CEUS in pregnancy.

Reference & country	Fetal outcome	Maternal outcome	Pregnancy and neonatal outcomes
Roberts et al. USA [32]	Not stated.	Not stated.	Not stated.
Mengjia et al. Japan [33]	Not stated.	Not stated.	Planned cesarean section at 34 weeks gestation after antenatal corticosteroids
Götzberger et al. Germany [34]	Not stated.	Transient mild elevation of lipase post-ERCP.	Not stated.
Geyer et al. Germany [35]	No fetal adverse events. No fetal contrast uptake detected during CEUS.	No maternal adverse events.	One vaginal delivery of a healthy neona 38 weeks gestation after 5 consecutive C Four cases with unknown pregnancy outcome.
Ordén et al. Finland & Sweden [36]	No fetal adverse events. **Acute fetal distress excluded using CTG analysis before, during, and after CEUS.**	No maternal adverse events.	Not stated.
Ordén et al. Finland [37]	No fetal adverse events. Similar increase in **short-term variation,** accelerations, and fetal movements **in CEUS and control group after** the procedure. No changes in umbilical artery blood flow velocity waveform.	No maternal adverse events.	6 premature deliveries (8.7%), 17 cesare sections (24.6%). F**ive premature neon with a 1 and 5-min APGAR score of b 7 and 6 respectively**, 17 NICU admissi
Schwarze et al. Germany [38]	No fetal adverse events.	No maternal adverse events.	Two cesarean sections at 32 and 35 wee gestation, one vaginal delivery at 35 we gestation, rest with delivery of unknown route. Neonatal outcome not stated.

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Schwarze et al. Germany [39]	No fetal adverse events.	No maternal adverse events.	Two vaginal births at 37 and 40 weeks g gestation, Three deliveries of unknown All healthy neonates.
Schwarze et al. Germany [40]	No fetal adverse events.	No maternal adverse events.	Not stated.
Denbow et al. England [41]	No fetal adverse events. Fetal heart rate and Doppler unaltered.	Not stated.	Uncomplicated pregnancy. Delivery by cesarean section at 30 weeks gestation. natal supportive neonatal care for prema
Kirkinen et al. Finland [42]	Not stated.	Not stated.	Immature rupture of membranes at the 2 week of gestation. Induction of labor. V delivery. Neonatal death 14 minutes pos partum due to immaturity.
Pintault et al. France [43]	Not stated.	Not stated.	Planned cesarean section at 32 weeks of gestation after repaired incomplete uteri rupture. Live birth.
Yin et al. China [44]	Not stated.	Not stated.	72 full-term deliveries, 27 preterm deliv 105 live births, 52 healthy neonates afte CEUS in the 3rd trimester.

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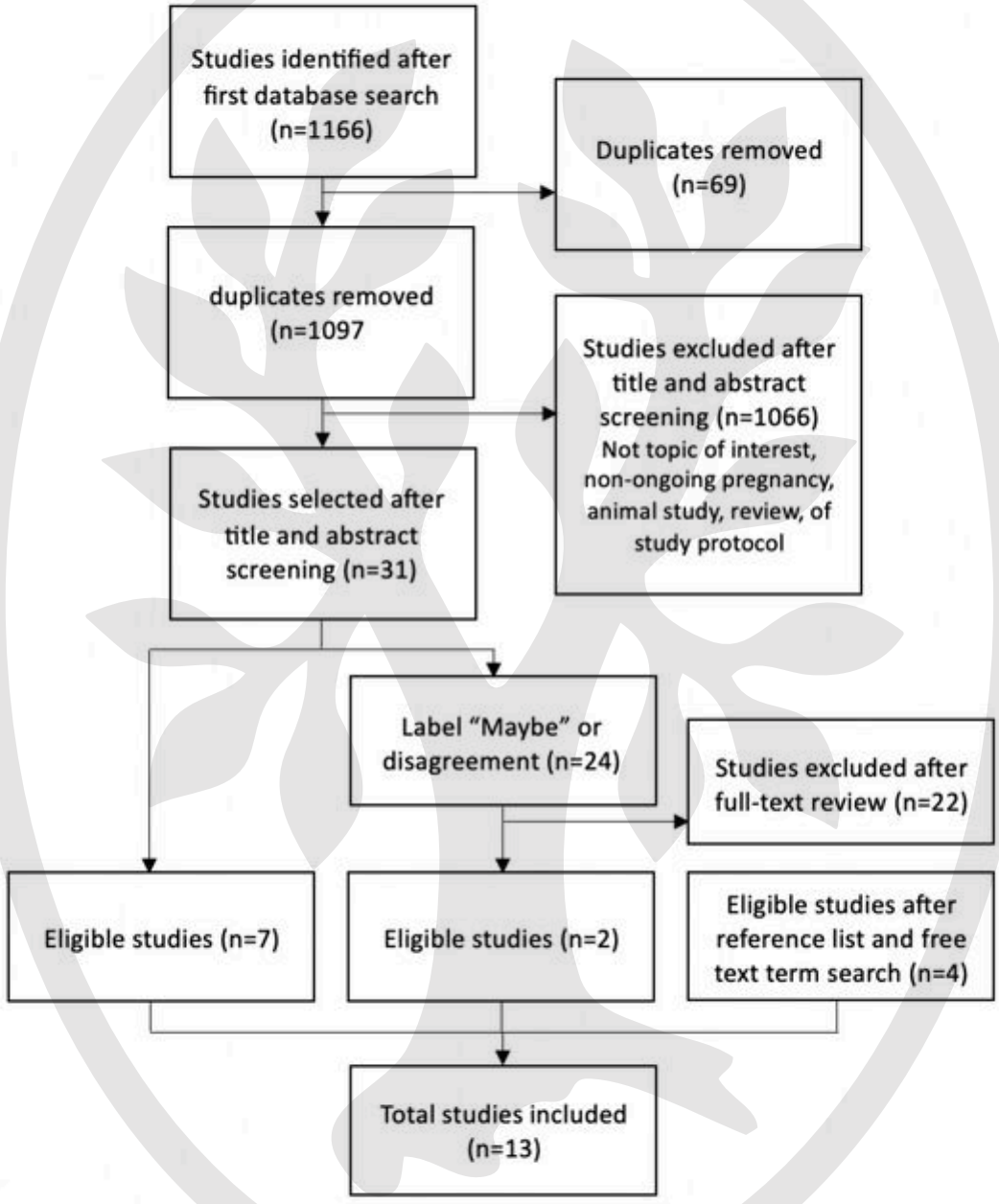

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