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Open fetal surgery for neural tube defects

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A B S T R A C T

The most common congenital defect of the central nervous system is myelomeningocele (MMC), which results in significant physical limitations for those affected. Neurologic injury associated with MMC begins with abnormal neurulation and is perpetuated by subsequent traumatic and toxic injury sustained in utero. Treatment historically has involved surgical closure of the MMC after birth along with neonatal management of the associated sequelae including cerebrospinal fluid diversion by ventricular shunting. With improvements in prenatal diagnosis, a defined antenatal natural history, and the concept of fetal intervention to arrest or reverse ongoing in utero damage, maternal–fetal surgery for MMC closure developed as a feasible therapy. Animal studies and early human studies investigating in utero MMC closure were promising, leading to Management of Myelomeningocele Study (MOMS trial). This prospective randomized multicenter trial comparing in utero fetal MMC (fMMC) closure to routine postnatal closure demonstrated a decreased need for shunting, reversal of hindbrain herniation, and improved neurologic function in the prenatal repair group, although maternal complications and prematurity were more frequently encountered. Because of the conclusion of the MOMS trial, fMMC closure has become a standard of care option for pregnancies complicated by a prenatal diagnosis of spina bifida. This article will provide background to the scope of MMC, review the MOMS trial data, and highlight the current clinical status of open fMMC closure.

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Background and significance of myelomeningocele

Approximately 300,000 babies worldwide and 1500 babies in the United States are born with spina bifida each year [1,2]. Myelomeningocele (MMC) is a form of spina bifida and is the most common congenital defect of the central nervous system. MMC is the result of the failure of the neural tube to close in the first four weeks after conception. This then results in abnormal neurulation characterized by an exposed spinal cord and nerves enclosed by a fluid-filled sac. Myeloschisis is a variant of MMC, also with exposed spinal cord and nerves, but the lesion is flat without a sac (Fig. 1). Both lesions result in similar clinical sequelae, and hence, they are simply referred to as MMC throughout the text. The abnormal development of the central nervous system related to an open neural tube defect results in hydrocephaly, hindbrain herniation, and exposed neural elements that become damaged by the toxic effects of amniotic fluid, leading to long-term morbidity and mortality.

The one-year survival rate for infants affected with spina bifida is 88–96%, and 75% will survive to adulthood [3,4]. The need for ventriculo-peritoneal shunting for cerebrospinal fluid diversion due to symptomatic hydrocephalous is required in over 80% of those affected with MMC [5]. Lesion level can be used to predict the likelihood of need for a shunt, with higher level lesions more likely to require a shunt [5]. Although shunts are often required for the treatment of symptomatic hydrocephalous, placement is associated with complications that can include infection, obstruction, displacement, and the need for multiple revisions [5,6]. The Arnold-Chiari II malformation, characterized by hindbrain herniation, brain stem abnormalities, and small posterior fossa, is diagnosed by imaging in over ¾ of patients [7–9]. This can lead to clinical sequelae that include swallowing difficulties, apnea, quadriparesis, and coordination challenges [7–9]. In approximately 39% of patients, the lesion levels correlate with functional motor levels; however, the functional level will be two levels higher or worse in over half [5]. Correlation with lesion level and wheelchair use is as follows: 90% with a thoracic lesion, 45% with a lumbar lesion, and 17% with a sacral lesion [10]. The majority of infants will be diagnosed with a foot deformity requiring intervention [11]. Because of nearly universal involvement of the sacral nerve roots, bladder and bowel incontinence are commonly associated with MMC, which are managed with bowel and bladder regimens that often require clean intermittent catheterization. Recurrent urinary tract infections, vesicoureteral reflux, and upper urinary tract dilation are common genitourinary manifestations of MMC [12]. Almost 1 in 3 adults living with spina bifida require daily assistance, and these individuals are at risk for unexpected death [13,14].

Clearly, the physical and medical ramifications of a neural tube diagnosis are substantial, and the financial impact and need for ongoing medical care can also be significant for families. Neonatal care costs are higher for babies born with spina bifida and they often have multiple hospitalizations throughout the first year of life [15,16]. As with many chronic medical conditions, medical expenditures for individuals with spina bifida are increased throughout the lifespan [17]. With this in mind,

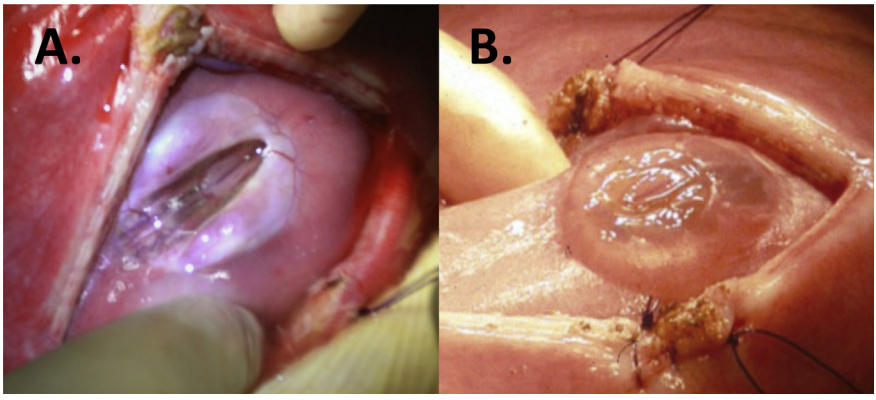

Fig. 1. Myelomeningocele with a covering sac and myeloschisis with no covering sac.

the cost-effectiveness of prenatal surgery for fMMC was evaluated, taking into account adverse outcomes including impact on subsequent pregnancies [18]. The study found that prenatal surgery saves $2,066,778 for every 100 cases of fMMC closure performed providing support as a cost-effective treatment [18].

MMC candidate for in utero treatment?

Before the treatment of fMMC, open fetal surgery was considered only in cases of life-threatening diagnoses. This paradigm changed with consideration of in utero fMMC closure. The basic tenets of fetal therapy were followed – the ability to make a reliable prenatal diagnosis, defined antenatal course, and long-term outcomes were well-known – making in utero closure plausible to improve long-term outcomes. Various animal models were used to explore the feasibility of in utero MMC closure, with sheep models most reliably mimicking human pathophysiology [19–25]. Spinal defects were created in midgestation sheep, exposing the lesion to the in utero environment for a prolonged period; then the defect was closed later in gestation using a latissimus dorsi flap with delivery at term [23]. The lambs that underwent in utero closure of the defect had near-normal motor function, intact sensation, improved bladder and bowel control, and reversal of hindbrain herniation compared to the control lambs who exhibited flaccid paraplegia, lack of sensation in the hind limbs, and bladder and bowel incontinence [23–25]. With promise as a viable fetal treatment based on results of these animal models, attention was then turned to human pilot studies.

The first attempts at human MMC closure were performed employing endoscopic techniques. This model used a maternal split-thickness skin graft to cover the neural placode in a minimally invasive fashion in two fetuses [26]. Outcomes were suboptimal, leading to the investigation of other techniques, including open maternal–fetal surgery. Subsequently, reports of open fMMC closure performed at 22–30 weeks of gestation came from Vanderbilt and the Children's Hospital of Philadelphia (CHOP) [27–30]. Both groups reported reversal of hindbrain herniation, with the group from Vanderbilt reporting continued hindbrain herniation in 38% compared to 95% in historical controls [30]. A significant decrease in the need for ventriculoperitoneal shunting was reported by both groups [29,30]. Motor function improved by at least two levels in most of the fetal closure patients in the CHOP series [29,30].

Despite the fact that these early human pilot studies were suggestive of decreased need for shunting, reversal of hindbrain herniation, and improved motor function, heavy skepticism remained regarding the true feasibility of performing fMMC closure as a standard option of care in affected pregnancies. Much of the debate stemmed from concern over patient selection bias and the absence of a true control group for comparison. The answer to the question of true benefit with fMMC closure would require a randomized prospective trial comparing open maternal–fetal surgery with routine neonatal surgery. Hence, this led to the development of the MOMS trial.

MOMS trial

Sponsored by the National Institutes of Health (NIH), the MOMS trial was a prospective randomized trial comparing open maternal–fetal surgery for fMMC closure with postnatal MMC closure [31]. The clinical care, including prenatal diagnostic imaging, fetal surgery, maternal care and delivery, and postnatal surgery, was performed at three centers – CHOP; Vanderbilt University; and University of California, San Francisco (UCSF). George Washington University served as the Data and Study Coordinating Center (DSCC). In the study workflow, patients were initially referred to the DSCC to determine potential candidacy in the MOMS trial. Then, if they met criteria for participation, patients were referred to one of the three clinical centers based on geographic location. Study protocols were followed closely with rigorous oversight. Inclusion and exclusion criteria are presented in Table 1. There were no backdoor options for fMMC closure during the trial as agreed upon by all U.S. fetal therapy centers.

Patients were evaluated at a fetal surgery center to determine maternal and fetal candidacy for MOMS participation. If a maternal–fetal pair met criteria, patients were randomized between 19.0 and

Table 1
Inclusion and exclusion criteria used in the MOMS trial.

Inclusion:
Singleton pregnancy
Gestational age 19.0–25.9 weeks
Maternal age ≥18 years
Lesion level T1-S1
Evidence of hindbrain herniation
Normal karyotype
U.S. resident
Exclusion:
Fetal anomaly unrelated to myelomeningocele
Multiple gestation
Kyphosis >30°
Increased risk for preterm birth (history of prior spontaneous preterm birth < 37 weeks, short cervix < 20 mm, history of incompetent cervix, cerclage)
Abnormal placentation (placenta previa, suspected placenta accreta, placental abruption)
BMI ≥ 35 kg/m^2
Uterine anomaly (fibroids, Mullerian abnormality, prior hysterotomy in the active portion of the uterus)
Maternal conditions that would place additional risk to maternal health, surgical risk, or impact the pregnancy (poorly controlled pregestational diabetes, poorly controlled hypertension, HIV+, and hepatitis B or C positivity)
Maternal-fetal Rh isoimmunization, Kell isoimmunization, or history of fetal neonatal alloimmune thrombocytopenia
Lack of support person
Maternal psychosocial limitations
Unable to follow-up or travel

25.9 weeks to either fetal surgery or neonatal surgery. Women randomized to fetal surgery remained in close proximity to the fetal surgery center until cesarean delivery, planned for 37 weeks. Women randomized to postnatal surgery were able to return home for ongoing prenatal care. They then returned to their assigned fetal surgery center for cesarean delivery at 37 weeks with neonatal surgical closure to follow. The neurosurgical teams were the same regardless of prenatal surgery or neonatal surgery. Follow-up was performed at 12 and 30 months.

Two primary outcomes were evaluated. The first primary outcome was a composite of fetal/neonatal death or the need for a cerebrospinal fluid shunt defined as either placement of a shunt or meeting objective criteria for shunt placement at 12 months of age. The second primary outcome was a composite score of the Mental Development Index of the Bayley Scales of Infant Development II and motor function adjusted for lesion level at 30 months of age. Secondary outcomes included maternal, fetal, and neonatal surgical, and pregnancy outcomes.

Although the study was powered to a total sample size of 200 patients, with 100 in each arm, the MOMS trial was stopped early after 183 patients were randomized due to demonstration of efficacy in the prenatal surgery group. Therefore, the original MOMS trial publication included 12-month outcomes on 158 infants and 30-month outcomes on 134 children. Benefit was noted for both primary outcomes in the prenatal surgery group compared to those in the postnatal surgery group. In particular, the need for shunt placement at one year was 40% in the prenatal group and 82% in the postnatal group. Hindbrain herniation was reversed in a large proportion of the prenatal surgery group, with evidence of hindbrain herniation seen in 64% of the prenatal closure group and 96% of the postnatal closure group. Furthermore, functional motor level was improved by two or more levels in 32% and by one or more levels in 11% of the prenatal surgery group compared to 12% and 9% in the postnatal repair group. Independent ambulation at 30 months was also seen more frequently in the prenatal surgery group than in the postnatal surgery group, 42% vs. 21%, respectively.

Despite the positive outcomes in the trial, numerous maternal, obstetric, and fetal complications were also identified. Prematurity was a significant issue with the average gestational age at delivery in the prenatal surgery group of 34.1 ± 3.1 weeks compared to 37.3 ± 1.1 weeks in the postnatal surgery group ($p < 0.001$). A proportion (13%) of the prenatal closure group delivered <30 weeks. The prematurity in the prenatal surgery group was largely attributable to complications unique to the fetal surgery that did not occur in the postnatal surgery group. These risk factors included chorionic membrane separation (prenatal: 26% vs. postnatal: 0%, $p < 0.001$), spontaneous membrane rupture (prenatal: 46% vs. postnatal: 8%,

p = 0.001), spontaneous preterm labor (prenatal: 38% vs. postnatal: 14%, p = 0.001), and oligohydramnios (prenatal: 21% vs. postnatal: 4%, p = 0.001). Pulmonary edema (prenatal: 6% vs. postnatal: 0, p = 0.03) and need for blood transfusion at delivery (prenatal: 9% vs. postnatal: 1%, p = 0.03) were the major maternal risk factors associated with prenatal surgery. The hysterotomy from the fetal surgery was inspected at delivery for each patient. Nearly 2/3 (64%) were well healed, with the remainder described as very thin (25%), having area of dehiscence (9%), and complete dehiscence (1%).

Since the publication of the original MOMS trial data in 2011, results from the full study cohort have been published, which further support and refine that data. The primary outcome occurred in 73% of the prenatal surgery group compared to 98% of the postnatal surgery group (p < 0.0001) in the full study cohort of 183 patients [32]. The actual shunt rate in the entire cohort was 44% in the prenatal surgery group and 84% in the postnatal surgery group (p < 0.0001), very similar to the rates seen in the original publication. Of those who required a shunt, the need for revision at one year of age was lower in the prenatal group than in the postnatal group, 15.4% and 40.2%, respectively. The number of revisions was also reduced in the prenatal surgery group. Ventricle size at prenatal evaluation was found to stratify risk for shunt requirement. In the prenatal closure group, a shunt was required in 20% with ventricles <10 mm, 45.2% with ventricles 10–15 mm, and 79% with ventricles ≥15 mm, compared to rates of 79.4%, 86%, and 87.5% in the postnatal group, respectively. The need for shunt was not correlated with lesion level, degree of hindbrain herniation, or gestational age at prenatal closure. The conclusion of this study identified the correlation with ventricle size and need for shunting. Furthermore, when ventricle size is 15 mm or larger at the time of prenatal evaluation, fMMC closure may not provide a benefit to the rate of shunting, in particular. A comparison of neurodevelopmental outcomes at 30 months of age for children with no hydrocephalus, shunted hydrocephalus, and unshunted hydrocephalus was performed on the MOMS trial cohort [33]. Testing included the Bayley II Mental and Psychomotor Indices, Peabody Developmental Motor Scales-2, and the Preschool Language Scale, 4th edition. Children who underwent prenatal closure constituted larger proportions of the no hydrocephalus and unshunted hydrocephalus groups. No neurodevelopmental differences were noted among the groups, although the children with the more severe hydrocephalus had poorer outcomes.

Analysis of urologic outcomes at 30 months of age revealed no difference in the need for clean intermittent catheterization in the prenatal closure group compared to the postnatal closure group [34]. Significantly less bladder trabeculation, vesicoureteral reflux, and open bladder neck was seen in the urologic evaluation of children who had undergone prenatal surgery; however, the implications of these findings are unclear.

Thirty-month outcomes for the full cohort of 183 patients in the MOMS trial confirmed the findings in the original publication that prenatal fMMC closure improves the primary outcome composite score of mental development and motor function [35]. Children who had undergone fMMC closure were more likely to ambulate independently than those who had postnatal closure, 44.8% vs. 23.9%, respectively. Functional level was improved ≥2 levels than expected by anatomic evaluation in 26.4% of prenatal surgery cases compared to that in 11.4% of postnatal surgery cases, and the prenatal surgery group was less likely to have a functional level ≥2 levels worse than expected compared to the postnatal surgery group (16.1% vs. 31.8%). Among those having prenatal surgery, the presence of hip, knee, and ankle movement; absence of a covering sac; and lesion level of ≤L3 were associated with independent ambulation. Male gender correlated to more significant improvement in functional level and psychomotor index than female gender in the prenatal surgery group. Motor function did not correlate with prenatal ventricle size or need for shunt. The conclusion of this report cautioned that counseling regarding outcomes related to need for shunt should be separate from counseling regarding outcomes related to distal motor function when parents are considering fMMC closure. Endurance of the outcomes related to prenatal surgery compared to those of postnatal surgery is being evaluated in the MOMS II trial. Results of childhood outcomes in this cohort at the age of 6–10 years are anxiously awaited.

Similarly, obstetric outcomes for the full MOMS cohort support the original data with increased rates of chorioamniotic membrane separation (33%), spontaneous membrane rupture (44%), oligohydramnios (20%), and spontaneous labor (42.9%) in the prenatal surgery group [36]. Pulmonary edema occurred in 5.5% of women who were randomized to prenatal surgery and none in the postnatal surgery group. The rate of maternal transfusion at delivery was 8.8% among the women

underwent prenatal surgery and 1.1% for the postnatal surgery group. Average gestational age at delivery in the entire prenatal surgery cohort was 34 weeks with 11% delivering <30 weeks. Risk factors associated with spontaneous rupture of membranes included earlier gestational age at surgery and chorioamniotic membrane separation. Oligohydramnios was deemed a risk factor for preterm delivery and nulliparity a risk factor for nonintact hysterotomy at delivery based on multivariate logistic regression analysis. Although operative times trended toward significance as a risk factor for these obstetric complications in univariate analysis, this was not confirmed in the logistic regression analysis. The impact of fetal diagnosis of MMC on parental and family stress was assessed in the MOMS trial cohort, and results showed improvements in the prenatal surgery group compared to the postnatal surgery group [37].

Post-MOMS technique and experience at CHOP

Centers performing fMMC closure in the United States, including CHOP, are generally following the perioperative management and surgical techniques similar to those employed in the MOMS trial [38,39]. Anesthesia typically involves a combination of general and epidural anesthesia with the epidural dual purposed for postoperative pain management. The surgeon's preference determines the laparotomy technique used, whether transverse or vertical, with placental position being taken into account for preoperative planning, as the hysterotomy is generally made opposite to the placental implantation site. Ultrasound is used to map the margins of the placenta, fetal position, and location of fetal parts before laparotomy to assist in planning the surgical approach. Once the laparotomy is performed and the uterus exposed, further evaluation of placental margins and fetal position is assessed. Because the hysterotomy is created in the fundal region, the fetus needs to be in the cephalic presentation to readily access the MMC with minimal manipulation of the uterine incision. If the fetus is in the breech presentation, cephalic version under ultrasound guidance is performed. Two full-thickness stay sutures are placed approximately 1 cm apart under continuous ultrasound guidance in a window free of placenta, umbilical cord, and fetal parts. The intervening uterine tissue is entered using electrocautery. Compression of the uterine tissue using atraumatic intestinal clamps along the anticipated hysterotomy line is performed, thereby facilitating deployment of the uterine stapling device [40]. Mineral oil is also used to pretreat the uterine stapling device to enhance deployment. A bloodless hysterotomy approximately 6–8 cm in length is created using the uterine stapling device and the fetal MMC (fMMC) defect is positioned within the hysterotomy. Warmed lactated Ringer's is continuously infused to maintain fetal warmth, buoyancy, and uterine distension through a sterile, flexible irrigation tube. Fetal heart rate and function are continuously monitored by real-time echocardiography. Fetal cardiac status is used to guide decision-making regarding adjustments to anesthetic levels, fetal positioning, and flow rates of the fluid infusion.

Once the fetus is positioned within the hysterotomy, fentanyl and vecuronium, as a weight-based dose, are delivered by intramuscular injection. The fMMC closure is then performed. The first step involves incising the skin to the level of the fascia in an elliptical fashion around the edge of the neural placode, releasing the connection to the sac and a multilayer closure is performed [41]. Because of the MOMS trial, we have utilized a closure technique in which membrane-lined myofascial flaps are created with monopolar needle point cautery, then sewn together over the neural placode in the midline (Fig. 2). This results in a tension-free, atraumatic closure that is watertight. The robust myofascial flaps prevent CSF leak and toxic exposure from the amniotic fluid and the dural-lined fascia overlies the neural tissue creating a dural-lined canal. The skin is then closed over the myofascial flaps. This more robust approach prevents the potential for inadequate closure that could lead to CSF leak or skin tethering to the neural placode and provides thick tissue coverage over the neural canal. An elliptical-shaped AlloDerm graft (LifeCell, Branchburg, N.J., USA) is used in situations when the skin cannot be brought together for a primary closure.

Making certain to suture the membranes along with the myometrium, the uterus is closed in two layers, interrupted full thickness sutures and a running inner layer. Lactated Ringer's is run through the irrigation tube to accumulate a sufficient level of amniotic fluid replacement as determined by ultrasound, and antibiotics are instilled in the amniotic cavity before the final suture being placed. The hysterotomy is covered with an omental flap, and the laparotomy is closed in typical layers.

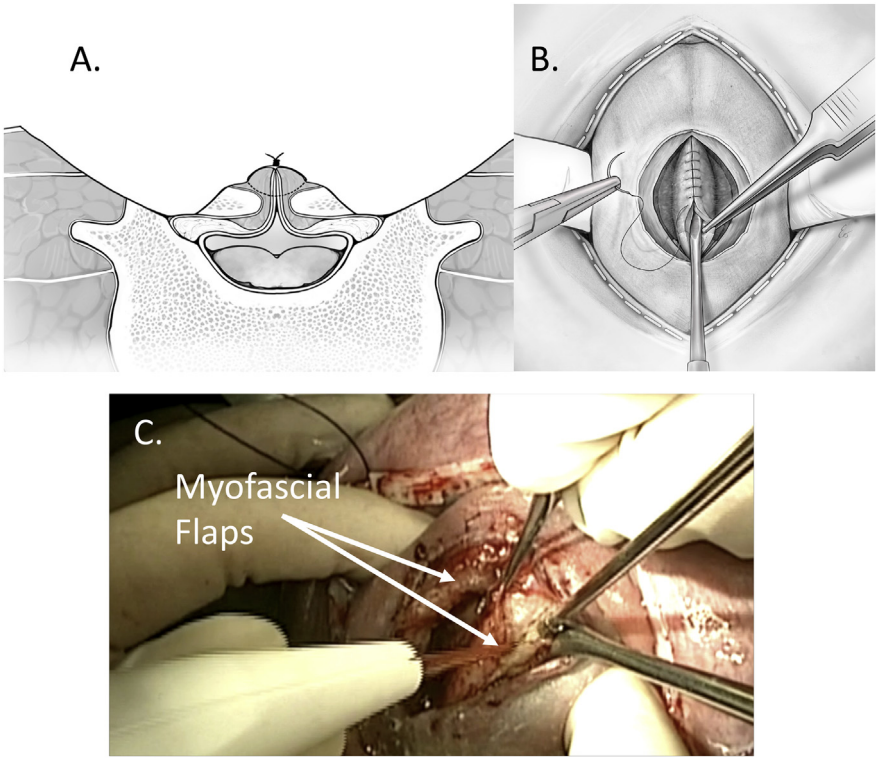

Fig. 2. Current technique for open closure of fetal myelomeningocele. (A) transverse schematic of myofascial flap closure demonstrating inner dural lining and outer layers of muscle and cartilage; (B) Suturing the mobilized myofascial flaps in the midline over the neural canal; (C) Operative view of mobilized myofascial flaps prior to closure.

At CHOP, we continue to use the perioperative tocolytic protocol used in the MOMS trial, including magnesium sulfate infusion, Indocin, and nifedipine. To mitigate perioperative fluid shifts, patients are encouraged to orally hydrate the night before surgery; then, we restrict fluid infusions intraoperatively and immediately postoperatively, which has essentially eliminated pulmonary edema in our patents. Patients typically stay in-house for about four days after surgery and are then discharged on modified activity. Follow-up visits are scheduled weekly and include an ultrasound to monitor amniotic fluid volume, hysterotomy, and membrane status, as well as fetal status. Delivery by cesarean is planned at 37 weeks. Patients return to their referring physicians for ongoing care and delivery, if this was arranged preoperatively, once they have remained stable for three weeks after surgery.

Earlier gestational age at fetal surgery was found to be a significant risk factor for the development of chorioamniotic membrane separation and premature rupture of membranes in a cohort of patients at CHOP [42]. Both chorioamniotic membrane separation and PPROM led to lower gestational age at delivery. A previous study reported an increased risk for PPROM when fetal surgery is performed prior to 23 weeks of gestation [43]. In our cohort, open maternal–fetal surgery for fMMC closure < 23 weeks was associated with an increased risk of both PPROM and chorioamniotic membrane separation [42]. Thus, our standard practice is to perform fMMC closure from 23 weeks through 25 weeks for 6 days to minimize these complications.

We have now performed over 250 fetal MMC closures at CHOP because of the conclusion of the MOMS trial. Outcomes for the first 100 cases have been published, and are similar to those of the MOMS trial [40]. Demographics and preoperative characteristics were similar between the CHOP experience and the MOMS trial (Table 2). Likely as a result of patient self-selection, the CHOP cohort was evaluated at an earlier gestational age (average 21 6/7 weeks), and patients underwent surgery at an earlier gestational age (23.3

Table 2
Comparison of outcomes from open fetal MMC closure.

	MOMS 2011 N = 91	Moldenhauer 2015 CHOP N = 100	Bennett 2014 Vanderbilt N = 43	Zaretsky 2017 Denver N = 49	Elbabaa 2017 St Louis N = 60	Moron 2018 Sao Paulo N = 237
Maternal race	85 (93.4%)	88 (88%)	41 (95%)	28 (57.1%)		
White	1 (1.1%)	4 (4%)	1 (2%)	1 (2%)		
Black	3 (3.3%)	6 (6%)	1 (2%)	4 (8.2%)		
Hispanic	2 (2.2%)	2 (2%)	0 (0%)	16 (32.7%)		
Other						
Maternal age, years	29.2 ± 5.2	29.7	29.4 ± 5.5	27.8 ± 4.3	27	30.9 ± 4.5
Female fetus	42 (46.2%)	52 (52%)	23 (53%)			45.3%
GA at eval., weeks	23.7 ± 1.4	21 6/7 (18 1/7–25 4/7)		23.2 ± 1.2		
Lesion level	4 (4.4%)	6 (6%)	0	L3 or lower =	L3/L4 = 50%	0.4%
Thoracic	25 (27.2%)	21 (21%)	7 (16%)	37 (75.5%)		5.5%
L1-L2	37 (40.7%)	66 (66%)	25 (58%)			69.5%
L3-L4	25 (27.5%)	7 (7%)	11 (26%)			24.6%
L5-S1						
GA @ Surgery, weeks	24.2	23.3 (20 2/7–25 6/7)	MOMS	23–25	24 3/7 (20 6/7–25 6/7)	25.2 ± 0.4
Operative time, min	105 ± 23.2	78.5 (54–106)			177 (94–290)	119.7 ± 7.6
Pulmonary edema	5 (5.5%)	2 (2%)				2.5%
Chorioamniotic membrane separation	30 (33%)	22/96 (22.9%)	0	20 (40.8%)		20.8%
Oligohydramnios	19 (20%)	6/96 (6.3%)	10 (24%)	0		23.3%
PPROM	40 (44%)	31/96 (32.3%)	9 (22%)			26.7%
Spontaneous labor	39 (42.9%)	36/96 (37.5%)	10 (24%)			24.2%
Blood transfusion at delivery	8 (8.8%)	3/89 (3.4%)	0			5 (2.1%)
Hysterotomy at delivery	57/88 (64.8%)	44/87 (50.6%)	36 (88%)	41/43 (95.4%)		3.8%
Intact	21/88 (23.9%)	36/87 (41.4%)	2 (4)	1 (2.3%)		
Thin	8/88 (12.0%)	6/87 (6.9%)	3 (7)	1 (2.3%)		
Area of dehiscence	2/88 (2.3%)	1/87 (1/1%)	0	0		
Complete dehiscence						
Perinatal death	2/91 (2.2%)	6/98 (6.1%)	2 (5%)		2/58 (3.4%)	3/237 (2.1%)
GA at delivery, wk	34.0 ± 3.0	34.3 (22 1/7–37 4/7)	34.4 ± 6.6	31.7 ± 3.8	34 4/7	33.6 ± 2.4
GA at delivery	10 (11.0%)	9/96 (9.4%)	2 (4%)	14/48 (29%)	>36–37 = 60%	6.8%
<30 weeks	35 (38.5%)	35/96 (36.4%)	12 (29%)	26/48 (54%)		45.3%
30–34	29 (31.9%)	26/96 (27.1%)	11 (27%)	8/48 (17%)		34.7%
35–36	17 (18.7%)	26/96 (27.1%)	16 (39%)	0		13.1%
>37						
Birth weight, g		2415.5 (501–3636)	2487 ± 631			2186 ± 506
Dehiscence at fetal repair site	10/77 (13%)	3/83 (3.6%)	3 (7%)			2.5%
Shunt placement (CSF Diversion)	44%	2/83 (2.4%)	14 (41%)		30/55 (54.5%)	
Reversal of HH	36%	71.1%			15/24 (62.5%)	71.4%

weeks) than the average gestational age at randomization of 23.6 ± 1.4 weeks in the MOMS trial. The CHOP cohort comprised a larger proportion of L3/L4 level lesions (66%) and smaller proportion of L5/S1 lesions (7%), which were more evenly distributed in the MOMS trial (38% L3/L4 and 29% L5/S1).

Similar to the MOMS trial, rates of preterm labor and membrane separation remain a common complicating factor of fMMC closure. The rates of PPROM (32%), pulmonary edema (2%), and maternal transfusion at delivery (3%) were lower in the CHOP cohort than in the MOMS trial, 46%, 6%, and 9%, respectively. Alterations in technique and perioperative management based on our large experience likely attributed to the reduction in these complications. The majority of patients in both the MOMS trial and the CHOP cohort were reported to have an intact hysterotomy site at delivery.

The average gestational age at delivery was comparable between the CHOP cohort (34.3 weeks) and the MOMS trial (34.1 weeks). Despite the similarity in overall gestational age at delivery, the CHOP

cohort had fewer deliveries <30 weeks (9.4%) than those in the MOMS trial cohort (13%). Dehiscence at the fetal repair site was lower in the CHOP cohort at 3.6% than in the 13% seen in the MOMS trial. Seventy-five percent of neonates in the CHOP cohort had no evidence of hindbrain herniation on imaging and 55% were evaluated to have a functional level one to five better than the lesion level at prenatal diagnosis. Apnea was a clinically significant factor in 58% of the CHOP cohort, compared to 36% of the MOMS cohort. Optimal care guidelines for the neonatal management of infants with MMC have been developed at CHOP, which includes standard monitoring in the intensive care nursery, and thus, detection of apnea may be more common in our cohort. Further investigation is warranted to evaluate the rate of apnea and associated risk factors in this group of neonates.

Post MOMS landscape and experience

Open maternal–fetal surgery for fMMC closure has become a standard of care option for pregnancies diagnosed with spina bifida in certain circumstances [44]. Along with acceptance of prenatal surgery for fMMC closure as a standard treatment option, an increasing number of centers are performing the procedure to meet the demand. Whether outcomes at an expanded number of centers could mirror the findings outside the MOMS trial has been questioned, and guidelines were developed to address those concerns [45,46]. The Fetal Myelomeningocele Consortium sponsored by the North American Fetal Therapy Network (NAFTNet) was created to provide a collaborative network for centers performing fMMC closure (naftnet.org). The fMMC Consortium registry was developed for all centers performing fMMC closure, regardless of the method, to contribute cases for outcomes monitoring and as a platform for future research. Currently, there are 25 centers worldwide actively participating in the fMMC Consortium and 16 centers participating in the registry. As the registry becomes mature, robust outcomes data, including maternal reproduction outcomes, are anticipated. An interactive global map of centers performing fMMC closure is available through the International Society of Prenatal Diagnosis website (ispdhome.org) based on center survey responses [39].

Multiple centers have now published their series of open fetal fMMC closure experience [47–50]. A comparison of the post-MOMS experiences and the MOMS trial data is presented in Table 2. In each of these reports, a degree of variation in technique is highlighted, although overall adherence to MOMS trial protocols is noted. The outcomes reported in each of these series are comparable to the MOMS trial data, suggesting that outcomes can be replicated outside of a rigorous trial. Ongoing outcomes monitoring is required to ensure that this trend will continue and centers performing fMMC closure should be transparent with patients and referring providers regarding their experience.

Although most centers performing open fMMC closure report continued general adherence to the MOMS trial protocol, some common alterations have occurred. Patients are no longer required to remain at the fetal surgery center for delivery post fMMC closure. Many return to their referring centers for ongoing prenatal care and delivery after fMMC closure. For this model to continue to be successful, ongoing communication between the fetal surgery center, the referral center, and the patient is essential. This model does create a challenge for outcomes monitoring, as it is difficult to standardize maternal and neonatal assessments across multiple institutions. The maternal BMI limit of 35 kg/m^2 in the MOMS trial has increased to 40 kg/m^2 in many centers including CHOP. As maternal obesity is a known risk factor for obstetric morbidity, this change in practice will need to be monitored closely.

As open maternal–fetal surgery for fMMC closure becomes more common, the potential for a growing number of women experiencing subsequent pregnancies after a fundal hysterotomy is imminent. It is imperative that women considering fMMC closure during an affected pregnancy are counseled regarding the potential for adverse outcomes in subsequent pregnancies, although the available supporting data are limited. In 16 subsequent pregnancies reported from women enrolled in the MOMS trial, 12.5% experienced uterine dehiscence after fMMC closure [51]. Forty-seven women who underwent open fetal surgery for multiple fetal diagnoses provided questionnaire responses regarding subsequent pregnancy outcomes [52]. Uterine rupture was reported in 14%, and uterine dehiscence was reported in 14%. Fertility after open fetal surgery did not appear to be impacted based on these responses.

Presently, there is no prescribed optimal method to evaluate the hysterotomy site for integrity in subsequent pregnancies after open fMMC closure. Therefore, subsequent pregnancy management recommendations include an interdelivery interval of at least two years, serial evaluation of the hysterotomy

site by ultrasound throughout the subsequent pregnancy and cesarean delivery by 37 weeks. Labor should be avoided in these women. Women presenting with vaginal bleeding, abdominal pain, contractions, decreased fetal movement, or alarming symptoms in a subsequent pregnancy after open fMMC closure should be promptly evaluated, and providers should have a low threshold for diagnosing uterine wall complications.

Conclusion

The MOMS trial data supported a decreased need for shunt placement, reversal of hindbrain herniation, and improved neurologic outcomes in the prenatal surgery group compared to those in the postnatal surgery group. Because these data became available, open maternal–fetal surgery for fMMC closure has become a standard of care treatment option for pregnancies complicated with spina bifida and is the only method with available level I evidence. Outcomes data reported by numerous centers are consistent with the MOMS trial data, supporting the concept that these outcomes can be replicated outside the confines of a rigorous trial. Reporting of ongoing transparent outcomes is required to ensure optimal maternal, fetal, and neonatal care is achieved. Future research should be aimed at improving selection criteria to optimize outcomes and investigation of operative techniques to decrease the risk of uterine rupture and dehiscence.

Conflict of interest

Dr. Flake and Dr. Moldenhauer have no conflicts of interest to disclose.

Practice points

- Open fetal MMC closure is the gold standard for in utero spina bifida closure as supported by level I evidence.
- In utero fMMC closure is associated with decreased need for shunting, reversal of hindbrain herniation, and improved motor outcomes.
- Preterm delivery related to obstetric complications is a major risk factor associated with open fMMC closure.
- The risk for uterine rupture or dehiscence related to the fundal hysterotomy in open fMMC closure exists in the fetal surgery pregnancy as well as any subsequent pregnancy.

Research agenda

- Evaluation of methods for hysterotomy to reduce maternal and obstetric morbidity in the index and subsequent pregnancies.
- Further define optimal selection criteria for fetal MMC closure to obtain optimal benefit.
- Continue with outcomes monitoring across centers.
- Sharing of techniques and management to optimize care.

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