

OBSTETRICS

Ultrasound-guided high-intensity focused ultrasound is technically feasible and safe for occluding placental vessels in early-onset twin-twin transfusion syndrome



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BACKGROUND: Twin-twin transfusion syndrome is a complication unique to monochorionic pregnancy, where shared placental vascular connections can lead to a circulatory imbalance, resulting in preterm delivery and attendant in utero or neonatal mortality. The only disease-modifying treatment is fetoscopic laser ablation of blood vessels, which has attendant risks of invasive intrauterine therapy.

OBJECTIVE: In this first-in-human technical feasibility and safety study, we investigated noninvasive, ultrasound-guided high-intensity focused ultrasound to occlude placental vascular targets as identified by color Doppler. The 2 outcomes were (1) safety: number/rate of patients experiencing significant iatrogenic harm, for first 14 days after high-intensity focused ultrasound and (2) efficacy: number/rate of targeted placental vessels which appear occluded at the end of a high-intensity focused ultrasound treatment cycle, assessed using comparison of color Doppler imaging of target anastomoses prehigh-intensity focused ultrasound and posthigh-intensity focused ultrasound exposure.

STUDY DESIGN: Participants with anterior placenta and early-onset twin-twin transfusion syndrome were recruited to a Phase 1a clinical trial with co-primary endpoints of safety and efficacy of vessel occlusion at 12 to 17⁺₆ weeks of gestational age.

RESULTS: Ten participants underwent targeted ultrasound-guided high-intensity focused ultrasound occlusion of placental blood vessels that connected the 2 circulations, verified by color Doppler imaging, in whom 27 of 30 (90%) targeted placental vessels were successfully occluded by ultrasound-guided high-intensity focused ultrasound. No treatment-related significant maternal or fetal adverse events were recorded, and 18 of 20 fetuses were alive 14 days post-treatment. Participants expressed positive attitudes toward ultrasound-guided high-intensity focused ultrasound, valuing clear and consistent communication and sufficient time to consider participation in the study.

CONCLUSION: In this Phase 1 study, ultrasound-guided high-intensity focused ultrasound showed a high rate of successful occlusion of placental vascular targets and no adverse side effects were observed within 14 days of treatment in women with early-onset twin-twin transfusion. While clinical efficacy of the technique could not be formally evaluated, 5 participants required fetoscopic laser and of the pregnancies treated, 12 of 20 neonates were alive at discharge.

Key words: anastomoses, monochorionic twins, noninvasive, placenta, safety, therapy

Introduction

Fetoscopic laser to treat twin-twin transfusion syndrome (TTTS) was pioneered by the US physician De Lia in the 1980s, with the aim of treating the cause rather than the symptoms of the condition.¹ This unique complication affects 15% of monochorionic diamniotic twins^{1,2}; the clinical manifestations result from anomalous placental anastomoses between the twin circulations, leading to vascular imbalance. A subsequent European multicenter study of selective occlusion of arteriovenous anastomoses on the vascular equator

showed reduced perinatal mortality and neurological sequelae.² However, while representing standard of care treatment, a reduction in mortality has not been confirmed by meta-analysis³ despite advances in the fetoscopic laser technique.⁴

Fetoscopic laser requires puncture of the skin, uterus, and amniotic cavity, thereby giving entry into the intrauterine space. No matter how skilled the practitioner, risks include previability preterm rupture of the membranes, miscarriage, or infection of the amniotic cavity.⁵ These complications make the use of fetoscopic laser surgery less compelling in early-stage TTTS where the prognosis is more favorable or at early gestational ages where the risks of intrauterine invasion are greater.⁶ Furthermore, technical challenges exist in women with anterior placentas, as the required shallow angle of the fetoscope

to the vessels can lead to incomplete visualization of vessels and suboptimal therapeutic effects from laser.

TTTS can be apparent from as early as the 12th week of gestation. Therefore, a noninvasive alternative treatment—were it shown to be clinically effective—would have advantages since the risks of uterine puncture and amniotic cavity entry are eliminated. Importantly, noninvasive treatment would not preclude the use of fetoscopic laser for progressive or recurrent TTTS at a later gestational age, when the risks of fetoscopic laser are lower. High-intensity focused ultrasound (HIFU) offers noninvasive technology with thermal and/or mechanical effects that can ablate soft tissue and occlude blood vessels. It has been used to treat related complications in monochorionic twins, such as twin reversed arterial perfusion sequence,⁷ and was able to occlude blood flow in half of the cases.

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AJOG at a glance

Why was this study conducted?

To determine if ultrasound-guided high-intensity focused ultrasound can safely and effectively occlude monochorionic placental vessels in early-onset twin-twin transfusion syndrome.

Key findings

In 10 participants, ultrasound-guided high-intensity focused ultrasound achieved a high rate (90%) of successful occlusion of targeted placental vessels in early anterior placenta twin-twin transfusion syndrome. No significant maternal or fetal adverse events occurred. However, half of the women required subsequent fetoscopic laser and 60% of fetuses survived to discharge.

What does this add to what is known?

Ultrasound-guided high-intensity focused ultrasound is a feasible, noninvasive method for selective placental vessel occlusion in early twin-twin transfusion syndrome with anterior placenta. While Phase 1 technical efficacy and procedural safety were established, clinical efficacy remains to be evaluated.

However, the use of HIFU to occlude flow in human placental vessels has not been investigated. Our previous studies using preclinical animal models of high human translational potential showed that HIFU technology was efficient and safe as a noninvasive method of selective occlusion of sheep placental vessels.^{8–10}

Imaging placental anastomoses using conventional color Doppler has been well described.¹¹ Importantly for the successful use of HIFU to occlude placental vessels, advances in Doppler imaging techniques¹² now allow noninvasive vascular imaging that is sensitive to low velocity flow within the monochorionic placenta.

Here, we present the ‘first-in-human’ experience of ultrasound-guided HIFU to occlude placental vessels in women with monochorionic diamniotic twins where TTTS presenting prior to 18 weeks of gestation was diagnosed and their referring fetal medicine experts judged that invasive therapy was not indicated because of gestational age or other factors. These results represent a completed Phase 1 human clinical trial whose primary outcome was to determine the technical feasibility and short-term procedural safety of using low flow Doppler and ultrasound-guided HIFU to identify and occlude placental vessels in the monochorionic placenta. While

we report maternal and fetal outcomes, these were a secondary outcome as the study was not powered for clinical efficacy in treating TTTS and furthermore no assumption was made that the placental vascular targets represented intertwin anastomoses.

Materials and methods**Study design**

The primary research objectives of this Phase 1a clinical trial of efficacy of vascular occlusion and safety of ultrasound-guided HIFU in TTTS were to determine (1) the proportion of vascular targets within the monochorionic placenta in which successful occlusion could be achieved and (2) the occurrence of any maternal or fetal adverse events resulting from attempted or successful occlusion within 14 days of treatment. The secondary research objectives were to establish the effect on stage of TTTS disease, the need for follow-on invasive procedures, the incidence of miscarriage, intrauterine fetal death, and maternal or fetal morbidity in the 2 weeks following exposure to ultrasound-guided HIFU.

The clinical trial was undertaken according to a Bryant and Day 2-stage design. This allows simultaneous assessment of 2 binary endpoints (efficacy of vascular occlusion and safety of

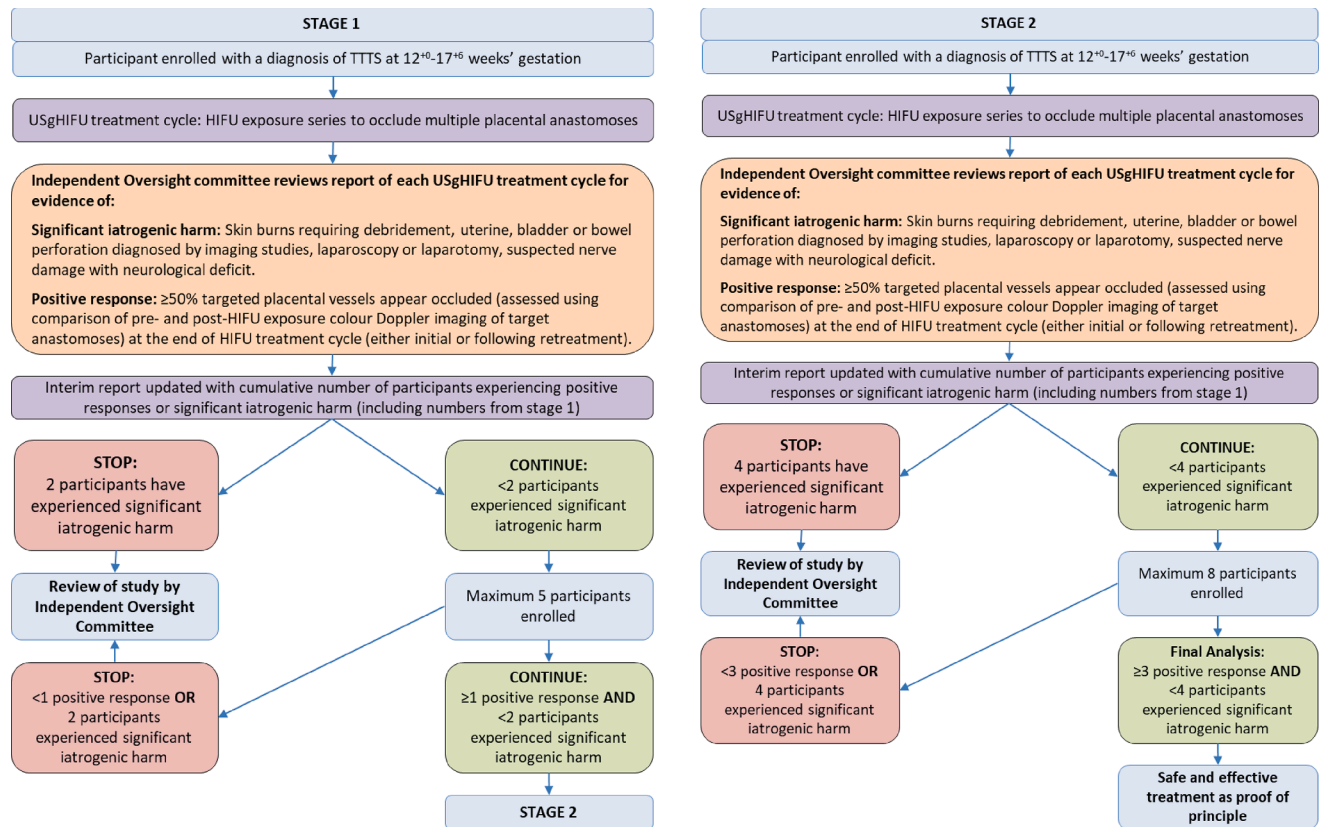
the intervention under investigation) in clinical trials where the intervention is such that the concept of dose escalation is not applicable. It incorporates a formal check in each successive participant of the cumulative number of positive responses and the number of participants experiencing iatrogenic harm (Figure 1), by an independent oversight committee (IOC), before allowing further recruitment. A qualitative substudy was conducted to explore acceptability of ultrasound-guided HIFU in TTTS.

Study population and participant identification

Participants were referred from UK and European fetal medicine centers by their treating clinicians for recruitment at a specialist fetal medicine unit in London, UK from January 2021 to June 2024. The trial was approved by the London Riverside Research Ethics Committee (REC reference 20/LO/0029) and was included in the National Institutes of Health Research Clinical Research Network Portfolio. The protocol was prospectively published on the ISCTRN trial registry.¹³ At recruitment, written informed consent for participation and publication of results was obtained.

Participants were eligible if aged more than 18 years and pregnant with an ongoing monochorionic diamniotic twin pregnancy diagnosed with stage II to IV TTTS between 12⁺⁰ and 17⁺⁶ weeks of gestation age and anterior placenta. TTTS was diagnosed using Quintero staging criteria¹⁴ modified to accept deepest vertical pocket of amniotic fluid <8 cm in the recipient twin where the donor was a “stuck twin” and all other features favored a diagnosis of TTTS. This more permissive definition was confirmed by the expert advisory group for this study and is consistent with a recent Delphi consensus¹⁵ and review of diagnostic criteria in TTTS.¹⁶ All participants had a preexisting diagnosis of TTTS made by an independent clinician prior to referral to the research team. Prior to inclusion, all potential participants also underwent advanced dynamic flow Doppler imaging of the

FIGURE 1
Bryant-Day 2-stage design for this study



The schema defines both positive responses and significant iatrogenic harms for this Phase 1 study, the criteria by which the outcome for each successive participant is to be evaluated by the Independent Oversight Committee (IOC). Based on these criteria, the continue/stop rules are applied to the cumulative number of positive responses and significant iatrogenic harms encountered by successive participants and determine whether (i) recruitment can proceed to the next participant or (ii) the study needs to be stopped for review by the IOC.

placenta using a 1.8 to 6.2 MHz convex probe (i8C1, Aplio i900, Canon Medical Systems) to identify suitable target placental vessels.¹²

In all cases, chorionicity was determined at 11 to 14 weeks of gestation using established methods.¹⁷ Gestational age was determined from the crown-rump length of the largest fetus¹⁸ in spontaneous pregnancies and in *in vitro* fertilization pregnancies by using the date of transfer and embryonic age. Exclusion criteria were body mass index (BMI) >35, single intrauterine fetal death or selective termination prior to recruitment, fetoscopic laser ablation of placental vessels prior to recruitment, higher order pregnancy (even if containing a monochorionic diamniotic pair), or inability to identify suitable

placental target vessels. All trial participants were eligible to take part in the qualitative substudy.

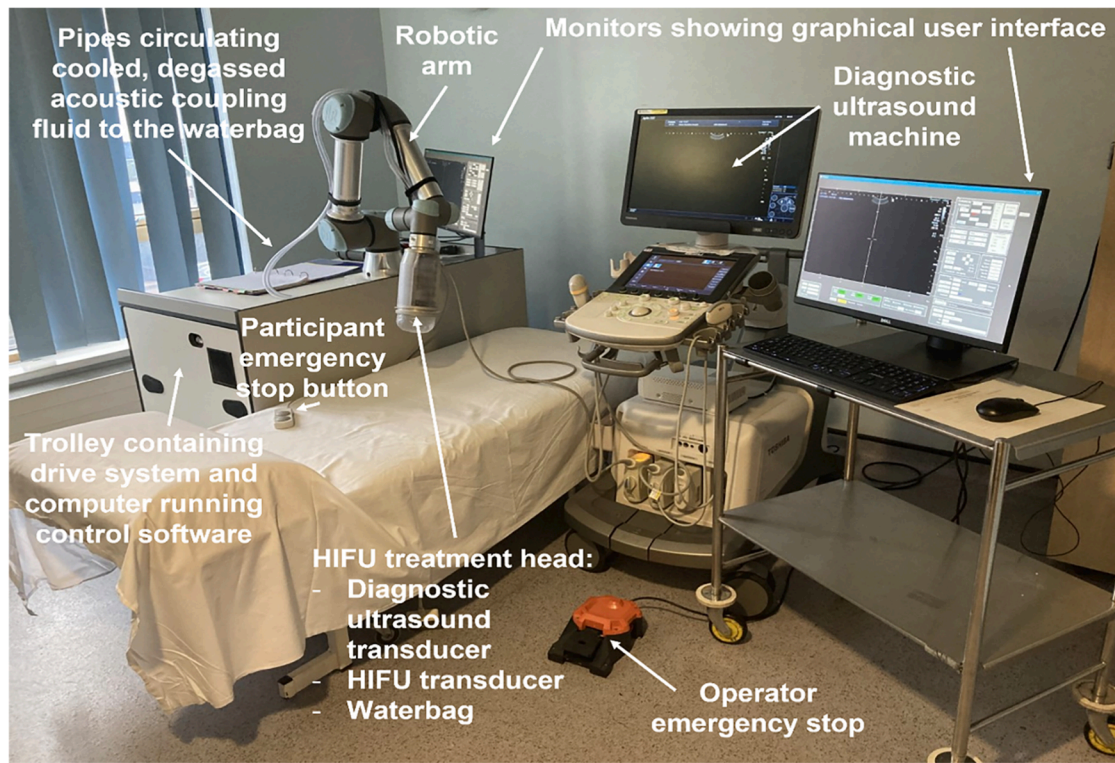
Sample size

The primary research objective of this Phase 1a study was technical efficacy of occluding placental vascular targets while avoiding iatrogenic harm to the mother. A Bryant and Day 2-stage design (Figure 1) with 85% power and 15% significance level for both positive response and significant iatrogenic harm was used to determine sample size.¹⁹ We assumed that the response probability if ultrasound-guided HIFU is inactive to be 10% and the response probability if ultrasound-guided HIFU is active to be 50%. The unacceptable rate of iatrogenic harm was set at 40%,

while the acceptable rate was set at 10%. Based on these conservative assumptions of technical efficacy of vascular occlusion and safety, we required up to 5 participants for stage 1 to be recruited. Subject to meeting the predefined safety and technical efficacy of vascular occlusion parameters, we required up to a further 8 participants for stage 2 to be completed.

Participants who were eligible and wished to be included (rather than opting to continue with standard care, including invasive treatments, if appropriate) were given at least 24 hours to confirm their decision. Following this, ultrasound-guided HIFU treatment was performed (day 0, see below). Follow-up visits which comprised an obstetric ultrasound scan to assess fetal wellbeing and TTTS stage,

FIGURE 2
Ultrasound-guided HIFU therapy system



The picture shows the robotic arm mounted on a trolley in relation to the HIFU and diagnostic ultrasound transducers and machine, and the coupling fluid cooling, degassing, and circulation system. The system is modular, designed to be moved to the patient bedside. The trolley contains the HIFU drive system and desktop computer equipment. The computer runs the graphical user interface software and controls communication with all the hardware components of the system. The system includes a participant emergency stop button, an operator emergency stop footswitch (which must be engaged to allow the robotic arm to move or the HIFU transducer to deliver energy), and both user interfaces have emergency stop buttons included in the software.

HIFU, high-intensity focused ultrasound.

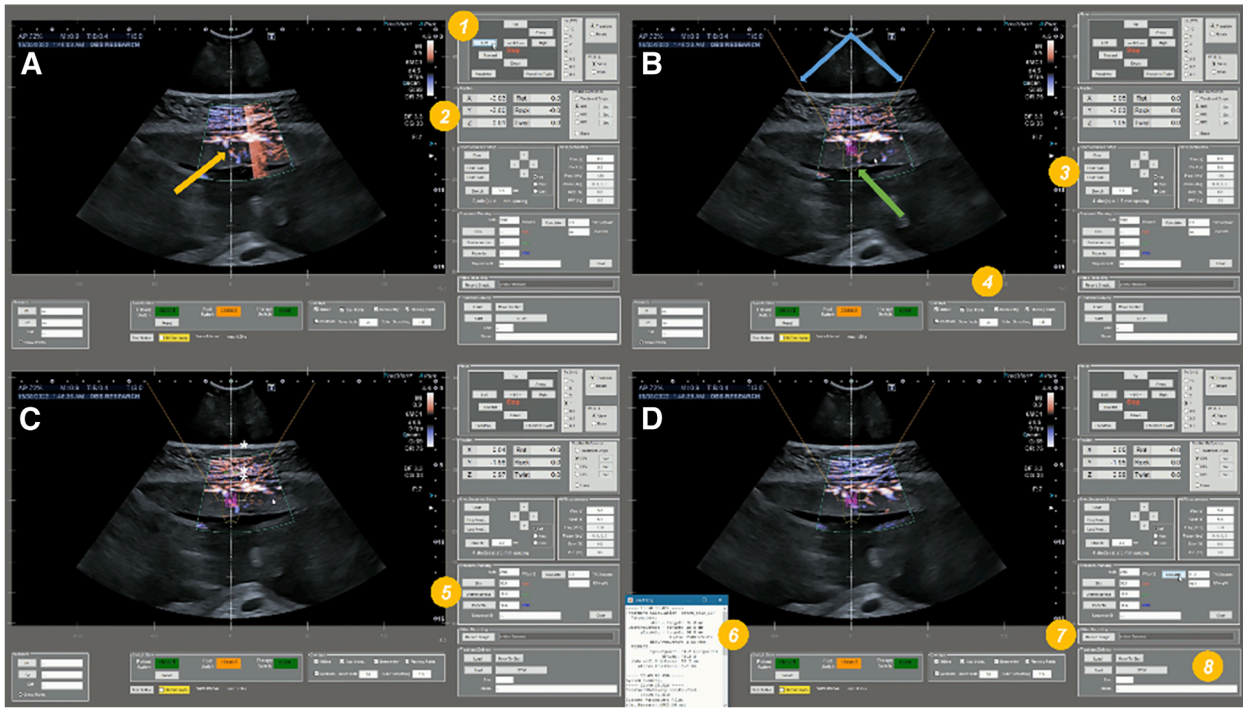
and an examination for evidence of maternal iatrogenic harm, took place on days 1, 3, 7, and 14. During this period, if indicated and appropriate, participants received invasive fetoscopic laser therapy undertaken in their referral unit. Participants completed a symptom diary for 14 days following ultrasound-guided HIFU treatment. The trial consent form included an option to consent to participation in the qualitative substudy.

Therapy system

An ultrasound-guided HIFU system was custom designed and built by the research team to meet the requirements of this trial (Figure 2). The HIFU transducer (H-175, Sonic Concepts, USA: frequency 1.66 MHz, outer diameter 110 mm, focal length 90 mm) contained a 50-mm diameter central aperture through which

a diagnostic transducer (PVT-382BT, Aplio i900, Canon Medical Systems) was inserted to allow real-time targeting of vessels. The HIFU and diagnostic transducers were co-aligned, with the HIFU transducer focus at a fixed position on the imaginary midline of the diagnostic transducer image. A 3-dimensional (3D) printed treatment head containing the diagnostic and therapeutic transducers allowed their mounting on a robotic arm (UR5e, Universal Robots, Denmark). A thin custom-shaped polythene water bag containing circulating, degassed, and temperature-controlled acoustic coupling medium was attached to the robotic arm. The water bag was coupled to the maternal skin using sterile paraffin liquid. An HIFU drive system (TPO105, Sonic Concepts, USA) powered the therapy transducer, the Radio Frequency (RF)

power was monitored using RF Wattmeters (22B, Sonic Concepts, USA), and an electronic relay ensured electrical isolation of the therapy transducer from the drive unless the system was ready to deliver a treatment. The robotic arm allowed 3D movement of the treatment head (controlled via a Universal Robots Polyscope script in communication with the control computer), with emergency stop hardware and software for both operators and study participants. The operator's graphical user interface was written in Matlab (Mathworks, Natick MA, USA) R2019b (Figure 3, Supplemental Video 1) running on a Windows 10 desktop computer. The entire system (including the scanner) was powered via a built-in, medically rated, electrical isolation transformer for participant and operator safety and underwent a formal quality assurance

FIGURE 3**Planning an USgHIFU exposure series using the graphical user interface**

The images A to D show screen captures of the graphical user interface (GUI) used to plan an USgHIFU exposure in a placental vascular target. The full video from which these screen captures are taken is provided as [Supplemental Video 1](#).

USgHIFU, ultrasound-guided high-intensity focused ultrasound.

check by the physicist and engineer prior to each treatment.

High-intensity focused ultrasound treatment protocol

All women were conscious during treatment, and no form of anesthesia or analgesia was used. Before treatment, all potential placental vascular targets were identified independently by the clinical researchers (Drs Shaw and Lees) using Doppler imaging, and then a joint agreement on target selection and order of treatment was reached in conjunction with the physicist and engineer (Dr Rivens and Mr Symonds-Taylor). The selection of vascular targets was based on: (1) the appearance of a vessel linking the twins' placental circulations, (2) estimation of vessel size and flow, (3) the depth of the vessel below the maternal skin, and (4) the separation of the target from maternal and fetal structures at risk of thermal injury, assessed using graphical user interface overlays of the

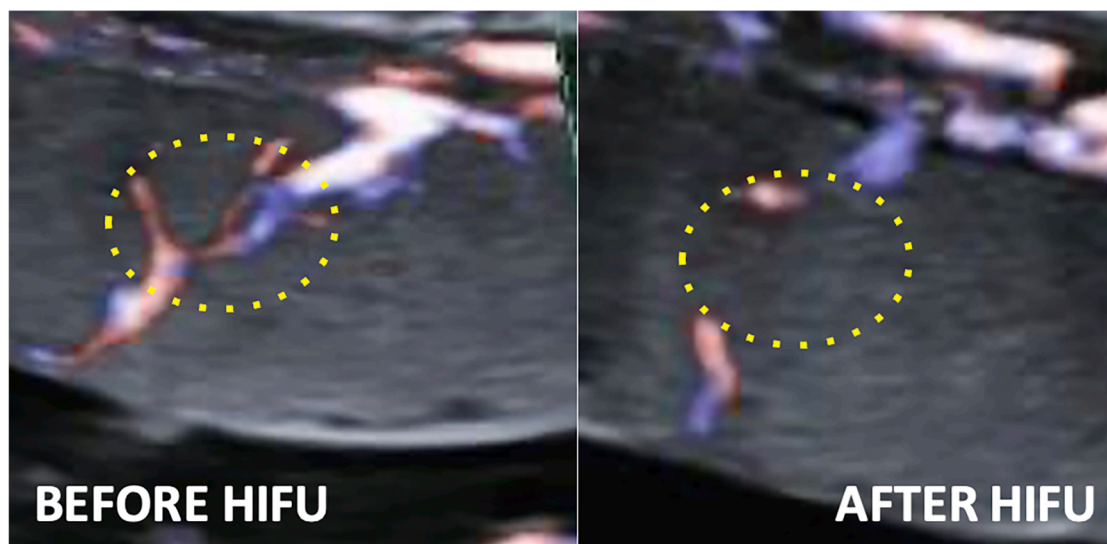
beam profile around the planned HIFU treatment positions. Consecutive HIFU exposures are referred to as an "HIFU exposure series". The number and positions of targets were reviewed after each exposure series, as fetal movement might prevent safe treatment, or altered blood flow from prior occlusions might prevent target identification. Treatment was deemed complete when either (1) no target vessel flow remained detectable on Doppler ultrasound or (2) the only remaining target vessel(s) could not be occluded using the maximum intensity identified to avoid hemorrhage in previous studies.

The ultrasound-guided HIFU system delivered a controlled amount of ultrasound energy, adjusted for the estimated attenuation of overlying tissues, through the intact maternal abdominal skin to the target vessel. The dimensions of the ellipsoidal HIFU focal zone (~1.1 mm wide) relative to the target vessel size meant that between 2 and 5 adjacent

exposures, spaced 2 mm apart in a line, were required to avoid missing the target. Each individual exposure lasted 5 seconds with a 5-second interval for tissue cooling and repositioning of equipment prior to subsequent exposures.

Target vessels were imaged using Doppler before, and immediately after the last therapeutic exposure, in a series (for at least 60 seconds), in the same 3D position. The system captures and stores a video of its graphical user interface, including the ultrasound equipment's Doppler imaging in real time. Successful occlusion of a vessel was defined as no detectable Doppler flow in real time seen by both treating investigators after HIFU treatment, using the same (or lower) velocity scale as the preexposure imaging (Figure 4). Where there was a failed occlusion (defined as residual detectable Doppler flow), the vessel could be reexposed using either the same treatment settings or those modified by using higher energy and/or more exposures

FIGURE 4
Color Doppler assessment of occlusion



The ultrasound image on the left shows pretreatment color Doppler imaging of placental vasculature. The intended target is ringed with yellow. The image on the right shows the same placental vessel and area after exposure of the target to HIFU, demonstrating “no flow” within the targeted vessel.

HIFU, high-intensity focused ultrasound.

and/or a slightly different target position, unless, as a result of the initial exposure series, there was: (1) evidence of maternal skin changes, (2) suspicion of fetal or other maternal injury, and (3) suspicion of vessel hemorrhage. There was no predefined limit to the number of retreatments which could be performed.

The maternal skin was inspected for evidence of coloration changes or damage before and after completion of each ultrasound-guided HIFU exposure series. Participants were asked to report any sensation experienced during, and immediately after, each exposure series with reference to a numerical grading scale (0–10). If there was evidence or suspicion of significant iatrogenic harm after any ultrasound-guided HIFU exposure series, the treatment protocol was halted. In women with a rhesus negative blood group, exposure to ultrasound-guided HIFU was managed as a potentially sensitizing event.

Pregnancy care

Ongoing pregnancy and delivery care, including further invasive therapy where required, was provided by

referring fetal medicine units in accordance with local and national guidance for monochorionic diamniotic twins.²⁰

Data collection and statistical analysis

Maternal demographic characteristics; ultrasound findings at the time of referral; ultrasound-guided HIFU procedure details; outcomes of visits at days 1, 3, 7, and 14; and symptom diaries were recorded in a MACRO electronic database.

Continuous data were assessed for normality using the Shapiro-Wilk test. For normally distributed data, mean $\pm$ standard deviation (SD) is reported; median and range were used for nonparametric data. Proportions of categorical data were described as a percentage of the relevant denominator.

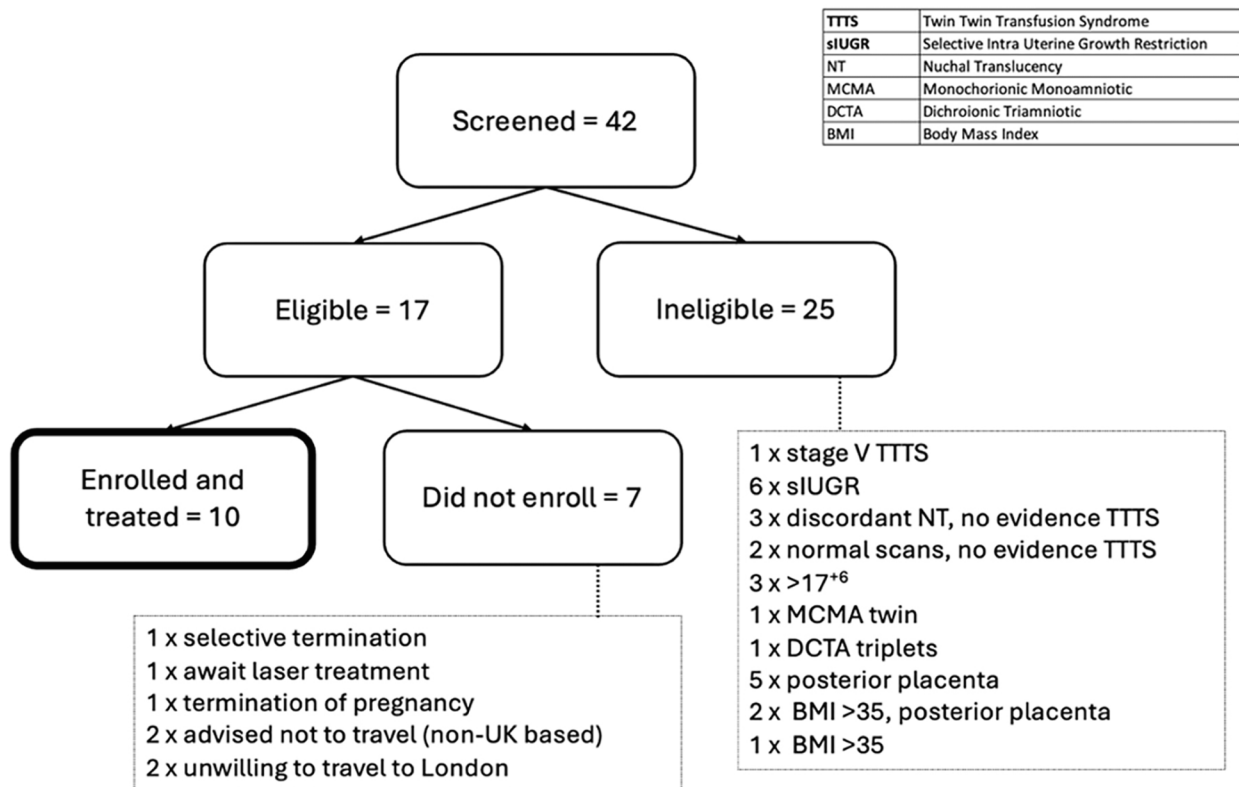
Those who consented to participation in the qualitative substudy were invited to take part in remote (online or telephone) semi-structured interviews. Interviews were audio-recorded with consent and transcribed. Data were uploaded to NVivo 12 (Lumivero, CO,

USA) and analyzed thematically, using both deductive (theory driven) and inductive (researcher driven) coding. The interview topic guide and deductive coding framework were designed to address substudy aims and known topics of relevance, as identified by the study team and the wider literature.

Results

Forty-two women were screened as potentially eligible for inclusion (Figure 5). Of these, 25 did not meet eligibility criteria. Of 17 who were eligible and offered recruitment, 10 consented to take part in the trial. This clinical trial report therefore details 10 participants with monochorionic diamniotic twin pregnancies who underwent ultrasound-guided HIFU treatment of TTTS at 15⁺ to 16⁺ weeks of gestation. At inclusion, 6 participants had stage II (cases 1, 2, 3, 6, 8, and 9) and 4 had stage III TTTS (cases 4, 5, 7, and 10; Table 1). The median age of participants was 34 years (range, 24–46), and median BMI was 25 (range, 20–29). In 8 women, the pregnancy was a result of spontaneous conception; 5 participants were nulliparous. None had relevant

FIGURE 5
Study participant flow diagram



medical histories. One participant had a previous cesarean delivery before 28 weeks of gestation.

After the 10th participant had completed treatment, the efficacy of vascular occlusion and harm data were reviewed by the IOC to consider stopping or continuing the trial. The lower confidence interval limit for efficacy of vascular occlusion was above our original assumption of 50%. The proportion of women experiencing significant iatrogenic harm was 0/10 (0%, 0% to 31%); the upper limit of the confidence interval is below the level of unacceptable harm (set at 40%). Given the observed performance of the customized ultrasound-guided HIFU system in terms of both technical efficacy and safety, the IOC approved completion of the second stage of the study after treating 10 of the planned 13 participants. Power for this smaller sample size was reduced to 80% from 85% while maintaining alpha at 15% using the

original conservative assumptions for harm and efficacy.

Clinical outcomes

Following ultrasound-guided HIFU treatment, in 8 pregnancies, both fetuses were alive on day 14, and in 2, there was a single intrauterine fetal death (Table 1). In one case, this occurred after a fetoscopic laser performed on day 7 for stable stage III TTTS (18⁺⁴); in the other case, the fetal death was identified at day 14 (19⁺³) following a day 7 scan which showed fully resolved TTTS. In a further 4 participants, by day 14, TTTS had resolved based on Quintero staging; however, in one of these, it later recurred leaving 3 in whom complete resolution was confirmed. Five participants required a fetoscopic laser in their referring units following HIFU treatment for stage III TTTS.

The study sample size was not designed to determine clinical efficacy. However, of 20 fetuses alive at the time

of treatment, 15 (75%) were live born and 12 (60%) survived to neonatal discharge. Placental examination was not undertaken as in all cases either delivery occurred remote from the treating site, or laser was undertaken, or both (Supplemental Table 1).

Primary outcome: technical efficacy

Based on comparison of pre-HIFU and post-HIFU exposure Doppler imaging, 27 of 30 targeted vessels were successfully occluded (90%). Specifically, 18/27 (67%) target vessels were occluded following the first ultrasound-guided HIFU exposure series; the remaining 9/27 were occluded following 2 ultrasound-guided HIFU exposure series. In 8 participants, treatment was deemed complete as there were no remaining targets left unoccluded. In one of the 2 in whom treatment was not considered complete, one vessel was exposed to ultrasound-guided HIFU but not occluded and on

TABLE 1
Fetal ultrasound changes before and after high-intensity focused ultrasound (HIFU) treatment

Participant	GA	Before HIFU treatment (day of treatment)						Outcome following HIFU treatment						Living fetuses day 14 after HIFU
		D/R DVP (cm)	D/R bladder filled	D/R UA EDF	D/R DV 'a' wave	D/R Hydrops present	D/R EFW discrepancy (%)	D/R DVP (cm)	D/R bladder present	D/R UA EDF	D/R DV 'a' wave	D/R Hydrops present	D/R EFW discrepancy (%)	
1	16+5	1.5/8.5	N/Y	+/+	+/+	N/N	38	2.7/6.3	Y/Y	+/+	+/+	N/N	24	2
2	16+2	1.3/5.7	N/Y	+/+	+/+	N/N	35	2.9/6.0	Y/Y	+/+	+/+	N/N	26	2
3 *	15+5	1.2/6.5	N/Y	+/+	+/+	N/N	2	2.3/6.8	Y/Y	+/+	+/-	N/Y	2	2
4	16+4	0.0/4.4	N/Y	+/+	+/-	N/N	31	3.0/5.5	Y/Y	+/+	+/+	N/N	17	2
5 *	16+5	0.0/7.6	N/Y	+/+	+/-	N/N	43	0.0/7.4	N/Y	+/+	+/-	N/N	27	2
6	17+6	1.5/6.1	N/Y	+/+	+/+	N/N	33	2.8/4.7	Y/Y	+/+	+/+	N/N	34	2
7 **	17+4	0.7/9	N/Y	+/+	+/-	N/N	28	0.0/10.8	N/Y	+/-	+/-	N/N	22	1
8	17+3	1.2/6.9	N/Y	+/-	+/+	N/N	20	0.0/9.8	S/Y	S/+	S/+	S/N	NA	1
9	16+6	1.4/8.5	N/Y	+/-	+/+	N/N	30	0.0/9.3	N/Y	-/-	+/+	N/N	56	2
10	15+6	0.6/8.7	N/Y	+/-	+/-	N/N	40	0.0/9.5	N/Y	+/+	+/-	N/N	31	2

The table shows gestational age (GA) at the time of inclusion in the study. The values reported show the ultrasound assessment of the donor (D) and recipient (R) twins' deepest vertical pool (DVP); bladder filling; characteristics of umbilical artery or ductus venosus waveforms; "a" represents positive umbilical artery end diastolic flow (UA EDF) or positive ductus venosus (DV) 'a' wave; "—" represents absent/reversed UA EDF or DV reversed 'a' wave; and the presence or absence of hydrops. The percentage difference in estimated fetal weight (EFW) was calculated as (EFW larger twin – EFW smaller twin)/EFW larger twin × 100. The values are on the day of treatment (day 0) and after 14 days, except for in participants 3 and 5 (denoted by *) where the findings are reported on day 10 following HIFU treatment as participants underwent fetoscopic laser treatment on day 11 in both cases and in participant 7 (denoted by **) where findings are reported on day 7 prior to fetoscopic laser treatment. S denotes readings not obtained following intrauterine fetal death. The final column reports the number of fetuses alive 14 days after HIFU treatment.

D/R, donor/recipient; DV, ductus venosus; DVP, deepest vertical pool; EFW, estimated fetal weight; GA, gestational age; HIFU, high-intensity focused ultrasound; N, No; NA, not applicable; UA EDF, umbilical artery end diastolic flow; Y, Yes.

resumption of the treatment after a break and repositioning of the participant, the target vessel could no longer be identified. Hence, the research team concluded there was likely to be an unoccluded target vessel remaining and fetoscopic laser treatment was required on day 11 post ultrasound-guided HIFU treatment. In the other participant, one vessel was exposed to 2 ultrasound-guided HIFU exposure series but could not be occluded and could not be retreated due to maternal discomfort (while most treatments lasted 2–3 hours, she developed back pain from lying still for >3 hours), with no evidence of iatrogenic harm. This participant required fetoscopic laser treatment on day 7 post ultrasound-guided HIFU treatment. In summary, while all participants had technically effective vascular occluding treatments according to the Bryant-Day model, when compared to the investigator intention for treatment, 8 had completed treatments and 2 had partially completed treatments.

For the 10 participants, the mean distances of the targets below the skin, uterine serosa, and utero-placental interfaces were 39 mm (SD ±10 mm), 21 mm (SD ±7 mm), and 15 mm (SD ±5 mm), respectively. The HIFU transducer delivered estimated in situ spatial-peak temporal-average intensities (ISPTAs) of 2.0 to 2.8 kW cm⁻² to the target vessels. Further details of the vascular targets, exposure characteristics, and outcomes for each HIFU exposure series are given in Table 2.

Primary outcome: safety and tolerability

There was no evidence of significant iatrogenic harm to either mothers or fetuses (defined in Figure 1) at the time of ultrasound-guided HIFU treatment or during the 14-day follow-up period. The custom-built ultrasound-guided HIFU system performed within the prespecified safety and operational parameters for all 30 targets of 40 exposure series and delivered the HIFU energy as intended in all cases based on review of imaging and RF wattmeter data. The circulated degassed acoustic couplant in the water bag was maintained at a

TABLE 2

Exposure characteristics and outcomes of ultrasound-guided high-intensity focused ultrasound exposure series by participant and vascular target

Participant	BMI	Vascular target	HIFU exposure series	Estimated in situ Intensity	Target depth (mm)	Number of exposures	Post HIFU exposure Doppler finding	Maternal sensation	Maternal skin
1	26	1	1.1	2800	43	4	No flow	Pain	Unchanged
		2	2.1	2250	45	4	Residual flow	None	Unchanged
		2.2	2500	47	3	No flow	Warmth	Unchanged	
2	29	1	1.1	2500	43	3	No flow	None	Unchanged
3	23	1	1.1	2500	50	3	No flow	Warmth	Unchanged
		2	2.1	2000	53	4	Residual flow	None	Unchanged
		2.2	2200	54	5	No flow	Warmth	Unchanged	
		3	3.1	2500	42	3	No flow	Warmth	Unchanged
4	25	1	1.1	2300	42	4	No flow	Warmth	Unchanged
		2	2.1	2500	46	3	Residual flow	Warmth	Unchanged
		2.2	2300	53	4	No flow	Warmth	Unchanged	
5	29	1	1.1	2400	40	5	Residual flow	Warmth	Unchanged
		1.2	2500	41	3	No flow	Warmth	Unchanged	
		2	2.1	2500	41	3	Residual flow	Warmth	Unchanged
		3	3.1	2500	36	4	No flow	Warmth	Unchanged
6	21	1	1.1	2300	39	4	Residual flow	Warmth	Unchanged
		1.2	2500	38	4	No flow	Warmth	Unchanged	
		2	2.1	2500	51	4	No flow	Warmth	Unchanged
		3	3.1	2600	42	5	No flow	Warmth	Unchanged
		4	4.1	2600	40	3	No flow	Warmth	Unchanged
7	24	1	1.1	2500	43	3	No flow	Hot needle *	Unchanged
		2	2.1	2400	45	3	No flow	Hot needle *	Unchanged
		3	3.1	2300	53	3	Residual flow	None	Unchanged
		3.2	2350	55	3	No flow	None	Unchanged	
		4	4.1	2400	43	4	Residual flow	Warmth	Unchanged
		4.2	2500	41	3	Residual flow	Pain *	Unchanged	
8	20	1	1.1	2200	25	3	Residual flow	Electric shock	Unchanged
		1.2	2500	25	3	No flow	Warmth	Unchanged	
		2	2.1	2500	26	2	Residual flow	Warmth	Unchanged
		2.2	2500	25	4	No flow	Warmth	Unchanged	
		3	3.1	2400	24	5	Residual flow	Warmth	Unchanged
		3.2	2350	25	5	No flow	Warmth	Unchanged	
		4	4.1	2500	31	3	No flow	None	Unchanged
		5	5.1	2500	27	4	No flow	Warmth	Unchanged
		6	6.1	2350	22	4	Residual flow	None	Unchanged
9	29	1	1.1	2300	49	4	No flow	Pain	Unchanged
10	24	1	1.1	2500	33	4	No flow	None	Unchanged
		2	2.1	2500	33	3	No flow	None	Unchanged
		3	3.1	2500	25	4	No flow	Hot needle	Unchanged
		4	4.1	2500	37	4	No flow	Warmth	Unchanged

temperature of 20.5°C (SD $\pm 0.4^\circ\text{C}$) and the dissolved oxygen level was 2.4 mg l⁻¹ (SD ± 0.7 mg l⁻¹).

Generally, the treatment was well tolerated by participants. Participants were able to independently stop the process of HIFU energy delivery during a planned HIFU exposure series for any reason, including pain or sensation. The patient stop facility was only used by one participant (Table 1) for 3 of 6 HIFU exposure series used in her treatment. All 10 participants experienced some sensation during at least one of the HIFU exposure series; in 5, this was limited to an abdominal warming sensation which was not painful and did not require the procedure to be stopped. In total, 24/40 HIFU exposure series resulted in a warming sensation. Where participants reported an abdominal warming sensation at some point during the procedure, none had any evidence of skin or uterine injury.

Three participants reported pain during an HIFU exposure series: in one, an HIFU single-exposure series performed at ISPTA 2.8 kW cm⁻² resulted in a strong heating sensation associated with transient pain (<30 seconds) but no injury. In another, a single HIFU exposure performed at ISPTA 2.3 kW cm⁻² series produced a sensation the participant reported as pain but did not halt the HIFU exposure series as she was willing to continue with further treatments as required. In a third, a HIFU exposure series performed at ISPTA 2.5 kW cm⁻² following which back pain required the HIFU exposure series to be prematurely stopped, and she needed a short treatment break to move around after delivery of the planned number of HIFU exposures in that series. Three participants described the feeling of a hot needle being inserted into the abdomen or the feeling similar to an electric shock inside the abdomen. This

affected 5 HIFU exposure series and resulted in 2 of the 5 HIFU exposure series being discontinued before completion of the planned number of exposures (both vessels were successfully occluded by the HIFU exposure series as delivered). Participants were asked to rate their abdominal and back pain scores at the end of all the HIFU exposures series (the day 0 score). The highest median abdominal and back pain scores (rated 0–10) on day 1 were 0 (range, 0–4) and 0 (range, 0–2); on day 2, the respective scores were 1 (range, 0–7) and 1 (range, 0–2). There were no other complications reported.

Acceptability: qualitative substudy findings

Seven participants took part in the qualitative substudy. Although experiences and outcomes varied, all participants supported the development of ultrasound-guided HIFU and remained positive about their involvement, even where pregnancies ended in perinatal loss. Four major themes were identified following analysis: ‘pressures of time’, ‘trust in the team’, ‘enduring discomfort’, and ‘first in human participation’. Key participant quotes are presented in Table 3.

Comment Principal findings

This early phase human study of efficacy and safety shows that ultrasound-guided HIFU shows a high rate of successful vascular occlusion with no adverse maternal or fetal side effects observed within 14 days of treatment. While limited in this study to women with anterior placenta and BMI less than 35, the technique has a high degree of accuracy in targeting and efficiency in occluding blood flow in human placental blood vessels. Furthermore, ultrasound-guided HIFU was associated with no adverse maternal outcomes or

injury; at its most severe, a short-lived sensation of heating and pain that did not result in injury or require analgesia. While clinical efficacy in treating TTTS was not the objective of this study, noninvasive treatment with ultrasound-guided HIFU does not preclude the use of fetoscopic laser for progressive or recurrent TTTS at a later gestational age, when the risks of fetoscopic laser are lower.

Results in the context of what is known

TTTS remains a major cause of morbidity and mortality for monochorionic twins due to placental anastomoses. The only available disease-modifying therapies remain invasive, with attendant sequelae including preterm rupture of membranes, preterm delivery, and maternal complications, which limit the gestational ages and stage of TTTS at which they can be recommended.^{4,21} In the 10 participants treated with ultrasound-guided HIFU, no adverse sequelae related to treatment within the 14-day post-treatment monitoring period were encountered.

Clinical implications

This Phase 1a study was designed to test technical efficacy and safety and not powered for clinical efficacy and pregnancy outcomes; however, we report these and the need for further treatment for completeness. All 10 participants had severe early-onset disease and there was stabilization or regression of TTTS in 5 following ultrasound-guided HIFU treatment. In all, the referring clinicians were Maternal Fetal Medicine specialists who judged that invasive therapy was not indicated because of gestational age or other factors. However, fetoscopic laser therapy was undertaken if and when clinically indicated. We report 60% babies surviving to neonatal discharge which is comparable to that of a recent systematic review of early TTTS

The table shows the characteristics and outcomes of each high-intensity focused ultrasound exposure series reported, including maternal sensation during exposure series and changes to skin noted after the end of the exposure series. Target depth reports the distance between the maternal skin and the vascular target while the maternal tissues were under a degree of compression by the water bag. Ultrasound-guided high-intensity focused ultrasound exposures stopped by the participant due to maternal sensation are denoted by *. Residual flow denotes incomplete vascular occlusion.

BMI, body mass index; HIFU, high-intensity focused ultrasound.

TABLE 3

Key qualitative substudy participant quotes

Pressures of time	Trust in the team	Enduring discomfort	First in human participation
Participant 002: 'I don't think we really realized exactly what we were taking part in until we got there... we'd got the basics I suppose, they told us they'd treat with ultrasound which was not going to be invasive... they'd kind of draw diagrams and explain exactly what would happen, and they had a couple of videos as well, so the more detailed things were left until we were there' Participant 001: 'It was very hard because everything seemed to progress quite quickly, and obviously we're in London, in a hospital we don't know, and we had to travel to get there which was quite stressful, I have other children to sort out with childcare and it was all at the last minute it wasn't easy trying to organize all that to get there the next day was quite hard, but we understood that it was a time pressured situation'	Participant 002: 'We trusted as well because... they said that if the babies are in this position tomorrow, they won't do it because it won't be safe. So I guess that increased our trust. Because we could see that they're not just going to do it any which way... they're actually going to be super careful about just being safe' Participant 007: 'First, my first thing was OK. Yes, I wanna do that. But then I was also a bit skeptic, because it's experimental... Is this real or not? Traveling to London, it's not just taking a car, right. It's a lot also because I was not feeling very well physically. Am I gonna do this? Will I be able to do this, travel this uh long... But then, because the doctor knew my doctor, they knew the doctors in London, it gave me a lot of confidence. And then talking, especially talking to the doctors in London... they called me and they gave me all information. They answered all questions I had. It was a no brainer for me to, to go through with it from that point, yeah'	Participant 005: 'Immediately felt at ease, all the doctors were very kind and caring. And I got on the couch and found the position comfortable... everything was going well I felt, and I must say that I did not have any kind of discomfort... the doctors had told me that maybe in the middle of the procedure a break was usually required, because the position maybe was a little uncomfortable or maybe a little pain, or annoyance. Instead fortunately I did not have any kind of discomfort... the only thing I remember but it was not really painful, is that maybe 3 4 sessions on the same area maybe I felt a little more heat, as if the area overheats a lot, but nothing more than that, everything was quite bearable.' Interviewer: And they gave you, you had some level of control if you needed to stop or pause the treatment at any time. Is that something that you used or you thought about using? Participant 007: 'I use that I think with every, yeah, I use it a lot... The difficult thing was I didn't expect it to be that difficult, but the fact that of course my 2 babies are in my stomach, so I wanna protect them with my life. And then I feel tired. I feel the pain like a hot needle going near them and it feels, you don't know how much pain is OK and how much pain is not OK, because of course it's still an experiment'	Participant 001: 'I did ask if it had been done to anybody else, to which she obviously replied it had not.... she was honest with us and said look they haven't used another human before, so that was hard to take... because we felt that they were positive about the ultrasound and obviously the laser, the statistics were not so good for that. Yeah, it was the scarier route to go down really, to be the first person and to have no real knowledge of anybody else who's been through that experience' Participant 002: 'It felt a real privilege to be offered this treatment, that's new, and also being part of the research, which is going to help other women in the future... I mean, it's incredible really, the technology. So I think me and my husband were both... quite awestruck' Participant 006: 'We were both pretty, like emotional to be honest, because you hear like the risks of laser and obviously we didn't really know much about this. But actually I think logically it kind of made sense to me that the whole idea was that like laser, gets rid of blood flow and that logically this is exactly the same thing. But it just means not having to make a hole inside me. So actually I think it was nice to know we had the opportunity to do something that was noninvasive and like low-risk to the babies'

treated with fetoscopic laser of 47.3% perinatal death rate.²²

While the number of vascular targets per participant might be less than are present based on our knowledge from postnatal placental studies,²³ the amniotic sac was undisturbed by the HIFU treatment and fetoscopic laser was not precluded and was undertaken without maternal complication in 5 participants. Therefore, this noninvasive treatment, if shown to be clinically effective with a

maintained low risk profile, could be used at earlier gestations and stages of TTTS, if needed. It could also be repeated at later gestational ages, as long as the placenta remains within the targeting distance (and energy) of the fixed focal length HIFU transducer.

Research implications

In this study, the use of Doppler imaging with high sensitivity to low velocity and small caliber vessels allowed the

identification, targeting, and occlusion of those intraplacental vessels that demonstrate transfusion of blood from the donor to recipient twin. In this early phase study, we were not able to demonstrate that these vessels corresponded to clinically relevant anastomoses. Nevertheless, assessment of directionality of blood flow is possible with Doppler imaging and with direct fetoscopic visualization. However, a recent study of fetoscopic laser has

suggested that such a technique might be associated with improved donor survival.²⁴ These questions in relation to biological mechanism of action (as neither placental injection nor histological studies were carried out) and proof of clinical efficacy remain to be examined.

Strengths and limitations

Both endoscopic laser and ultrasound-guided HIFU have technical limitations. With endoscopic laser, an anterior placenta limits endoscopic access to, and visualization of, the vascular anastomoses due to the shallow angle that the endoscope makes with the placenta.²⁵ For ultrasound-guided HIFU, the opposite is true: a posterior placenta requires a greater focal depth transducer with higher energy output than an anterior placenta. This risks inadvertent damage due to power deposition in a fetus lying in the path of the HIFU beam to the target and degradation of the ultrasound image quality. While the focal length/energy limitations could be overcome with a different therapy transducer design, the ultrasound-guided HIFU system described here cannot be used when the placenta is posteriorly implanted on the uterus. In that situation, HIFU energy passing through one or more fetuses to reach the target would pose both a risk of iatrogenic harm to the fetuses and disruption of the HIFU energy transmission. Further technical barriers remain to more widespread use of the ultrasound-guided HIFU technique: we restricted treatments to participants with BMI <35 because of difficulties encountered when imaging and treating through adipose tissue.²⁶

Additionally, it should be recognized that an ultrasound-guided HIFU system with the necessary power output and focal properties is not available commercially, and hence a bespoke device with appropriate focal distance and size and power output was constructed for this indication. This system also integrated high-quality commercially available Doppler vascular imaging optimized for low velocity flow in small

blood vessels. This allowed the operators to identify placental vessels joining the twins' circulations¹¹ in a way that is not possible using conventional color Doppler. Our preclinical studies⁸ show that HIFU occlusion works well with vessels within the parenchyma. Hence, HIFU efficacy of vascular occlusion is likely to be significantly lower for superficial vessels, due to the lack of surrounding tissue, and this is an area where laser is likely to reflect the best treatment choice.

The positioning and HIFU targeting systems used custom-designed software and a graphical user interface that facilitated precise position and targeting information. These advances were central to the high degree of efficacy in vascular occlusion reported: accurate imaging of the blood vessels in the placenta is a prerequisite for targeting using HIFU.

While the feedback from 7 participants was positive, 3 participants declined to take part in the qualitative substudy, and as such not all participant voices are represented. It is notable that for the 3 who declined, TTTS was not resolved following treatment. Although we have accounts from 4 substudy participants for whom TTTS was also not resolved following treatment, any future studies should aim to include as full a range of participant experiences as possible.

Conclusion

Ultrasound-guided HIFU treatment of early gestational onset TTTS is technically feasible in women with anterior placenta. It has high efficacy in occluding placental vessels (90%) based on Doppler evaluation, caused no adverse maternal or fetal effects within 14 days of treatment, and was compatible with subsequent fetoscopic laser treatment of residual or recurrent symptoms in half of the participants. There was no evidence of short-term procedural harm; however, long-term safety of the intervention has not been demonstrated. Furthermore, while there were some early signs of efficacy of vascular occlusion based on Doppler evaluation in this safety/technical efficacy study, clinical outcomes are not a

research objective of a Phase 1 study. Clinical effectiveness and outcomes remain unproven and to be determined by a Phase 2 study of appropriate sample size. Nevertheless, participant accounts suggest ultrasound-guided HIFU was an acceptable and valued treatment option. The need for clear and consistent communication, coupled with sufficient time to consider treatment options, was highlighted.

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article. ■

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