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Fetal surgery for spina bifida: Past, present, future

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ABSTRACT

Open spina bifida or myelomeningocele (MMC) is a common birth defect that is associated with significant lifelong morbidity. Little progress has been made in the postnatal surgical management of the child with spina bifida. Postnatal surgery is aimed at covering the exposed spinal cord, preventing infection, and treating hydrocephalus with a ventricular shunt. Experimental and clinical evidence suggest that the primary cause of the neurologic defects associated with MMC is not simply incomplete neurulation, but rather chronic, mechanical and amniotic-fluid induced chemical trauma that progressively damages the exposed neural tissue during gestation. The cerebrospinal fluid leak through the MMC leads to hindbrain herniation and hydrocephalus. *In utero* repair of open spina bifida is now performed in selected patients and presents an additional therapeutic alternative for expectant mothers carrying a fetus with MMC. In the past, studies in animal models and clinical case series laid the groundwork for a clinical trial to test the safety and efficacy of fetal MMC repair. In the present, a prospective, randomized study (the MOMS trial) has shown that fetal surgery for MMC before 26 weeks' gestation may preserve neurologic function, reverse the hindbrain herniation of the Chiari II malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt. However, this study also demonstrates that fetal surgery is associated with significant risks related to the uterine scar and premature birth. In the future, research will expand our understanding of the pathophysiology of MMC, evaluate the long-term impact of *in-utero* intervention, and to refine timing and technique of fetal MMC surgery using tissue engineering technology.

Introduction

Open spina bifida or myelomeningocele (MMC) is a devastating congenital defect of the central nervous system for which there is no cure. The natural history of MMC includes a constellation of findings which correlate with the proximal anatomic extent of the defect. MMC is characterized by protrusion of the meninges and spinal cord through open vertebral arches leading to lifelong paralysis. In addition, MMC patients are often limited by various degrees of mental retardation, bowel and bladder dysfunction, and orthopedic disabilities. While the etiology of MMC remains poorly understood, primary failure of either neural tube or mesenchymal closure at the caudal neuropore in the embryonic period results in exposure of the developing spinal cord to the uterine environment.[1,2] Without protective tissue coverage, secondary destruction of the exposed neural tissue by trauma or amniotic fluid may occur throughout gestation. Until 15 years ago, treatment of MMC consisted of surgical closure of the spinal canal at birth and lifelong supportive care. Since that time the clinical experience with midgestational human repair has been shown to improve neurologic function and reduce morbidity from hydrocephalus and the Arnold–Chiari II malformation by reversal of the hindbrain herniation component. This review will focus on the rationale for *in utero* repair in the context of pathologic observations and animal models of MMC, outcomes from human fetal MMC repair including the recently completed Management of Myelomeningocele Study (MOMS trial), and future research challenges.

Advances in prenatal diagnosis now permit diagnosis of spina bifida as early as the first trimester, and extensive research into the etiology of neural tube defects has elucidated both genetic and micronutrient causes.[3] While substantial progress could be made in preventing this disorder through folic acid supplementation, the impact of this preventative approach has leveled off.[4,5] Consequently, spina bifida affects 1 in 3000 live births.[6-8] Not included in this figure are the estimated 25–40% of MMC pregnancies in which the fetus is aborted.[9,10] Mothers who choose to continue the pregnancy must prepare for a child with significant care needs and high medical expenses. Despite aggressive intervention, nearly 14% of all spina bifida neonates do not survive past 5 years of age, with the mortality rising to 35% in those with symptoms of brainstem dysfunction secondary to the Arnold–Chiari malformation.[11] While 70% of patients have an I.Q.

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above 80, only half are able to live independently as adults, even with adapted accommodations.[12] The emotional and financial impact on the family and community are enormous. No recent data are available, but in 1994 the cost of care exceeded $500 million per year (in 1992 dollars) in the United States alone.[13]

In addition to motor and sensory deficits due to the spinal cord lesion, significant complications in MMC come from hydrocephalus, the Arnold–Chiari II malformation, and spinal cord tethering at the site of surgical repair. Hydrocephalus, defined as any enlargement of the cerebral ventricles, occurs in more than 85% of patients with MMC.[14] More than 80% of spina bifida patients require placement of shunts to prevent the neurologic and intellectual compromise that accompanies significant ventriculomegaly, and 46% have complications of shunts within the first year of placement.[15,16] Almost all patients with MMC also have the Arnold–Chiari II malformation, characterized by descent of the cerebellar vermis through the foramen magnum, elongation and kinking of the medulla, caudal displacement of the cervical spinal cord and medulla, and obliteration of the cisterna magna.[17] Descent of the hindbrain through the foramen magnum can lead to brain stem compression, the leading cause of mortality in children with MMC.[18] Clinical presentation of this malformation depends on the age of the child, but typically it includes dysfunction of the cerebellum, medullary respiratory center, and cranial nerves IX and X as well as hydrocephalus. Surgical management for symptomatic hindbrain herniation is beneficial in only selected patients and consists of a ventricular shunt, though some patients ultimately require laminectomy and decompression of the cranio–cervical junction.[19,20] Tethering is fixation of the spinal cord secondary to adhesions between the previously exposed neural elements and the surrounding tissues, leading to tension on the neural axis. The diagnosis is confirmed radiographically, usually after a patient develops progressive worsening of neurologic function. While surgical release can limit further damage in some patients, the functional decline may be irreversible in others.[21,22] Therapeutic interventions aimed at preventing these complications could significantly impact the quality of life of children with MMC. *In utero* intervention may hold the key for reversing the hindbrain herniation, limiting the need for ventriculoperitoneal shunting due to hydrocephalus, and preventing late loss of function due to tethering.

Rationale for *in utero* intervention

The neural damage in MMC may be primarily the result of defective spinal cord development, a secondary event resulting from damage to the exposed spinal cord by the intrauterine milieu, or both—the "two-hit hypothesis". The two-hit hypothesis states that primary congenital abnormalities in anatomic development allow a relatively normal spinal cord to become secondarily damaged by amniotic fluid exposure, direct trauma, hydrodynamic pressure, or a combination of these factors. It is this secondary damage which may be ameliorated by early fetal surgical repair.

There are many observations that support this premise. Hutchins and colleagues performed a pathologic examination of the spinal cords of 8 stillborn human fetuses with MMC and carefully described the relationships of the spinal cord, meninges, and dermal–epidermal junction.[23] There were varying degrees of neural tissue loss at the site of the defect, but normal appearing dorsal and ventral horns were present at the proximal aspect of the lesion. This group was among the first to suggest the two-hit pathophysiology since they attributed these alterations to injuries occurring subsequent to primary neural tube formation. A study of 10 additional fetuses produced similar findings.[24]

Additional support for the two-hit hypothesis of spinal cord damage comes from sonographic observation of fetuses with MMC. Multiple studies have assessed the quality, frequency, and presence of fetal leg movements during fetal development, only to report inconsistency between prenatal and postnatal function. Korenromp used sonography to document normal flexion and extension at the hips and knees as early as 16–17 weeks in MMC fetuses.[25] Sival studied the leg movements of 13 fetuses with MMC and compared the results to postnatal function.[26] Only one of the 13 had abnormal leg movements prenatally, but 11 had abnormal postnatal leg movements. The leg movements seen prenatally could be secondary to spinal arc reflexes rather than of cerebral origin, thus permitting motion without electrical impulses through damaged segments of spinal cord. Alternately, the leg motions could come from the cerebrum through an intact spinal cord that is damaged secondarily throughout gestation, in labor and/or at delivery. As is illustrated by these studies, accurate neurologic assessment *in utero* of the fetus with MMC remains a challenge.

Further support for the theory of acute neurologic damage comes from studies demonstrating improved neurologic outcomes following cesarean section *prior* to the onset of labor. Luthy reported 160 infants with MMC and compared outcomes based on vaginal delivery, cesarean section prior to the onset of labor, and cesarean section after the onset of labor. Delivery by cesarean section before the onset of labor resulted in better motor function at 2 years of age than with vaginal delivery or delivery by cesarean section after a period of labor.[27] In a subsequent report by this same group, the cesarean section groups were further stratified into patients with or without preoperative rupture of the amniotic membranes.[28] They noted improved outcomes, as measured by the difference in the mean between anatomic level and motor level, in those who had cesarean section after onset of labor but before rupture of membranes, as compared to those who underwent cesarean section after onset of labor with rupture of membranes. They concluded that labor prior to membrane rupture causes minimal injury to the protruding nervous tissue while loss of amniotic fluid with labor after membrane rupture may lead to traumatic injury.

While other studies have indicated that cesarean section for MMC may not impact neurologic outcome, no group has compared vaginal delivery with elective cesarean section of vertex fetuses prior to onset of labor or rupture of membranes in a randomized, controlled fashion.[29,30] Until such a study is performed, it is common obstetrical practice that fetuses with MMC are delivered by cesarean section prior to the onset of labor or rupture of membranes to minimize potential trauma to the spinal cord.

Insight into the protection provided by spinal cord coverage also comes from analysis of some of the less severe variants of spinal dysraphism which are interesting "experiments of nature". In cervical dysraphism, a cystic sac containing neuroglial tissue bulges through open posterior vertebral elements, but remains covered by a thick layer of skin. The neurological examination in these patients is typically normal or near normal.[31] Lipomyelomeningocele involves a spinal dysraphism in which a lipoma covers the neural elements, generally preventing herniation of the cord through the defect. Compared to MMC patients, patients with lipomeningocele typically have more mild neurologic deficits including retained bowel and bladder continence, despite significant dysplasia of the caudal spinal cord.[32] In hemimyelocele, half of the dysrhaphic spinal cord is devoid of dura and openly exposed to the uterine environment while the remaining half is covered with a dural membrane. In a study of 16 patients with this disorder, Duckworth reported that the dural encapsulated portion of the cord remained in complete continuity and corresponded to a lower extremity with normal or only mildly