Surgical Management of Myelomeningocele

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ABSTRACT

Myelomeningocele (MMC) is one of the most common abnormalities of the central nervous system that causes significant neurological impairment. Traditionally, treatment consisted of postnatal closure with the management of the complications, such as ventricular shunting. MMC is a plausible candidate for in-utero surgery because of the mechanism of neurologic damage that begins with abnormal neurulation and continues throughout gestation. Researchers discussed the benefits of in-utero closure prior to the publication of the prospective randomized multicenter Management of Myelomeningocele Study (MOMS trial). Compared to postnatal repair with maternal complications and prematurity as trade-offs, prenatal repair reduced shunting, reversed hindbrain herniation, and improved neurological function. This article discusses the diagnosis, evaluation, long-term follow-up, surgical options, and innovative treatment for fetal myelomeningocele.

Keyword: Myelomeningoceles; Hydrocephalus; Fetal surgery; Management of Myelomeningocele Study; Postnatal surgery; Prenatal surgery

Abbreviations: Myelomeningoceles (MMCs); Neural tube defects (NTDs); Maternal serum alpha-fetoprotein (MSAFP); Cerebrospinal fluid (CSF); Magnetic resonance imaging (MRI); The Management of Myelomeningocele Study (MOMS); Ventriculoperitoneal (VP); endoscopic third ventriculostomy (ETV); Chiari II malformation (C2M); Premature rupture of membranes (PROM); Tethered spinal cord (TSC); Platelet-rich plasma (PRP); Placental mesenchymal stem cells (PMSCs); Platelet-derived growth factor (PDGF); Vascular endothelial growth factor (VEGF); Epidermal growth factor (EGF); Platelet-derived factor 4 (PF-4); Insulin-like growth factor (IGF-1); Transforming growth factor-beta (TGF-b)

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INTRODUCTION

Myelomeningoceles (MMCs) are a common subset of spina bifida occurring in roughly 1 in 1000 births globally [1]. Epidemiologically, MMCs are described under the general term neural tube defects (NTDs). There are significant differences between geographical locations in NTD prevalence, specifically between the U.S. and many European nations, compared to China, where it is significantly higher [2]. MMCs are congenital birth defects involving the incomplete closing of the caudal neuropore followed by the continued development of neural arches and skin, specifically taking place during the fourth week of gestation [3]. This malformation leads to an opening in the spinal cord dorsally, usually at a vertebral level with a lack of development of vertebral arches. Agenesis and closing defects expose the neural placode to impactful traumas from the uterine wall and amniotic fluid [3]. Although MMC impacts all portions of the spine, the more proximal the lesion, the worse the potential for possible ambulation [4]. MMCs involve an open spinal dysraphism that may present with many other malformations with varying morbidities such as defects of the corpus callosum, brainstem, and heterotopias [5]. Prenatal diagnosis of MMC is most common, giving time for potential termination of pregnancy if needed, and typically involves ultrasound or a positive maternal serum alpha-fetoprotein (MSAFP) test [6]. Diagnosis via ultrasounds is best seen in the sagittal plane, as the cystic extension is best visualized. Common clinical manifestations include hydrocephalus, Arnold-Chiari II malformation, and musculoskeletal abnormalities [3]. The Arnold-Chiari II malformation occurs in nearly all patients born with an MMC and typically involves caudal displacements of the cerebellum and deformities of the third and fourth ventricles [7]. Hydrocephalus, a defect involving abnormal cerebrospinal fluid (CSF) movement from the ventricles to its specific absorption point, can be lethal if untreated [8-10]. Studies have further shown the role that hydrocephalus plays in MMC outcomes, particularly the increase in mortality in patients with both hydrocephalus and MMC [9]. Many risk factors have been implicated in MMC development such as folate deficiency, teratogen exposure, and genetic abnormalities [1]. Folate deficiency has been seen to be the strongest non-genetic risk factor for the development of MMC, and recent pushes to increase folic acid in the United States agriculture have been associated with a decrease in prevalence of spina bifida nationally [11]. Prevention peri-conceptually by folic acid intake has also been shown in various trials, further establishing these folate fortification programs [1]. Neurological disability in MMC has often been looked at as a "two-hit" process [3]. The first hit being the lack of neural tube closure and the second hit being further neurodegeneration in utero. This concept led to attempts to fix the vertebral lesion during fetal development in cases of failed closure [1]. MMC babies who do survive to birth need to have surgical intervention to close the defects followed by further management of other clinical manifestations [4]. In this review, we aim to provide a comprehensive overview of MMCs including their diagnosis, clinical manifestations, surgical intervention, and an insight into emerging treatments in the field.

DIAGNOSIS

Early diagnosis of myelomeningoceles can ensure appropriate management [12,13]. Myelomeningoceles are diagnosed using a combination of clinical examination and imaging studies. Ultrasound and magnetic resonance imaging (MRI) is common in diagnosing myelomeningoceles prenatally [14-17]. Genetic testing can also diagnose myelomeningoceles, as neural tube defects can be associated with chromosomal abnormalities and genetic syndromes [12]. Myelomeningoceles may be diagnosed after birth in some cases through physical examination (e.g., neurological deficits, orthopedic abnormalities, etc.) and imaging studies. A multidisciplinary team approach involving neurosurgeons, neonatologists, geneticists, and other specialists can further optimize outcomes for infants with myelomeningoceles.

Ultrasound

Ultrasound is a non-invasive, using high-frequency sound waves to create images of the fetus, typically used in the first and second trimesters of pregnancy [14,15]. In the first trimester, its use can help to evaluate fetal anatomy, growth, and screen for fetal anomalies. In the second trimester of pregnancy, its use can detect the features of myelomeningocele (i.e., detection of an open neural tube defect, cystic sac, ventriculomegaly). In the third trimester of pregnancy, its use can monitor fetal growth, amniotic fluid volume, and evaluate the size and location of the myelomeningocele, as well as detect any associated anomalies (e.g., hydrocephalus or clubfoot). Ultrasound can be used to identify the presence of myelomeningocele and evaluate fetal growth and development; however, its accuracy is not guaranteed and may not provide enough detail for management or surgical planning [17].

MRI

In contrast, MRI is more sensitive and specific than ultrasound in detecting myelomeningoceles as it uses a powerful magnetic field and radio waves to produce detailed images of the body and internal structures [14,15,18]. MRI scans are generally done during the second and third trimesters of pregnancy. In the first trimester of pregnancy, it may be challenging to detect myelomeningoceles as the fetal spine is still developing; however, there may be some indirect features to suggest the possibility of a neural tube defect (e.g., abnormally shaped or dilated ventricle, absence of the normal midline echo complex) [12]. Thus, these findings may prompt further evaluation in the second or third trimester. In the second and third trimesters, a cystic sac, herniation of neural tissue into the sac, and possible brainstem kinking or distortion may be visualized via MRI as well as hydrocephalus, Chiari malformation, or spinal cord tethering [12,14,18]. MRI can provide highly detailed information on the size and location of the lesion, as well as identify any associated anomalies.

Genetic Diagnosis

Genetic evaluation for myelomeningocele can have significant implications for management and counseling [12,19] Physicians can perform fetal karyotyping on amniotic fluid or chorionic villus samples obtained through amniocentesis or chorionic villus sampling, as well as advanced genomic testing (e.g., exome sequencing).19,20 Certain genetic conditions have been shown to associate with myelomeningocele (e.g., Trisomy 13 & 18, Mackel-Gruber syndrome, VACTERL/VATER associations), [21-24] Several genes have been linked as potential risk factors (e.g., VANGL1 & 2, MTHFR, PAX3, CTNNB1), [21,25,26] although, genetic mutant mice strains describe more than 40 gene mutations associating with neural tube defects [21] These genetic markers guide the underlying mechanisms involved in myelomeningocele development, although, their complete association and effects are not yet fully understood and remain to be investigated thoroughly.

Postnatal Evaluation

Postnatal physical examination may reveal myelomeningocele as a visible sac or bulge on the back, as well as any associated neurological deficits and orthopedic abnormalities [27]. Imaging studies can further evaluate the extent of the lesion and identify any associated anomalies, where MRI is typically the preferred modality [14]. Genetic testing may be used in the postnatal evaluation as well, mainly if there is a suspicion of a genetic syndrome or chromosomal abnormality; furthermore, genetic testing may also be recommended for parents or siblings of children with myelomeningocele, as they may be at higher risk of having a child with the condition. When myelomeningocele is diagnosed postnatally, prompt referral to a specialized center is recommended for further evaluation and management, in addition to evaluating the extent of the lesion and any associated anomalies. Treatment options may include surgery to repair the defect and management of associated conditions. While postnatal evaluation is essential to the diagnosis of a myelomeningocele, prenatal diagnosis is preferred, when possible, as it allows for earlier identification of the lesion and prompt referral to specialized centers for counseling and further evaluation. Prenatal diagnosis can also reduce the risk of complications associated with postnatal repair, such as infection and the need for a ventriculoperitoneal shunt. Both genetic and postnatal evaluation for myelomeningoceles is not typically the primary diagnostic evaluation modalities.

MOMS Trial: Diagnosis

The Management of Myelomeningocele Study (MOMS) trial was a significant study that compared prenatal versus postnatal repair of myelomeningoceles [27]. The trial demonstrated the importance of prenatal diagnosis and counseling to identify high-risk pregnancies and guide appropriate management, as well as that prenatal repair resulted in better long-term outcomes for the infant in terms of motor function, the ability to walk independently, the need for shunts compared to postnatal repair, and was a significant step in establishing open fetal myelomeningocele repair as the standard of care [13,27].

Prenatal diagnosis of myelomeningoceles is crucial in determining optimal timing and defect repair approach as it allows for early lesion identification and prompt referral to specialized centers for counseling and further evaluation. Furthermore, prenatal diagnosis can reduce the risk of complications associated with the postnatal repair, such as infection and the need for a ventriculoperitoneal shunt; nevertheless, optimal timing and patient selection for surgery is essential to risk minimalization associated with surgery and to improve outcomes. In the MOMS trial, two perinatal deaths were reported in each group, highlighting the importance of careful patient selection and counseling [27]. In the prenatal-surgery group, intrauterine fetal death and neonatal death due to prematurity were diagnosed (26 and 23 weeks, respectively),

and in the postnatal-surgery group, two neonates died with severe symptoms of the Chiari II malformation despite shunt management [27]. Prenatal diagnosis and counseling can help identify higher-risk pregnancies and guide appropriate management to minimize the risks associated with birth and surgery.

HYDROCEPHALUS

Hydrocephalus is a common physiological disorder of the CSF that causes abnormal cerebral ventricle expansion [28]. Clinical symptoms, radiological images, and measurements of the CSF pressure are frequently utilized in the diagnosis of hydrocephalus [29]. The patient's age, reason for the obstruction, its location, its duration, and how rapidly it started all have an impact on the clinical diagnosis of hydrocephalus [30].

Prenatal ultrasound, a diagnostic imaging technique that uses high-frequency sound waves and a device to produce images of blood vessels, tissues, and organs, can detect hydrocephalus, prenatally [31]. Fetal ultrasounds are used to observe internal organs in action and to measure blood flow through specific vessels [31]. For most cases, hydrocephalus does not present until the third trimester of pregnancy and thus may not be visible on earlier fetal ultrasounds [31].

Congenital hydrocephalus can be diagnosed either at birth or after diagnostic testing. Commonly, congenital hydrocephalus is evident at birth [33]. Congenital hydrocephalus is usually identified by an abnormally large head [29]. It is characterized by a number of symptoms, including a tense and bulging fontanelle, a disjunction of sutures, a thin and shiny scalp with strikingly visible veins, stiff arms and legs that are prone to contractions, "the setting sun" look (pupils are close to the lower eyelid), breathing problems, poor feeding, the infant's inability to bend or move their neck or head, and delayed developmental milestones [29]. If hydrocephalus is not addressed, it can result in death, physical and mental impairment, and irreversible harm to the brain [34]. Frequent CSF shunt failures raise patient morbidity and mortality, and as such hydrocephalus in MMC patients must be carefully taken into account [33].

Treatment for persistent hydrocephalus involves surgically inserting a ventricular shunt [31]. The CSF is transferred by the shunt to another area of the body where it can be absorbed. The most frequent form of shunts is called a ventriculoperitoneal (VP) shunt [31]. This typically drains CSF from the lateral ventricle to the peritoneal cavity. In kids, it has the benefit that the distal peritoneal part can be kept in place for a longer time and won't need to be changed as the child grows [31]. A ventriculoatrial shunt, or VA shunt, is the other prevalent type. A ventriculoatrial shunt (VA) shunt is the second prevalent type [35]. CSF is shunted into the right ventricle via the superior vena cava and jugular vein [36]. The majority of patients who receive a VA shunt also have comorbidities like peritonitis, have undergone significant abdominal surgery, or are obese. Only if the aforementioned interventions are unsuccessful is a ventriculo-pleural shunt the next step [36].

A randomized controlled study called the MOMS was conducted to evaluate the safety and effectiveness of prenatal MMC repair versus traditional postnatal repair [37]. Prenatal surgery for MMC seeks to reduce spinal cord damage brought on by in utero chemical and mechanical injuries. Early results from nonrandomized trials suggested that this approach might reduce or reverse hindbrain herniation and reduce the necessity for VP shunting post-delivery.38 According to MOMS, prenatal surgical closure as opposed to postnatal surgical closure led to a lower rate of VP shunt placement (40% vs. 82%), a lower rate of hindbrain herniation (64% vs. 96%), and a higher rate of being able to independently walk without orthotics at 30 months of age (42% vs. 21%). 39 Given that one of the main benefits of prenatal surgery for MMC, as determined by MOMS, is the reduction in the requirement for a VP shunt (postnatal), it is crucial to take into account pediatric neurosurgeons' practices regarding the management of hydrocephalus when comparing the advantages of surgical prenatal closure versus surgical postnatal closure of the neural tube [39]. Additionally, a minimally invasive operation known as endoscopic third ventriculostomy (ETV) is becoming more common as a substitute or in tandem with VP shunts. ETV makes a small opening in the floor of the third ventricle of the brain, enabling fluid to flow into its regular pathway [39].

An open neural tube defect of the spine known as spina bifida cystica or MMC is linked with the Chiari II malformation (C2M).40 In at least 80% of instances, the condition coexists with hydrocephalus. There are several skull and brain anomalies present, such as a tiny posterior fossa, herniation of the brainstem and cerebellum, and a low-lying tentorium with a pronounced incisura [41]. Cerebrospinal fluid leakage through the meningocele can result in Chiari malformation, followed by hydrocephalus. This necessitates the placement of a VP shunt after birth. However, the growing option of prenatal surgery can help alleviate the need to place a VP shunt

after birth. MMC in-utero surgical repair can reduce the risk of fetal hindbrain herniation [42]. As a result, problems like C2M and hydrocephalus that are linked to MMC at delivery can be avoided. According to one study, between 24 and 25 weeks of pregnancy, three successive fetuses with prenatally diagnosed MMC underwent in-utero repair. Cesarean deliveries took place at 37 weeks gestation without any major issues [43]. Examinations performed following delivery were typically uneventful. MRI scans show that, as soon as six weeks after prenatal myelomeningocele surgery, hindbrain herniation has improved [38].

Long-term follow-up

Myelomeningoceles may have several long-term impacts, even after surgical intervention. Some broad categories include neurological complications, learning disabilities, bowel and urinary deficits, motor function outcomes, and orthopedic results. Neurologic function may deteriorate overtime, which may lead to severe disability leading into adulthood without vigilant monitoring and treatment. Typically, neurological deficits can be traced back to an underlying cause; the most common reason is shunt malfunction, followed by a tethered cord [44]. To evaluate symptomatic manifestations, it is essential to have a baseline to compare to (CT and MRI scans, muscle tests, neurological exam, etc.). Shunt malfunctions are the most common complications post-myelomeningocele surgeries. This may require prompt revision but can be challenging to identify due to variable presentations on a population level, while similar symptoms may manifest for a specific patient [44]. Another common complication is a tethered cord, generally due to scar tissue at the closure site. While scar tissue is common, only 10-30% of patients develop tethered cords [45,46] Surgical repair usually leads to resolution of symptoms, although incidences of retethering have been reported in 31% of patients [46].

Myelomeningoceles are commonly associated with Chiari II malformations [47], which is an important factor influencing executive function outcomes in patients. Discussion of executive function will be further elaborated subsequently, but one direct physiologic outcome is cervical canal compression. Chiari II malformations have heterogenous presentations, which leads to only 5-10% that meet the criteria for surgical intervention/decompression [48]. Symptoms can vary from vocal cord paresis, apnea, swallowing deficits, and more [47]. Prenatal surgical intervention seems to improve radiographic appearance. Recent outcomes of the MOMS suggest that prenatal surgery, overall, does lead to improved motor function and psychomotor development. (The MOMS Clinical trial looked at 30-month outcomes for patients randomized to either prenatal or postnatal repair) [49]. Despite these overall results, the specific correlation of surgical intervention for Chiari II malformations must be further elucidated.

Another sequela of myelomeningocele surgical interventions is hydromyelia: a widening of the central canal of the spinal cord due to a buildup of cerebrospinal fluid. Hydromyelia may result from shunt malformation or untreated hydrocephalus. Hydromyelia may not always present with symptoms. Stable patients have some degree of hydromyelia 50% of the time; other patients may have segmental or severe holocord hydromyelia. In the latter cases, symptoms range from urologic issues, pain, motor/sensory deficits, and progressive scoliosis. Treatment depends on the presentation, symptoms, and identifying the root cause (e.g.: shunt malfunction). Typical surgical interventions may include fenestration or shunting to the peritoneal cavity or subarachnoid space, although these methods may lead to an increase in deficits [50].

In addition to the neurological deficits mentioned above, neurogenic bladder dysfunction is quite common amongst myelomeningocele patients [51,52]. It is very important to monitor urinary function, as urinary stasis or improper bladder function may be the only sign of neurological dysfunction. Without proper treatment, bladder dysfunction can lead to further renal dysfunction as well [51,52]. Management options range from clean intermittent catheterization to pharmacologic agents (anticholinergics, antibiotics, botulinum toxin) to surgical options – namely, bladder augmentation, bladder neck/outlet surgery, or neurosurgical intervention if the root cause is a tethered cord, for example. Bowel function is also very commonly affected in almost all myelomeningocele patients, presenting with dysmotility (that may lead to constipation and fecal impaction), poor sphincter control, and fecal incontinence (in 60-70% of patients) [51,53]. Management generally includes oral laxatives, suppositories, enemas, and more [54]. Lastly, the most recent data from the MOMS trial showed that despite prenatal surgery (as opposed to postnatal intervention), bladder and bowel management continue to be an ongoing challenge [55].

Motor function is also another area that requires long-term follow-up. Myelomeningoceles are commonly associated with scoliosis, as well as congenital skeletal deformities of the hip,

foot, and ankle [56]. Predictors of independent ambulation include in utero ankle, knee, and hip movement, the absence of a sac over the lesion, and myelomeningocele lesions below L3. Scoliosis occurs most often in children with lesions above L2. However, postnatal motor function does not have any correlation to prenatal ventricular size or postnatal shunt placement [49]. One study that had a median follow-up age of 10 years resulted in 79% community ambulators, 9% household ambulators, and 14% wheelchair dependent patients.55 Data from the MOMS trial involving follow-up at 30-months illustrated that boys show better improvement in functional and psychomotor development index overall [49].

Lastly, the MOMS trial also looked at cognitive and executive functioning. Generally, most myelomeningocele patients have typical intelligence, but may develop learning disabilities, such as poor executive skills, attention deficits, and memory issues. One of the biggest associations is the presence of Chiari II malformations [57]. The MOMS trial measured executive functioning at 30 months using the Behavior Rating Inventory of Executive Function indices (Global Executive Composition, Metacognition Index, and Behavioral Regulation Index) and measured adaptive behaviors via Adaptive Behavioral Assessment System II. Deficits in both executive functioning and adaptive behaviors was seen, with the need for shunting being especially associated with significant behavioral regulation deficits. However, there was no effect on cognitive development at 30 months [49].

MANAGEMENT

Studies suggest that the main cause of neurologic defects caused by MMC is not neural underdevelopment but chemical trauma caused by the amniotic fluid and mechanical trauma from the uterine wall. Hydrocephalus and hindbrain herniation are caused by cerebrospinal fluid leaks through the MMC [58]. Prenatal versus postnatal repair of myelomeningocele was compared in MOMS published in 2011. We can tell that the approach to MMC has changed since this study was conducted and before it was conducted. There were a significant decrease in postnatal VP shunt placements in children receiving prenatal repair, which resulted in the study being stopped early for efficacy. Motor function and hindbrain herniation were also improved during the in-utero MMC repair. Nevertheless, this study demonstrated that fetal surgery can result in significant risks, including uterine scarring and premature birth. Following the MOMS trial, prenatal MMC repairs became the standard of care for qualified patients [59].

MMC repair in utero can be done openly, fetoscopically, or with a hybrid approach that combines a maternal laparotomy and an endoscopic procedure on the fetus. Overall, there are two types of surgery for MMC repair in utero: Open fetal surgery, Fetoscopic fetal surgery. The MOMS trial has advocated open fetal surgery for the closure of fetal MMCs.

MOMS outcome: In comparison with postnatal MMC repair, prenatal MMC repair has more obstetrical complications. Shunt placement rates were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group ($P<0.001$). The proportion of infants without hindbrain herniation at 12 months was in the prenatal-surgery group (36%) and the postnatal-surgery group (4%). Prenatal-surgery participants had a significantly higher Bayley Mental Development Index score and a significant difference between functional and anatomical levels at 30 months compared with postnatal-surgery participants ($P = 0.007$).

There must be a balance between the potential benefits of prenatal surgery and the risks associated with prematurity and maternal morbidity. Results of the MOMS trial showed that prenatal MMC repair had increased preterm births (81.3%), spontaneous labor (42.9%), spontaneous membrane separation (42.9%), chorioamniotic membrane separation (33%), oligohydramnios (20%), maternal transfusion (8.8%), and placental abruption (6.6%). The prenatal repairs had an incidence of preterm delivery of 81.3% compared to the postnatal repairs which had an incidence of 16.3%. The rate of preterm deliveries was higher in mothers who had previously had prenatal MMC repair (56.3%) than post-natal MMC repair (5.9%) [60].

MOMS2 outcome: Compared with children with a standard postnatal repair for myelomeningocele, children with prenatally repaired myelomeningocele performed better on self-care, motor function, and mobility measures. Prenatal repair children not only walked more frequently, but they also needed fewer braces and assistive devices. Compared with children in the postnatal repair group, their gaits were faster, and their ability to walk up and down stairs was a better-all indicator that they were able to perform daily motor activities more easily. There were fewer contractures and better motor strength in children with prenatal repair. In addition, the prenatal repair group had fewer hindbrain herniations, which may explain why they were able to chew and swallow food more easily than the postnatal repair group [61].

The rate of premature rupture of membranes (PROM) and preterm birth was higher after percutaneous fetoscopic repair than after open repair. In comparing percutaneous fetoscopic repair with fetoscopic repair via maternal laparotomy, there was no significant difference in the preterm birth rate. Studies comparing fetoscopic and open surgery found that both procedures had comparable mortality rates, ventriculoperitoneal shunt placement, hindbrain herniation reversal, CA membrane separation, and placental abruption rates.

In a meta-analysis, Kabagambe et al. demonstrated that both surgical approaches resulted in VPS placement: 43% for the percutaneous approach and 40% for the open approach. Neurologic evaluation postnatally assessing motor response relative to MMC level did not differ between fetoscopic and open repair.62 According to follow-up analyses of the MOMS, innovations in the minimally invasive fetoscopic repair of MMC may reduce the high rate of preterm PROM, premature birth, and other obstetrical complications [60,63]. Cesarean delivery is required after open fetal surgery during subsequent pregnancies due to the possibility of uterine rupture. Several studies have suggested fetoscopy might improve obstetric outcomes [64].

Open Fetal Surgery

The procedure is conducted during the 22nd to 25th week of pregnancy via laparotomy surgery from the maternal abdomen, followed by a hysterotomy to repair the fetal MMC. The circulation of the placenta will be maintained throughout the surgery. During surgery, fetal lie and part evaluations, along with real-time monitoring of the fetal heart and placental location by sonography, are essential [65,66].

When the fetal MMC has been closed, a warm ringer lactate solution will restore amniotic fluid before the uterus is closed completely. Postoperatively, pregnant women are administered a course of tocolytic agents. Some studies report obstetric, maternal, and fetal complications following intrauterine fetal MMC closure [67,68]

Fetoscopic Fetal Surgery

There has been a growing interest in minimally invasive fetal surgery in the management of potentially operable congenital malformations during pregnancy. Compared to open fetal surgery, fetal endoscopy provides similar postnatal outcomes. There is a lower risk of maternal and fetal morbidity. Endoscopic fetal surgery can be performed laparoscopically or entirely percutaneously [69]. The MMC was covered by collagen, biocellulose patches, or bilaminar skin substitutes under the primary skin closure method [70].

In cases of fetoscopic fetal MMC repair, there has been a higher incidence of cerebrospinal fluid (CSF) leakage from the side of the repair, which necessitates postnatal revision [62]. There is a record for the shortest operative time in an open approach (54-130 minutes), an entirely percutaneous approach (98-480 minutes), and a laparotomy-assisted fetoscopic approach (145-450 minutes) [71]. It is noteworthy that 60% of mothers who underwent the hybrid approach delivered vaginally. All three approaches did not differ in mortality, shunt placement, reversal of Arnold-Chiari II malformation or functional improvement [3].

EMERGING TREATMENT

MMC management is complicated and requires a multidisciplinary care approach. Recently, there has been a shift towards preference for surgical MMC defect repair, when possible, during prenatal period vs repairing soon after delivery. The goals however are to prevent further damage to the spinal cord, to prevent cord infection, and improve overall neurologic outcomes for the patients. Patients with MMC are susceptible to various diseases with hydrocephalus and Chiari malformation type II (CMTII) being the most commonly observed defects [72-75].

Prenatal encapsulation of a spina-bifida lesion can preserve neurological function and prevent or reverse hindbrain herniation. This has been shown by various experimental investigations employing animal models. These studies point to a “two-hit” hypothesis as a cause of ultimate neurologic deficit where primary spinal cord injury is brought on by the prolonged exposure of neuronal-sensitive components in the amniotic fluid or trauma, and then the failure of normal neural-tube closure serves as the second hit mechanism which results in the presentation of MMC [76]. This theory served as the foundation for the MOMS, which aimed to repair the defect hypothesizing as a better repair in the prenatal period. The results of this study were released in 201127,76. In this randomized controlled experiment, 183 women who were < 26 weeks pregnant were randomly assigned to either prenatal surgery or standard postnatal repair [27,77]. Despite pregnancy-related issues like preterm birth occurring more frequently, the outcomes of the patients who received prenatal repair were positive [27,77,78]. For instance, less than half of them needed a shunt to be installed78. Also, the patients’ CMTII rates were lower, and their

motor and cognitive abilities were improved [27]. Although clinically significant, tethered spinal cord (TSC) is frequently considered a late-occurring issue, but according to the MOMS study, fetal closure of the MMC appears to be linked to increase rate of earlier onset of TSC 27. Numerous fetal medicine centers have published their "post-MOMS" experiences on fetal surgery for spina bifida and many more are still studying the results [79]. For instance, the PRIUM study (NCT01983345) has been carried out in France from 2014 to 2021 to introduce prenatal repair as a potential standard of care after the results of MOMS trial were published. With the development of new minimally invasive procedures and strategies for in utero surgery for spina bifida the therapeutic landscape has grown more complex.

Clinicaltrials.gov has a list of several studies that look into novel myelomeningocele management strategies in an effort to enhance newborn outcomes. One of the areas of interest includes use of platelet-rich plasma (PRP) to improve healing after the repair. Historically, PRP is employed in conditions where tissue renewal is crucial, such as orthopedic indications, wound healing, face rejuvenation, hair restoration, and other disorders. Both surgical and non-surgical wounds can benefit from the use of PRP, particularly in individuals who have slow cell turnover, insufficient blood supply, or poor wound healing. In a study with 40 participants, NCT05711355, PRP was given to babies with meningomyelocele after corrective surgery to reduce CSF leaks and expedite the healing of the neuronal tissue in the immature sac. The results will be compared with the control arm (surgery without PRP) to assess the differences in outcomes and observe frequency of associated complications. An autologous concentration of human platelets of PRP, can be made from venous blood by properly centrifuging the blood. Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived factor 4 (PF-4), insulin-like growth factor (IGF-1), and transforming growth factor-beta (TGF-b) are among the various growth factors present in the PRP [80,81]. The findings have not yet been publicized but will provide essential insight into the role of PRP in MMC repairs.

An ongoing clinical study, NCT02230072, is investigating the effectiveness of minimally invasive MMC repair with the goal of reducing maternal fetal risk and improving outcomes when compared to open prenatal repair, as demonstrated and emphasized in the MOMS trial. Chorioamniotic separation, placental abruption, preterm membrane rupture, and early birth were among the complications in the MOMS trial27. They are using a minimally invasive procedure called fetoscopy, which was developed to lessen the risks to mothers during open uterine fetal surgery while preserving similar or even improved fetal benefit as observed in the MOMS study, perhaps possibly enabling vaginal delivery during labor. To further augment the durability of repair performed, another study, NCT03794011, is being conducted comparing fetoscopy repair with and without patch hypothesizing improved outcomes with a thicker repair and less dehiscence or CSF leak with the "patch repair". In the past, it has been demonstrated that using a human umbilical cord patch prevented hindbrain herniation, restored epidermal, dermal, and subcutaneous tissue layers, and retained neurologic function [82,83]. Thereafter, the umbilical cord patch was successfully applied in two human infant cases which exhibited reversible hindbrain herniation, and showed skin growth three to four weeks postpartum, with an intact patch site and no CSF leakage [82]. NCT03794011 study will however utilize commercially available bovine skin-based collagen matrix, Durepair patch, as an additional step in closing of the MMC repair in the experimental arm to assess difference in durability of repair and any associated acute and long-term outcomes as the patients will be followed for up to 5 years.

Tissue engineering-based approaches that enable total tissue coverage of spina bifida defects while actively promoting spinal cord regeneration have gained traction recently due to their potential to enhance repair outcomes by augmenting neurologic function in afflicted patients [84-86]. A favorable three-dimensional (3D) milieu for donor-derived brain progenitor cells of either human or rodent origin was demonstrated in an ex-vivo preclinical investigation using fibrin-based hydrogels87. Moreover, it has been shown that hydrogel patches would support continuing neuronal differentiation and axonal regeneration in slice cultures and be biocompatible with prenatal MMC spinal cord tissue [87]. Small animal models have also been used in other preclinical research to examine transamniotic stem cell therapy (TRASCET), particularly the use of mesenchymal stromal cells as an alternative to the open MMC repair procedure [88,89]. Following these studies, large animal models were utilized where early gestational placental mesenchymal stem cells (PMSCs) were used to supplement fetal MMC repair in MMC defects in utero to improve the neurologic outcomes [89-93]. Studies conducted both in vivo and in vitro showed that PMSCs have neuroprotective properties, which increase the density of large motor neurons in the exposed spinal cord tissue [89-93]. A higher postnatal motor function is correlated with a higher large motor neuron density in the ovine

MMC model, which allows lambs who would otherwise have hindlimb paralysis to walk [93,94]. The CuRe trial, NCT04652908, is an ongoing study that aims to make use of the remarkable capacity for regeneration of the fetal environment as well as that of placental mesenchymal stem cells. It was hypothesized that the use of stem cells would enhance fetal repair of MMC and further alleviate the sustained spinal cord damage and provide better recovery and long-term outcomes. They will contrast the results of MMC repair using commercially available dural graft extracellular matrix seeded with placental mesenchymal stem cells with standard repair. The evaluation of the intervention's safety and effectiveness is one of the desired measurable outcomes. This study will offer crucial insight regarding efficacy of this treatment in MMC repair and possibly improve outcomes significantly and may even be added to the fetoscopy technique in the future as more data comes out for these procedures regarding complications and long term maternal-fetal outcomes.

Another team of researchers used amniotic fluid-based tissue-engineered amniocytes to repair defects in the rat fetal neural tube, illustrating the therapeutic potential of amniotic fluid-based tissue engineering. In this short-term pilot research, the epidermis was produced using human fibroblasts and collagen type I, while the dermal layer was made from keratinocytes derived from iPSCs of human amniotic fluid. The long-term efficacy of these stem cell-based strategies for functional spinal cord regeneration cannot be demonstrated in any of the available rodent MMC models [95].

CONCLUSION

MMC is a congenital malformation that causes permanent disability. Foods enriched with folic acid have decreased MMC prevalence, although the prevalence of MMC remains high. Based on the MOMS trial, Prenatal repair significantly improved the treatment of MMC, resulting in a reduction in the need for VP shunts, reversal of hindbrain herniation, and improved outcomes for motor function. However, it is associated with an increased risk of maternal complications and prematurity. The MOMS2 trial will report long-term outcomes and provide additional data about cognition, motor function, brain morphology, urologic outcomes, spina bifida-associated outcomes, quality of life, and maternal reproductive function at the age of 6-10. The open repair of the maternal-fetal can lead to complications, including uterine dehiscence and fetal complications of preterm delivery. However, during fetoscopic MMC repair, there is a high rate of dehiscence and leakage at the repair site, which require postnatal revision. If the technique can be optimized to overcome PROM and the need for postnatal revision of the repair, the percutaneous fetoscopic approach to MMC repair may offer a more effective alternative to the open approach. Fetoscopic MMC repairs have not yet been compared to open fetal MMC repairs for long-term cognitive, behavioral, and functional outcomes. As a result of the potential for uterine rupture following open fetal surgery, subsequent pregnancies will require a cesarean section. Fetoscopic MMC repair allows spontaneous vaginal delivery based on the outcomes of Belfort and colleagues' fetoscopic MMC repair [96].

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

BLW and MRHS was the major contributor to the design of the study. AR and MK, and SL were responsible for writing the first manuscript. MRHS and MK and RR, and AR were responsible for revising the manuscript and validating the included studies. MRHS and MK contributed to editing graphs. BLW and MRHS conceived the study and were responsible for the overall direction and planning. All authors contributed to the article and approved the submitted version.

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