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Percutaneous transuterine fetal cerebral embolisation to treat vein of Galen malformations at risk of urgent neonatal decompensation: study protocol for a clinical trial of safety and feasibility

Alfred Pokmeng See ,[1] Louise E Wilkins-Haug,[2] Carol B Benson,[3] Wayne Tworetzky,[4] Darren B Orbach [5]

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For numbered affiliations see end of article.

Correspondence to
Dr Darren B Orbach; Darren.Orbach@childrens.harvard.edu

ABSTRACT

Introduction Although endovascular techniques have improved outcomes in vein of Galen malformations (VOGM), there is still a high rate of morbidity and mortality, particularly among cases with decompensation in the neonatal period. The dimension of the draining venous sinus on fetal imaging correlates with the risk of neonatal decompensation. In fetuses within this high-risk group who do not have end-organ injury, there is a theoretical therapeutic opportunity to reduce the arteriovenous shunt before the normal physiological changes of birth precipitate decompensation. This study investigates the safety and potential benefit of treating a VOGM in utero, which has not been previously studied.

Methods and analysis This study aims to enroll 20 subjects: pregnant women with a fetus harbouring a high-risk VOGM (defined on MRI by a narrowest medial-lateral width greater than 8 mm in the draining venous sinus). Unfortunately, the subset of fetuses with in utero end-organ injury is ineligible, because the late stage of pathology is not amenable to recovery from a cerebrovascular intervention, likely not even in utero. This study aims to alter the physiology before such developments accrue.

At or after 23 weeks of gestation, a transuterine transposterior fontanelle needle puncture to the torcular allows ultrasound-guided deployment of coils to embolise the draining venous malformation.

This study has 97.5% power to detect major safety events at 30% or greater, and 80% power to detect a reduction in the rate of neonatal intervention from 80% to 30%. In the staged study design, an interval evaluation after 11 patients invokes study termination if safety events occur above the allowed threshold.

Ethics and dissemination The institutional review boards at Mass General Brigham and Boston Children's Hospital (BCH) reviewed and approved this protocol. The BCH Department of Radiology and a patient family philanthropic donation fund this study. The trial results will be published in peer-reviewed journals and presented at scientific conferences.

Trial registration number NCT04434729

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a treatment not previously studied, fetal intervention for vein of Galen malformation.
⇒ This is a prospective non-controlled study to evaluate the feasibility and safety of such a treatment, although it may also suggest effectiveness.
⇒ The staged study design creates a planned interval evaluation to interrupt enrolment if the study is futile.
⇒ Subjects undergo a fetal treatment at 23 weeks or later at a single study institution, Brigham and Women's Hospital, by the specific specialised interdisciplinary team from Brigham and Women's Hospital and Boston Children's Hospital.

INTRODUCTION

Incidence

Vein of Galen malformation (VOGM) is the most frequently diagnosed fetal cerebrovascular anomaly, likely occurring in approximately 1:58 100 deliveries.[1] The malformation is thought to represent a preserved embryonic 'choroidal phase' of brain vasculature, with arterial connections to a midline venous channel, the median prosencephalic vein of Markowski, which normally involutes by the 11th week of gestation.[2] By dint of non-regression of the prosencephalic vein with continued direct arterial inflow, the Markowski vein balloons to become the characteristic midline varix seen in VOGM.

A third of newborns with VOGM are clinically stable and able to be discharged from the neonatal intensive care unit (NICU) to undergo elective outpatient embolisation of their VOGM[3]; this cohort will henceforth be referred to as the *infantile treatment* (IT) cohort. However, the remaining two-thirds of patients acutely decompensate in the perinatal period due to physiological changes

following delivery and require urgent embolisation as neonates[4]; this group will be referred to as the *neonatal at risk* (NAR) cohort. The placental circulation provides a massive low-resistance sump in utero, likely protecting both heart and brain from the effects of massive overflow; for this reason, only a small minority of fetuses with VOGM manifest severe cardiac failure or evidence of parenchymal brain injury. However, this placental sump is lost immediately post partum,[5 6] and after the delivery of the placenta, there is increased systemic resistance which will typically reduce flow through the foramen ovale and the ductus arteriosus, leading to closure.[7] Although the normal cardiopulmonary transition at birth results in a decrease in pulmonary vascular resistance and a 10-fold increase in pulmonary flow, the low-resistance circuit within the VOGM can lead to competition across the patent ductus arteriosus. In VOGM, the high-flow shunt and resultant increased venous return through the superior vena cava is associated with a high-preload high-output cardiac failure, beginning with the right ventricle. Right-to-left ductal flow of up to 50% of the right ventricular output is seen, which may limit pulmonary perfusion and blood oxygenation. Over 80% of the cardiac output passes through the vascular malformation, with resultant systemic and coronary hypoperfusion and lactic acidosis.[7] Similar to the peripheral organ hypoperfusion, the brain itself can also suffer from a steal phenomenon as well as from venous hypertension, with resultant parenchymal injury in the neonatal period. Additionally, the cerebral ventricles can be directly obstructed by mass effect with resultant hydrocephalus, or arterialised inflow directly to the venous varix in the malformation can impede cerebral spinal fluid absorption, which typically relies on low venous pressure.

Neonatal medical management targets reduction of systemic vascular resistance as well as pulmonary vascular resistance. Reduced systemic vascular resistance can reduce cardiac stress and improve peripheral perfusion. Pulmonary vasodilatation and reduced pulmonary vascular resistance can provide the same benefit to the right ventricle. The patent ductus arteriosus provides a protective low-resistance alternative outlet for the otherwise excessive right ventricular preload.[7] In this regard, suprasystemic pulmonary arterial pressure and quantity of superior vena cava flow return are sometimes used as metrics of the severity of the cardiac stress secondary to the malformation.[5 8] The vasoactive-inotropic score has been proposed to as a predictor of clinical outcomes based on severity.[9]

Current interventions for early decompensation

Nearly 90% of cases with high-output cardiac failure (the NAR cohort) are refractory to medical intervention with diuresis for preload reduction, milrinone for peripheral vasodilatation and cardiac inotropy, and prostaglandin E_2 for patency of the ductus arteriosus.[8] Despite these measures, progressive cardiopulmonary failure is common, with cardiogenic shock in 59% of cases and myocardial ischaemia in 30%–66% of cases.[5 8] Although historically, these cases were nearly uniformly fatal, the development of endovascular interventions in the late 1980s and early 1990s significantly improved the rate of survival. The initial technique involved percutaneous transtorcular coil embolisation of the venous varix using fibred coils aimed at thrombosis and closure,[10] but endovascular cerebral transarterial embolisation has become the standard of care at nearly all high-volume centres.[11] Neonatal endovascular embolisation of the arteriovenous shunt has as its goal reduction of the cardiac burden but may often not result in radiographic cure, and flow reduction is balanced with the risk of complication, markedly elevated in the neonatal population. There has not been a study of a prenatal intervention. Endovascular approaches, whether through an arterial approach or a venous approach, are not feasible in utero with current tools and technology.

Burden of disease

However, even with state-of-the-art management, there is a high rate of mortality and morbidity. Of the cases with medically refractory neonatal decompensation, a considerable percentage suffer from severe brain injury, severe cardiogenic shock or multiorgan failure, and many centres may not offer further intervention.[8] With significant heterogeneity of inclusion criteria for treatment across centres, neurointerventional case series reporting treatment outcomes have been historically subject to selection bias. A major advantage of the results reported in Lecce *et al* and Gopalan *et al* is that they result from a national UK series, whereby all cases are referred to a single centre of excellence.[3 4] For the NAR cohort, the UK group reports a mortality rate of approximately 40% and a severe neurocognitive morbidity rate of 50% in the survivors. For the IT cohort, they report a mortality rate of 10% and a severe neurocognitive morbidity rate of 30% in the survivors, despite care at an experienced tertiary referral centre.[4]

From the fetal perspective, the situation is even more grim. A pooled analysis from two national referral centres in France and Italy reported 49 cases over 17 years, with late termination of pregnancy, fetal death or neonatal death in 55%.[12] In this group, neonates had a 33% mortality rate. Another group reported a systematic review including antenatal diagnosis and found a higher rate of 54% perinatal mortality.[13]

Determination of high-risk patients

Patients with VOGM are typically observed after birth in the NICU for clinical changes, with the possibility of urgent intervention. Central to the current standard of care protocol for management of neonates with VOGM was the development of the Bicêtre criteria, which aggregates over different organ systems to identify patients who have multiorgan injury with a low chance of recovery using the current standard of care, allowing for triage of newborns to (1) urgent embolisation (for middle scores

on the Bicêtre scale) and (2) 'therapeutic abstention' (for severe scores) or deferred elective embolisation (for mild scores).[11] However, this clinical scoring system describes existing organ injury in order to predict survivability. Therefore, early proactive interventions cannot be guided by these criteria.

There have been attempts to define fetal characteristics that may inform a progressive risk of decompensation.[12 14] Paladini *et al* described tricuspid regurgitation as a predictor of brain injury and both tricuspid regurgitation and VOGM varix volume larger than 20 mL as predictors of severe neurological impairment, death or late termination due to severe fetal brain anomalies.[12] This association was significant, with 20 of 29 cases involving a VOGM >20 mL having a poor outcome. However, the need for intervention was not described in this analysis and these results have not been replicated. A subset analysis suggested that volume over 40 mL may also be at increased risk of late gestational progression. With a larger cohort from the USA and a systematic review of multiple intracranial vascular measurements on fetal MRI, the mediolateral width of the straight or falcine sinus at its point of tightest constriction was found to most robustly correlate with neonatal decompensation necessitating endovascular intervention, more than any other measured vascular parameter, that is, this variable reliably predicted eventual presentation of the fetus in the NAR cohort after delivery.[14] This particular parameter is consistent with physiological intuition, as the point of tightest constriction of the venous sinus draining the prosencephalic varix is a definitive limiting point on overall flow return from the malformation to the systemic circulation. At a threshold of falcine sinus width of ≥8 mm, the investigators found an 88% likelihood of the fetus falling into the NAR group after birth.

METHODS AND ANALYSIS

Objective

This study aims, first, to determine the safety of fetal embolisation for patients with VOGM, and, second, to evaluate the efficacy of fetal embolisation for patients with VOGM. This is a prospective, single-arm, non-randomised, interventional study applying a one-time intervention of fetal embolisation, followed by assessments every 2–4 weeks until delivery per standard of care, followed by postnatal neurological assessments every 6 months for 2 years of adjusted gestational age. Clinical outcomes will be compared with historical cohorts of patients with VOGM.

The primary outcome is a composite of events within the first week after intervention, plus any events thereafter between embolisation and delivery. Safety endpoints include fetal death, fetal intracranial parenchymal or extra-axial haemorrhage, or maternal death, blood loss requiring transfusion, or other procedure-related morbidity within 7 days of the fetal embolisation. Intracranial petechial haemorrhage, which can develop spontaneously, and in which there is no mass effect and rarely neurological sequelae, would not be included in the endpoint. Safety endpoints between the embolisation and parturition include intraprocedural or postprocedural morbidity to the fetus or mother, preterm delivery from abruption, infection, rupture of membranes, contractions or fetal compromise, maternal blood transfusion or unanticipated surgery, or new fetal brain injury on MRI.

The efficacy outcome is a composite of avoidance of three events within the first 30 postnatal days: urgent neonatal embolisation, neonatal death or neonatal brain MRI with parenchymal injury affecting more than 10% of the supratentorial brain volume.

Study conditions

This study evaluates a potential fetal treatment for VOGM in subjects who are at risk of fetal or early neonatal decompensation and morbidity, who have not already suffered from significant brain injury.

Inclusion and exclusion criteria

Pregnant women with a fetus harbouring a VOGM, in which the medial-lateral width of the draining venous sinus of the malformation (the falcine or straight sinus) on fetal MRI measures 8 mm or greater at its point of greatest constriction, are candidates. The mother must be 18 years or older and able to provide consent, and the fetus gestational age should be between 23 weeks and term (VOGM is not seen on imaging before 22–23 weeks, likely due to its small size early in gestation). For the procedure, the mother should be eligible for continuous lumbar epidural anaesthesia and be able to travel to the study site for study evaluation, the intervention and follow-up visits.

Exclusion criteria are: extensive fetal brain parenchymal injury/gliosis (>10% of supratentorial brain volume), irreversible fetal non-brain organ injury (eg, hydrops fetalis as a manifestation of heart failure, a finding which portends fatal outcome in fetuses with VOGM), fetuses with VOGM in whom the straight sinus or falcine sinus draining the prosencephalic varix measures less than 8 mm on fetal MRI, severe maternal obesity pre-pregnancy as defined by body mass index of 40 or greater, fetuses with major congenital anomalies, evidence of preterm labour, rupture of membranes or abruption, maternal coagulopathy (International Normalized Ratio >1.2, Prothrombin Time/Partial Thromboplastin Time above normal ranges for the laboratory, platelets $<(100\times10^9/L)$), medical disease requiring current anticoagulation including maternal deep vein thrombosis, maternal medical history that would preclude epidural anaesthesia, multifetal pregnancy, placenta previa or accrete, participation in another fetal study that influences maternal and fetal morbidity and mortality and known maternal hypersensitivity to 316LM stainless steel.

Participants, recruitment and screening

Direct outreach to the potential subjects has been made via VOGM online family support group sites. Outreach to

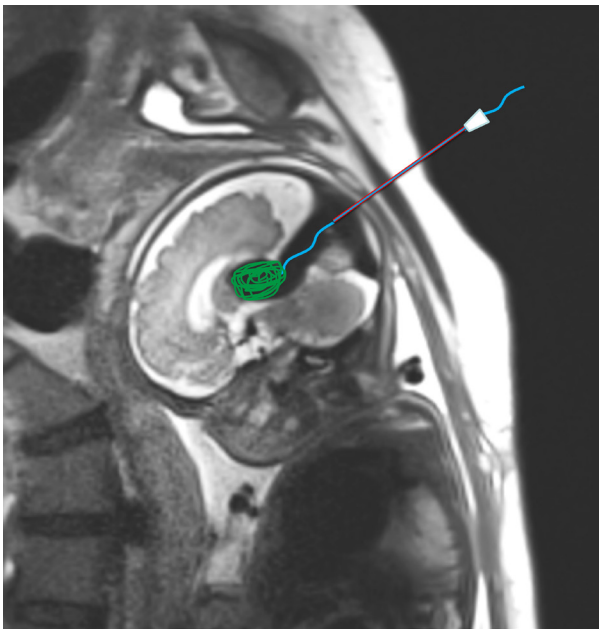

Figure 1 Illustration of technique. This T2 sequence fetal MRI illustrates a patient with a vein of Galen malformation (VOGM). The procedure is completed by a collaboration between a high-risk Maternal Fetal Medicine specialist introducing a transuterine 19 G needle (red) under ultrasound guidance into the confluence of sinuses and allows access into the varix for a microcatheter (blue) to deliver coils for embolisation (green).

healthcare providers managing this pathology has been made through presentation at national and international maternal fetal medicine meetings, fetal cardiology meetings and neuroradiology and neurosurgery meetings and forums. Individual letters with information about the study were sent as well to maternal-fetal medicine practices throughout the USA, and outreach through physician social media has been made to maternal-fetal medicine and fetal cardiology practices, specialising in high-risk obstetric patients.

The study cohort will consist of 20 subjects, enrolled over 3 years at Boston Children's Hospital and Brigham and Women's Hospital. The study opens for enrolment in September 2022 and is expected to complete enrolment at the end of 2025.

Fetal MRI is reviewed to confirm the diagnosis of VOGM, to assess the fetal brain parenchyma and to measure the calibre of the draining venous sinus, typically on a T2-weighted coronal MRI section. Maternal medical history and fetal ultrasound and echocardiography provide the remainder of the data for screening. After confirmation of eligibility, a licensed physician investigator will discuss the study with the potential subject.

Consent methodology

Written (and where needed, translated) institutional review board (IRB)-approved research information and written consent is made available to potential subjects including the father of the fetus if possible; for those who do not speak English, a medical interpreter will be present if needed for discussions. The study information will be reviewed with both parents by a licensed physician investigator in the Boston Children's Hospital Maternal Fetal Care Center. Per federal guidelines, if the parents wish to continue enrolment, both parents are required to consent; however, if the father is unavailable, incompetent or temporarily incapacitated, or if the pregnancy resulted from rape or incest, then only the mother's consent is required. Consent may be withdrawn at any time throughout the course of the study.

Intervention

Subjects undergo a single fetal intervention—a maternal percutaneous, ultrasound-guided, transuterine 19 G needle placement, with transcranial fetal ultrasound guidance of the needle tip via the posterior fontanelle into the fetal torcular herophili (confluence of sinuses) (figure 1). The 19 G needle is attached to continuous flush via a rotating haemostatic valve, and a microcatheter (Headway 21, MicroVention, Aliso Viejo, California) is introduced into the hub of the needle via the valve, and guided over a microwire (Asahi Chikai black 18 soft tip, Asahi Intecc USA, Irvine, California) to the prosencephalic varix. Embolisation will occur using platinum detachable coils (Target XXL and XL, Stryker Neurovascular, Fremont, California). Detachable platinum coils are approved for use in adults and are regularly used off label for paediatric brain embolisations, including neonatal and infant VOGMs. The same catheters, wires and coils used typically in neonatal embolisations will be used in the fetal intervention. A dedicated radiologist with specialisation in fetal sonography and fetal image guidance for procedures provides real-time imaging guidance, with no radiation exposure, during puncture and catheter navigation. Real-time ultrasound also provides flow visualisation with colour Doppler and the flow waveform.

The mother undergoes epidural anaesthesia and is positioned in left uterine displacement for conventional ultrasonography to identify the placenta and fetal orientation. External cephalic version or transvaginal fetal manipulation may be required to position the fetus for transcranial torcular puncture.

Using a protocol well established for fetal transuterine needle-guided cardiac interventions,[15] the fetus receives intramuscular analgesia and neuromuscular blockade and ultrasound guidance is used for transuterine, transposterior fontanelle puncture for torcular access and catheterisation of the venous varix with a microcatheter and microwire. These are used to deploy detachable platinum coils for a planned varix packing density of 15%–20% via a predetermined number, length and size of coils (based on venous varix volume, as measured on fetal MRI). This packing density has been found to result in significant flow diminution and clinical improvement in neonates with VOGM, without resulting in complete occlusion and thrombosis of the varix.

Procedures		Screening and Baseline (Visit 1)	Study Intervention (Visit 2)	Pre-delivery follow up visits (clinical care)	6 month visit (Visit 3) ± 1 month	12 month visit (Visit 4) ± 1 month	18 month visit (Visit 5) ± 1 month	24 month visit (Visit 6) ± 1 month
Signed Consent Form		X						
Assessment of Eligibility Criteria		X						
Review of Medical History		X						
Review of Concomitant Medications		X	X	X	X	X	X	X
Study Intervention			X					
Fetal ultrasound, fetal echocardiogram, and fetal MRI		X		X				
Assessment of Adverse Events			X	X	X	X	X	X
Neurological assessments	Vineland Adaptive Behavior Scales				X	X	X	X
	REEL				X	X	X	X
	CBCL						X	X
	Bayley Exam						X*	X*

Figure 2 Plot of schedule of events. Grid of study activities at each study visit. CBCL, Child Behavior Checklist; REEL, Receptive-Expressive Emergent Language Test.

Following embolisation, colour Doppler ultrasound will visualise changes in varix flow and the flow waveform associated with the embolisation.

Follow-up and quality control

After fetal intervention, the mother will be monitored in the inpatient setting at least overnight, with continuous fetal heart rate monitoring (figures 2 and 3). The mother will receive tocolytics for 12 hours or longer, as guided by the maternal fetal medicine specialist. At 3–6 hours after the procedure, interval ultrasound of the placenta, cervix and fetal brain will be evaluated for procedural complication.

Fetal ultrasound, echocardiogram and MRI are performed at 24–48 hours after procedure and then every 2–4 weeks until delivery.

Delivery will be planned to occur at Brigham and Women's Hospital, with clinical determination of the mode of delivery and timing of delivery based on optimising maternal and fetal well-being.

Postnatal care will be in the NICU with an echocardiogram and MRI on the first postnatal day. Additional clinical interventions, including potential embolisation or serial imaging, will be guided by clinical standard of care,

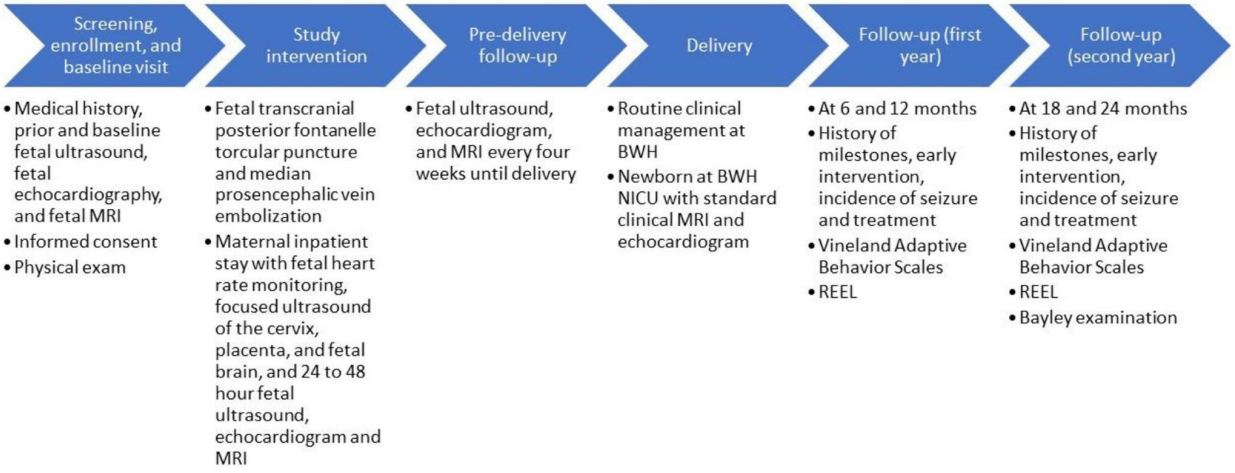

Figure 3 Participant timeline. A linear flow diagram describing each of the study visits and the assessments completed at each encounter. BWH, Brigham and Women's Hospital; NICU, neonatal intensive care unit; REEL, Receptive-Expressive Emergent Language Test.

in identical fashion to neonates who have not undergone fetal embolisation.

For intubated neonates with VOGM, extubation is considered in patients who are normotensive, with normal cardiac rate and rhythm, and awake with spontaneous, regular breathing and mean airway pressure <10 cm H_2O and fractional inspired oxygen less than 0.25. Before discharge from the NICU, neonates must feed well, gain weight, maintain thermal autoregulation in an open crib and maintain stable respirations.

Study follow-up will occur at 6-month intervals. At these visits, seizure incidence and treatment, early intervention and neurological development will be assessed, either in person or by telephone. Neurodevelopmental testing is assessed with standardised testing: the Vineland Adaptive Behavior Scales, the Receptive-Expressive Emergent Language Test, the Child Behavior Checklist and, if in person, the Bayley examination.

Metrics

The primary study endpoint is an evaluation of safety, within a week of the intervention, as well as from the intervention to parturition. Evaluation is made for fetal or maternal death, fetal intracranial haemorrhage with mass effect or neurological sequelae, procedural morbidity to the fetus or mother, preterm delivery from abruption, infection, rupture of membranes, labour or fetal compromise, blood transfusion or unanticipated surgery for the mother or new fetal brain injury on MRI.

The secondary endpoint is an evaluation of efficacy in preventing particular neonatal events within the first 30 postnatal days. These events are an urgent need for neonatal embolisation (historically 80% in the NAR cohort), neonatal death (historically 40%) and further brain injury in more than 10% of the supratentorial volume on postnatal MRI (historically 30%). A separate efficacy metric will evaluate neurocognitive development at 24 months.

Secondary metrics related to the procedure include technical attributes such as procedure times for fetal positioning and navigation from the transfontanelle site to the varix, as well as the coil embolisation. Other technical features include vessel perforation, the number of coils deployed and imaging changes (colour Doppler change after embolisation, change in waveform after embolisation).

Follow-up metrics include fetal imaging changes in the brain (new parenchymal injuries on fetal MRI, intracranial haemorrhage or expansion of ventricular or extra-axial fluid space), heart (worsening left and right ventricular function on fetal echocardiogram, development or worsening of pulmonary hypertension) or other organs (pleural effusions, pericardial effusions or hydrops fetalis). After birth, new parenchymal brain injury and death are additional final follow-up metrics.

Statistical analysis

There are two components in the sample size considerations: the safety endpoint and the efficacy endpoint. For each endpoint, there are two stages. The primary outcome, safety of fetal transuterine transfontanelle venous intervention, is evaluated in the first 11 patients. If three subjects reach any of the triggering safety endpoints (maternal death, fetal death or fetal non-petechial intracranial haemorrhage), the intervention is deemed unsafe and the study will be stopped. In the second stage, with an additional nine patients, the safety threshold would be four or more patients manifesting triggering safety events. To test the null hypothesis of safety events at a proportion of >30%, this could achieve a type I error rate of 0.097 with a power of 97.5%.

In the first stage of 11 patients, if six or more patients reach the non-efficacy or futility endpoint, that is, negative neonatal events occur (neonate requiring urgent embolisation due to cardiopulmonary failure or neonate with new parenchymal brain injuries on MRI in over 10% of the supratentorial brain volume), then the intervention is deemed ineffective and the study will be stopped. In the second stage, the futility threshold would be 10 or more patients. This would test the null hypothesis that the intervention is efficacious in ≤40% of cases versus the alternative hypothesis that it is efficacious in ≥70%, with a type I error rate of 0.099 and a power of 90.2%.

For the secondary outcome of efficacy, fetuses with VOGMs measuring>8 mm in the straight sinus or falcine sinus historically have 88% likelihood of requiring neonatal intervention.[14] Using a conservative estimate of 80% requiring such intervention, with a goal of 50% absolute reduction in the need for neonatal intervention to a rate of 30%, the proposed 20-patient cohort would have 80% power to demonstrate statistically significant efficacy of the study intervention.

Monitoring

The study will be overseen by the Data and Safety Monitoring Board (DSMB), composed of five senior members of faculty of medical schools not affiliated with the study, who are experts in neonatal medicine, paediatric neurointerventions, newborn medicine with expertise in VOGM management, maternal-fetal medicine and fetal cardiology.

ETHICS AND DISSEMINATION

This study investigates the safety, feasibility and efficacy of treating VOGMs in the fetus, with the potential to alter the pathophysiology of the condition before irreversible decompensation develops at birth. In the absence of an animal model of VOGM and a fetal model of VOGM, the study design is based on clinical experience in the treatment of neonates with VOGMs and on preclinical in vitro models.

The trial results will be published in peer-reviewed journals and at conferences.

Prior experience

Technical feasibility has been investigated with an anatomically accurate ultrasound phantom constructed out of polyvinyl alcohol cryogel, which simulates the brain parenchyma, surrounding a fluid-filled inner cavity, which simulates the sinus and venous varix. Morphology and calibre of the phantoms was based on fetal MRI scans from patients treated at our centre. The cryogel phantoms have allowed confirmation of the technical ability to assess the malformation and visualise coil deployment. Furthermore, the relationship of the venous varix and the falcine/straight sinus to the torcular represents a unique anatomical configuration, not present in other pathology. Therefore, although the pathology has been demonstrated in a physical model, there is no reasonable preclinical in vivo study. As mentioned above, phantom data were submitted to both the IRBs and US Food and Drug Administration (FDA) as part of the approval process, and were submitted for publication under separate cover.

The design of the intervention is based on clinical experience in treating neonates with VOGMs. In endovascular treatment, metallic coils can be applied to a density of 15%–25% of the volume. In neonatal VOGM cases, this embolisation aims to reduce the flow but not occlude the malformation. Review of six cases where the flow reduction interrupted high-output cardiac failure suggests that a density of 13%–22% can significantly diminish the flow. Therefore, with a fetal intervention goal of reducing flow to reduce neonatal decompensation, this study aims to achieve 15%–20% packing.

Despite the simulation and evidence-based projection of treatment response, there are unknown features of fetal physiology which may alter the response, and fetal torcular puncture, as designed in this study, is not otherwise described.

Risks

The study intervention, by its nature as a fetal procedure, presents risks to the mother and the fetus. The mother can experience haemorrhage and need for blood transfusion or surgery. There may be direct injury to the mother's abdomen, uterus, placenta, umbilical cord, bladder or bowel, which may require additional observation, medical treatment or surgical treatment. Premature labour and placental abruption are particular risks of transuterine intervention, and further complications may result in limited future reproductive ability. The mother is also exposed to procedural risks including allergic reactions, anaesthesia risks, including death.

The fetus is likewise susceptible to risks from the procedure, which may injure the placenta, umbilical cord, or induce preterm delivery. Other potential risks of fetal intervention include infection, haemorrhage or injury of fetal structures, and allergic reaction to or intravascular absorption of the fetal anaesthetic agents. Specific to the percutaneous transfontanelle intervention, there is a risk of intracranial haemorrhage, seizure, epilepsy or other neurological disorders, brain ischaemia. Due to embolisation of the VOGM, there is a risk of inadvertent thrombosis or occlusion or dissection or perforation of vessels.

Limitations

This study will assess the technical feasibility, safety and potential benefit of a fetal transuterine transposterior fontanelle puncture for ultrasound-guided coil embolisation of the median prosencephalic varix in fetuses with VOGM deemed to be at high risk of severe neonatal decompensation. Although the study is designed to confidently demonstrate the feasibility and identify an unacceptable procedural risk, the small size of this study may not clearly delineate subtle yet clinically relevant benefits of fetal intervention compared with neonatal or infant intervention. Several assumptions represent potential pitfalls.

The approach to treatment is a transvenous coil embolisation, which is sometimes used in neonatal VOGM care, but is not typically the first-line option in postnatal care. However, due to technical limitations, intracranial transarterial embolisation, used as first-line therapy in most neonates, is not currently feasible. Ultrasound rather than fluoroscopy eliminates radiation risk. Transposterior fontanelle access allows for a percutaneous approach rather than requiring an open fetal surgery, which would almost certainly incur greater risk. Based on historical experience with percutaneous transtorcular embolisation after birth, which was an early approach to VOGM embolisation, haemorrhage from the puncture site was not cited as a source of complications. This was also borne out in our institutional experience with direct torcular access through a burr hole. Finally, our team's experience in direct fetal transcardiac needle puncture for valve dilatation is not associated with significant morbidity from haemorrhage through the myocardium or pericardium. In addition to assumptions regarding reasonable risks of this fetal procedure, this therapy relies on the premise of similar response to treatment during the fetal state of VOGM.

The design of this study presumes that the response to venous embolisation in a fetus is similar to that of a neonate, and this is unknown, given that there have not to date been fetal interventions for brain arteriovenous shunts. Furthermore, the extent of embolisation to achieve clinically significant changes is unknown. Extent of embolisation has not been reported in VOGM, so we applied packing density as a surrogate metric, although it is most commonly used in the treatment of arterial brain aneurysms. There have not been precise studies in the degree of VOGM embolisation, whether from transarterial or transvenous approaches. Therefore, we rely on internal review of cases with a more concretely observable clinical outcome: interruption of high-output cardiac failure. The VOGM pathophysiology may be more or less responsive to intervention than expected. There may be secondary response to treatment, potentially interacting in unexpected ways with fetal physiology, possibly

involving recruitment of alternate arterial or venous pathways.

This study evaluates the clinical phenotype of treated patients and is not designed to evaluate physiological changes or molecular-level responses to changes in arteriovenous shunting related to treatment, given the limited availability of quantitative metrics in VOGMs and the lack of tissue specimens.

Finally, although this is a fetal treatment of a congenital malformation, it neither cures nor reverses the malformation, and is targeted towards reducing the risk of the overall natural history clinical course, in cases of NAR VOGMs.

Ethics

This study was reviewed and approved by the IRB at Partners (Mass General Brigham) and at Boston Children's Hospital, and adheres to the principles outlined in the World Medical Association's Declaration of Helsinki statement of ethical principles for medical research involving human subjects.

The study has additionally been approved through an investigational device exemption by the FDA. As no animal models that resemble either the anatomy or physiology of VOGM are extant, fetal brain ultrasound phantoms were designed by the Boston Children's Hospital simulations group using real fetal patient MRI models, and these phantoms underwent preprocedure MRI for planning, needle-guided microcatheter coil embolisation and post-treatment verification of accurate coil deployment using MRI and direct visualisation. Phantom data were submitted to both the IRBs and FDA as part of the approval process, and are submitted for publication under a separate cover. No further preclinical study is feasible at this time. Although the intervention represents a greater than minimal risk to the mother and the fetus, this study risk is likely comparable or less than the risk of neonatal decompensation and urgent neonatal embolisation. This is based on clinical experience with maternal percutaneous fetal transuterine cardiac interventions and based on the historical experience with percutaneous transfontanelle venous embolisation for neonatal and infant VOGMs. Maternal procedure-related morbidity is expected to be low, with rates similar to those seen in needle-guided transuterine fetal cardiac interventions. For the subject population, there is potential benefit to the fetus in avoiding injury to the brain, heart, lungs and other organs, with an associated reduction in morbidity and mortality.

Study recruitment is broad and varied, including direct patient channels as well as via referring providers who diagnose and care for fetuses with VOGMs. There is therefore no systematic selection for particular groups or exclusion of vulnerable or at-risk populations. Exclusion criteria are based on medically and scientifically required limitations, such as the need to safely undergo a percutaneous transuterine procedure under epidural anaesthesia, and the need to adhere to the study follow-up evaluation.

Individual subjects may withdraw at any time. An investigator may also terminate individual subject participation if a clinical adverse event, laboratory abnormality or medical condition puts ongoing participation into conflict with the best interest of the subject. One such specific instance, as determined by our group's experience with fetal cardiac transuterine needle-guided interventions, would be inability to achieve ideal fetal position after over 40 min with epidural analgesia in one attempt, or up to one additional attempt more than 24 hours later.

Ongoing study performance will be overseen by the primary investigator, senior author on this report (DBO), as well as additional direction by the DSMB, who review all serious adverse events and evaluate stoppage criteria and study continuation. Examples of early termination include unexpected significant risk to the mother or fetus, protocol non-adherence or incomplete data collection. For subject safety, study continuation is evaluated on an ongoing basis and at a prespecified sensitivity analysis after the first 11 patients before further enrolment in stage 2. Thus, if three safety events occur or if six efficacy events occur, the study will be stopped, even if stage 1 enrolment is incomplete. Likewise, if four cumulative safety events or 10 cumulative efficacy events occur during stage 2, the study will be stopped.

No inducements, monetary or otherwise, will be offered to terminate a pregnancy; individuals engaged in the research will have no part in any decisions as to the timing, method or procedures used to terminate a pregnancy; and individuals engaged in the research will have no part in determining the viability of a neonate.

Registration

Fetal treatment of Galenic malformations is registered with the ClinicalTrials.gov database with identifier NCT04434729 (https://clinicaltrials.gov/ct2/show/NCT04434729). It was first registered on 17 June 2020.

Sources of funding

This study is supported by Boston Children's Hospital Radiology funding and a philanthropic gift, without other funding sources.

Treatment product is purchased directly from the manufacturer, Stryker Neurovascular, based on precalculated coil size and coil counts for the specific enrolled case.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Next steps

The fetal treatment of VOGM is currently recruiting eligible participants through contact with the principal investigator and the Boston Children's Hospital Maternal Fetal Medicine Care Center.

Author affiliations
[1]Department of Neurosurgery, Boston Children's Hospital, Boston, Massachusetts, USA
[2]Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[3]Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[4]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA
[5]Department of Radiology (Neurointerventional), Boston Children's Hospital, Boston, Massachusetts, USA

Contributors APS: neurointerventional technique and equipment of the protocol design; drafting and critical revisions of the manuscript. LEW-H: obstetrical and fetal medical and ethical components of the protocol design; preliminary validation studies in preclinical model of fetal vein of Galen malformation intervention; critical revisions of the manuscript. CBB: fetal interventional and radiographic evaluation components of the protocol design; preliminary validation studies in preclinical model of fetal vein of Galen malformation intervention; critical revisions of the manuscript. WT: fetal interventional evaluation and contribution to design protocol based on pioneering analogous protocols for fetal cardiac intervention; revisions of the manuscript. DBO: conceptualisation of fetal intervention in vein of Galen malformation, neurointerventional technique and equipment, and safety and efficacy outcome measure of the protocol design; preliminary validation studies in preclinical model of fetal vein of Galen malformation intervention; critical revisions of the manuscript. All authors have read and approved the manuscript.

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Competing interests APS is on the scientific advisory board for Microbot Medical with CSF diverting implants. CSF diversion represents a rare intervention in infants with vein of Galen malformations, but every effort is made to avoid CSF diversion in the VOGM population, and this is not a component of the intervention studied or reported here.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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ORCID iDs
Alfred Pokmeng See http://orcid.org/0000-0003-3634-4692
Darren B Orbach http://orcid.org/0000-0002-1793-3398

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