Fetal Surgery in Zurich: Key Features of Our First Open in utero Repair of Myelomeningocele

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Introduction

The first description of apparently secondary, that is, in utero acquired, damage to the pathologically exposed spinal cord within the myelomeningocele (MMC) lesion dates back to 1956.[1] For obvious reasons, the significance of this observation regarding therapeutic consequences was not recognized until fetal surgery became a reality in the 1980s.[2] Only then was the hypothesis born that early in utero intervention might stop the ongoing neural tissue destruction and so reduce the neurologic deficit otherwise seen at birth.[3]

Compelling experimental[4,5] as well as preliminary clinical[6–10] evidence collected over the past two decades have led to the conclusion that fetal surgery for MMC may be an effective novel therapy to ameliorate the neurologic outcome. Lastly, a recently published prospective, controlled, and randomized study (Management of Myelomeningocele Study [MOMS] Trial)[11] has, for the very first time, generated sound data showing that in utero repair can be recommended as a novel standard of care for selected fetuses with MMC. This is a report on the first fetus with MMC operated under the published criteria, principles, and procedures set forth by the MOMS Trial at the Zurich Center for Fetal Diagnosis and Therapy.

Case Report

Diagnostic Work-up

A healthy 37-year-old 4G3P was diagnosed with a female fetus suffering from a spina bifida in the 19th week of gestation. On ultrasound, the fetus had a classical cystic lumbosacral myelomeningocele (MMC) (cranial level = lumbar 3), the typical Chiari II malformation, and a moderate ventriculomegaly (13 mm). The fetus demonstrated bilateral lower extremity movements at hip, knee, ankle, and toe levels. The bladder showed normal cycling and the stomach was visible. No other malformations were identified. The placenta completely covered the anterior uterine wall. Fetal magnetic resonance imaging (MRI) at 19 + 4 weeks of gestational age confirmed these findings, but additionally revealed an aqueductal stenosis (►Fig. 1a).

In summary, both mother and fetus met all inclusion criteria for fetal surgical repair according to the MOMS Trial while they did not fulfill any of the exclusion criteria.[11]

Prenatal Counseling

Parents were counseled nondirectively in several sessions by pediatric surgeons, obstetricians, and anesthesiologists with particular focus on all known risks and potential benefits associated with maternal–fetal surgery and also with all

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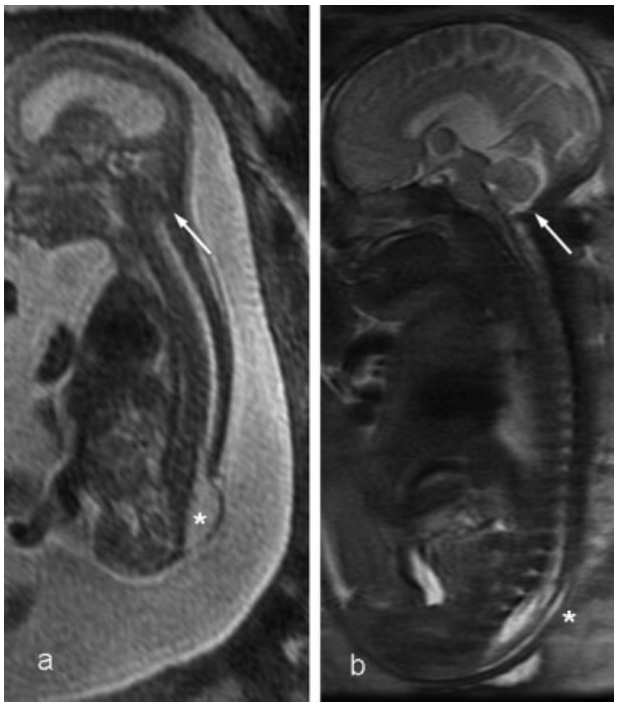

Fig. 1 (a) Preoperative fetal MRI at 20 weeks of gestation. Sagittal single shot fast spin echo sequence showing the MMC lesion (asterisk) with associated hindbrain herniation (white arrow) and ventriculomegaly. (b) Postoperative fetal MRI at 34 weeks of gestation. Sagittal single shot fast spin echo sequence showing an intact MMC closure site. The hindbrain herniation is reversed. Dysplastic mesencephalic tectum. MMC, myelomeningocele; MRI, magnetic resonance imaging.

problems and handicaps presumably present if standard postnatal care was chosen. They were given ample time for decision making and were also informed that whatever decision they made they could change at any time.

The parents decided to pursue fetal surgery. A written informed consent was obtained.

Maternal–Fetal Surgery

Maternal–fetal surgery was performed according to the current techniques used within the MOMS Trial framework.[11] Three days before the intervention, lung maturation was induced with 24 mg betamethasone. To prevent postoperative contractions, the mother received 50 mg indomethacin preoperatively. The mother underwent deep inhalation anesthesia with desflurane, remifentanil, and neuromuscular relaxation. A transverse supraumbilical laparotomy was performed; the uterus was exteriorized and opened on the posterior wall at a safe distance from the placenta. The fetus was positioned in such a way that the cystic MMC lesion came to lie within the hysterotomy.

The cystic sac was then resected taking care not to touch the exposed, nonneurulated, but macroscopically intact, spinal cord tissue (►**Fig. 2a**). The easily identifiable filum terminale was clearly under tension that was completely released after untethering. Since the open dura mater was difficult to identify, a bilateral paraspinal myofascial flap, medially comprising the open dura, was raised and sewn over the cord (►**Fig. 2b**). After extensive mobilization, the skin could be closed primarily over the defect (►**Fig. 2c**). Total fetal blood loss was an estimated 8 mL (approximately 8 to 10% loss of total blood volume).

Ultrasound monitoring showed normal heart rate and myocardial contractility of the fetus throughout the intervention.

The uterus was closed using an inner running suture and outer single stitches. Amniotic fluid was substituted with 500 mL Ringer's lactate containing 2 g of ceftriaxone as antibiotic prophylaxis. An omental flap was sewn over the closure site for additional sealing. The maternal laparotomy was closed in layers.

In summary, the operation was performed without significant problems and the principle goals of the intervention including preserved maternal–fetal safety as well as solid multilayer defect closure over the nontouched intact spinal cord were reached.

Postoperative Maternal–Fetal Management and Evolution

To prevent contractions, an infusion with high dose magnesium was started (6 g loading dose, followed by 4 g/h for the first 3 hours, then 3 g/h for the next 33 hours) and the mother also received three doses of 50 mg indomethacin. After 3 days, a continuous long-term tocolysis was started using

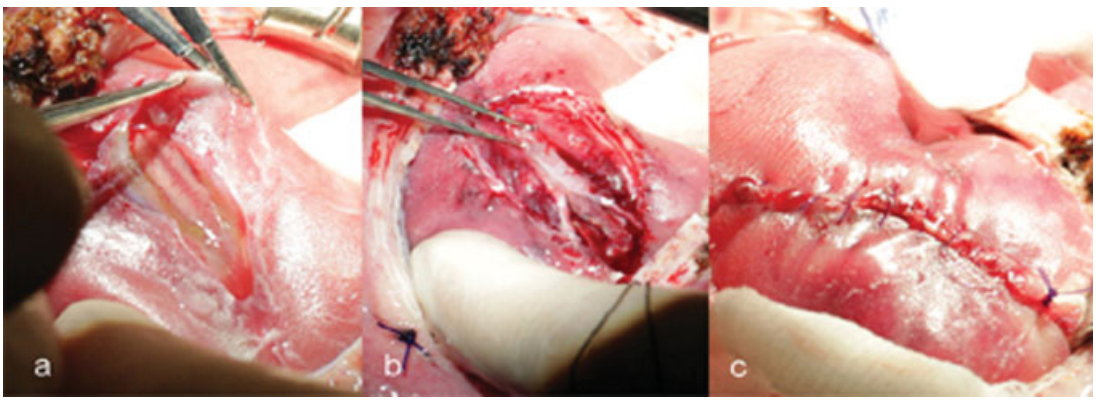

Fig. 2 (a) MMC lesion; (b) closure of the dura mater; and (c) fetal skin closure. MMC, myelomeningocele.

nifedipine 120 mg/d. For thromboprophylaxis, we used low molecular heparin and pneumatic stockings. Epidural catheter analgesia allowed optimal pain control for the first 2 postoperative days. The mother was mobilized on postoperative day 2 and discharged home 4 weeks after the intervention.

Continuous monitoring of fetal heart rate and uterine activity was normal throughout the postoperative course.

A scan, 6 hours after the intervention, demonstrated anhydramnios suggesting amniotic fluid leakage into the maternal peritoneal cavity although no free fluid was seen in the maternal abdomen. For the remainder of gestation, the fetus remained in the breech presentation with extended legs, already present preoperatively.

Postoperatively, peak velocity in the middle cerebral artery was 2.7 standard deviation (SD) above mean values, indicating mild fetal anemia. It increased to 3.7 SD within 1 week and normalized by 2 weeks after the operation. Heart rate and myocardial contractility were always normal, and there were no signs of fetal hydrops. The fetal bladder was almost empty for 1 week. Thereafter, normal cycling was again present, and small pockets of amniotic fluid were detected. The amniotic fluid index remained below 5. The ventricle size was 11 mm during the first 2 postoperative weeks, but then gradually increased to 20 mm before delivery. Hindbrain herniation reversed completely within 8 weeks (►Fig. 1b). Active feet and toe movements were present throughout.

Cesarean Section

Cesarean section was performed on a semielective basis at the gestational age of 35 + 0 weeks, approximately 8 hours after rupture of membranes and onset of mild labor. There was no uterine dehiscence detectable.

The baby girl (head circumference 32.5 cm [percentile: 50 to 75], weight 2,030 g [percentile: 10 to 25], and length 43 cm [percentile: 3 to 10]) adapted normally (Apgar 8/8/9). The repair site was solidly healed (►Fig. 3). Due to prolonged breech presentation, legs and trunk were in a fixed jackknife position.

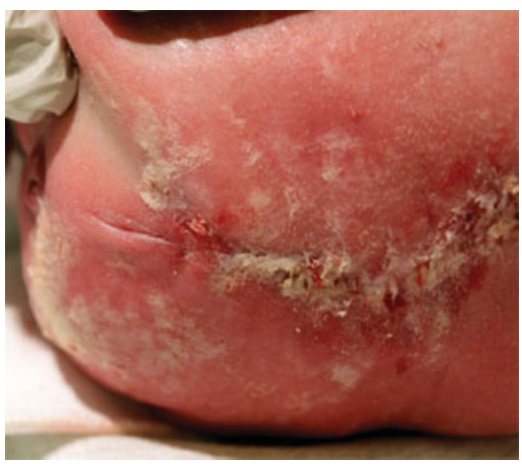

Fig. 3 Picture taken immediately after birth showing a healed wound and covered spina bifida.

The mother exhibited an uneventful postoperative course and was discharged home on postoperative day 6.

Postnatal Clinical Evolution during the First Year of Life

The key features of the first 12 months postpartum can be summarized as follows: Vital parameters were always normal. Regarding growth, the baby developed along the third percentile for length and body weight. Peripheral neurology showed a mild to moderate paraparesis below L4 representing a more favorable motor capacity than usually expected when compared with similar postnatal repair.

With regard to hydrocephalus, head circumference increased gradually from the percentile P3 (birth) to P50 (6 months) without clinically significant signs of increased cerebral pressure. Over the ensuing 2 months, the baby demonstrated an overproportional growth of the neurocranium, developed mild signs for increased cerebral pressure, and head circumference crossed P90. Repeat MRI demonstrated significant ventriculomegaly (►Fig. 4), in all likelihood due to the still present aqueductal stenosis (present already before fetal surgery), while hindbrain herniation was still reversed. At 8 months of life, a ventriculoperitoneal shunt was therefore inserted with an uneventful postoperative course up to date.

Urologically, the baby is voiding spontaneously under a regimen of oxybutynin instillation twice a day.

The baby demonstrated a renal insufficiency with the highest creatinine level of 273 µmol/L at day 5 of life that gradually decreased to 48 µmol/L (normal range < 35 µmol/L) at the age of 11 months. Despite an extensive diagnostic work-up, the reason for this kidney dysfunction could not be conclusively determined.

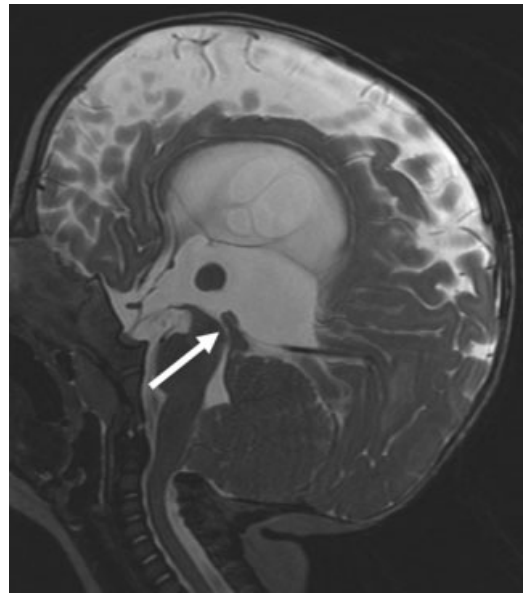

Fig. 4 MRI at the 8 months of age; sagittal T2-weighted fast spin echo sequence: small posterior fossa, no cerebellar herniation. Dysplastic mesencephalic tectum and missing flow void at the level of the cerebral aqueduct (arrow). MRI, magnetic resonance imaging.

Defecation occurs spontaneously and on a regular basis without soiling.

Finally, a bilateral hip dislocation, consequent to the fetal breech position (present before fetal surgery) was reduced surgically at 4 months of life after casting failed.

Discussion

This is one of the first open fetal spina bifida repairs conducted outside the United States. More importantly, it is, to the best of our knowledge, the first intervention performed outside the three U.S.-trial centers after the ground breaking evidence resulting from the "MOMS" clinical trial was published.[11] Of note, this "premiere" surgery was carefully orchestrated with our partner institution, the Center for Fetal Diagnosis and Treatment of the Children's Hospital of Philadelphia. In particular, the current concepts, guidelines, and standard operating procedures of the MOMS Trial regarding prenatal diagnostic work-up, maternal–fetal surgery, and postoperative management were adopted.[11] Importantly, one of the world's most experienced fetal surgeons (coauthor Alan Flake) assisted the operation and acted as advisor during the critical perioperative phase. It is our firm conviction that the latter is an indispensable strategic element to guarantee the best possible setting for this most sophisticated and extremely demanding enterprise. Clearly, a failure to organize the best expertise is hardly justifiable medically and ethically in front of patient and mother, and, moreover, it jeopardizes the successful spawn of this youngest surgical discipline to a few more select centers.

Definitely, the aforementioned MOMS Trial is by far the largest prospective, randomized clinical trial ever performed to compare prenatal versus postnatal surgery. And it is the first to convincingly demonstrate a clear-cut benefit for the fetal surgery cohort in that almost all crucial outcome parameters were clearly in favor of in utero intervention as opposed to conventional postnatal care.[11] Of note, the unequivocal results even led to a premature ending of the trial after 183 out of the planned 200 patients were enrolled.

The key findings of the MOMS Trial were that fetal surgery markedly reduced the need for hydrocephalus shunting (fetal surgery 40% vs. postnatal care 82%) and significantly improved motor as well as developmental outcomes at 30 months. On the other hand, fetal surgery was associated with a higher risk of preterm delivery and uterine dehiscence at delivery.[11]

We found similar advantageous effects in our case, in particular, complete reversal of hindbrain herniation, spontaneous micturition with no need for clean intermittent catheterization, and a better than expected peripheral neurology. Although these findings are substantial benefits attributable in all likelihood to prenatal intervention, they are somewhat preliminary since the follow-up period is only 1 year.

The need for late ventriculoperitoneal shunting at 8 months of life calls for a judicious consideration. The hindbrain herniation, present preoperatively, resolved almost completely before birth as typically seen after fetal surgery.[11–15] During the first 6 months, there was a slightly overproportional head growth and there were no signs for increased intracranial pressure (ICP). Therefore, we expected a high likelihood that shunting would not be mandatory. Somewhat surprisingly, we then witnessed an unfavorable evolution with increasing signs for elevated ICP and a head circumference that rapidly crossed the 97th percentile mandating shunt placement. Here, the question arises whether shunting was required because of aqueductal stenosis, identified before fetal surgery. We did not find any current literature describing an association between MMC and aqueductal stenosis. Therefore, it remains unclear whether this patient is a true nonresponder regarding shunt avoidance after fetal surgery (like the 40% of the MOMS Trial), or whether it was a rather unfortunate and uncommon coincidence of spina bifida and aqueductal stenosis leading to aqueductal stenosis-induced/coinduced hydrocephalus.[16]

Another issue is the leakage-induced oligohydramnios (also seen in 21% of the MOMS Trial fetal surgery cases) and its possible negative impact. Apparently, there was no clinically significant effect on lung development and function in that the baby demonstrated normal respiration at all times. Likewise, oligohydramnios has probably not played a major role in the pathogenesis of hip dislocation. Rather, this pathology is a consequence of the breech presentation the fetus demonstrated already before fetal intervention.

A completely unexpected finding was a marked transient renal insufficiency of unclear origin. We hypothesize that a combined effect of indomethacin[17,18] (via renal artery constriction) and anemia, another drug-related side effect, or a nonprocedure-related cause (e.g., hypodysplastic kidneys) might have played a role. Despite extensive investigation, we could not find enough evidence to corroborate either explication, although a pharmacological problem is most likely. Moreover, there is no report on procedure-related kidney problems in the context of fetal surgery.

Of utmost importance, maternal safety was perfectly preserved as there were no significant problems or complications throughout the entire course.

In summary, we report our first case was successfully managed in accord with the recently published MOMS Trial framework and provide preliminary outcome data. Although in utero surgery can now be recommended as new standard of care for select fetuses with MMC, the paucity of cases as well as both delicacy and intricacy of fetal surgery mandate these patients be pooled in a few centers worldwide and the interventions be exclusively performed by appropriately trained and highly qualified fetal surgeons.

Conflict of Interest

None

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