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Implementation Process and Evolution of a Laparotomy-Assisted 2-Port Fetoscopic Spina Bifida Closure Program

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Abstract
Introduction: Prenatal closure of open spina bifida via open fetal surgery improves neurologic outcomes for infants in selected pregnancies. Fetoscopic techniques that are minimally invasive to the uterus aim to provide equivalent fetal benefits while minimizing maternal morbidities, but the optimal technique is undetermined. We describe the development, evolution, and feasibility of the laparotomy-assisted 2-port fetoscopic technique for prenatal closure of fetal spina bifida in a newly established program. ***Methods:*** We conducted a retrospective cohort study of women consented for laparotomy-assisted fetoscopic closure of isolated fetal spina bifida. Inclusion and exclusion criteria followed the Management of Myelomeningocele Study (MOMS). Team preparation involved observation at the originating center, protocol development, ancillary staff training, and surgical rehearsal using patient-matched models through simulation prior to program implementation. The primary outcome was the ability to complete the repair fetoscopically. Secondary maternal and fetal outcomes to assess performance of the technique were collected prospectively. ***Results:*** Of 57 women screened, 19 (33%) consented for laparotomy-assisted 2-port fetoscopy between February 2017 and December 2019. Fetoscopic closure was completed in 84% (16/19) cases. Over time, the technique was modified from a single- to a multilayer closure. In utero hindbrain herniation improved

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in 86% (12/14) of undelivered patients at 6 weeks postoperatively. Spontaneous rupture of membranes occurred in 31% (5/16) of fetoscopic cases. For completed cases, median gestational age at birth was 37 (range 27–39.6) weeks and 50% (8/16) of women delivered at term. Vaginal birth was achieved in 56% (9/16) of patients. One newborn had a cerebrospinal fluid leak that required postnatal surgical repair. ***Conclusion:*** Implementation of a laparotomy-assisted 2-port fetoscopic spina bifida closure program through rigorous preparation and multispecialty team training may accelerate the learning curve and demonstrates favorable obstetric and perinatal outcomes.

Introduction

Open spina bifida (OSB) remains the commonest nonlethal central nervous system birth defect with increased mortality in adulthood secondary to complications of hydrocephalus and Chiari malformation [1]. The Management of Myelomeningocele Study (MOMS) established the benefits of prenatal closure via hysterotomy compared to traditional postnatal closure [2], at the expense of a higher rate of prematurity and the obstetric sequelae of hysterotomy.

The maternal and obstetric risks of uterine rupture after OSB closure [3, 4] provide impetus for exploring less invasive techniques that preserve fetal benefits but minimize risks for the mother and her future children. Fetoscopic OSB closure has been performed through either a percutaneous or laparotomy-assisted approach [5–8]. While both share the technical challenges of achieving watertight closure of the defect, the percutaneous fetoscopic approach has been hampered by higher spontaneous rupture of membranes (SROM) and preterm birth rates than open OSB closure. In contrast, laparotomy-assisted fetoscopy allows surgical fixation of the membranes to the myometrium potentially prolonging pregnancy [9, 10].

Recognizing that treatment outcomes may relate to center and management team experience [11], we established a laparotomy-assisted fetoscopic OSB closure program in a step-wise fashion. In this study, we outline the process for establishing the program and evaluate the feasibility of introducing this technique outside the originating center measured by the ability to complete the procedure fetoscopically and its performance by secondary maternal and fetal outcomes.

Materials and Methods

This is a retrospective cohort study of patients with fetal OSB evaluated for prenatal closure eligibility at our center between February 2017 and December 2019. The study was conducted following STROBE guidelines [12], under an investigational device exemption (IDE) from the US Food and Drug Administration (FDA) for use of the fetoscopy equipment for this novel indication (ClinicalTrials.gov: NCT03090633). The study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00123834). Recruitment was paused at the beginning of the COVID-19 pandemic, and the cohort includes all delivered patients at that point.

Screening and Inclusion

All patients underwent a detailed anatomic survey, fetal echocardiogram, and magnetic resonance imaging (MRI) [13], amniocentesis, and multispecialty consultations. Preoperative ventriculomegaly was defined as a lateral ventricle measurement >10 mm on ultrasound. Patients meeting the MOMS trial inclusion criteria [2] with preserved fetal lower extremity movement were offered fetoscopic OSB closure. All patients signed written informed consent for laparotomy, and fetoscopic OSB closure with optional conversion to hysterotomy if fetoscopic closure was not feasible.

Program Implementation

Institutional support guided by a national position statement was gathered from all departments involved in the care of children with OSB to offer prenatal closure as a treatment option [14]. A dedicated multispecialty surgical team of experienced maternal-fetal intervention specialists, pediatric neurosurgeons, obstetric anesthesiologists, and nursing was established [15, 16]. After literature review and direct observation of several surgical approaches, we decided to pursue a laparotomy-assisted 2-port fetoscopic approach.

Weekly training sessions using a tabletop simulator were instituted to practice individual surgical steps and coordination between surgeons and to determine the optimal instrumentation and suture material [17]. The training goal was to achieve stable simulation times for the surgical milestones. In preparation for clinical cases, individual patient-matched 3D-printed models were generated from prenatal ultrasound volumes with a silicone skin covering and incorporated into surgical practice sessions in order to better anticipate intraoperative circumstances [18].

Surgical Technique

Fetoscopic OSB closure was planned between 19 and 25^{+6} weeks gestation under maternal general endotracheal and adjunctive epidural anesthesia. A transverse lower abdominal incision was followed by uterine exteriorization. External version was performed when necessary to orient the fetus into cephalic presentation. The location of the superior port was determined by placental location and fetal position. At least 2 stay sutures were used to plicate the membranes to the uterine wall, and 2 12 Fr (4 mm) ports (Cook Inc., West Des Moines, IA, USA) were introduced under ultrasound guidance using either Seldinger or sharp technique. Amnioreduction was followed by humidified (after case 5) carbon dioxide (CO_2) insufflation at a pressure of 8–10 mm Hg (Insuflow; Lexion Medical, St Paul, MN, USA). The second port was placed in line with the defect approximately 5 cm away from the initial

port under direct visualization using a hysteroscopy sheath with a 0° telescope or ventriculoscope (both Karl Storz, Tuttlingen, Germany). Fetal weight-based analgesia (rocuronium [0.5 mg/kg], atropine [40 μg/kg], and fentanyl [3 μg/kg]) were administered. Intraoperative fetal surveillance was performed using continuous ultrasound monitoring. Fetal venous blood gases were drawn if there was concern about fetal status [19], and rescue medications were available to treat fetal bradycardia. If intrauterine resuscitation was unsuccessful and the fetus was >24 weeks gestation or if there was concern for maternal status, delivery was performed.

The neurosurgical portion of the procedure was initially performed by a sharp release of the placode followed by skin closure using interrupted sutures of 3-0 poliglecaprone (Monocryl; Ethicon, Somerville, NJ, USA) secured with an extracorporeal sliding knot in a single-layer approach. In the next iteration of the technique, placode dissection was followed by development of a myofascial flap bilaterally. A dural substitute (Durepair Regeneration Matrix; Medtronic, Minneapolis, MN, USA or DuraGen Dural Regenerative Matrix; Integra, Plainsboro, NJ, USA) was placed over the placode to provide an additional barrier to reduce tethering, followed by approximation of the myofascial flap with interrupted mattress sutures. The skin was closed with a series of interrupted mattress sutures or continuously using a barbed suture of 3-0 poliglecaprone (Monocryl; Ethicon, Somerville, NJ, USA). Lateral relaxing incisions were performed using monopolar electrocautery with or without sharp dissection (Colorado Microdissection Needle; Stryker, Kalamazoo, MI, USA or Karl Storz, Tuttlingen, Germany) if needed to allow for primary skin closure. Once fetal OSB closure was complete, CO_2 insufflation was discontinued and uterine fluid volume was restored with warmed normal saline. Each port was removed, and the insertion sites were closed with a running 2-0 polyglactin (Vicryl; Ethicon, Somerville, NJ, USA) suture, followed by an imbricating layer. Seprafilm was placed over the port sites, according to the surgeon's discretion. The maternal abdomen was closed in a standard fashion.

Perioperative Care

Perioperative management to address the risks for preterm labor (PTL) used our previously published approach [16]. Vaginal progesterone (200 mg) was initiated up to 1 week before surgery and continued postoperatively. For tocolysis, oral indomethacin (100 mg) was given preoperatively, and intravenous magnesium sulfate was initiated after induction of anesthesia (4 g bolus then 2 g/h) then titrated overnight to achieve uterine quiescence. Oral indomethacin was titrated over the first 48 h. Nifedipine 10–20 mg every 6–8 h was used for maintenance tocolysis if there was persistent uterine irritability or preterm contractions. Cervical cup pessary (Bioteque, San Jose, CA, USA) was offered for postoperative cervical shortening <25 mm [16].

A modified enhanced recovery after surgery protocol was instituted [20]. Postoperative pain was managed with a multimodal approach using epidural anesthesia until postoperative day 2, followed by a quadratus lumborum block and scheduled acetaminophen [21]. Lidocaine patches and oral oxycodone were administered for breakthrough pain. Sequential compression devices with or without heparin administration were used for thrombotic prophylaxis.

After hospital discharge, outpatient weekly surveillance included maternal vital signs and ultrasound evaluation of membrane status, amniotic fluid volume, fetal motor function, and for signs of reversing hindbrain herniation. Follow-up fetal MRI was performed after 6 weeks in all undelivered patients to assess for improvement of hindbrain herniation. Obstetric complications such as SROM or PTL were promptly addressed according to standard of care. Timing and mode of delivery were determined using standard obstetric indications.

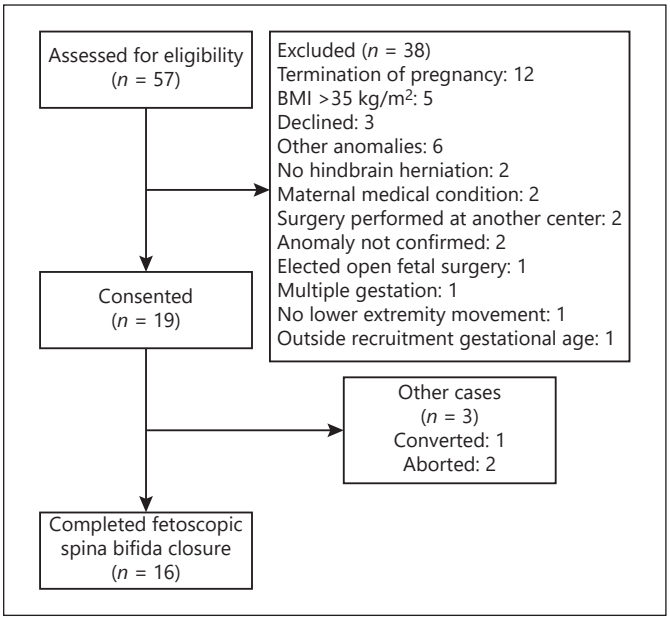


Fig. 1. Flow diagram of participants screened, providing informed consent and procedure performed.

Postnatal Care

After birth, neonates were admitted to the intensive care unit. Discharge follow-up included coordinated transition into the local spina bifida clinic at the Kennedy Krieger Institute or one closer to the family's residence. Assessment of motor function is planned at 30 months of age.

The primary outcome of this study was the ability to perform entire OSB closure fetoscopically. Secondary outcomes included SROM, PTL, preterm birth, gestational age (GA) at delivery, vaginal delivery, and improvement in hindbrain herniation in utero. Study data were collected and managed using REDCap electronic data capture tools hosted at the Johns Hopkins University [22, 23]. Descriptive statistics and comparisons made between groups are reported using standard parametric and nonparametric tests based on the distribution of the data using IBM SPSS Statistics 25. A p value of <0.05 was considered statistically significant.

Results

Ten cases were initially approved under the IDE, but the number has expanded gradually with ongoing monitoring by the FDA. Of 57 patients evaluated, 19 (33%) were consented for fetoscopic OSB closure (18 under IDE

Table 1. Baseline characteristics of the study population

Characteristic	$N = 19$
Maternal age	31.1±7.2
Race	
Caucasian	12 (63)
Black	1 (5)
Hispanic	6 (32)
Other	0 (0)
Married	17 (90)
Body mass index at enrollment, kg/m^2	27.3±3.5
Current smoker	1 (5)
Family history of neural tube defect	2 (10)
Nulliparous	5 (26)
Cervical length, mm	37.6±6.6
Anterior placenta	14 (74)
Lesion type	
Myelomeningocele	12 (63)
Myeloschisis	7 (37)
Lesion level on ultrasound	
Thoracic	1 (5)
L_1–L_2	2 (11)
L_3–L_4	9 (47)
L_5–S_1	7 (37)
Club foot	3 (16)
Ventriculomegaly	11 (58)
>15 mm preoperatively	3 (16)

Data are mean ± standard deviation, or *n* (%).

Table 2. Intraoperative data for the entire study population

Intraoperative detail	Fetoscopic ($n = 16$)	Unsuccessful ($n = 3$)
GA at surgery, weeks	25.1 [22.9–25.9]	24.7±0.8
Total laparotomy time, min	317 [263–458]	331±178
Total fetoscopy time,[a] min	225±54	275±16
Insufflation duration, min	190±55	107 [17–198]
Fetal repair completed	16/16 (100)	1/3 (33)
Total fetal closure time,[b] min	145±62	142 [124–161]
Multilayer closure	4 (25)	1/3 (33)
Dural matrix used	6 (38)	1/3 (33)
Relaxing incisions performed	3 (19)	0/3 (0)
Humidified CO_2 used	11 (69)	2/3 (67)
Total IVF volume, mL	2,724±1,013	3,400±1,905
Estimated blood loss, mL	150 [100–600]	4,300±5,047

Data are median [range], mean ± standard deviation, or *n*/*N* (%). CO_2, carbon dioxide; IVF, intravenous fluid; GA, gestational age. [a] From the first port inserted until second port removed. [b] From the beginning of placode dissection to end of last stitch.

and one experimental procedure prior to IDE submission). Thirty-eight women were excluded (Fig. 1). Participants were predominantly Caucasian and multiparous, with a mean body mass index of 27.3 ± 3.5 kg/m^2. The upper border of the lesion was in the lumbosacral region for the majority of cases, and 11 (58%) had cerebral ventriculomegaly preoperatively (Table 1).

Nineteen fetoscopic cases were attempted. Sixteen cases (84%) were completed entirely fetoscopically. Surgery was carried out at a median GA of 25.1 (range 22.9–25.9) weeks. Mean total fetoscopy time was 225 ± 54 min, and mean duration of uterine insufflation was 190 ± 55 min. Fetoscopy time is longer since second port placement, subsequent removal, amnioreduction, and amnioinfusion straddle the uterine insufflation portion of the procedure. The time required for closure of the fetal lesion was 145 ± 62 min. For the 5 cases with a multilayer closure, fetoscopy time was 268 ± 27 min, with 165 ± 69 min of insufflation, and required 173 ± 40 min to close the fetal lesion. Relaxing incisions were performed in 3 cases with myeloschisis (unilateral [$n = 1$]; bilateral [$n = 2$]) to achieve a primary skin closure. Simulation times for both placode dissection and individual sutures were also recorded for 8 preoperative simulation sessions as well as the corresponding operative times. Both placode, dissection time and suture time were shorter in the simulated setting (4.8 ± 1.8 min vs. 19.8 ± 12.2 min and 9.2 [range 5.6–19.7] min vs. 17 [range 5–77] min, respectively).

Intraoperative data are presented stratified by the type of procedure (Table 2), and individual case details are available upon request. Three cases were unsuccessful. One case was performed without insufflation due to concern of retroamniotic CO_2 tracking requiring conversion to hysterotomy to complete OSB closure. One required emergency cesarean delivery for fetal bradycardia that persisted, despite resuscitation efforts after uterine exteriorization while preparing for port placement. One case required emergent cesarean delivery to control myometrial hemorrhage. There were no maternal deaths. Maternal complications including significant blood loss requiring transfusion ($n = 2$) and intensive care unit admission ($n = 2$) were limited to unsuccessful cases (Table 2).

Hindbrain herniation improved in 12/14 (86%) cases by ultrasound and MRI performed 6 weeks postoperatively. Localized chorion-amnion separation was identified on ultrasound in 7/16 (44%) completed fetoscopic cases at a GA of 28.8 ± 3.3 weeks. There was no difference in the SROM rate, GA at SROM, or delivery timing for those who had chorion-amnion separation or cases where humidified CO_2 was used (χ^2 and Mann-Whitney U, all $p > 0.05$, respectively). Fetoscopy to delivery interval was

longer when membrane status appeared normal (88.3 ± 14 days vs. 60.3 ± 32.3 days, Mann-Whitney U, $p = 0.043$).

For the completed cases, median delivery GA was 37 (range 27–39.6) weeks and 8/16 (50%) patients delivered at term. Nine of 16 women (56%) had vaginal birth, and 4/7 (57%) of cesarean births were for breech presentation. All port sites inspected at cesarean delivery were intact. Neonatal intensive care unit admission had a median length of stay of 9 (range 2–101) days. One newborn had a cerebrospinal fluid leak on the first day of life requiring surgical repair. All newborns with relaxing incisions had uncomplicated complete healing by secondary intention.

Discussion

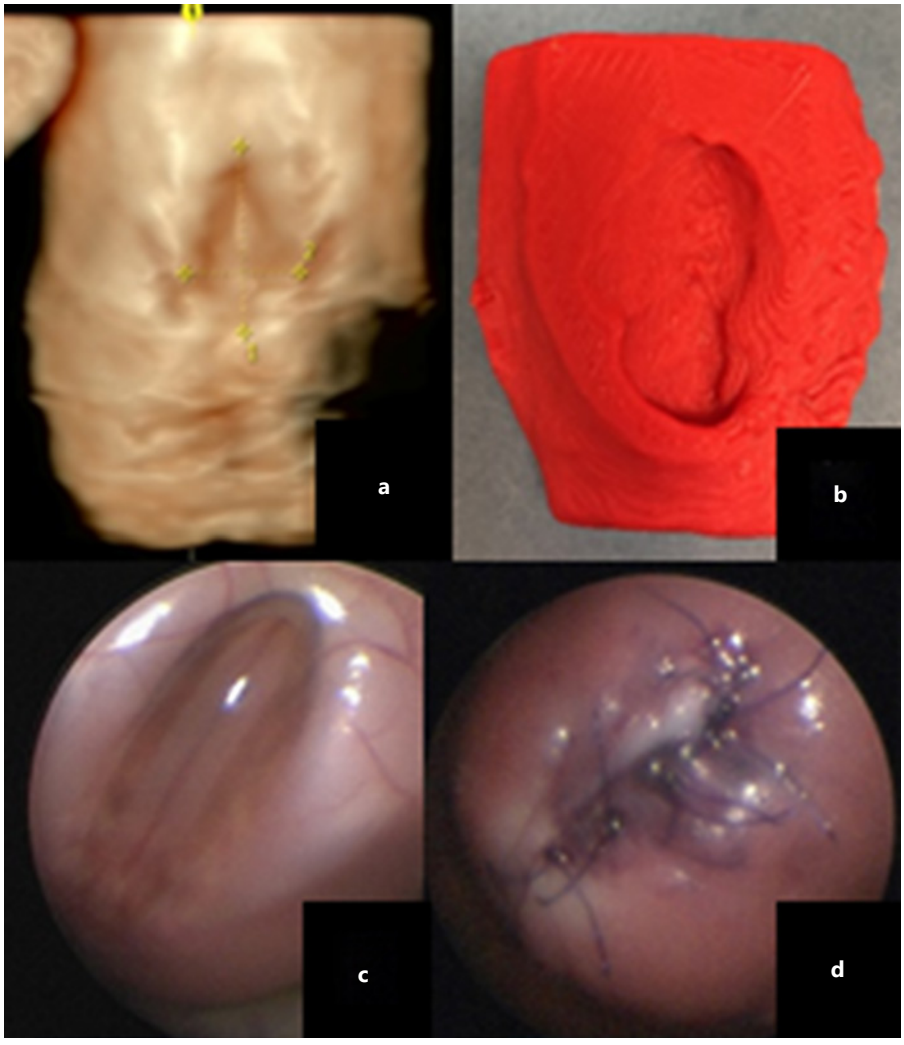
Adoption of fetoscopic OSB closure is rapidly accelerating worldwide, but the optimal surgical technique is undetermined. The process we describe to implement a laparotomy-assisted 2-port fetoscopic OSB closure program aligns with guidance from the International Fetoscopic Myelomeningocele Repair Consortium, demonstrating feasibility with over 80% surgical success even during the learning curve phase [24]. Although this cohort represents a heterogeneous group due to transition to using humidified CO_2 and a more complex multilayer closure, delivery at ≥37 weeks occurred in 50% of patients and 69% delivered at ≥35 weeks for completed cases. Half of the patients had vaginal birth. No uterine scar complications were encountered, and all inspected port sites were well-healed. Only one newborn required revision of the surgical site.

Our data support that the laparotomy-assisted fetoscopic approach for OSB closure mitigates the risk of SROM with fetoscopy for fetal OSB closure while avoiding risks associated with hysterotomy. Approximately 30% of patients had SROM, which is less frequent than following percutaneous fetoscopic surgery [6, 9, 25–27] and similar to rates after open fetal surgery [2, 3, 28, 29] and other laparotomy-assisted fetoscopic series [7–9]. Intraoperative complications largely occurred when the procedure could not be completed fetoscopically, predominantly related to concerns regarding membrane tenting or chorion-amnion separation at the time of initial port placement, which is consistent with the technical challenges reported with the percutaneous approach [27, 30]. Open communication and mentoring from the originating group allowed our team to incorporate their experiential knowledge from the beginning.

The potential for fetal acidosis from CO_2 based on ovine model observations is one of the major concerns with fetoscopic OSB closure [31–34]. However, partial insufflation with heated, humidified CO_2 appears to lessen both fetal acid base changes [35, 36] and the inflammatory reaction in the peritoneum and fetal membranes that may contribute to SROM compared to cold, dry CO_2 [36–38]. For these reasons, we switched to heated humidified CO_2. Differences between the human and ovine placenta as well as the higher concentration of carbonic anhydrase [39] in human fetal tissues has been suggested as the reason for greater tolerance of CO_2 in human fetuses with only modest changes in acid-base status, as we previously reported [8, 18]. Additional observations in membrane status and brain microstructure between fetuses that have undergone open fetoscopic closure for spina bifida using humidified CO_2 and those that underwent open fetal surgery show no demonstrable differences and provide additional affirmation that exposure to heated humidified CO_2 is not detrimental to human fetuses [40, 41]. Ongoing efforts to minimize fetal CO_2 exposure and evaluate any sequelae are important factors for fetoscopic OSB closure.

The simulation model used for surgical rehearsal was felt to be a critical contributor to successfully building a cohesive operative team to minimize clinical errors. Incorporation of a second neurosurgeon occurred effortlessly as well as harmonization of 2 different surgical specialists. The 2-port technique is a substantial departure from standard laparoscopic skill set that most surgeons learn during operative training [17]. The role of a third port in decreasing operative time and maintaining membrane integrity remains an important consideration. The use of patient-matched models was particularly informative for our team in that specific aspects or challenges for each procedure could be better anticipated (Fig. 2) [18]. Concurrent clinical practice and repetitive surgical rehearsal provide an opportunity to strategically target ways to improve surgical technique and efficiency and to identify opportunities for new product development. However, longer surgery times likely reflect significant limitations of the current simulator to address the full range of surgical challenges associated with the procedure. Assuring that the clinical resources are capable of managing the full spectrum of potential complications for both the mother and fetus is also an important additional safeguard.

In order for fetoscopic OSB closure to become an equivalent surgical alternative to open fetal closure, obstetric and fetal outcomes must be commensurate or better. Commitment to long-term follow-up of these children and ongoing collaboration in the consortium are key



Color version available online

Fig. 2. Ultrasound 3D rendering of a fetal myeloschisis (**a**), 3D print of the lesion (**b**), intraoperative appearance of the myeloschisis (**c**), and after fetoscopic closure (**d**).

measures to optimize surgical technique and verify if outcomes through childhood and beyond are comparable to other fetal OSB closure methods [10]. If long-term outcomes for the fetoscopic approach rival those of open surgery, the surgical approach chosen can be based on the particular case characteristics with shared decision-making between the physician and patient, rather than commitment to a single technique.

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Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00123834). All patients included provided written informed consent (ClinicalTrials.gov, NCT03090633). Trial registration for the protocol titled "Fetoscopic repair of isolated fetal spina bifida" can be located at https://www.clinicaltrials.gov/ct2/show/NCT03090633?cond=fetal+spina+bifida+fetoscopy&draw=2&rank=1.

Conflict of Interest Statement

J.L.M. received funding from the Fetal Health Foundation and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01). A.A.B. received funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U10). E.B.J. received funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD100540). The remaining authors did not report any potential conflicts of interest.

Author Contributions

All designated as authors have met all 4 criteria for authorship, provided critical review, approved this submission, and agreed to be accountable for this work.

Data Availability Statement

Data included in this study are available upon request by contact with the corresponding author.

Funding Sources

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