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Proceedings of the First Annual Meeting of the International Fetoscopic Myelomeningocele Repair Consortium

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BACKGROUND

Prenatal myelomeningocele (MMC) repair has significant advantages over postnatal repair, as was demonstrated by the Management of Myelomeningocele Study (MOMS) in 2011[1]. This multicenter randomized controlled trial demonstrated that prenatal compared with postnatal repair significantly reduced the rate of ventriculoperitoneal shunt placement in the first 12 months of postnatal life and improved motor function, evidenced by a higher proportion of ambulatory infants at 30 months[1]. In MOMS, access to the fetal spinal defect was via a laparotomy with uterine exteriorization and hysterotomy, with consequent procedure-associated maternal and fetal risks, including increased risk of uterine rupture, need for Cesarean section in the index pregnancy and future pregnancies, and higher rate of preterm birth as well as perinatal mortality in future pregnancies[1–3]. Other complications more prevalent in the prenatal-repair group were: chorioamniotic membrane separation, spontaneous rupture of the membranes, oligohydramnios, placental abruption, pulmonary edema and need for maternal transfusion at delivery[1,2].

Fetoscopic *in-utero* spina bifida repair was introduced with the objective of reducing the maternal and fetal/neonatal complications/risks of open hysterotomy repair, while at the same time preserving the neurologic benefits for the child[4–14]. Two different minimally invasive approaches have been developed and are currently being used in several centers worldwide: a totally percutaneous technique[5–10] and an open fetoscopic technique on an exteriorized uterus[11–14].

THE INTERNATIONAL FETOSCOPIC MMC REPAIR CONSORTIUM

After initial discussions about the different fetoscopic MMC repair techniques during the 26th Fetal Medicine Foundation World Congress in Slovenia in 2017, the idea of developing an international consortium for the study of fetoscopic MMC repair was originated by Kypros Nicolaides. He asked Michael Belfort, Denise Lapa and Elena Carreras to establish the Consortium and to facilitate a forum in which all groups performing fetoscopic MMC repair could work together transparently and collaboratively.

The bylaws of the Consortium were established in December 2017 and a formal invitation to participate was sent out to all groups performing such surgery during the first half of 2018. The requirements for membership of the Consortium were then established by mutual agreement between the different centers that showed interest in being part of this initiative. These requirements include: first, submission of an approved protocol, providing a detailed description of the inclusion and exclusion criteria for surgery, the technique used and the plan for a minimum of 30 months of follow-up for patients who undergo fetoscopic MMC repair; second, submission of a copy of their Institutional Review Board or Ethics Committee approval letter; third, submission of an Investigational Device Exemption (IDE) approval letter from the Food and Drug Administration (FDA) for those centers located in the USA; fourth, provision of details regarding simulation training for their team, including, for example, the frequency of simulations, participants

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and systems; fifth, submission of a signed data sharing and confidentiality agreement; and sixth, performance of at least one case of fetoscopic MMC repair.

The primary mission of the Consortium is to advance knowledge on fetoscopic MMC repair by fostering cooperative clinical research into this technique. To achieve this objective, the centers participating in the Consortium have formally agreed to provide accurate and complete data to a common registry. The data, including obstetric, perinatal, neurosurgical, neurodevelopmental and neurological outcomes, are modeled on the data structure of the MOMS trial[1]. These data will be reviewed and discussed by designated representatives of each participating center, with the stated intent of providing peer oversight, and the shared data will be presented transparently on an annual basis at a meeting held in conjunction with the World Congress in Fetal Medicine, under the auspices of The Fetal Medicine Foundation.

SUMMARY OF PRESENTATIONS AT FIRST MEETING OF THE CONSORTIUM

Participants were asked to present a summary of their surgical results and related studies. For centers with greater experience and those in which the surgical technique had undergone different iterations, representatives were asked to present their center data excluding the 'learning curve'. The main points from the presentations are given in Appendices S1 and S2 and are summarized below. The results from centers that had, at the time of the meeting, performed five or more procedures with delivery are summarized in Tables 1–3. Centers that were not yet performing fetoscopic MMC repair surgery but were interested in developing this approach at their institutions (listed in Appendix S3) were also invited to this meeting and participated in the discussions.

Percutaneous fetoscopic double-layer closure using three or four ports

This procedure, developed by Dr Denise Lapa[7], essentially involves the following steps: first, general anesthesia is given; second, ultrasound-guided amnioinfusion of 500 mL warmed saline/ringer is performed; third, three 11-Fr and one 5-mm balloon-tipped laparoscopic trocars are inserted percutaneously; fourth, almost all amniotic fluid is removed, and heated and humidified carbon dioxide (CO_2) is insufflated into the uterus; fifth, an endoscope, graspers, scissors and needle driver are passed through the ports; sixth, the placode is released and the skin edges are undermined to allow their approximation in the midline; seventh, a dural patch is placed over the defect and then a bilateral aponeurosis flap is sutured in the midline; eighth, the skin is closed. In cases in which skin approximation is not possible, a bilaminar skin substitute is placed over the dural patch and sutured to the skin edges.

Denise Lapa (Hospital Israelita Albert Einstein, São Paulo, Brazil)

Fetal surgery by a totally percutaneous fetoscopic technique was carried out on 80 cases, but data from only the last 60 consecutive cases were presented since the first 20 cases were considered to be part of the learning curve and had been published previously[7]. The inclusion criteria were neural tube defect located at any level, provided the parents understood the severity of the defect, gestational age at surgery between 24.0 and 28.9 weeks, presence of hindbrain herniation, no other major abnormalities and normal karyotype. Excluded were patients with placenta previa, alloimmunization, multiple gestation, positive serology for HIV or hepatitis B or C, and maternal conditions increasing the risk for surgery or anesthesia (such as uncontrolled diabetes or hypertension). Insufflated CO_2 was heated and humidified in only the last eight survivors.

The median (range) gestational age at the time of surgery was 26.6 (24.0–28.9) weeks; there were 58 live births, one fetal death and one pregnancy termination. The median gestational age at delivery was 32.5 (26.9–40.7) weeks, and the rate of preterm prelabor rupture of the membranes (PPROM) was 67% (39/58). Of the 58 survivors, five (9%) had cerebrospinal fluid (CSF) leakage and six (10%) required revision of the repair at birth.

At the time of reporting, 30 children were ≥ 12 months of age, of which 14 (47%) required a ventriculoperitoneal shunt or third ventriculostomy. Follow-up at ≥ 30 months of age found that 59% (10/17) of infants were ambulatory. Bladder function was assessed in 37 of 58 survivors at a median age of 22 (range, 1–60) months and in 24 (65%) there were no signs of neurogenic bladder;

Table 1 Technical details of techniques for fetoscopic *in-utero* myelomeningocele repair performed by six most experienced groups

Lead investigator	*Technique*	*Trocars* (n)	*Layers of closure* (n)	*Patch*	*Relaxing incisions*	*Heated/ humidified* CO_2
Denise Lapa	Percutaneous	3–4	2	Dural +/– artificial skin	No	Yes, in last 9 cases
Michael Belfort	Laparotomy, exteriorized uterus	2	3	Dural	+/–	Yes
Elena Carreras	Laparotomy, exteriorized uterus	3	2	+/– Dural	+/–	Yes, in last 2 cases
Jose L. Peiro	Laparotomy, exteriorized uterus	3	2–3	Dural +/– artificial skin	+/–	Heated
Jena Miller	Laparotomy, exteriorized uterus	2	1	None	+/–	Yes, in last 3 cases
Gerardo Sepulveda	Laparotomy, exteriorized uterus	3	1	None	+/–	No

+/–, use if necessary to achieve skin closure. CO_2, carbon dioxide.

Table 2 Surgical and postoperative characteristics of cases presented by six most experienced groups

Lead investigator	n	*Years*	*GA at surgery (weeks)*	*Stillbirth*	*PPROM at:*		*GA at delivery (weeks)*	*Delivery at:*		*Vaginal birth*	*Uterine dehiscence**
					< 37 weeks	*< 34 weeks*		*< 37 weeks*	*< 30 weeks*		
Denise Lapa	Total 80	2013–2018	26.6 (24.0–28.9)	1/59 (2)	39/58 (67)	39/58 (67)	32.5 (26.9–40.7)	53/58 (91)	11/58 (19)	13/58 (22)	0/45 (0)
	Learning curve 20										
	Results of last 60†				3/8 (38)¶	3/8 (38)¶	34.5 (31.6–40.7)¶	2/8 (25)¶	0/8 (0)¶		
Michael Belfort	Total 45	2017– 2018	25.0 (24.0–26.0)	0/10 (0)	2/10 (20)	1/10 (10)	37.7 (31.1–40.9)	3/10 (30)	0/10 (0)	7/10 (70)	0/3 (0)
	Learning curve 33										
	Results of last 10‡										
Elena Carreras	Total 38	2017–2018	24.4 (23.6–27.4)	1/9 (11)	3/8 (38)	2/8 (25)	35.6 (25.6–37.3)	6/8 (75)	2/8 (25)	4/8 (50)	0/4 (0)
	Learning curve 29										
	Results of last 9										
Jose L. Peiro	Total 14	2015–2018	25.3 (23.8–25.8)	1/11 (9)	4/10 (40)	4/10 (40)	34.0 (30.2–37.0)	9/10 (90)	0/10 (0)	3/10 (30)	0/7 (0)
	Learning curve 0										
	Results of last 11§										
Jena Miller	Total 8	2017–2018	25.1 (22.9–25.9)	0/8 (0)	2/8 (25)**	2/8 (25)**	36.9 (29.9–39.9)	4/8 (50)	1/8 (13)	5/8 (63)	0/3 (0)
	Learning curve 0										
	Results of all 8										
Gerardo Sepulveda	Total 5	2016–2018	26.3 (25.7–28.0)	1/5 (20)	1/4 (25)	1/4 (25)	35.4 (34.0–37.4)	3/4 (75)	0/4 (0)	2/4 (50)	0/2 (0)
	Learning curve 0										
	Results of all 5										

Data are presented as median (range) or *n/N* (%). *In cases of Cesarean delivery. †One pregnancy termination. ‡Two cases intended for presentation of results had not delivered at time of reporting. §Three cases intended for presentation of results had not delivered at time of reporting. ¶Insufflated carbon dioxide (CO_2) heated and humidified in last eight survivors (one termination). **Both cases in which humidified CO_2 was not used. GA, gestational age; PPROM, preterm prelabor rupture of membranes.

Table 3 Neurosurgical and motor information for infants presented by six most experienced groups

Lead investigator	Survived (n)	Findings at birth			Complete reversal of HBH	Assessment ≥ 12 months		Neurogenic bladder
		CSF leak	Need for repair revision	Motor function*		Shunt or ETV†	Walking	
Denise Lapa	58	5 (9)	6 (10)	34/40 (85)	26/29 (90) (≥ 12 months)	14/30 (47)	10/17 (59)	13/37 (35)**
Michael Belfort	10	0 (0)	0 (0)	8/10 (80)	9/10 (90)‡	1/10 (10)§	4/14 (29)¶ 10/14 (71)¶	—
Elena Carreras	8	0 (0)	0 (0)	8/8 (100)	4/5 (80)‡	1/8 (13); 1/3 (33)	—	—
Jose L. Peiro	10	0 (0)	0 (0)	10/10 (100)	8/10 (80)‡	2/10 (20); 2/6 (33)	—	—
Jena Miller	8	0 (0)	0 (0)	5/7 (71)	7/8 (88)‡	0/8 (0); 0/1 (0)	—	—
Gerardo Sepulveda	4	2 (50)	1 (25)	4/4 (100)	NA	3/4 (75); 1/1 (100)	—	—

Data are presented as *n* (%) or *n*/*N* (%) unless stated otherwise. *Motor function assessed at birth, when compared with anatomical level of lesion, was one or more levels better than expected. †Need for hydrocephalus treatment, expressed as ratio of patients who received treatment from total of cases delivered; and from total of cases ≥ 12 months of age at time of presentation, if different. ‡Assessed *in utero*. §No case in this group was ≥ 12 months of age at time of presentation. ¶No case was ≥ 30 months at time of presentation; data are walking independently ($n = 4$) and walking with assistance ($n = 10$), from total series of 45 cases. **Bladder function assessed in 37 of 58 survivors at median age of 22 (range, 1–60) months. CSF, cerebrospinal fluid; ETV, endoscopic third ventriculostomy; HBH, hindbrain herniation; NA, not assessed.

none of these children was taking medication for bladder dysfunction or infection, and none required intermittent catheterization.

It was concluded that large MMC defects may be treated successfully *in utero* using a totally percutaneous fetoscopic technique, but that PPROM and preterm birth remain a challenge; the incidence of these complications is likely to be reduced by the introduction of heating and humidification of the insufflated CO_2; among the last eight cases analyzed (excluding one termination), the median gestational age at birth increased to 34.5 weeks and the rate of PPROM decreased to 38% (3/8).

Yuval Gielchinsky (Hadassah-Hebrew University Medical Center, Jerusalem, Israel)

Fetal surgery was reported for four cases; the first was performed by Dr Lapa with the assistance of the team of Dr Gielchinsky, and the second by Dr Gielchinsky with his team, under the supervision of Dr Lapa and her team. The subsequent two cases were performed independently by Dr Gielchinsky's team. The inclusion and exclusion criteria and technique were essentially the same as those of Dr Lapa, described above. After removal of amniotic fluid, heated CO_2 was insufflated into the uterus without the use of a humidifier. The median (range) gestational age at the time of surgery was 25.7 (24–28) weeks and at delivery was 32.3 (30–33) weeks. All cases had PPROM, at a median (range) gestational age of 30 (28–32) weeks. All babies survived and there were no cases with CSF leakage or requiring revision of the repair at birth. Two (50%) babies underwent ventriculoperitoneal shunt placement within the first 12 months.

Masami Yamamoto (Universidad Los Andes, Santiago de Chile, Chile)

Fetal surgery was reported for two cases; the first was performed by Dr Lapa with her team assisting, and the second was performed by Dr Yamamoto's team under the guidance of the teaching team. The inclusion and exclusion criteria and technique were essentially the same as those of Dr Lapa, described above. After removal of amniotic fluid, CO_2 was insufflated into the uterus without heating or humidification. Surgery was performed at 27 weeks' gestation, PPROM occurred at 29 weeks and delivery occurred at 33 and 36 weeks, respectively. Neither case had CSF leakage at birth and neither required postnatal repair. Postnatal ventriculoperitoneal shunt placement was carried out in one of the two cases.

Lynn Simpson (Columbia University Medical Center, New York, NY, USA)

Fetal surgery was reported for one case; this was performed by Dr Simpson's team under the guidance of Dr Lapa. The technique was essentially the same as that of Dr Lapa, described above. Surgery was performed at 27.3 weeks, PPROM occurred at 28.5 weeks and the baby was delivered at 29.2 weeks. There was no CSF leakage at birth and the baby did not require postnatal repair. A temporary ventricular subgaleal shunt was placed in the neonatal period and was removed subsequently.

Exteriorized uterus fetoscopic single-/double-/triple-layer closure using two or three ports

This procedure essentially involves the following steps: first, general anesthesia is given, laparotomy is performed, the uterus is exteriorized and the fetus is gently manipulated into position using ultrasound guidance; second, either two or three 10–12-Fr cannulas are introduced between the uterine wall and amniotic cavity (in some centers, plication sutures are placed to fix the membranes to the uterine wall prior to insertion of the cannulas); third, amniotic fluid is withdrawn and CO_2 is insufflated into the uterus (in some centers, the CO_2 is

heated and humidified); fourth, an endoscope, graspers, scissors and needle driver are passed through the ports; fifth, the placode is dissected; sixth, in centers using single-layer closure, the skin is sutured over the open defect, in centers using double-layer closure, a dural patch is placed over the defect before suturing the skin, and in centers using triple-layer closure, a dural patch is placed over the defect and then durafascial or myofascial flaps are cut parallel to the spinal defect and sutured in the midline before suturing the skin. If needed, relaxing skin incisions (15–20 mm lateral to the defect) are created to allow midline apposition of the skin edges.

Michael Belfort (Texas Children's Hospital, Houston, TX, USA)

Fetal surgery was reported for 45 cases, but the focus was on the last 12 patients, in whom a two-port technique with triple-layer closure and placement of a dural patch was used. The inclusion and exclusion criteria were the same as those in the MOMS trial[1]. The membranes were plicated to the uterine wall before port insertion. Insufflated CO_2 was heated and humidified. In the 12 cases, the median (range) gestational age at surgery was 25.0 (24.0–26.0) weeks. Ten cases had been delivered by the time of this presentation and their median (range) gestational age at delivery was 37.7 (31.1–40.9) weeks. The PPROM rate was 20% (2/10). All babies were liveborn. No case had repair dehiscence or leakage of CSF at birth. This appeared to be a major advantage of the triple-layer closure, because, in the previous series of single-layer closures, the CSF leak rate was 25%. None of the 10 children was ≥ 12 months of age at the time of reporting. One (10%) case required a ventriculoperitoneal shunt during the first week after delivery.

Longer-term follow-up was presented for the entire cohort of fetoscopically repaired infants; none of the patients had reached 30 months of age for evaluation, but, of 14 cases at 24–30 months, four (29%) were able to walk independently and 10 (71%) walked with assistance. From a neurodevelopmental standpoint, patients underwent Developmental Profile 3 and Capute Scales with Gessell testing at 6–28 months and at 2–22 months, respectively, with the proportion of abnormalities in different areas ranging from 5% to 60% in the former and 7% to 70% in the latter.

Data were also presented which showed that, first, the use of uterotonics for induction and augmentation of labor following fetoscopic repair is apparently safe and well-tolerated[15] and, second, fetal and postnatal growth after fetoscopic MMC repair is not significantly different from that after open-hysterotomy MMC repair in the same center[16].

Elena Carreras (Hospital Universitari Vall d'Hebron, Barcelona, Spain)

Fetal surgery was reported for nine cases. The inclusion and exclusion criteria were the same as those in the MOMS trial[1]. A three-port technique with double-layer closure was used and, in the last two patients, a dural patch was inserted. The membranes were plicated to the uterine wall before port insertion. In the last two cases the insufflated CO_2 was heated and humidified. The median (range) gestational age at surgery was 24.4 (23.6–27.4) weeks and at delivery was 35.6 (25.6–37.3) weeks. There were eight survivors and one fetal death. The PPROM rate was 38% (3/8). No case had repair dehiscence or leakage of CSF at birth. Only three of the eight children were ≥ 12 months at the time of reporting and one (33%) of them required a ventriculoperitoneal shunt.

Jose Luis Peiro (Cincinnati Children's Hospital, Cincinnati, OH, USA)

Fetoscopic surgery was reported for 14 cases, three of whom were still pregnant at the time of reporting. The inclusion and exclusion criteria were the same as those in the MOMS trial[1]. A three-miniport (6-, 10- or 12-Fr) technique with double- or triple-layer closure with placement of a single or double dural patch over the placode and skin closure, with or without a skin substitute, over the patch/es was used. Membranes were not plicated before port insertion but the port sites were always closed with absorbable sutures after removal. Insufflated CO_2 was heated. The median (range) gestational age at surgery was 25.3 (23.8–25.8) weeks and at delivery was 34.0 (30.2–37.0) weeks. There were 10 live births and one fetal death associated with a hypercoiled umbilical cord. The PPROM rate was 40% (4/10). No case had repair dehiscence or leakage of CSF at birth. Only six of the 10 children were ≥ 12 months at the time of reporting and 2/6 (33%) required a ventriculoperitoneal shunt (one at 9 months and the other at 26 months of age).

Jena Miller (Johns Hopkins Center for Fetal Therapy, Baltimore, MD, USA)

Fetal surgery was reported for eight cases. The inclusion and exclusion criteria were the same as those in the MOMS trial[1], but with an additional inclusion criterion of preservation of lower extremity movement. A two-port technique with single-layer closure and no patch was used. The membranes were plicated to the uterine wall before port insertion. In the last three cases, the insufflated CO_2 was heated and humidified. The median (range) gestational age at surgery was 25.1 (22.9–25.9) weeks and at delivery was 36.9 (29.9–39.9) weeks. The PPROM rate was 25% (2/8) and both cases were treated prior to the use of humidified CO_2 insufflation. No case had repair dehiscence or leakage of CSF at birth. Only one of the eight children was ≥ 12 months at the time of reporting and that child had not required a ventriculoperitoneal shunt.

Dr Miller also reported that, in a study of a series of four pairs of fetal blood-gas samples obtained at the beginning and end of surgery, there were no abnormal acid–base results, indicating that exposure to prolonged

periods of CO_2 insufflation did not cause profound fetal acidemia[12].

Gerardo Sepulveda (Hospital Christus Muguerza Alta Especialidad, Monterrey, Mexico)

Fetal surgery was reported for five cases. The inclusion and exclusion criteria were the same as those in the MOMS trial[1], but with extension of the upper gestational age to 28 weeks. A three-port technique with single-layer closure and no patch was used. The membranes were plicated to the uterine wall before port insertion. The insufflated CO_2 was not heated or humidified. There were four survivors and one fetal death. The median (range) gestational age at surgery was 26.3 (25.7–28.0) weeks and at delivery was 35.4 (34.0–37.4) weeks. The PPROM rate was 25% (1/4). In two babies, there was CSF leakage at birth and one needed revision of the repair. In three of the four babies, a ventriculoperitoneal shunt was needed during the first postnatal year.

Dr Sepulveda suggested that, although their results were poorer than those in the MOMS trial, the technique may still be better than postnatal repair in their low-resource environment. He acknowledged some opportunities for improvement, including heating and humidification of CO_2 gas for insufflation and use of a dural patch to reduce postnatal leakage.

Julien Stirnemann (Necker-Enfants Malades Hospital, Paris, France)

Fetal surgery was reported for two cases. The inclusion and exclusion criteria were the same as those in the MOMS trial[1]. A two-port technique with triple-layer closure was used, similar to that described by Dr Belfort. The membranes were plicated to the uterine wall before port insertion. Heated and humidified CO_2 was used. Surgery was performed at 24 weeks' gestation in one case and 25 weeks in the other, and PPROM followed by delivery occurred at 35 and 33 weeks, respectively. At birth, in one case there was leakage of CSF requiring repair and in the second there was no leakage. The first baby required ventriculoperitoneal shunting and the second had a temporary subgaleal shunt.

DISCUSSION

The attendees of the first meeting of the International Fetoscopic MMC Repair Consortium participated in a lively discussion, highlighted a number of positions and stated needs for the field to progress. These are discussed below.

Need for a Registry and Consortium

All participants agreed that the establishment of the Consortium under the auspices of The Fetal Medicine Foundation is important and they all committed to reporting their data to the Registry in a transparent and standardized manner. The bylaws of the Consortium were presented, discussed and agreed upon.

Advantages of fetoscopic MMC repair

All groups agreed that fetoscopic MMC repair surgery decreases some of the most significant maternal risks related to the open-hysterotomy approach. These include dehiscence or thinning of the hysterotomy scar, uterine rupture and need for multiple Cesarean-section deliveries. None of the presenting groups had observed dehiscence of the port access sites in patients who had a Cesarean delivery, which contrasts with the 36% rate of non-intact hysterotomy scar reported in the MOMS trial[1].

Most centers performing fetoscopic repair now offer the option of vaginal delivery, which is a clear benefit. Another advantage of the fetoscopic approach is the potential for a term delivery without prolonged stay in a neonatal intensive care unit. This has important physical, neurobehavioral and psychological benefits for the mother-baby dyad.

The neurological outcomes reported, based on current publications, seem equivalent to those from the MOMS trial[1]. The experience reported by Dr Lapa suggests that the incidence of neurogenic bladder may be lower than that reported by the MOMS trial[1], which, to some extent, could be attributable to the biocellulose patch used in the totally percutaneous technique. In fact, comparison of follow-up at 12–30 months may underestimate the potential long-term benefits, such as avoiding the need for surgery to untether the cord (because tethered-cord syndrome is commonly diagnosed only after 30 months). From animal studies, it is likely that cord tethering will be reduced because the biocellulose itself separates the dura mater from the adjacent tissues[17]. However, this issue is complicated by non-standard reporting methodology, incomplete data, different terminology and definitions, and the use of different tests and timing of assessments.

Different fetoscopic techniques for access to the fetus

Two distinct surgical techniques to gain access to the fetus for fetoscopic repair of MMC lesions were identified by the presenting groups: a completely percutaneous approach and an exteriorized-uterus approach. While there are variations of each technique that have been adopted by different groups, including differences in the number of ports, use of surgical instruments and abdominal incisions, there exist two distinct camps predicated on the use of an open-abdomen *vs* a percutaneous approach.

It was agreed that there is an urgent need for all teams to report the same neurological and neurobehavioral outcomes in a standardized fashion. The groups further decided that larger numbers of cases are needed, along with specified metrics and transparent reporting of long-term outcomes, before any method can be favored over the other.

The proponents of each of the two techniques stated publicly that, once data on all outcomes can be compared appropriately, they would be prepared to change their approach to whichever method is determined, in an

evidence-based manner, to be optimal. This would undoubtedly be one of the most important achievements of the Consortium.

Need to reduce rate of PPROM and membrane separation

Regardless of the technique of fetoscopic repair, there is still a relatively high rate of associated membrane damage and rupture. There are a number of potential reasons for this: separation of the membranes at the time of port insertion, drying of the membranes by the CO_2, toxic effect of CO_2 on the membranes, trauma to the membranes during surgery, overdistention of the uterus by excessive CO_2 pressure, manipulation of the uterus and fetus during surgery, replacement of the amniotic fluid by crystalloid solution and subclinical infection caused by exposure of the internal uterine surfaces to the outside environment. Which one, or combination, of these possible causes is responsible is difficult to determine.

Suggested solutions included humidification and heating of the CO_2 to diminish the effects of desiccation of the membranes, as well as plication of the membranes to the uterine wall prior to port insertion. There was general acceptance of the need for all teams to adopt the use of heated and humidified gas.

Use of CO_2 gas

There was general acceptance by the participants that the risk/benefit ratio of CO_2 use is acceptable. Reasons for differences in response to intrauterine CO_2 insufflation between ovine and human fetuses were discussed and the different placentation and physiology was highlighted. From a pragmatic standpoint, the cumulative experience from over 100 cases shows that acute fetal CO_2 gas exposure is not associated with any obvious adverse perinatal outcome.

The rate of intraoperative fetal distress was extremely low, certainly comparable with that reported in the MOMS trial[1]. Also, based on the experience of the participants with more experience and longer follow-up, infant development appeared to be similar to that in the MOMS trial[1]. As Registry data accumulate, we will be able to evaluate more patients in terms of developmental tests and longer-term follow-up. These results are of the utmost importance to this working group.

Need to unify neurosurgical technique

The need for a standardized approach to achieve a watertight neurosurgical closure was also discussed. Again, standardized metrics and data are lacking and subjective opinion is strong. The use of patches was debated, with differences of opinion regarding the use of relaxing incisions *vs* interposition patches as the best way to achieve a watertight closure in a myeloschisis or large MMC lesion. The proponents of relaxing incisions maintained that an intact skin closure over the spinal defect was preferable to an open lesion that healed by endothelial ingrowth under a patch, because it reduced the risk for neonatal infection and provided thicker coverage of the defect. The proponents of patches were critical of the large flank defects that result from relaxing incisions and stated that neurological outcomes with a bilaminar patch are excellent. Medium- and long-term neonatal outcome data will potentially answer this question, but there is an urgent need for reliable information specifically addressing the issues of subclinical and overt infection from open wounds at birth, and the thickness of the defect coverage over time (as well as any attendant complications, such as cord tethering and symptomatic hydrocephalus).

Another aspect of this discussion focused on the number of layers used in the closure. There was general agreement that myofascial flaps should be used, but there was no agreement on the need to cover the placode with a patch prior to closing the lesion. The team from Texas Children's Hospital presented data showing significant improvements in outcome following their adoption of a triple-layer closure technique that includes the use of myofascial flaps sutured over a bovine collagen patch followed by skin closure. The use of interrupted sutures *vs* running sutures for skin closure was also discussed, with no definitive conclusion.

Learning process

The process for implementation of a fetoscopic MMC repair program has followed a common pattern regardless of the technique used, and consisted of: first, gathering a multidisciplinary team, generally composed of maternal–fetal medicine specialists, pediatric neurosurgeons and pediatric surgeons, and reaching consensus on the need for such a program; second, securing institutional support for the program; third, traveling to an experienced center to observe one or more cases; and fourth, engaging in simulations and/or animal-model surgeries. Once they are ready to perform their first few procedures, most centers will arrange for one or more members of the team whose approach they are emulating to be present to oversee and guide their surgery.

The need for more than simply assembling a multidisciplinary surgical team was highlighted. It was generally agreed that any program offering this surgery should have the necessary neonatal intensive care unit and neonatology services, as well as a multidisciplinary spina bifida clinic (with pediatric neurosurgeons, urologists, orthopedic surgeons, physical and occupational therapists, social workers and other teams) to address comprehensively the long-term physical, psychological and social needs of these patients.

Participants agreed that the above sequence is a proper and ethical way to proceed, in order to implement this complicated surgery in new centers. The importance of ongoing training of the entire team, using different simulation systems, is key for the technical success of their surgeries. It is for this reason that proof of the use of a simulation system in each of the participating

centers is one of the requirements for participation in the Consortium.

Need for oversight of all programs

Various participants commented on the importance of oversight of all programs in order to guarantee ethical and peer-accepted performance of this procedure. This was agreed upon as an important way to ensure patient protection while, at the same time, allowing responsible innovation.

The procedure should only be performed under the oversight of an Ethics Committee or Institutional Review Board, but participants were encouraged to add further levels of oversight, such as a Data Safety Review Board and/or Fetal Therapy Board. All sites should be registered on Clintrials.gov, and all participating sites in the USA must have an FDA IDE.

As new sites proliferate, it is hoped that they will all join the Consortium and report their data and outcomes in a transparent and accurate manner. All currently participating sites have committed to appropriate peer review of their data by a central executive group consisting of representatives from each center. In this way an effective peer-review system can be instituted.

CONCLUSIONS

The main conclusions of this meeting include the following general points of agreement by participants: first, regarding the essential requirements to become part of this Consortium and the objectives and responsibilities that such membership entails; and, second, to continue submitting their data to the common Registry and to critical analysis and peer review of the accumulated collective data.

Although a solid consensus for the adoption of a unified fetoscopic MMC repair technique cannot be reached at this point, all stakeholders in the group agree that it is one of the main objectives of this group. Comparing data from the different centers performing the different techniques (including any modifications of each technique) is key in order to reach this goal.

The teams with the greatest experience are committed to transferring their knowledge and agreed to offer advice and help when requested. Knowledge sharing may be through lectures, simulation workshops, clinical observerships and research fellowships, as well as through frank discussion at the Consortium meetings.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Details of percutaneous fetoscopic approach

Appendix S2 Details of exteriorized-uterus fetoscopic approach

Appendix S3 List of new centers interested in introducing fetoscopic myelomeningocele repair