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**Design of a safety and feasibility study of percutaneous transuterine fetal cerebral embolization to treat vein of Galen malformations at risk of urgent neonatal decompensation**

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Title: Design of a safety and feasibility study of percutaneous transuterine fetal cerebral embolization to treat vein of Galen malformations at risk of urgent neonatal decompensation

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Public title: Fetal Embolization of Vein of Galen Malformations

Scientific title: Fetal Embolization of Vein of Galen Malformations

Countries of Recruitment: United States of America

Health condition studied: Vein of Galen malformations

Intervention: Percutaneous, needle-guided transuterine fetal embolization of vein of Galen malformation using detachable coils

Study type: Interventional single group open label

Date of first enrollment: pending

Sample size: 20 participants

Recruitment status: Recruiting

Primary outcomes: safety (maternal and fetal) – fetal or maternal death or fetal intracranial hemorrhage within seven days of intervention; procedural morbidity to the fetus or mother, or preterm delivery from abruption, infection, rupture of membranes, or labor or fetal compromise, or maternal blood transfusion or unanticipated surgical intervention, or presence of new, procedure-related brain injury on fetal imaging.

Key secondary outcomes: efficacy – prevention of (i) urgent neonatal embolization requirement, (ii) neonatal death, or (iii) brain injury affecting more than 10% of the supratentorial volume.

Ethics approval and consent to participate: Approved on 5/26/2020 by Boston Children’s Hospital IRB and on 6/24/20 by Mass General Brigham IRB

Word count: 4849
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 draining 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 physiologic 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 twenty subjects: pregnant women with a fetus harboring 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 are 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 trans-posterior fontanelle needle puncture to the torcular allows ultrasound-guided deployment of coils to embolize 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 eleven patients and 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.
Article summary, strengths and limitations of this study:

- This is a treatment not previously studied, fetal intervention for VOGM
- 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 enrollment 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 specialized interdisciplinary team from Brigham and Women’s Hospital and Boston Children’s Hospital.

Trial 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 June 17, 2020.

Keywords (3–10): Vein of Galen Malformations, Cerebral Veins, Fetal Therapies, Fetal Embolization
Introduction

Incidence

Vein of Galen malformation (VOGM) is the most frequently diagnosed fetal cerebrovascular anomaly, likely occurring in approximately 1:25,000 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 to undergo elective outpatient embolization of their VOGM; (3) this cohort will henceforth be referred to as the infantile treatment cohort, IT. However, the remaining two thirds of patients acutely decompensate in the perinatal period due to physiologic changes following delivery and require urgent embolization as neonates; (4) this group will be referred to as the neonatal at risk cohort, NAR. 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 postpartum, (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 arterialized inflow
directly to the venous varix in the malformation can impede cerebral spinal fluid (CSF) 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 (VIS) 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 vasodilation and cardiac inotropy, and prostaglandin E2 for
patency of the ductus arteriosus.(8) Despite these measures, progressive cardiopulmonary failure is common, with
cardiogenic shock in 59% of cases and myocardial ischemia 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 trans-torcular coil
embolization of the venous varix using fibered coils aimed at thrombosis and closure,(10) but endovascular
cerebral trans-arterial embolization has become the standard of care at nearly all high-volume centers.(11)
Neonatal endovascular embolization 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 study of a pre-natal intervention.
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 severe brain injury, severe cardiogenic shock, or multi-organ failure, and many centers may not offer further intervention. With significant heterogeneity of inclusion criteria for treatment across centers, 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 United Kingdom series, whereby all cases are referred to a single center of excellence. 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 center.

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

Determination of high-risk patients

Patients with VOGM are typically observed after birth in the neonatal intensive care unit 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 (i) urgent embolization (for middle scores on the Bicêtre scale), (ii) “therapeutic abstention” (for severe scores), or deferred elective embolization (for mild scores). 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. 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. 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 United States and a systematic review of multiple intracranial vascular measurements on fetal MRI, the medio-lateral 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, i.e. this variable reliably predicted eventual presentation of the fetus in the NAR cohort after delivery. 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 embolization for patients with VOGM, and, second, to evaluate the efficacy of fetal embolization for patients with VOGM. This is a prospective, single-arm, non-randomized, interventional study applying a one-time intervention of fetal embolization, followed by assessments every four weeks until delivery per standard of care, followed by post-natal neurological assessments every six months, for two years of adjusted gestational age. Clinical outcomes will be compared to historical cohorts of VOG patients.

The primary outcome is a composite of events within the first week after intervention, plus any events thereafter between embolization and delivery. Safety endpoints include fetal death, fetal intracranial parenchymal or extra-
axial hemorrhage, or maternal death, blood loss requiring transfusion, or other procedure-related morbidity within
seven days of the fetal embolization. Intracranial petechial hemorrhage, 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 embolization and parturition include intra-procedural or post-procedural 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 thirty post-natal days: urgent
neonatal embolization, 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
decompenation and morbidity, who have not already suffered significant brain injury.

Inclusion and exclusion criteria

Pregnant women with a fetus harboring 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 anesthesia and be able to travel to the study site for study evaluation, the intervention, and follow-up
visits.

Cases are excluded if the fetus harbors extensive fetal brain parenchymal injury (> 10% of the supratentorial brain
volume), irreversible fetal non-brain organ injury, major congenital anomalies, multi-fetal pregnancy, placenta
previa or accreta, or in cases of preterm labor, rupture of membranes, or abruption. Maternal exclusion criteria
include coagulopathy (INR >1.2, or abnormal prothrombin time or partial thromboplastin time per laboratory ranges), thrombocytopenia (platelets < 100 thousand per microliter) or comorbidity requiring anticoagulation, severe pre-pregnancy obesity (BMI of 40 or greater, precluding fetal positioning and needle-guided access), medical history precluding epidural anesthesia, or 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 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 United States, and outreach through physician social media has been made to maternal-fetal medicine and fetal cardiology practices, specializing in high-risk obstetric patients.

The study cohort will consist of 20 subjects, enrolled over three years enrolling at Boston Children’s Hospital and Brigham and Women’s Hospital.

Fetal MRI is reviewed to confirm the diagnosis of VOGM, to assess the fetal brain parenchyma, and to measure the caliber 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) 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, and 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 enrollment, 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 19G needle placement, with transcranial fetal guidance of the needle tip via the posterior fontanelle into the fetal torcular herophili (confluence of sinuses). The 19G needle is attached to continuous flush via a rotating hemostatic valve, and a microcatheter (Headway 21, Microvention, Aliso Viejo, CA) 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, CA) to the prosencephalic varix. Embolization will occur using platinum detachable coils (Target XXL and XL, Stryker Neurovascular, Fremont, CA). Detachable platinum coils are approved for use in adults and are regularly used off-label for pediatric brain embolizations, including neonatal and infant VOOGMs. The same catheters, wires, and coils used typically in neonatal embolizations will be used in the fetal intervention. A dedicated radiologist with specialization 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 visualization with color Doppler and the flow waveform.

The mother undergoes epidural anesthesia 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 developed for fetal transuterine needle-guided cardiac interventions,(15) the fetus receives intramuscular analgesia and neuromuscular blockade and ultrasound guidance is utilized for transuterine, trans-posterior-fontanelle puncture for torcular access and catheterization 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 pre-determined number, length, and size of coils (based on venous varix volume, as measured on fetal MRI).
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.

Following embolization, color Doppler ultrasound will visualize changes in varix flow and the flow waveform associated with the embolization.

**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 1 and 2). 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 to 48 hours post-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 optimizing maternal and fetal well-being.

Postnatal care will be in the neonatal intensive care unit with an echocardiogram and MRI on the first post-natal day. Additional clinical interventions, including potential embolization or serial imaging will be guided by clinical standard of care, in identical fashion to neonates who have not undergone fetal embolization.

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 H₂O 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 six-month intervals. At these visits, seizure incidence and treatment, early intervention, and neurologic development will be assessed, either in person or by telephone. Neurodevelopmental testing is assessed with standardized 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 hemorrhage with mass effect or neurological sequelae, procedural morbidity to the fetus or mother, preterm delivery from abruption, infection, rupture of membranes, labor 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 thirty post-natal days. These events are urgent need for neonatal embolization (historically 80% in the NAR cohort), neonatal death (historically 40%), and further brain injury in more than 10% of the supratentorial volume on post-natal 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 trans-fontanelle site to the varix, as well as the coil embolization. Other technical features include vessel perforation, the number of coils deployed, and imaging changes (color Doppler change after embolization, change in waveform after embolization).

Follow-up metrics include fetal imaging changes in the brain (new parenchymal injuries on fetal MR, intracranial hemorrhage, 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 or 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 trans-fontanelle 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 hemorrhage), the intervention is deemed unsafe and the study will be stopped. In the second stage, with an additional 9 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, i.e. negative neonatal events occur (neonate requiring urgent embolization 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 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 faculty of medical schools not affiliated with the study, who are experts in neonatal medicine, pediatric 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 in absence of a fetal model of VOGM, the study design is based on clinical experience in the treatment of neonates with VOGMs and on pre-clinical in vitro models.

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 caliber of the phantoms was based on fetal MRI scans from patients treated at our center. The cryogel phantoms have allowed confirmation of the technical ability to assess the malformation and visualize 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 pre-clinical in vivo study. As mentioned above, phantom data was submitted to both the IRBs and FDA as part of the approval process, and is 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 embolization 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 hemorrhage 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 labor 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, anesthesia risks, including death.

The fetus is likewise susceptible to risks from the procedure, which may injure the placenta, umbilical cord, or induce pre-term delivery. Other potential risks of fetal intervention include infection, hemorrhage or injury of fetal structures, and allergic reaction to or intravascular absorption of the fetal anesthetic agents. Specific to the percutaneous trans-fontanelle intervention, there is risk of intracranial hemorrhage, seizure, epilepsy, or other neurological disorders, brain ischemia. Due to embolization 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 trans-posterior fontanelle puncture for ultrasound guided coil embolization 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 to neonatal or infant intervention. Several assumptions represent potential pitfalls.

The approach to treatment is a transvenous coil embolization, which is sometimes used in neonatal VOGM care, but is not typically the first-line option in post-natal care. However, due to technical limitations, intracranial transarterial embolization, used as first-line therapy in most neonates, is not currently feasible. Ultrasound rather than fluoroscopy eliminates radiation risk. Trans-posterior fontanelle access allows for a percutaneous approach rather than requiring an open fetal surgery, which would almost certainly incur greater risk. However, this presumes that the response to venous embolization 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. 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 physiologic 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 institutional review boards (IRB) at Partners (Mass General Brigham, MGB), and at Boston Children’s Hospital.

The study has additionally been approved through an investigational device exemption (IDE) 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 pre-procedure MRI for planning, needle-guided microcatheter coil embolization, and post-treatment verification of accurate coil deployment using MRI and direct visualization. Phantom data was submitted to both the IRBs and FDA as part of the approval process, and is submitted for publication under separate cover. No further pre-clinical 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 embolization. This is based on clinical experience with maternal percutaneous fetal transuterine cardiac interventions and based on the historical experience with percutaneous trans-fontanelle venous embolization 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 anesthesia, 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 minutes 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 Data and Safety Monitoring Board (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 enrollment in stage 2. Thus, if three safety events occur or if six efficacy events occur, the study will be stopped, even if stage 1 enrollment is incomplete. Likewise, if four cumulative safety events or ten 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.
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 June 17, 2020.

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 pre-calculated coil size and coil counts for the specific enrolled case.

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

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.

Abbreviations

- VOGM – vein of Galen malformations
- MRI – magnetic resonance imaging
- IT – infantile treatment
- NAR – neonatal at risk
- CSF – cerebrospinal fluid
- VIS – vasoactive-inotrope score
- DSMB – Data and Safety Monitoring Board
511 IRB – Institutional Review Board
512 MGB – Mass General Brigham
513 IDE – investigational device exemption
514 FDA – U.S. Food and Drug Administration
Figures

Figure 1. Plot of schedule of events
Grid of study activities at each study visit.

Figure 2. Participant timeline
A linear flow diagram describing each of the study visits and the assessments completed at each encounter.
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Declarations

Ethical approval and consent to participate

This study was evaluated and approved independently by the Mass General Brigham Institutional Review Boards (2020P000216) and the Boston Children's Hospital's Institutional Review Board (IRB-P00034727).

Consent for publication

Not applicable

Availability of data and materials

Individual clinical trial participant-level data will not be shared for this small trial in a rare disease with a small and interconnected community of patients.

Author contributions

APS – Neurointerventional technique and equipment of the protocol design; drafting and critical revisions of the manuscript

LEW – 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 – Conceptualization 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
Provenance and peer review

Not commissioned; externally peer reviewed.

Acknowledgements

Not applicable

Organizational structure and responsibilities

Eligibility committee

- Richard L. Robertson Jr., M.D., Head of the Department of Radiology at Boston Children's Hospital, Harvard Medical School
- Janet Soul, M.D., Director, Fetal-Neonatal Neurology Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School
- Darren B. Orbach, M.D., Ph.D., Chief, Neurointerventional Radiology, Boston Children's Hospital, Harvard Medical School
- Louise E. Wilkins-Haug, M.D., Ph.D., Division Director, Maternal Fetal Medicine and Reproductive Genetics, Brigham and Women's Hospital, Harvard Medical School

Confidentiality

The study protocol, documentation, and data are held in strict confidence, and will not be released to any unauthorized third party without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records for the study subjects. Future use and research on the data from this study will be deidentified with a code maintained on a password-protected computer.

Funding statement
This study is supported by a research fund granted to the senior author by the Boston Children’s Hospital Radiology Department (Sage Schermerhorn Image-Guided Therapy Chair), as well as a philanthropic donation of seed funding to support the first three procedures performed (Haas Family Cerebral Interventions Research Fund), without other funding sources.

Competing interests statement

APS is on the scientific advisory board for Microbot Medical Ltd. 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.

LEW, CBB, WT, and DBO report no potential conflicts of interest.
### SCHEDULE OF EVENTS

| 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               |                                  |                              |                                              |                                  |                                   |                                   |                                   |
| Assessment of Eligibility Criteria|                                  |                              |                                              |                                  |                                   |                                   |                                   |
| Review of Medical History         |                                  |                              |                                              |                                  |                                   |                                   |                                   |
| Review of Concomitant Medications | X                                |                              |                                              | X                                | X                                 | X                                 | X                                 |
| Study Intervention                |                                  |                              |                                              |                                  |                                   |                                   |                                   |
| Fetal ultrasound, fetal echocardiogram, and fetal MRI | X                                |                              |                                              |                                  |                                   |                                   |                                   |
| Assessment of Adverse Events      | X                                | 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*                                |
Screening, enrollment, and baseline visit

- Medical history, prior and baseline fetal ultrasound, fetal echocardiography, and fetal MRI
- Informed consent
- Physical exam

Study intervention

- Fetal transcranial posterior fontanelle torcular puncture and median prosencephalic vein embolization
- Maternal inpatient stay with fetal heart rate monitoring, focused ultrasound of the cerebrum, placenta, and fetal brain, and 24 to 48 hour fetal ultrasound, echocardiogram and MRI

Pre-delivery follow up

- Fetal ultrasound, echocardiogram, and MRI every four weeks until delivery

Delivery

- Routine clinical management at BWH
- Newborn at BWH NICU with standard clinical MRI and echocardiogram

Follow-up (first year)

- At 6 and 12 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL

Follow-up (second year)

- At 18 and 24 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL
- Bayley examination

BWH – Brigham and Women’s Hospital
REEL – Receptive-Expressive Emergent Language Test
CBCL – Child Behavior Checklist to assess emotional and behavioral function
| Section/item          | Item No | Description                                                                                                                                                                                                 | Lines          |
|----------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Administrative information |         |                                                                                                                                                                                                           |                |
| Title                | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                               | Lines 1-2      |
|                      | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                     | Lines 91-93, Lines 485-487 |
|                      | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                                                                                    | Lines 27-49    |
| Protocol version     | 3       | Date and version identifier                                                                                                                                                                                 | Lines 48-49    |
| Funding              | 4       | Sources and types of financial, material, and other support                                                                                                                                                 | Lines 489-491, Lines 647-651 |
| Roles and responsibilities | 5a     | Names, affiliations, and roles of protocol contributors                                                                                                                                                     | Lines 28-29    |
|                      | 5b      | Name and contact information for the trial sponsor                                                                                                                                                         | Lines 21-31    |
|                      | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Lines 623-624, Lines 640-645 |
|                      | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Lines 629-638  |
| Introduction         |         |                                                                                                                                                                                                           |                |
### Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention  

Lines 109-202

6b Explanation for choice of comparators  

Line 159, 210-211

### Objectives

7 Specific objectives or hypotheses  

Line 205-224

### Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  

Lines 207-210

### Methods: Participants, interventions, and outcomes

#### Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained  

Lines 255-256

#### Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)  

Lines 230-253, 263-270, 281-283

#### Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered  

Lines 272-299

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)  

Lines 466-470

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  

NA – single procedural intervention

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial  

NA – single procedural intervention
Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Lines 213-224, Lines 327-348

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Figures 1 and 2. Lines 258-261, 273, 301-315, 322-325

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Lines 350-370

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size Lines 247-253

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions NA – single arm

Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned NA – single arm

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions NA – single arm
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | NA – single arm |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | NA – single arm |

**Methods: Data collection, management, and analysis**

| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Lines 327-348 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | None – small study population with single intervention and short follow-up |

| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Lines 640-645 |

| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Lines 350-370 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | None |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | None – small study population with single intervention and short follow-up |

**Methods: Monitoring**
Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Lines 372-375, 472-479

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Lines 74-75, 86, 351-356, 359-363, 476-479

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Lines 472-479

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Lines 472-479

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Lines 48-49, 77-80, 441-443

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Lines 472-479

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Lines 263-270

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable None

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Lines 640-645
### Declaration of interests

28 Financial and other competing interests for principal investigators for the overall trial and each study site

Lines 653-657

### Access to data

29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Lines 605-607

### Ancillary and post-trial care

30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

NA - none

### Dissemination policy

31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Lines 640-645

31b Authorship eligibility guidelines and any intended use of professional writers

None

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Lines 605-607

### Appendices

#### Informed consent materials

32 Model consent form and other related documentation given to participants and authorised surrogates

Available upon request

#### Biological specimens

33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

NA – no specimens
**Percutaneous transuterine fetal cerebral embolization to treat vein of Galen malformations at risk of urgent neonatal decompensation: study protocol for a clinical trial of safety and feasibility**

| Journal:        | BMJ Open               |
|-----------------|------------------------|
| Manuscript ID   | bmjopen-2021-058147.R1 |
| Article Type:   | Protocol               |
| Date Submitted by the Author: | 02-Mar-2022 |
| Complete List of Authors: | See, Alfred; Boston Children’s Hospital, Neurosurgery Wilkins-Haug, Louise; Brigham and Women’s Hospital Department of Obstetrics and Gynecology Benson, Carol; Brigham and Women’s Hospital Department of Radiology Tworetzky, Wayne; Boston Children’s Hospital Orbach, Darren; Boston Children’s Hospital, Department of Radiology |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Neurology, Cardiovascular medicine, Paediatrics |
| Keywords:        | NEUROSURGERY, Fetal medicine < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Paediatric neurosurgery < PAEDIATRIC SURGERY |
Title: Percutaneous transuterine fetal cerebral embolization to treat vein of Galen malformations at risk of urgent neonatal decompensation: study protocol for a clinical trial of safety and feasibility

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Public title: Fetal Embolization of Vein of Galen Malformations

Scientific title: Fetal Embolization of Vein of Galen Malformations

Countries of Recruitment: United States of America

Health condition studied: Vein of Galen malformations

Intervention: Percutaneous, needle-guided transuterine fetal embolization of vein of Galen malformation using detachable coils

Study type: Interventional single group open label

Date of first enrollment: pending

Sample size: 20 participants

Recruitment status: Recruiting

Primary outcomes: safety (maternal and fetal) – fetal or maternal death or fetal intracranial hemorrhage within seven days of intervention; procedural morbidity to the fetus or mother, or preterm delivery from abruption, infection, rupture of membranes, or labor or fetal compromise, or maternal blood transfusion or unanticipated surgical intervention, or presence of new, procedure-related brain injury on fetal imaging.

Key secondary outcomes: efficacy – prevention of (i) urgent neonatal embolization requirement, (ii) neonatal death, or (iii) brain injury affecting more than 10% of the supratentorial volume.

Ethics approval and consent to participate: Approved on 5/26/2020 by Boston Children’s Hospital IRB and on 6/24/20 by Mass General Brigham IRB

Word count: 4849
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 physiologic 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 twenty subjects: pregnant women with a fetus harboring 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 are 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 trans-posterior fontanelle needle puncture to the torcular allows ultrasound-guided deployment of coils to embolize 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 eleven 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.

Article summary, strengths and limitations of this study:

- This is a treatment not previously studied, fetal intervention for VOGM
- 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 enrollment 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 specialized interdisciplinary team from Brigham and Women’s Hospital and Boston Children’s Hospital.

Trial 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 June 17, 2020.

Keywords (3–10): Vein of Galen Malformations, Cerebral Veins, Fetal Therapies, Fetal Embolization
Introduction

Incidence

Vein of Galen malformation (VOGM) is the most frequently diagnosed fetal cerebrovascular anomaly, likely occurring in approximately 1: 58,100 deliveries. 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. 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 to undergo elective outpatient embolization of their VOGM; this cohort will henceforth be referred to as the infantile treatment cohort, IT. However, the remaining two thirds of patients acutely decompensate in the perinatal period due to physiologic changes following delivery and require urgent embolization as neonates; this group will be referred to as the neonatal at risk cohort, NAR. 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 postpartum, 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. 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 arterialized inflow directly to the venous varix in the malformation can impede cerebral spinal fluid (CSF) 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 (VIS) 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 vasodilation and cardiac inotropy, and prostaglandin E₂ for patency of the ductus arteriosus.(8) Despite these measures, progressive cardiopulmonary failure is common, with cardiogenic shock in 59% of cases and myocardial ischemia 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 trans-torcular coil embolization of the venous varix using fibered coils aimed at thrombosis and closure,(10) but endovascular cerebral trans-arterial embolization has become the standard of care at nearly all high-volume centers.(11) Neonatal endovascular embolization 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 study of a pre-natal 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 severe brain injury, severe
cardiogenic shock, or multi-organ failure, and many centers may not offer further intervention.(8) With significant
heterogeneity of inclusion criteria for treatment across centers, 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 United Kingdom series, whereby all cases are
referred to a single center 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 center.(4)

From the fetal perspective, the situation is even more grim. A pooled analysis from two national referral centers 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 neonatal intensive care unit 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 (i) urgent embolization (for middle scores on the Bicêtre scale), (ii) “therapeutic abstention” (for severe scores), or deferred elective embolization (for mild scores). 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. 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. 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 United States and a systematic review of multiple intracranial vascular measurements on fetal MRI, the medio-lateral 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, i.e. this variable reliably predicted eventual presentation of the fetus in the NAR cohort after delivery. 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 embolization for patients with VOGM, and, second, to evaluate the efficacy of fetal embolization for patients with VOGM. This is a prospective, single-arm, non-randomized, interventional study applying a one-time intervention of fetal embolization, followed by assessments every 2-4 weeks until delivery per standard of care, followed by post-natal neurological assessments every six months.
months, for two years of adjusted gestational age. Clinical outcomes will be compared to historical cohorts of VOGM patients.

The primary outcome is a composite of events within the first week after intervention, plus any events thereafter between embolization and delivery. Safety endpoints include fetal death, fetal intracranial parenchymal or extra-axial hemorrhage, or maternal death, blood loss requiring transfusion, or other procedure-related morbidity within seven days of the fetal embolization. Intracranial petechial hemorrhage, 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 embolization and parturition include intra-procedural or post-procedural 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 thirty post-natal days: urgent neonatal embolization, 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 decompenensation and morbidity, who have not already suffered significant brain injury.

Inclusion and exclusion criteria

Pregnant women with a fetus harboring 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 anesthesia and be able to travel to the study site for study evaluation, the intervention, and follow-up visits.

Cases are excluded if the fetus harbors extensive fetal brain parenchymal injury (> 10% of the supratentorial brain volume), irreversible fetal non-brain organ injury, major congenital anomalies, multi-fetal pregnancy, placenta previa or accreta, or in cases of preterm labor, rupture of membranes, or abruption. Maternal exclusion criteria include coagulopathy (INR >1.2, or abnormal prothrombin time or partial thromboplastin time per laboratory ranges), thrombocytopenia (platelets < 100 thousand per microliter) or comorbidity requiring anticoagulation, severe pre-pregnancy obesity (BMI of 40 or greater, precluding fetal positioning and needle-guided access), medical history precluding epidural anesthesia, or 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 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 United States, and outreach through physician social media has been made to maternal-fetal medicine and fetal cardiology practices, specializing in high-risk obstetric patients.

The study cohort will consist of 20 subjects, enrolled over three years at Boston Children’s Hospital and Brigham and Women’s Hospital. The study opens for enrollment in September 2022 and is expected to complete enrollment 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 caliber 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) 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, and 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 enrollment, 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 19G 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 19G needle is attached to continuous flush via a rotating hemostatic valve, and a microcatheter (Headway 21, Microvention, Aliso Viejo, CA) 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, CA) to the prosencephalic varix. Embolization will occur using platinum detachable coils (Target XXL and XL, Stryker Neurovascular, Fremont, CA). Detachable platinum coils are approved for use in adults and are regularly used off-label for pediatric brain embolizations, including neonatal and infant VOGMs. The same catheters, wires, and coils used typically in neonatal embolizations will be used in the fetal intervention. A dedicated radiologist with specialization 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 visualization with color Doppler and the flow waveform.

The mother undergoes epidural anesthesia 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 utilized for transuterine, trans-posterior-fontanelle puncture for torcular access and catheterization 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 pre-determined 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.

Following embolization, color Doppler ultrasound will visualize changes in varix flow and the flow waveform associated with the embolization.

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 to 48 hours post-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 optimizing maternal and fetal well-being.

Postnatal care will be in the neonatal intensive care unit with an echocardiogram and MRI on the first post-natal day. Additional clinical interventions, including potential embolization or serial imaging will be guided by clinical standard of care, in identical fashion to neonates who have not undergone fetal embolization.
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 H₂O 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 six-month intervals. At these visits, seizure incidence and treatment, early intervention, and neurologic development will be assessed, either in person or by telephone. Neurodevelopmental testing is assessed with standardized 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 hemorrhage with mass effect or neurological sequelae, procedural morbidity to the fetus or mother, preterm delivery from abruption, infection, rupture of membranes, labor 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 thirty post-natal days. These events are urgent need for neonatal embolization (historically 80% in the NAR cohort), neonatal death (historically 40%), and further brain injury in more than 10% of the supratentorial volume on post-natal 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 trans-fontanelle site to the varix, as well as the coil embolization. Other technical features include vessel perforation, the number of coils deployed, and imaging changes (color Doppler change after embolization, change in waveform after embolization).
Follow-up metrics include fetal imaging changes in the brain (new parenchymal injuries on fetal MR, intracranial hemorrhage, 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 or 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 trans-fontanelle 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 hemorrhage), the intervention is deemed unsafe and the study will be stopped. In the second stage, with an additional 9 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, i.e. negative neonatal events occur (neonate requiring urgent embolization 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 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 faculty of
medical schools not affiliated with the study, who are experts in neonatal medicine, pediatric 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 in absence of a fetal model of VOGM, the study design is based on clinical
experience in the treatment of neonates with VOGMs and on pre-clinical 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 caliber of the phantoms was based on fetal MRI scans from
patients treated at our center. The cryogel phantoms have allowed confirmation of the technical ability to assess
the malformation and visualize 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 pre-clinical
*in vivo* study. As mentioned above, phantom data was submitted to both the IRBs and FDA as part of the approval
process, and is 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
embolization 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 hemorrhage 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 labor 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, anesthesia risks, including death.

The fetus is likewise susceptible to risks from the procedure, which may injure the placenta, umbilical cord, or induce pre-term delivery. Other potential risks of fetal intervention include infection, hemorrhage or injury of fetal structures, and allergic reaction to or intravascular absorption of the fetal anesthetic agents. Specific to the percutaneous trans-fontanelle intervention, there is risk of intracranial hemorrhage, seizure, epilepsy, or other neurological disorders, brain ischemia. Due to embolization 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 trans-posterior fontanelle puncture for ultrasound guided coil embolization 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 to neonatal or infant intervention. Several assumptions represent potential pitfalls.

The approach to treatment is a transvenous coil embolization, which is sometimes used in neonatal VOGM care, but is not typically the first-line option in post-natal care. However, due to technical limitations, intracranial transarterial embolization, used as first-line therapy in most neonates, is not currently feasible. Ultrasound rather than fluoroscopy eliminates radiation risk. Trans-posterior 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 trans-torcular embolization after birth, which was an early approach to VOGM embolization, hemorrhage 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 hemorrhage 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. However, this assumption presumes that the response to venous embolization 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 embolization to achieve clinically significant changes is unknown. Extent of embolization 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 embolization, whether from transarterial or transvenous approaches. Therefore, we rely on internal review of cases with more a concretely observable clinical outcomes: 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 physiologic 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 institutional review boards (IRB) at Partners (Mass General Brigham, MGB), 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 (IDE) 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 pre-procedure MRI for planning, needle-guided microcatheter coil embolization, and post-treatment verification of accurate coil deployment using MRI and direct visualization. Phantom data was submitted to both the IRBs and FDA as part of the approval process, and is submitted for publication under separate cover. No further pre-clinical 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 embolization. This is based on clinical experience with maternal percutaneous fetal transuterine cardiac interventions and based on the historical experience with percutaneous trans-fontanelle venous embolization 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 anesthesia, 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 minutes 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 Data and Safety Monitoring Board (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 enrollment in stage 2. Thus, if three safety events occur or if six efficacy events occur, the study will be stopped, even if stage 1 enrollment is incomplete. Likewise, if four cumulative safety events or ten 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.

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 June 17, 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 pre-calculated coil size and coil counts for the specific enrolled case.

**Patients 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.

**Abbreviations**

- VOGM – vein of Galen malformations
- MRI – magnetic resonance imaging
- IT – infantile treatment
- NAR – neonatal at risk
- CSF – cerebrospinal fluid
- VIS – vasoactive-inotrop score
- DSMB – Data and Safety Monitoring Board
- IRB – Institutional Review Board
- MGB – Mass General Brigham
- IDE – investigational device exemption
- FDA – U.S. Food and Drug Administration
Figures

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

Figure 2. Plot of schedule of events

Grid of study activities at each study visit.

Figure 3. Participant timeline

A linear flow diagram describing each of the study visits and the assessments completed at each encounter.
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Declarations

Ethical approval and consent to participate

This study was evaluated and approved independently by the Mass General Brigham Institutional Review Boards (2020P000216) and the Boston Children's Hospital's Institutional Review Board (IRB-P00034727).

Consent for publication

Not applicable

Availability of data and materials

Individual clinical trial participant-level data will not be shared for this small trial in a rare disease with a small and interconnected community of patients.

Author contributions

APS – Neurointerventional technique and equipment of the protocol design; drafting and critical revisions of the manuscript

LEW – 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 – Conceptualization 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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Acknowledgements
Not applicable

Organizational structure and responsibilities
Eligibility committee
- Richard L. Robertson Jr., M.D., Head of the Department of Radiology at Boston Children's Hospital, Harvard Medical School
- Janet Soul, M.D., Director, Fetal-Neonatal Neurology Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School
- Darren B. Orbach, M.D., Ph.D., Chief, Neurointerventional Radiology, Boston Children's Hospital, Harvard Medical School
- Louise E. Wilkins-Haug, M.D., Ph.D., Division Director, Maternal Fetal Medicine and Reproductive Genetics, Brigham and Women’s Hospital, Harvard Medical School

Confidentiality
The study protocol, documentation, and data are held in strict confidence, and will not be released to any unauthorized third party without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records for the study subjects. Future use and research on the data from this study will be deidentified with a code maintained on a password-protected computer.

Funding statement

This study is supported by a research fund granted to the senior author by the Boston Children’s Hospital Radiology Department (Sage Schermerhorn Image-Guided Therapy Chair), as well as a philanthropic donation of seed funding to support the first three procedures performed (Haas Family Cerebral Interventions Research Fund), without other funding sources.

Competing interests statement

APS is on the scientific advisory board for Microbot Medical Ltd. 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. LEW, CBB, WT, and DBO report no potential conflicts of interest.
# SCHEDULE OF EVENTS

| 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                                | X                                | X                                | X                                |
| Fetal ultrasound, fetal echocardiogram, and fetal MRI | X | | X | | | | |
| Assessment of Adverse Events       | X                                | X                           | X                                           | X                                | X                                | X                                | X                                |
| Neurological assessments           |                                  |                             |                                             | X                                | X                                | X                                | X                                |
| Vineland Adaptive Behavior Scales  |                                  |                             |                                             |                                  |                                  |                                  |                                  |
| REEL                               |                                  |                             |                                             | X                                | X                                | X                                | X                                |
| CBCL                               |                                  |                             |                                             | X                                |                                  |                                  |                                  |
| Bayley Exam                        |                                  |                             |                                             |                                  |                                  | X*                               | X*                               |
**Screening, enrollment, and baseline visit**
- Medical history, prior and baseline fetal ultrasound, fetal echocardiography, and fetal MRI
- Informed consent
- Physical exam

**Study intervention**
- Fetal transcranial posterior fontanelle torcular puncture and median prosencephalic vein embolization
- Maternal inpatient stay with fetal heart rate monitoring, focused ultrasound of the cerebrum, placenta, and fetal brain, and 24 to 48 hour fetal ultrasound, echocardiogram and MRI

**Pre-delivery follow-up**
- Fetal ultrasound, echocardiogram, and MRI every four weeks until delivery

**Delivery**
- Routine clinical management at BWH
- Newborn at BWH NICU with standard clinical MRI and echocardiogram

**Follow-up (first year)**
- At 6 and 12 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL
- Bayley examination

**Follow-up (second year)**
- At 18 and 24 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL

BWH – Brigham and Women’s Hospital
REEL – Receptive-Expressive Emergent Language Test
CBCL – Child Behavior Checklist to assess emotional and behavioral function
### SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Lines |
|--------------|---------|-------------|-------|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Lines 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Lines 91-93, Lines 485-487 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Lines 27-49 |
| Protocol version | 3 | Date and version identifier | Lines 48-49 |
| Funding | 4 | Sources and types of financial, material, and other support | Lines 489-491, Lines 647-651 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Lines 28-29 |
| | 5b | Name and contact information for the trial sponsor | Lines 21-31 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Lines 623-624, Lines 640-645 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Lines 629-638 |

**Introduction**

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*For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml*
### Background and rationale
6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

6b Explanation for choice of comparators

### Objectives
7 Specific objectives or hypotheses

### Trial design
8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

### Methods: Participants, interventions, and outcomes

#### Study setting
9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

#### Eligibility criteria
10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

#### Interventions
11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

NA – single procedural intervention
Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
| Method | Section | Description | Notes |
|--------|---------|-------------|-------|
| **Blinding (masking)** | 17a | Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how | NA – single arm |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | NA – single arm |

**Methods: Data collection, management, and analysis**

| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Lines 327-348 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Lines 640-645 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Lines 350-370 |
| | 20b | Methods for any additional analyses (e.g., subgroup and adjusted analyses) | None |
| | 20c | Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation) | None – small study population with single intervention and short follow-up |

**Methods: Monitoring**
Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
| Section                        | Number | Description                                                                                                                                                                                                 | Pages       |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Declaration of interests      | 28     | Financial and other competing interests for principal investigators for the overall trial and each study site                                                                                              | Lines 653-657|
| Access to data                | 29     | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators                                                                | Lines 605-607|
| Ancillary and post-trial care | 30     | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation                                                                                  | NA - none   |
| Dissemination policy          | 31a    | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Lines 640-645|
|                               | 31b    | Authorship eligibility guidelines and any intended use of professional writers                                                                                                                               | None        |
|                               | 31c    | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code                                                                                             | Lines 605-607|
| Appendices                    |        |                                                                                                                                                                                                      |             |
| Informed consent materials    | 32     | Model consent form and other related documentation given to participants and authorised surrogates                                                                                                           | Available upon request|
| Biological specimens          | 33     | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA – no specimens |
Percutaneous transuterine fetal cerebral embolization to
treat vein of Galen malformations at risk of urgent neonatal
decompensation: study protocol for a clinical trial of safety
and feasibility

| Journal        | BMJ Open          |
|----------------|-------------------|
| Manuscript ID  | bmjopen-2021-058147.R2 |
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| Date Submitted by the Author | 06-May-2022 |
| Complete List of Authors | See, Alfred; Boston Children's Hospital, Neurosurgery Wilkins-Haug, Louise; Brigham and Women's Hospital Department of Obstetrics and Gynecology Benson, Carol; Brigham and Women's Hospital Department of Radiology Tworetzky, Wayne; Boston Children's Hospital Orbach, Darren; Boston Children's Hospital, Department of Radiology |
| Primary Subject Heading | Obstetrics and gynaecology |
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| Keywords       | NEUROSURGERY, Fetal medicine < OBSTETRICS, Prenatal diagnosis < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Paediatric neurosurgery < PAEDIATRIC SURGERY |
Title: Percutaneous transuterine fetal cerebral embolization to treat vein of Galen malformations at risk of urgent neonatal decompensation: study protocol for a clinical trial of safety and feasibility

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Public title: Fetal Embolization of Vein of Galen Malformations

Scientific title: Fetal Embolization of Vein of Galen Malformations

Countries of Recruitment: United States of America

Health condition studied: Vein of Galen malformations

Intervention: Percutaneous, needle-guided transuterine fetal embolization of vein of Galen malformation using detachable coils

Study type: Interventional single group open label

Date of first enrollment: pending

Sample size: 20 participants

Recruitment status: Recruiting

Primary outcomes: safety (maternal and fetal) – fetal or maternal death or fetal intracranial hemorrhage within seven days of intervention; procedural morbidity to the fetus or mother, or preterm delivery from abruption, infection, rupture of membranes, or labor or fetal compromise, or maternal blood transfusion or unanticipated surgical intervention, or presence of new, procedure-related brain injury on fetal imaging.

Key secondary outcomes: efficacy – prevention of (i) urgent neonatal embolization requirement, (ii) neonatal death, or (iii) brain injury affecting more than 10% of the supratentorial volume.

Ethics approval and consent to participate: Approved on 5/26/2020 by Boston Children’s Hospital IRB and on 6/24/20 by Mass General Brigham IRB

Word count: 4849
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 physiologic 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 twenty subjects: pregnant women with a fetus harboring 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 are 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 trans-posterior fontanelle needle puncture to the torcular allows ultrasound-guided deployment of coils to embolize 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 eleven 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.

**Article summary, strengths and limitations of this study:**

- This is a treatment not previously studied, fetal intervention for VOGM
- 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 enrollment 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 specialized interdisciplinary team from Brigham and Women’s Hospital and Boston Children’s Hospital.

**Trial 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 June 17, 2020.

**Keywords (3–10):** Vein of Galen Malformations, Cerebral Veins, Fetal Therapies, Fetal Embolization
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 to undergo elective outpatient embolization of their VOGM; (3) this cohort will henceforth be referred to as the infantile treatment cohort, IT. However, the remaining two thirds of patients acutely decompensate in the perinatal period due to physiologic changes following delivery and require urgent embolization as neonates; (4) this group will be referred to as the neonatal at risk cohort, NAR. 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 postpartum, (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 arterialized inflow
directly to the venous varix in the malformation can impede cerebral spinal fluid (CSF) 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 (VIS) 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 vasodilation and cardiac inotropy, and prostaglandin E₂ for
patency of the ductus arteriosus.(8) Despite these measures, progressive cardiopulmonary failure is common, with
cardiogenic shock in 59% of cases and myocardial ischemia 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 trans-torcular coil
embolization of the venous varix using fibered coils aimed at thrombosis and closure,(10) but endovascular
cerebral trans-arterial embolization has become the standard of care at nearly all high-volume centers.(11)

Neonatal endovascular embolization 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 study of a pre-natal 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 severe brain injury, severe
cardiogenic shock, or multi-organ failure, and many centers may not offer further intervention.(8) With significant
heterogeneity of inclusion criteria for treatment across centers, 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 United Kingdom series, whereby all cases are
referred to a single center 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 center.(4)

From the fetal perspective, the situation is even more grim. A pooled analysis from two national referral centers 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 neonatal intensive care unit 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 (i) urgent embolization (for middle scores on the Bicêtre scale), (ii) “therapeutic abstention” (for severe scores), or deferred elective embolization (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 United States and a systematic review of multiple intracranial vascular measurements on fetal MRI, the medio-lateral 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, i.e. 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 embolization for patients with VOGM, and, second, to evaluate the efficacy of fetal embolization for patients with VOGM. This is a prospective, single-arm, non-randomized, interventional study applying a one-time intervention of fetal embolization, followed by assessments every 2-4 weeks until delivery per standard of care, followed by post-natal neurological assessments every six
months, for two years of adjusted gestational age. Clinical outcomes will be compared to historical cohorts of
VOGM patients.

The primary outcome is a composite of events within the first week after intervention, plus any events thereafter
between embolization and delivery. Safety endpoints include fetal death, fetal intracranial parenchymal or extra-
axial hemorrhage, or maternal death, blood loss requiring transfusion, or other procedure-related morbidity within
seven days of the fetal embolization. Intracranial petechial hemorrhage, 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 embolization and parturition include intra-procedural or post-procedural 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 thirty post-natal days: urgent
neonatal embolization, 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 significant brain injury.

Inclusion and exclusion criteria

Pregnant women with a fetus harboring 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 anesthesia 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 (e.g. hydrops fetalis as a manifestation of heart failure, a finding which portends fatal outcome in fetuses with vein of Galen malformation), 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 (BMI) of 40 or greater, fetuses with major congenital anomalies, evidence of preterm labor, rupture of membranes or abruption, maternal coagulopathy (INR > 1.2, PT/PTT above normal ranges for the lab, platelets <100), medical disease requiring current anticoagulation including maternal deep vein thrombosis, prior maternal medical history that would preclude epidural anesthesia, multi-fetal 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 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 United States, and outreach through physician social media has been made to maternal-fetal medicine and fetal cardiology practices, specializing in high-risk obstetric patients.

The study cohort will consist of 20 subjects, enrolled over three years at Boston Children’s Hospital and Brigham and Women’s Hospital. The study opens for enrollment in September 2022 and is expected to complete enrollment 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 caliber 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) 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, and 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 enrollment, 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 19G 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 19G needle is attached to continuous flush via a rotating hemostatic valve, and a microcatheter (Headway 21, Microvention, Aliso Viejo, CA) 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, CA) to the prosencephalic varix. Embolization will occur using platinum detachable coils (Target XXL and XL, Stryker Neurovascular, Fremont, CA). Detachable platinum coils are approved for use in adults and are regularly used off-label for pediatric brain embolizations, including neonatal and infant VOGMs. The same catheters, wires, and coils used typically in neonatal embolizations will be used in the fetal intervention. A dedicated radiologist with specialization 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 visualization with color Doppler and the flow waveform.
The mother undergoes epidural anesthesia 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 utilized for transuterine, trans-posterior-fontanelle puncture for torcular access and catheterization 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 pre-determined 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.

Following embolization, color Doppler ultrasound will visualize changes in varix flow and the flow waveform associated with the embolization.

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 to 48 hours post-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 optimizing maternal and fetal well-being.
Postnatal care will be in the neonatal intensive care unit with an echocardiogram and MRI on the first post-natal day. Additional clinical interventions, including potential embolization or serial imaging will be guided by clinical standard of care, in identical fashion to neonates who have not undergone fetal embolization.

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 H₂O 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 six-month intervals. At these visits, seizure incidence and treatment, early intervention, and neurologic development will be assessed, either in person or by telephone. Neurodevelopmental testing is assessed with standardized 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 hemorrhage with mass effect or neurological sequelae, procedural morbidity to the fetus or mother, preterm delivery from abruption, infection, rupture of membranes, labor 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 thirty post-natal days. These events are urgent need for neonatal embolization (historically 80% in the NAR cohort), neonatal death (historically 40%), and further brain injury in more than 10% of the supratentorial volume on post-natal 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 trans-fontanelle site to the varix, as well as the coil embolization. Other technical features include vessel perforation, the number of coils deployed, and imaging changes (color Doppler change after embolization, change in waveform after embolization).

Follow-up metrics include fetal imaging changes in the brain (new parenchymal injuries on fetal MR, intracranial hemorrhage, 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 or 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 trans-fontanelle 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 hemorrhage), the intervention is deemed unsafe and the study will be stopped. In the second stage, with an additional 9 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, i.e. negative neonatal events occur (neonate requiring urgent embolization 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 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 faculty of medical schools not affiliated with the study, who are experts in neonatal medicine, pediatric 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 in absence of a fetal model of VOGM, the study design is based on clinical experience in the treatment of neonates with VOGMs and on pre-clinical 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 caliber of the phantoms was based on fetal MRI scans from patients treated at our center. The cryogel phantoms have allowed confirmation of the technical ability to assess the malformation and visualize 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 pre-clinical
in vivo study. As mentioned above, phantom data was submitted to both the IRBs and FDA as part of the approval process, and is 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 embolization 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 hemorrhage 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 labor 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, anesthesia risks, including death.

The fetus is likewise susceptible to risks from the procedure, which may injure the placenta, umbilical cord, or induce pre-term delivery. Other potential risks of fetal intervention include infection, hemorrhage or injury of fetal structures, and allergic reaction to or intravascular absorption of the fetal anesthetic agents. Specific to the percutaneous trans-fontanelle intervention, there is risk of intracranial hemorrhage, seizure, epilepsy, or other neurological disorders, brain ischemia. Due to embolization 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 trans-posterior fontanelle puncture for ultrasound guided coil embolization 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 to neonatal or infant intervention. Several assumptions represent potential pitfalls.

The approach to treatment is a transvenous coil embolization, which is sometimes used in neonatal VOGM care, but is not typically the first-line option in post-natal care. However, due to technical limitations, intracranial transarterial embolization, used as first-line therapy in most neonates, is not currently feasible. Ultrasound rather than fluoroscopy eliminates radiation risk. Trans-posterior 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 trans-torcular embolization after birth, which was an early approach to VOGM embolization, hemorrhage 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 hemorrhage 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. However, this design of this study presumes that the response to venous embolization 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 embolization to achieve clinically significant changes is unknown.

Extent of embolization 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 embolization, whether from transarterial or transvenous approaches. Therefore, we rely on internal review of cases with more a concretely observable clinical outcomes: 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 physiologic 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 institutional review boards (IRB) at Partners (Mass General Brigham, MGB), 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 (IDE) 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 pre-procedure MRI for planning, needle-guided microcatheter coil embolization, and post-treatment verification of accurate coil deployment using MRI and direct visualization. Phantom data was submitted to both the IRBs and FDA as part of the approval process, and is submitted for publication under separate cover. No further pre-clinical 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 embolization. This is based on clinical experience with maternal percutaneous fetal transuterine cardiac interventions and based on the historical experience with percutaneous trans-fontanelle venous embolization 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 anesthesia, 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 minutes 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 Data and Safety Monitoring Board (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 enrollment in stage 2. Thus, if three safety events occur or if six efficacy events occur, the study will be stopped, even if stage 1 enrollment is incomplete. Likewise, if four cumulative safety events or ten 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 June 17, 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 pre-calculated coil size and coil counts for the specific enrolled case.

Patients 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.

Abbreviations

VOGM – vein of Galen malformations
MRI – magnetic resonance imaging
IT – infantile treatment
NAR – neonatal at risk
CSF – cerebrospinal fluid
VIS – vasoactive-inotrop score
DSMB – Data and Safety Monitoring Board
IRB – Institutional Review Board
MGB – Mass General Brigham
537 IDE – investigational device exemption

538 FDA – U.S. Food and Drug Administration
Figures

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

Figure 2. Plot of schedule of events

Grid of study activities at each study visit.

Figure 3. Participant timeline

A linear flow diagram describing each of the study visits and the assessments completed at each encounter.
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Declarations

Ethical approval and consent to participate

This study was evaluated and approved independently by the Mass General Brigham Institutional Review Boards (2020P000216) and the Boston Children's Hospital's Institutional Review Board (IRB-P00034727).

Consent for publication

Not applicable

Availability of data and materials

Individual clinical trial participant-level data will not be shared for this small trial in a rare disease with a small and interconnected community of patients.

Author contributions

APS – Neurointerventional technique and equipment of the protocol design; drafting and critical revisions of the manuscript

LEW – 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 – Conceptualization 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

Provenance and peer review

Not commissioned; externally peer reviewed.

Acknowledgements

Not applicable

Organizational structure and responsibilities

Eligibility committee

- Richard L. Robertson Jr., M.D., Head of the Department of Radiology at Boston Children’s Hospital, Harvard Medical School
- Janet Soul, M.D., Director, Fetal-Neonatal Neurology Program, Department of Neurology, Boston Children’s Hospital, Harvard Medical School
- Darren B. Orbach, M.D., Ph.D., Chief, Neurointerventional Radiology, Boston Children’s Hospital, Harvard Medical School
- Louise E. Wilkins-Haug, M.D., Ph.D., Division Director, Maternal Fetal Medicine and Reproductive Genetics, Brigham and Women’s Hospital, Harvard Medical School

Confidentiality
The study protocol, documentation, and data are held in strict confidence, and will not be released to any unauthorized third party without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records for the study subjects. Future use and research on the data from this study will be deidentified with a code maintained on a password-protected computer.

**Funding statement**

This study is supported by a research fund granted to the senior author by the Boston Children’s Hospital Radiology Department (Sage Schermerhorn Image-Guided Therapy Chair), as well as a philanthropic donation of seed funding to support the first three procedures performed (Haas Family Cerebral Interventions Research Fund), without other funding sources.

**Competing interests statement**

APS is on the scientific advisory board for Microbot Medical Ltd. 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.

LEW, CBB, WT, and DBO report no potential conflicts of interest.
## SCHEDULE OF EVENTS

| 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                               | X                               |
| Neurological assessments                       |                                  |                             |                                             |                                 |                                 |                                 |                                 |
| Vineland Adaptive Behavior Scales              |                                  |                             |                                             |                                 | X                               | X                               | X                               |
| REEL                                           |                                  |                             |                                             |                                 | X                               | X                               | X                               |
| CBCL                                           |                                  |                             |                                             |                                 |                                 | X                               | X                               |
| Bayley Exam                                    |                                  |                             |                                             |                                 |                                 |                                 | X*                              | X*                              |
Screening, enrollment, and baseline visit
- Medical history, prior and baseline fetal ultrasound, fetal echocardiography, and fetal MRI
- Informed consent
- Physical exam

Study intervention
- Fetal transcranial posterior fontanelle torcular puncture and median prosencephalic vein embolization
- Maternal inpatient stay with fetal heart rate monitoring, focused ultrasound of the cervix, placenta, and fetal brain, and 24 to 48 hour fetal ultrasound, echocardiogram and MRI

Pre-delivery follow up
- Fetal ultrasound, echocardiogram, and MRI every four weeks until delivery

Delivery
- Routine clinical management at BWH
- Newborn at BWH NICU with standard clinical MRI and echocardiogram

Follow-up (first year)
- At 6 and 12 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL
- Bayley examination

Follow-up (second year)
- At 18 and 24 months
- History of milestones, early intervention, incidence of seizure and treatment
- Vineland Adaptive Behavior Scales
- REEL

BWH – Brigham and Women’s Hospital
REEL – Receptive-Expressive Emergent Language Test
CDCL – Child Behavior Checklist to assess emotional and behavioral function
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

| Section/item | Item No | Description | Lines |
|--------------|---------|-------------|-------|
| Administrative information |  |  | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Lines 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | Lines 91-93, Lines 485-487 |
|  | 2b | All items from the World Health Organization Trial Registration Data Set | Lines 27-49 |
| Protocol version | 3 | Date and version identifier | Lines 48-49 |
| Funding | 4 | Sources and types of financial, material, and other support | Lines 489-491, Lines 647-651 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | Lines 28-29 |
|  | 5b | Name and contact information for the trial sponsor | Lines 21-31 |
|  | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Lines 623-624, Lines 640-645 |
|  | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Lines 629-638 |
| Introduction |  |  | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | Lines 109-202 |
|--------------------------|----|-----------------------------------------------------------------------------------------------------------------|----------------|
|                          | 6b | Explanation for choice of comparators                                                                             | Line 159, 210-211 |
| Objectives               | 7  | Specific objectives or hypotheses                                                                                   | Line 205-224   |
| Trial design             | 8  | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | Lines 207-210   |

**Methods: Participants, interventions, and outcomes**

| Study setting           | 9  | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Lines 255-256   |
|-------------------------|----|-----------------------------------------------------------------------------------------------------------------|----------------|
| Eligibility criteria    | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Lines 230-253, 263-270, 281-283 |
| Interventions           | 11a| Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Lines 272-299   |
|                         | 11b| Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Lines 466-470   |
|                         | 11c| Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | NA – single procedural intervention |
|                         | 11d| Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA – single procedural intervention |
**Outcomes**

Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

**Participant timeline**

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

**Sample size**

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

**Recruitment**

Strategies for achieving adequate participant enrolment to reach target sample size.

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

**Sequence generation**

Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

**Allocation concealment mechanism**

Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

**Implementation**

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.
Blinding (masking) 17a Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how

NA – single arm

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

NA – single arm

Methods: Data collection, management, and analysis

Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Lines 327-348

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

None – small study population with single intervention and short follow-up

Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Lines 640-645

Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Lines 350-370

20b Methods for any additional analyses (e.g., subgroup and adjusted analyses)

None

20c Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)

None – small study population with single intervention and short follow-up

Methods: Monitoring
Data monitoring

21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Lines 372-375, 472-479
Lines 629-638

Harms

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Lines 472-479

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Lines 472-479

Ethics and dissemination

Research ethics approval

24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Lines 48-49, 77-80, 441-443

Protocol amendments

25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Lines 472-479

Consent or assent

26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Lines 263-270

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

None

Confidentiality

27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Lines 640-645
| Section                                      | Line(s)    | Information                                                                 |
|----------------------------------------------|------------|-----------------------------------------------------------------------------|
| Declaration of interests                     | 28         | Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data                               | 29         | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care                | 30         | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy                         | 31a        | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
|                                              | 31b        | Authorship eligibility guidelines and any intended use of professional writers |
|                                              | 31c        | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| Appendices                                   |            |                                                                             |
| Informed consent materials                   | 32         | Model consent form and other related documentation given to participants and authorised surrogates Available upon request |
| Biological specimens                         | 33         | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable NA – no specimens |