Original Research

Fetoscopic Open Neural Tube Defect Repair

Development and Refinement of a Two-Port, Carbon Dioxide Insufflation Technique

Michael A. Belfort, MD, PhD, William E. Whitehead, MD, Alireza A. Shamshirsaz, MD, Zhoobin H. Bateni, MD, Oluyinka O. Olutoye, MD, PhD, Olutoyin A. Olutoye, MD, David G. Mann, MD, Jimmy Espinoza, MD, Erin Williams, MD, Timothy C. Lee, MD, Sundeep G. Keswani, MD, Nancy Ayres, MD, Christopher I. Cassady, MD, Amy R. Mehollin-Ray, MD, Magdalena Sanz Cortes, MD, PhD, Elena Carreras, MD, Jose L. Peiro, MD, Rodrigo Ruano, MD, PhD, and Darrell L. Cass, MD

OBJECTIVE: To describe development of a two-port fetoscopic technique for spina bifida repair in the exteriorized, carbon dioxide-filled uterus and report early results of two cohorts of patients: the first 15 treated with an iterative technique and the latter 13 with a standardized technique.

METHODS: This was a retrospective cohort study (2014–2016). All patients met Management of Myelomeningocele Study selection criteria. The intraoperative approach was iterative in the first 15 patients and was then standardized. Obstetric, maternal, fetal, and early neonatal outcomes were compared. Standard parametric and nonparametric tests were used as appropriate.

RESULTS: Data for 28 patients (22 endoscopic only, four hybrid, two abandoned) are reported, but only those with a complete fetoscopic repair were analyzed (iterative technique [n=10] compared with standardized technique [n=12]). Maternal demographics and gestational age (median [range]) at fetal surgery (25.4 [22.9–25.9] compared with 24.8 [24–25.6] weeks) were similar, but delivery occurred at 35.9 (26–39) weeks of gestation with the iterative technique compared with 39 (35.9–40) weeks of gestation with the standardized technique ($P<.01$). Duration of surgery (267 [107–434] compared with 246 [206–333] minutes), complication rates, preterm prelabor rupture of membranes rates (4/12 [33%] compared with 1/10 [10%]), and vaginal delivery rates (5/12 [42%] compared with 6/10 [60%]) were not statistically different in the iterative and standardized techniques, respectively. In 6 of 12 (50%) compared with 1 of 10 (10%), respectively ($P=.07$), there was leakage of cerebrospinal fluid from the repair site at birth. Management of Myelomeningocele Study criteria for hydrocephalus–death at discharge were met in 9 of 12 (75%) and 3 of 10 (30%), respectively, and 7 of 12 (58%) compared with 2 of 10 (20%) have been treated for hydrocephalus to date. These latter differences were not statistically significant.

CONCLUSION: Fetoscopic open neural tube defect repair does not appear to increase maternal–fetal complications as compared with repair by hysterotomy, allows for vaginal delivery, and may reduce long-term maternal risks.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, https://clinicaltrials.gov, NCT02230072.

(Obstet Gynecol 2017;0:1–10)

DOI: 10.1097/AOG.0000000000001941

Open neural tube defect is associated with significant motor and cognitive impairment. The Management of Myelomeningocele Study[1] showed

From the Departments of Obstetrics and Gynecology, Neurosurgery, Surgery, Anesthesiology, Pediatrics, and Radiology, Baylor College of Medicine, and Texas Children's Fetal Center, Houston, Texas; and the Departments of Obstetrics and Gynecology and Surgery, Vall D'Hebron Hospital, Barcelona, Spain.

Supported by grants from the Sterling Turner Foundation, O'Quinn Foundation, Fondren Foundation, and Tramuto Foundation.

Presented in part at the 36th Annual Meeting of the Society for Maternal-Fetal Medicine, February 4–6, 2016, Atlanta, Georgia; and at the 37th Annual Meeting of the Society for Maternal-Fetal Medicine, January 23–28, 2017, Las Vegas, Nevada.

The authors thank Lawrence McCullough, PhD, for help with oversight and outcome review.

Each author has indicated that he or she has met the journal's requirements for authorship.

Corresponding author: Michael A. Belfort, MD, PhD, Department of Obstetrics and Gynecology, Baylor College of Medicine, Texas Children's Hospital Pavilion for Women, 6651 Main Street, Houston TX 77030; email: Belfort@bcm.edu.

Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/17

that prenatal open neural tube defect repair lowers the risk of hydrocephalus and improves motor outcomes at 30 months of age. The hysterotomy required is, however, associated with significant maternal and fetal risk making a less invasive method desirable. Initial attempts at fetoscopic surgery in a gas-filled uterus had poor outcomes (Bruner JP, Tulipan NE, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero [letter]. Am J Obstet Gynecol 1997;176:256–7)[2,3] and led to abandonment of this approach in the United States. Researchers in Europe and Brazil[4–6] developed percutaneous fetoscopic techniques for open neural tube defect repair, but these have been complicated by high rates of preterm prelabor rupture of membranes (PROM) before 32 weeks of gestation[7,8] and by preterm delivery (Bruner et al, Am J Obstet Gynecol).[2–10] Currently there are few data supporting an improved risk–benefit profile for the fetoscopic compared with the open uterus technique, and none of the published series has allowed for vaginal delivery.

This study represents the clinical endpoint of a program that was developed in an animal model[11,12] and then advanced with the hope of developing a reliable, safe, fetoscopic technique in humans that affords satisfactory fetal access, produces equivalent neurosurgical results to the open method, allows vaginal delivery, and decreases the maternal and obstetric risks of open fetal surgery. The aims of the current study were to describe the progressive development of our exteriorized uterus, carbon dioxide insufflation fetoscopic technique (2011–2016) and to compare our early experience (first 12 patients–iterative technique) with our next 10 patients (standardized technique). We also aimed to compare results with our standardized technique with those from other groups performing fetoscopic open neural tube defect repair.

MATERIALS AND METHODS

This retrospective cohort study (per Strengthening the Reporting of Observational Studies in Epidemiology guidelines)[13] included all fetoscopic procedures at our center between April 2014 and September 2016 including those that were converted to open (hybrid; n=4) or abandoned (abandoned; n=2). Oversight was provided by the U.S. Food and Drug Administration, Baylor College of Medicine institutional review board (H-34680, H-38479), our Fetal Therapy Board, and a Data Safety Monitoring Board. All patients agreed to open fetal surgery before being offered the experimental fetoscopic procedure. Inclusion and exclusion criteria were per the Management of Myelomeningocele Study trial (Box 1).[1] All patients understood that per-protocol fetoscopic procedures would be converted to hybrid if deemed necessary for a technically better or safer procedure and that the case could be abandoned (and the pregnancy continued with postnatal open neural tube defect repair) if the fetus did not tolerate the surgery and did not need immediate delivery or if the findings at the time of surgery were different from what was expected and surgery was not advisable. All patients underwent preoperative fetal echocardiogram, comprehensive fetal ultrasound scan, and magnetic resonance imaging (to document the degree of hindbrain herniation).

All patients were managed per our standard protocol involving steroid administration (23–34 weeks of gestation), prophylactic tocolysis (preoperative indomethacin or nifedipine and intra- and postoperative magnesium sulfate), and prophylactic antibiotics (cefazolin or, if allergic, clindamycin and gentamicin).

All patients had general endotracheal anesthesia (1–3 minimum alveolar concentration sevoflurane). Fetal anesthesia was with intramuscular opioid (fentanyl 5–10 micrograms/kg), anticholinergic (atropine 20 micrograms/kg), and muscle relaxant (vecuronium 0.3 mg/kg) into the buttock or extremity using a long 22-gauge needle passed through one of the operating ports.

The fetal surgical technique we used for fetoscopic surgery with carbon dioxide insufflation has been previously described.[14–16] The uterus was exteriorized through a low transverse abdominal incision

Box 1. Inclusion and Exclusion Criteria

Inclusion Criteria

- Singleton pregnancy
- Myelomeningocele with the upper boundary located between T1 and S1
- Evidence of hindbrain herniation
- Gestational age of 19–25.9 weeks at randomization
- A normal karyotype
- U.S. residency
- Maternal age of at least 18 y

Exclusion Criteria

- A fetal anomaly unrelated to myelomeningocele
- Severe kyphosis
- Risk of preterm birth (including short cervix and previous preterm birth)
- Placental abruption
- Body mass index (kg/m^2) of 35 or more
- Contraindication to surgery, including previous hysterotomy in the active uterine segment

Adapted from criteria reported in the Management of Myelomeningocele Study.[1]

and the fetus then manipulated into position using an external version technique. Under ultrasound guidance, two 2/0 polydioxanone stitches were placed to plicate the membranes to the uterine wall. In the iterative technique, four sutures were placed in a box pattern, whereas, in the standardized technique, only two parallel sutures were placed. A 12-French port was then introduced between the sutures into the amniotic cavity (Seldinger technique). Approximately 300 mL of amniotic fluid was withdrawn and carbon dioxide was insufflated (0.5 L/min, 12±2 mm Hg) through a heater–humidifier. A pediatric cystoscope (iterative) or a straight endoscope (standardized) was placed into the gas pocket through the port. Under fetoscopic vision plication sutures, and one or two additional ports, were then placed. In the first 15 patients we developed an iterative technique that initially used two ports and then moved to three ports for six patients (numbers 6–9, 12, and 14) with a combination of 5-French, 7-French, 12-French, and 16-French ports. In addition, we tried different instruments, needles, and sutures (barbed monofilament, braided, monofilament standard, braided Quikstitch) and closure techniques. After 15 attempted cases (11 fetoscopic, three hybrid, one abandoned) we standardized our approach from patient 16 to use two ports (12 French) (Fig. 1), a straight endoscope, interrupted vertical mattress sutures, and a knot pusher to deliver an extracorporeally tied modified Meltzer knot in a braided polyglactin–monocryl suture (10 standardized, one hybrid, one abandoned).

For neurosurgical repair, in all patients, the spinal cord was released sharply by cutting the arachnoid membrane between the placode and junctional zone. Primary closure was achieved with a single, unified layer of skin and dura with interrupted or running vertical mattress stitches used to evert the skin edges. Relaxing skin incisions (15–20 mm lateral to the defect) were cut before the repair at the discretion of the neurosurgeon (W.E.W.) if needed to bring the skin edges together (Video 1, available online at http://links.lww.com/AOG/A936; Fig. 2); these were allowed to heal by secondary intention. No patches or extraneous materials (glues) were used in any closure.

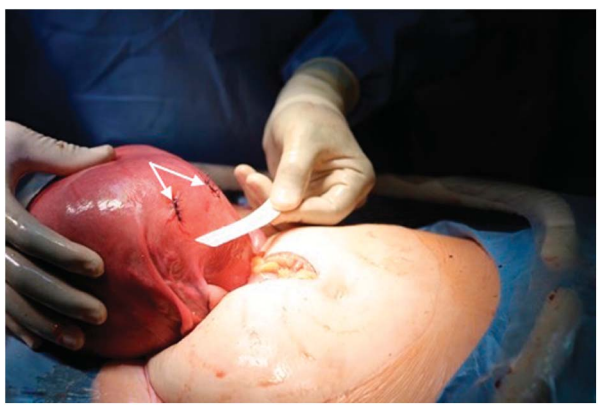

Fig. 1. Image of a patient's uterus and the two port sites (*arrows*) after completion of the fetoscopic surgery.
Belfort. Fetoscopic Meningomyelocele Repair. Obstet Gynecol 2017.

Video 1. Fetoscopic open neural tube defect repair. This video shows the initial and final (standardized) fetoscopic repair techniques used by the team at Texas Children's Hospital to effect fetoscopic open neural tube defect repair. Video created by Mr. Wally Crow. Used with permission.

Fetal surveillance was accomplished using near continuous echocardiography to monitor fetal heart rate and function. If in utero resuscitation was unsuccessful, the protocol called for delivery; if successful, the operation was either continued or abandoned based on clinical judgment. If fetoscopic repair was not thought possible, the fetoscopic procedure was converted to our standard open technique. On completion of both iterative and standardized cases, warmed lactated Ringer's solution with nafcillin (1,000 mg/L) was infused to achieve a normal amniotic fluid index. All patients had postoperative tocolysis per protocol with any, or a combination of, nifedipine (10 mg PO every 6 hours),

Scan this image to view Video 1 on your smartphone.

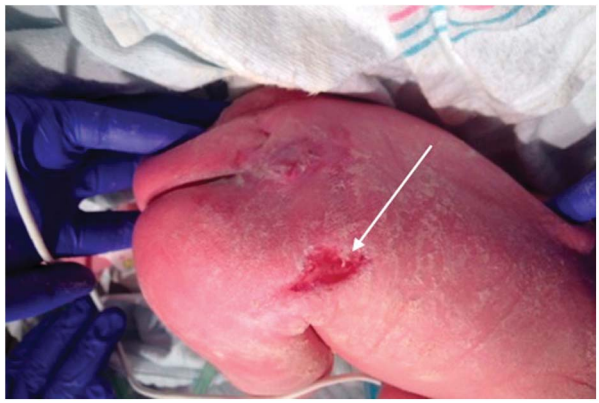

Fig. 2. A healed repair at birth with evidence of a healing relaxing incision (*arrow*).
Belfort. Fetoscopic Meningomyelocele Repair. Obstet Gynecol 2017.

indomethacin (25 mg PO every 6 hours for 48 hours), terbutaline (0.25 mg subcutaneous×two doses), magnesium sulfate (2-g/h intravenous infusion), and epidural analgesia followed by oral opioids. Patients were discharged to modified bed rest at a nearby facility (Ronald McDonald House) once stable and returned weekly for follow-up. Monthly comprehensive ultrasound examination started at 30–32 weeks of gestation, and fetal magnetic resonance imaging was performed at 6 weeks postprocedure to help in planning the mode of delivery (vaginal delivery if the skin lesion appeared closed). Weekly biophysical profile and Doppler studies began at 34 weeks of gestation. In the event of preterm PROM, management in both groups was the same (standard preterm PROM protocol with steroids, latency antibiotics,

Table 1. Baseline Characteristics of and Intraoperative Data for the Study Populations

Characteristic	Fetoscopic (n=22)	Iterative (n=12)	Standardized (n=10)	*P*	Hybrid (n=4)	Abandoned (n=2)	MOMS Trial (n=78)
Maternal age (y)	27.5 [19–38]	28.5 [21–38]	25 [19–37]	.42	25 [24–29]	29 [21–37]	29±5
Race or ethnic group							
White	9/22 (41)	4/12 (33)	5/10 (50)	.67	0/4 (0)	1/2 (50)	73/78 (94)
Black	1/22 (5)	1/12 (8)	0/10 (0)	1.00	0/4 (0)	0/2 (0)	1/78 (1)
Hispanic	12/22 (55)	7/12 (58)	5/10 (50)	1.00	4/4 (100)	1/2 (50)	2/78 (3)
Other	0/22 (0)	0/12 (0)	0/10 (0)	—	0/4 (0)	0/2 (0)	2/78 (3)
Nulliparity	7/22 (32)	2/12 (17)	5/10 (50)	.18	2/4 (50)	1/2 (50)	33/78 (42)
BMI at screening (kg/m^2)	26 [22–35]	27.3 [23.3–33.9]	26 [22–35]	.63	28.7 [27–37.6]	31.8 [29–34.7]	26±4
Anterior placenta	11/22 (50)	6/12 (50)	5/10 (50)	1.00	1/4 (25)	0/2 (0)	36/78 (46)
GA at surgery (wk)	25 [22.9–25.9]	25.4 [22.9–25.9]	24.8 [24–25.6]	.63	24.4 [22.7–25.9]	23.9 [23.9–24]	23.6±1.4
Prior uterine surgery	5/22 (23)	4/12 (33)	1/10 (10)	.32	0/4 (0)	0/2 (0)	11/78 (14)
EFW less than 10%*	2/22 (9)	2/12 (17)	0/10 (0)	.48	1/4 (25)	0/2 (0)	NA
Cervix length* (mm)	38 [28–50]	36 [28–50]	39 [28–46]	.82	35 [30–47]	37 [34–40]	39±7
Lesion level*							
T12 or less	2/22 (9)	1/12 (9)	1/10 (10)	1.00	1/4 (25)	0/2 (0)	4/78 (5)
L1–L2	3/22 (14)	1/12 (9)	2/10 (20)	.57	0/4 (0)	1/2 (50)	21/78 (27)
L3–L4	14/22 (64)	10/12 (83)	4/10 (40)	.07	3/4 (75)	1/2 (50)	30/78 (38)
L5–S1	3/22 (14)	0/12 (0)	3/10 (30)	.08	0/4 (0)	0/2 (0)	23/78 (29)
Myeloschisis*	5/22 (23)	1/12 (9)	4/10 (40)	.14	4/4 (100)	0/2 (0)	NA
Club foot or feet*	3/22 (14)	2/12 (17)	1/10 (10)	1.00	0/4 (0)	0/2 (0)	20/78 (26)
Ventriculomegaly†	16/22 (73)	10/12 (83)	6/10 (60)	.35	3/4 (75)	1/2 (50)	NA
Ventriculomegaly 14 mm or greater	5/22 (23)	3/12 (25)	2/10 (20)	1.00	0/4 (0)	0/2 (0)	NA
Operating time (min)	250 [107–434]	267 [107–434]	246 [206–333]	.27	284 [225–313]	129 [95–163]	105.2±21.8
EBL (mL)	50 [25–300]	55 [25–150]	50 [50–300]	.72	50 [50–100]	42.5 [35–50]	NA
Relaxing incisions	7/22 (32%)	2/12 (17)	5/10 (50)	.17	3/4 (75)	—	NA
Intraoperative resuscitation required	0/22 (0%)	0/12 (0)	0/10 (0)	—	0/4 (0)	1/2 (50)	NA

MOMS, Management of Myelomeningocele Study; BMI, body mass index; GA, gestational age; EFW, estimated fetal weight; NA, data not reported and therefore not available; EBL, estimated blood loss.
Data are median [range], mean±standard deviation, or n/N (%) unless otherwise specified.
P determined by Mann-Whitney *U* test and Fisher exact test as appropriate.
* Based on data recorded from the preoperative ultrasound examination.
† Ventriculomegaly was defined as an atrial width 10 mm or greater.

and delivery chorioamnionitis). In all fetoscopic patients delivered by cesarean, the uterine port scars were inspected.

At birth, all neonates were admitted to the neonatal intensive care unit for comprehensive multidisciplinary evaluation and respiratory support if needed. Transcranial ultrasonography was performed to evaluate the degree of ventriculomegaly within the first 48 hours after delivery. Participants were followed closely for the development of hydrocephalus and neurogenic bladder.

Data from the iterative, standardized, hybrid, and abandoned groups are presented in Table 1, but only those cases that were completed fetoscopically were analyzed statistically (iterative compared with standardized) (Tables 2–4). Standard descriptive statistics and parametric and nonparametric testing were used as appropriate. Parametric data are presented as mean±standard deviation, and nonparametric data are presented as median (range; $P<.05$). We also presented our data with those recently published in a systematic review[1,6] (Table 4).

RESULTS

Between April 2014 and September 2016, 28 fetoscopic cases had been attempted, of which 22 were completed fetoscopically (79%); four (15%) myeloschisis cases (two in each group) were converted to hybrid when it was deemed that a better repair could be achieved using an open approach, and two (7%) cases were abandoned without repair being attempted: one case was the result of fetal bradycardia from maternal hypothermia, which resolved with therapy (ultimately delivered by cesarean at term with postnatal repair) and one case was abandoned after fetoscopy revealed a skin-covered meningocele without a visible placode (confirmed at delivery). The four cases converted to hybrid (because they had a hysterotomy and an open repair) and the two abandoned (because they did not have any repair) were excluded from the analysis but individual (Appendix 1, available online at http://links.lww.com/AOG/A937) and aggregate (Table 1) data are presented in the tables. No significant differences were seen when they were included in their respective fetoscopic group in an intent-to-treat analysis (data not shown). Data are presented here because a port was placed, fetoscopy with carbon dioxide insufflation was carried out, and the pregnancy was allowed to continue.

We compiled individual patient data (Appendix 1, available online at http://links.lww.com/AOG/A937), baseline characteristics, and pertinent intraoperative details (Table 1) and maternal outcomes (Table 2). Gestational age at delivery and repair-to-delivery interval were significantly different. In patients who had cesarean delivery (arrest of descent or fetal intolerance of labor), the port sites were all noted to be well healed.

Birth weight in the iterative technique group was significantly lower than in the standardized technique group (Table 3). There were no other major differences in neonatal nonneurologic complications, but numbers are too small to generalize. No infant in either group has died. Reversal of hind brain herniation (per magnetic resonance imaging at 30–32 weeks of gestation) was similar in the iterative (55%) and standardized (60%) groups, but more of the iterative technique cases had cerebrospinal fluid (CSF) leakage at birth (50% compared with 10%, $P=.07$). Two participants in the iterative technique group had repair in the operating room; all other leaks were successfully stopped at the bedside with one to three simple sutures or with only a Steristrip. One iterative technique case (neonate who was delivered en caul 4 days postoperatively at 26 weeks of gestation) required a shunt and repair revision for a late CSF leak from a persistent pseudomeningocele. No neonate had a wound dehiscence as defined by exposed neural elements or a defect larger than 2×2 mm. Lesion level, motor function, and anatomic level were similar. Using the Management of Myelomeningocele Study criteria for hydrocephalus or death, there was no significant difference between the iterative and standardized groups (9/12 [75% compared with 3/10 [30%], $P=.08$). Table 4 lists our standardized fetoscopic technique results with those of recently published series.[1,6]

DISCUSSION

This study represents the clinical endpoint of a program that began with a sheep model,[11,12] was further developed in a fetoscopy simulator, and was then finalized in the sheep model before use in humans. It highlights a number of important findings. Fetoscopic surgery in carbon dioxide gas can be effectively performed for open neural tube defect repair with acceptable short-term maternal and obstetric risk. Nonneurologic neonatal results are comparable with those seen after open fetal surgery, with a low respiratory distress syndrome rate. Neonatal neurologic outcomes are encouraging but long-term data are needed, preventing any direct comparisons with Management of Myelomeningocele Study outcomes.[1] Our standardized technique compares favorably with those of others performing fetoscopic repair.[4–9] Our unified closure technique allows effective repair without patches, extensive dissection, or tissue flaps.

Table 2. Maternal Outcomes

Outcome	Fetoscopic (n=22)	Iterative (n=12)	Standardized (n=10)
GA at PROM (wk)	34 [30.1–35.9]	33.6 [30.1–35.9]	34 (n=1)
PROM* (weeks of gestation)	5/22 (23)	4/12 (33)	1/10 (10)
Less than 30	0/22 (0)	0/12 (0)	0/10 (0)
30–34 6/7	3/22 (14)	2/12 (17)	1/10 (10)
35	2/22 (9)	2/12 (17)	0/10 (0)
GA at delivery (wk)	38.1 [26–40]	35.9 [26–39]	39 [35.9–40]
Delivery (weeks of gestation)			
Less than 30	1/22 (5)	1/12 (8)	0/10 (0)
30–34 6/7	4/22 (18)	4/12 (33)	0/10 (0)
35–36 6/7	3/22 (14)	2/12 (17)	1/10 (10)
37	14/22 (64)	5/12 (42)	9/10 (90)
Vaginal delivery	11/22 (50)	5/12 (42)	6/10 (60)
Scheduled cesarean delivery	2/22 (9)	2/12 (17)	0/10 (0)
Repair-to-delivery interval (wk)	12.9 [0.4–15.1]	11.4 [0.4–14.1]	14.4 [10.3–15.1]
PROM to delivery (d) (no. of patients)	4±5 (5)	2±2 (4)	13±0 (1)
Placental abruption	2/22 (11)	1/12 (8)	1/10 (10)
Chorioamniotic membrane separation	7/22 (32)	5/12 (45)	2/10 (20)
Oligohydramnios	3/22 (14)	2/12 (17)	1/10 (10)
Pulmonary edema	2/22 (9)	2/12 (17)	0/10 (0)
Chorioamnionitis	0/22 (0)	0/12 (0)	0/10 (0)
Well-healed port sites	11/11 (100)*	7/7 (100)*	4/4 (100)*
Port site adhesions	3/11 (27)*	2/7 (29)*	1/4 (25)
Omental adhesions	3/11 (27)	2/7 (29)	1/4 (25)
Blood transfusion after fetal surgery	0/22 (0)	0/12 (0)	0/10 (0)
Maternal hospital length of stay (d)	5 [3–8]	5 [5–8]	6.5 [2–8]

MOMS, Management of Myelomeningocele Study; GA, gestational age; PROM, prelabor rupture of membranes; NA, data not reported and therefore not available.
Data are median [range], n/N (%), or mean±standard deviation unless otherwise specified.
P determined by Mann-Whitney *U* test and Fisher exact test as appropriate.
Bold indicates significant values.

* Seven iterative and four standardized cases were available for evaluation of the port site scars.

Table 3. Fetal, Early Neonatal, and Neurologic Outcomes

Outcome	Fetoscopic (n=22)	Iterative (n=12)	Standardized (n=10)
Birth weight (g)	2,870 [870–3,856]	2,468 [870–3,460]	3,225 [2,554–3,856]
Birth weight less than the 10th percentile	2/22 (9)	2/12 (17)	0/10 (0)
Fetal demise	0/22 (0)	0/12 (0)	0/10 (0)
Apgar score at 5 min less than 7	1/22 (5)	1/12 (8)	0/10 (0)
Ventilation	1/22 (5)	1/12 (8)	0/10 (0)
RDS	1/22 (5)	1/12 (8)	0/10 (0)
Sepsis	0/22 (0)	0/12 (0)	0/10 (0)
NEC	0/22 (0)	0/12 (0)	0/10 (0)
PVL	0/22 (0)	0/12 (0)	0/10 (0)
PDA	0/22 (0)	0/12 (0)	0/10 (0)
Retinopathy	0/22 (0)	0/12 (0)	0/10 (0)
Length of stay in NICU (d)	12 [2–253]	20 [2–253]	9 [5–22]
Perinatal death	0/22 (0)	0/12 (0)	0/10 (0)
Reversal of hindbrain herniation†	12/21 (57)	6/11 (55)	6/10 (60)
CSF leakage at birth	7/22 (32)	6/12 (50)	1/10 (10)
Repair dehiscence	0/22 (0)	0/12 (0)	0/10 (0)
Repair in OR	2/22 (9)	0/12 (0)	2/10 (20)
Repair in NICU	6/22 (27)	6/12 (50)	0/10 (0)
Upper level of lesion			
T12	2/22 (9)	1/12 (8)	1/10 (10)
L1–L2	3/22 (14)	1/12 (8)	2/10 (20)
L3–L4	14/22 (64)	10/12 (83)	4/10 (40)
L5–S1	3/22 (14)	0/12 (0)	3/10 (30)
Motor level: birth vs time of diagnosis			
2 or more levels better	12/22 (55)	7/12 (58)	5/10 (50)
1 level better	4/22 (18)	1/12 (8)	3/10 (30)
No change	5/22 (23)	4/12 (33)	1/10 (10)
One level worse	0/22 (0)	0/12 (0)	0/9 (0)
2 or more levels worse	1/22 (5)	0/12 (0)	1/10 (10)
Motor level after surgery			
Improved	16/22 (73)	8/12 (67)	8/10 (80)
No change	5/22 (23)	4/12 (33)	1/10 (10)
Got worse	1/22 (5)	0/12 (0)	1/10 (10)
Meets MOMS criteria for shunt or death	12/22 (55)	9/12 (75)	3/10 (30)
Treated for hydrocephalus at 12 mo or less	9/22 (41)	7/12 (58)	2/10 (20)

MOMS, Management of Myelomeningocele Study; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; PDA, patent ductus arteriosus; NICU, neonatal intensive care unit; CSF, cerebrospinal fluid; OR, operating room; NA, data not reported and therefore not available.
Data are median [range], mean±standard deviation or as numerator/denominator (percentage) as appropriate unless otherwise specified. *P* values determined by Mann-Whitney *U* test and Fisher exact test as appropriate. Bold indicates significant values.

* One neonate in the abandoned group had a wound infection after postnatal repair that required reexploration.

† Based on fetal magnetic resonance imaging performed at approximately 6 weeks after the repair (one patient delivered 4 days after surgery and did not get a magnetic resonance image).

P	Hybrid (n=4)	Abandoned (n=2)	MOMS Trial (n=78)
—	33.7 (n=1)	—	—
.32	1/4 (25)	0/2 (0)	36/78 (46)
—	0/4 (0)	0/2 (0)	NA
1.00	1/4 (25)	0/2 (0)	NA
—	0/4 (0)	0/2 (0)	NA
<.01	37 [34.1–37.1]	38.9 [38.3–39.4]	34.1±3.1
1.00	0/4 (0)	0/2 (0)	10/78 (13)
.10	1/4 (25)	0/2 (0)	26/78 (33)
1.00	0/4 (0)	0/2 (0)	26/78 (33)
.03	3/4 (75)	2/2 (100)	16/78 (21)
.67	0/4 (0)	0/2 (0)	0/78 (0)
.48	3/4 (75)	0/2 (0)	48/78 (62)
<.01	11.7 [10.3–14.3]	NA	NA
—	2±0 (1)	—	NA
1.00	0/4 (0)	0/2 (0)	5/78 (6)
.38	2/4 (50)	0/2 (0)	20/78 (26)
1.00	0/4 (0)	0/2 (0)	16/78 (21)
.48	0/4 (0)	0/2 (0)	5/78 (6)
—	0/4 (0)	0/2 (0)	2/78 (3)
1.00	4/4 (100)	2/2 (100)	49/76 (64)
1.00	3/4 (75)	1/2 (50)	NA
1.00	3/4 (75)	1/2 (50)	NA
—	0/4 (0)	0/2 (0)	7/78 (9)
.65	6 [5–7]	5.5 [4–7]	NA

Finally, our technique allows the mother to carry the fetus to term or near term and have a vaginal delivery.

Fetoscopic surgery in a carbon dioxide environment has not been enthusiastically received largely as a result of concerns about poor fetal and neonatal

P	Hybrid (n=4)	Abandoned (n=2)	MOMS Trial (n=78)
<.01	2,572 [1,927–3,260]	3,227 [3,120–3,335]	2,383±688
.48	1/4 (25)	0/2 (0)	3/78 (4)
—	0/4 (0)	0/2 (0)	NA
1.00	0/4 (0)	0/2 (0)	NA
1.00	0/4 (0)	0/2 (0)	NA
1.00	0/4 (0)	0/2 (0)	16/77 (21)
—	0/4 (0)	0/2 (0)	4/77 (5)
—	0/4 (0)	0/2 (0)	1/77 (1)
—	0/4 (0)	0/2 (0)	4/77 (5)
—	0/4 (0)	0/2 (0)	3/77 (4)
—	0/4 (0)	0/2 (0)	NA
.36	13 [4–21]	21.5 [5–38*]	NA
—	0/4 (0)	0/2 (0)	2/78 (3)
1.00	4/4 (100)	NA	25/70 (36)
.07	0/4 (0)	0/2 (0)	NA
—	0/4 (0)	NA	10/77 (13)
.19	0/4 (0)	NA	NA
.02	0/4 (0)	NA	NA
1.00	1/4 (25)	0/2 (0)	NA
.57	0/4 (0)	1/2 (50)	NA
.07	3/4 (75)	1/2 (50)	NA
.08	0/4 (0)	0/2 (0)	NA
1.00	3/4 (75)	0/2 (0)	20/62 (32)
.29	0/4 (0)	1/2 (50)	7/62 (11)
.32	1/4 (25)	1/2 (50)	14/62 (23)
—	0/4 (0)	0/2 (0)	13/62 (21)
.45	0/4 (0)	0/2 (0)	8/62 (13)
.65	3/4 (75)	NA	27/62 (44)
.32	1/4 (25)	NA	14/62 (23)
.45	0/4 (0)	NA	21/62 (34)
.08	0/3 (0)	1/2 (50)	53/78 (68)
.10	0/4 (0)	0/2 (0)	31/78 (40)

Table 4. Standardized Technique Compared With Currently Published Data From Other Groups Performing Fetoscopic Repair

	Standardized Technique, Belfort et al, 2017	Pedreira et al, 2016[7]	Kohl, 2014[4]; Degenhardt et al, 2014[8]	Adzick et al, 2011[1]
Approach	Fetoscopic—exteriorized uterus	Fetoscopic—percutaneous	Fetoscopic—percutaneous	Open—hysterotomy
No. of patients	10	10	51	78
Operative outcomes				
Operative time (min)	246 [206–333]	242±89	223±40	105±22
Incomplete neural tube repair at fetal surgery	0 (0/10)	20 (2/10)	1.9 (1/51)	0 (0/78)
Maternal outcome				
Placental abruption	0 (0/10)	10 (1/10)	0 (0/51)	6.4 (5/78)
Pulmonary edema	0 (0/10)	0 (0/10)	1.9 (1/51)	6.4 (5/78)
Chorioamnionitis	0 (0/10)	0 (0/10)	5.9 (3/51)	2.6 (2/78)
Oligohydramnios	10 (1/10)	40 (4/10)	13.7 (7/51)	20.5 (16/78)
Chorioamniotic membrane separation	20 (2/10)	40 (4/10)	3.9 (2/51)	25.6 (20/78)
Preterm PROM	10 (1/10)	100 (10/10)	84.3 (43/51)	46.2 (36/78)
Time of preterm PROM (wk)	34.0±0.0	30.2±2.7	29.7±3.1	—
Hemorrhage requiring transfusion at delivery	0 (0/7)	0 (0/10)	0 (0/51)	9 (7/78)
Vaginal delivery	60 (6/10)	0 (0/10)	0 (0/51)	0 (0/78)
Uterine thinning or hysterotomy dehiscence	0 (0/4)	0 (0/10)	0 (0/51)	35.5 (27/76)
Fetal and neonatal outcomes				
Mean GA at birth (wk)	38.5±1.2	32.4±1.9	32.9±2.7	34.1±3.1
Preterm birth at less than 30 wk of gestation	0 (0/10)	11.1 (1/9)	11.8 (6/51)	12.8 (10/78)
Respiratory distress syndrome	0 (0/10)	0 (0/9)	NA	20.8 (16/77)
Postnatal additional surgery to cover ONTD	0 (0/10)	28.6 (2/7)	NA	2.6 (2/77)
Reversal of hindbrain herniation	60 (6/10)	85.7 (6/7)	NA	35.7 (25/70)
Shunt placement or ETV at 12 mo or less	20 (2/10)	42.8 (3/7)	NA	40.3 (31/77)
Surgery for tethered cord	0 (0/10)	0 (0/7)	NA	7.8 (6/77)
CM decompression surgery	0 (0/10)	0 (0/7)	NA	1.3 (1/77)
Perinatal mortality	0 (0/10)	20 (2/10)	7.8 (4/51)	2.6 (2/78)

PROM, prelabor rupture of membranes; NA, data not reported and therefore not available for comparison; GA, gestational age; ONTD, open neural tube defect; ETV, endoscopic third ventriculostomy; CM, cisterna magna.
Data are median [range], % (n/N), or mean±standard deviation unless otherwise specified.
Management of Myelomeningocele Study trial data are included for reference.

outcomes, high reported rates of preterm PROM and preterm birth (Bruner et al, Am J Obstet Gynecol),[2–9] a less than acceptable open neural tube defect repair,[10,19] and the safety of intrauterine carbon dioxide.[17–19] The concerns about the obstetric and nonneurologic fetal and neonatal outcomes are not supported by our study although numbers are small. The issue of carbon dioxide causing fetal acidosis is more difficult. Modern fetoscopic and anesthetic techniques can to a great extent minimize these largely theoretical concerns, which were based on data from animal models (with different placentation[20] to humans) using anesthetic agents no longer in use.[20,21] We saw no acute fetal heart rate, rhythm, or functional imaging abnormalities during the surgeries (except for one case of slowly progressive fetal bradycardia that started before carbon dioxide was introduced, was associated with progressive maternal hypothermia, and which reversed when maternal temperature was restored). We did not see anything suggestive of an episode of severe prenatal fetal acidosis[22] during the surgery, during prenatal follow-up, or after birth (Table 3). In addition, as these children have been followed up, there has not been any evidence suggestive of a prenatal period of acidosis.

The preterm PROM rate, gestational age at delivery, and short-term neonatal outcomes in our fetoscopic cases compare favorably with that in the Management of Myelomeningocele Study[1] and other fetal surgery trials (Bruner et al, Am J Obstet Gynecol) (Table 4).[2–9] The results of fetoscopic open neural tube defect repair require longer follow-up and numbers are small. One of the major concerns with our technique initially was the CSF leak rate. We recorded any leakage of CSF, but in no case was there a wound dehiscence as defined by wound breakdown (exposed neural elements or large

incisional defect [greater than 2×2 mm]). The leaks were closed with a Steristrip or one to two simple sutures at the bedside (except for one iterative technique case repaired at 3 months for a late leak and one standardized technique case with a thin [but still watertight] skin covering). It may be misleading to equate wound dehiscence as reported in the Management of Myelomeningocele Study[1] (and which required revision of the repair) with what we report as a CSF leak. Over time, and with the introduction of our standardized technique, there was a reduction in CSF leakage at birth from 50% (6/12) to 10% (1/10) in the last 10 participants. Reversal of hindbrain herniation results are encouraging, but we do not have 12-month postnatal data. In addition, although we have not had any cases of tethered cord, this is clearly something that requires long-term follow-up.

This study demonstrates that vaginal delivery is an option after fetal fetoscopic repair. From an obstetric standpoint, this obviously is a major finding. Strengths of the study include: 1) a new technique for fetoscopic surgery (exteriorized uterus, warmed–humidified carbon dioxide, plicated membranes, two-port approach, fetoscopically created relaxing incisions, and a unified single-layer open neural tube defect closure with a high rate of success without the need for a patch or extensive surgery); and 2) demonstration of an ethically acceptable risk–benefit profile that may open up a new era in fetal surgery fostering further development and innovation. Weaknesses include 1) the small sample size, 2) the iterative nature of the technique to arrive at a standardized approach, 3) the need for laparotomy and general anesthesia, and 4) lack of long-term neurodevelopmental outcome data.

We believe that under carefully controlled and monitored experimental conditions, more research into the development of the carbon dioxide-filled uterus as a surgical space is justified.

REFERENCES

1. Adzick NS, Thom EA, Spong CY, Brock JW III, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011;364:993–1004.
2. Bruner JP, Richards WO, Tulipan NB, Arney TL. Endoscopic coverage of fetal myelomeningocele in utero. Am J Obstet Gynecol 1999;180:153–8.
3. Farmer DL, von Koch CS, Peacock WJ, Danielpour M, Gupta N, Lee H, et al. In utero repair of myelomeningocele: experimental pathophysiology, initial clinical experience, and outcomes. Arch Surg 2003;138:872–8.
4. Kohl T. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. Ultrasound Obstet Gynecol 2014;44:515–24.
5. Pedreira DA, Zanon N, de Sá RA, Acacio GL, Ogeda E, Belem TM, et al. Fetoscopic single-layer repair of open spina bifida using a cellulose patch: preliminary clinical experience. J Matern Fetal Neonatal Med 2014;27:1613–9.
6. Joyeux L, Engels AC, Russo FM, Jimenez J, Van Mieghem T, De Coppi P, et al. Fetoscopic versus open repair for spina bifida aperta: a systematic review of outcomes. Fetal Diagn Ther 2016;39:161–71.
7. Pedreira DA, Zanon N, Nishikuni K, Moreira de Sá RA, Acacio GL, Chmait RH, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol 2016;214:111.e1–111.e11.
8. Degenhardt J, Schürg R, Winarno A, Oehmke F, Khaleeva A, Kawecki A, et al. Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. Ultrasound Obstet Gynecol 2014;44:525–31.
9. Verbeek RJ, Heep A, Maurits NM, Cremer R, Hoving EW, Brouwer OF, et al. Fetal endoscopic myelomeningocele closure preserves segmental neurological function. Dev Med Child Neurol 2012;54:15–22.
10. Graf K, Kohl T, Neubauer BA, Dey F, Faas D, Wanis FA, et al. Percutaneous minimally-invasive fetoscopic surgery for spina bifida aperta. Part III: postnatal neurosurgical interventions in the first year of life. Ultrasound Obstet Gynecol 2016;47:158–61.
11. Fontecha CG, Peiro JL, Sevilla JJ, Aguirre M, Soldado F, Fresno L, et al. Fetoscopic coverage of experimental myelomeningocele in sheep using a patch with surgical sealant. Eur J Obstet Gynecol Reprod Biol 2011;156:171–6.
12. Peiro JL, Fontecha CG, Ruano R, Esteves M, Fonseca C, Marotta M, et al. Single-Access Fetal Endoscopy (SAFE) for myelomeningocele in sheep model I: amniotic carbon dioxide gas approach. Surg Endosc 2013;27:3835–40.
13. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014;12:1500–24.
14. Belfort MA, Whitehead WE, Ball R, Silver R, Shamshirsaz AA, Ruano R, et al. Fetoscopic amniotic band release in a case of chorioamniotic separation: an innovative new technique. AJP Rep 2016;6:e222–5.
15. Belfort MA, Shamshirsaz AA, Whitehead WE, Ball R, Silver R, Ruano R, et al. Unusual pleuroamniotic shunt complication managed using a two-port in-CO2 fetoscopic technique: technical and ethical considerations. Ultrasound Obstet Gynecol 2016;47:123–4.
16. Belfort MA, Whitehead WE, Shamshirsaz AA, Ruano R, Cass DL, Olutoye OO. Fetoscopic repair of meningomyelocele. Obstet Gynecol 2015;126:881–4.
17. Gratacós E, Wu J, Devlieger R, Van de Velde M, Deprest JA. Effects of amniodistention with carbon dioxide on fetal acid-base status during fetoscopic surgery in a sheep model. Surg Endosc 2001;15:368–72.
18. Luks FI, Deprest J, Marcus M, Vandenberghe K, Vertommen JD, Lerut T, et al. Carbon dioxide pneumoamnios causes acidosis in fetal lamb. Fetal Diagn Ther 1994;9:105–9.
19. Flake A. Percutaneous minimal-access fetoscopic surgery for myelomeningocele–not so minimal! Ultrasound Obstet Gynecol 2014;44:499–500.
20. Wilkening RB, Meschia G. Current topic: comparative physiology of placental oxygen transport [published erratum appears in Placenta 1992;13:309]. Placenta 1992;13:1–15.
21. Sabik JF, Assad RS, Hanley FL. Halothane as an anesthetic for fetal surgery. J Pediatr Surg 1993;28:542–6.

22. Moise KJ Jr, Tsao K, Papanna RM, Bebbington MW. Fetoscopic repair of meningomyelocele. Obstet Gynecol 2015; 126:674.

23. Soni S, Moldenhauer JS, Spinner SS, Rendon N, Khalek N, Martinez-Poyer J, et al. Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele repair. Am J Obstet Gynecol 2016; 214:647.e1–7.

24. Moldenhauer JS, Soni S, Rintoul NE, Spinner SS, Khalek N, Martinez-Poyer J, et al. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther 2015;37:235–40.