Childs Nerv Syst
DOI 10.1007/s00381-011-1662-z

ORIGINAL PAPER

Intrauterine myelomeningocele repair Postnatal results and follow-up at 3.5 years of age — initial experience from a single reference service in Brazil

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Received: 22 September 2011 / Accepted: 13 December 2011

Abstract
Purpose Present the outcomes of six cases submitted to intrauterine myelomeningocele (MMC) repair.
Methods Descriptive observational study of six children submitted to antenatal surgical repair of MMC between 26 and 27 weeks gestation. All deliveries were through cesarean section. The following neonatal variables were assessed: gestational age at delivery, birth weight, Apgar scores, need for intubation, duration of hospital stay and need for postnatal shunt procedures. After 3.5 years, the children were evaluated using the Columbia Mental Maturity Scale or Denver II tests and the Hoffer Ambulation Scale.
Results All deliveries were preterm at a mean gestational age of 32+4 weeks and mean birth weight was 1,942 g. Two infants had Apgar scores <7 at 1 min and 1 at 5 min. Ventricular–peritoneal shunts were placed in two cases. All six children are alive: five have normal cognitive development and one has a neuropsychomotor developmental delay. Two children had normal leg movements, a sacral functional level and are community ambulators. Three children had upper lumbar anatomical level lesions and one had a lower thoracic level lesion at the time of fetal surgery. One child, with an L1–L2 anatomical level lesion, in noambulatory and fully dependent on a wheelchair for mobility.
Conclusion Antenatal surgical repair of MMC reduced the need for postnatal shunt placements. Despite preterm delivery, the cognitive development of most children at 3.5 years was normal. Antenatal surgery seemed to improve lower limb motor function in these cases.

Keywords Myelomeningocele · Intrauterine surgery · Postnatal results · Cognitive results · Motor results

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Introduction

Myelomeningocele (MMC) is one of the most frequent congenital malformations of the central nervous system. Despite its decreasing prevalence in the past decades due to folic acid supplementation and to interruption of affected pregnancies, over 1,500 infants are born with this malformation in the USA each year [1]. The estimated costs for the treatment of these patients reach $500 million per year [2], and each MMC patient will spend approximately $350,000 throughout his lifetime to treat the condition and its complications [3].

Most MMC patients have reduced mobility and will require special equipment, such as braces, orthoses, crutches and

Published online: 29 December 2011

wheelchairs. According to the level of their lesion, many will also have urinary and fecal incontinence. Additionally, a substantial proportion of these patients will need to have surgeries to correct associated malformations, such as club feet, or spinal deformities, such as kyphoscoliosis. Over 80% of the patients with MMC have ventriculomegaly, increased intracranial pressure and brain damage and will need cerebrospinal fluid shunting surgeries during the neonatal period.

After years of animal studies and bioengineering progress, in 1998 MMC started to be corrected in uterus in humans. The first surgeries took place in two American centers (Children's Hospital of Philadelphia and Vanderbilt University Medical Center [4, 5]). Up to the present, over 250 fetal MMC surgeries have been performed all over the world [6] and preterm delivery is the most frequent complication reported. Over the years, in order to increase the maternal and fetal safety of this procedure and to improve outcomes, several different protocols have been proposed and tested. Apparently, the ideal period for the performance of these surgeries is between 19 and 26 weeks [7].

A multicentric randomized trial was carried out in the USA to test the safety and effectiveness of this procedure for the treatment of MMC. The Management of Myelomeningocele Study (MOMS) involved three different centers specialized in fetal medicine (University of California–San Francisco, Children's Hospital of Philadelphia and Vanderbilt University Medical Center [8]).

Between 2003 and 2004, the Department of Obstetrics of São Paulo Federal University (São Paulo, Brazil), performed six intrauterine corrections of MMC, in an attempt to improve the outcomes of these cases. Three and a half years after this initial experience, we felt compelled to analyze the current developmental status of these six children. We present a critical analysis of the risks and benefits of this surgery based on the experience obtained in our setting.

Methods

Between 2003 and 2004, six fetal surgeries for the correction MMC were performed at São Paulo Hospital, UNIFESP (São Paulo, SP, Brazil). All participants were being managed at UNIFESP's high-risk antenatal care clinic and all infants continue to be followed by the pediatric and neurology teams of this university. This study was approved by the institution's review board, and all six mothers gave written informed consent.

The selection criteria for enrollment in the experimental fetal MMC surgery program were: gestational age 21–27 weeks at entry, fetal spinal cord defect below T12 involving up to seven vertebrae, normal spinal curve and ventricular atrium diameter below 16 mm on obstetric ultrasound. Cases with any of the following were excluded: contraindication for general anesthesia, severe maternal comorbidities (e.g., cardiac or pulmonary diseases or coagulation disorders), maternal psychiatric disorders, prior preterm births or history of contractions in current pregnancy, multiple pregnancy, other fetal malformations (except club feet) or chromosomal anomalies, fetal growth restriction, oligohydramnios or polyhydramnios, low-lying placenta or vaginal bleeding or chronic infections (such as toxoplasmosis, rubella, cytomegalovirus, hepatitis B or C and HIV).

All surgeries were performed between the 25th and 27th weeks of gestation. After hysterotomy, the fetus was gently positioned so that his spine coincided with the uterine incision and the neurosurgery team proceeded with correction of the MMC. The time of fetal exposure was short, which was why a magnifying lens and not a surgical microscope were used while the defect was repaired. The placode was isolated and the dura mater broadly exposed. Closure was performed in two layers, using absorbable 6.0 Monocryl thread and fibrin glue was spread on the suture. The fetus was then returned to the uterine cavity (Figs. 1 and 2).

All infants were delivered though cesarean section. Five occurred at São Paulo Hospital and one patient was delivered in another maternity (Pro-Matre Paulista, São Paulo, SP, Brazil) because she went into premature labor soon after preterm rupture of membranes and lived closer to that hospital. UNIFESP's neonatology and neurosurgery teams cared for all the infants, including the one that was delivered in the other hospital.

After 3 years, all mothers were asked to bring their children for additional assessments and neurological examination. The mothers were interviewed by the first author who collected

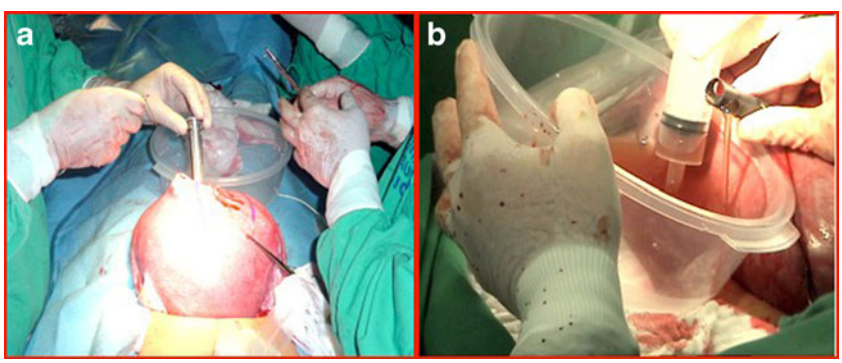

Fig. 1 **a** Insertion of the Almodin–Moron trochanter into the uterine cavity; **b** amniotic fluid is removed through the trochanter

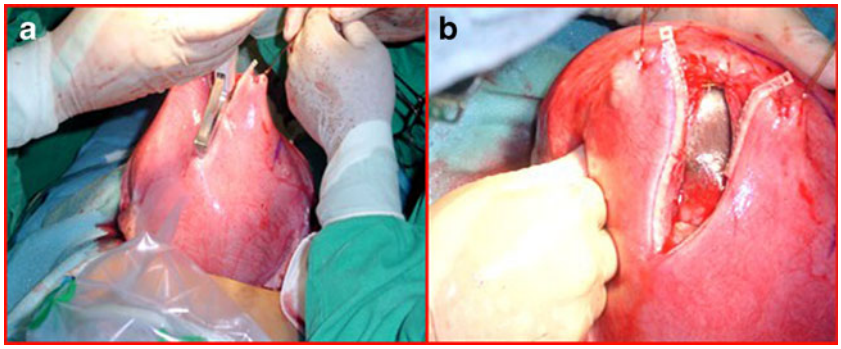

Fig. 2 **a** Myometrial incision using a staple gun; **b** hemostatic staples along the uterine borders

information on the need for cerebrospinal fluid shunting surgeries, the number of urinary infection episodes, the need for intermittent urinary catheter placement, hydronephrosis, neurogenic bladder (diagnosed through urodynamic test and urethrocystography) orthopedic problems or surgeries.

The Columbia Mental Maturity Scale (CMMS) test was used to assess cognitive development (general reasoning ability). This test is validated by the Brazilian College of Psychology and was applied by psychologist who had no knowledge of the type of surgery performed on the children managed at the clinic. Children with scores above 60 were considered normal. The Denver II test for neuropsychomotor development was used for children unable to take the CMMS. This screening test is used to evaluate cognitive and behavioral problems in preschool children. The test is divided into four domains: (a) social/personal (aspects related to socialization), (b) fine motor function (eye–hand coordination and handling of small objects), (c) language (sounds, ability to understand and use language) and (d) gross motor functions (ability to sit, walk or jump). The test was administered by UNIFESP pediatricians who assessed a total of 125 items related to these four domains. The results were graded according to the expected age pattern.

Motor strength was assessed by a physiotherapist from the pediatric neurology department, without previous knowledge of the type of surgery performed. The patients' level of functional walking ability at home and in the community was assessed using the Hoffer Functional Ambulation scale [9]. The children were grouped into four classes, according to their deambulation status — (1) community ambulators: capable of walking indoors and outside, may need crutches, braces and/or a wheelchair only for long journeys outside their community; (2) household ambulators: able to walk only indoors and with the help of equipments, able to transfer from wheelchair to bed with little or no help, may need to use a wheelchair for some activities at home or school and depend on it for all other activities in their community; (3) non-functional or therapeutical ambulators: able to walk only during therapy, use wheelchairs for displacement from one place to the other and for all their transportation needs; (4) nonambulators: wheelchair-bound, can transfer from the wheelchair to the bed when needed. Spinal cord injury level was categorized as (1) thoracic: no sensation below hips and no strength of the muscles that pass through the hip joint or below; (2) high lumbar: some sensation below hips, some strength in hip adductor or knee flexors or extensor muscles; (3) lower lumbar: strength in knee flexor or ankle dorsiflexor muscles or in hip adductors; (4) sacral level: strength in one or more of the latter muscles, strength in plantar or toe flexors.

Results

Pregnancy and delivery data

The mean interval between fetal surgery and delivery was 44.5 days, ranging from 11 to 56 days. On average, the women were discharged 7 days after surgery, ranging from 4 to 16 days. Three women were re-admitted because of preterm labor or to receive amnioinfusions. Mean gestational age at delivery was 32.4 weeks, ranging from 28+4 to 34+5 weeks.

Three of the cases (50%) had oligohydramnios on at least one of the post-surgery ultrasounds; amnioinfusion (with warm saline) was performed in two cases. The mean interval between diagnosis of oligohydramnios and delivery was 3 weeks. None of the infants had pulmonary hypoplasia. Preterm labor occurred in five cases (83.3%). One case received tocolytics twice after the surgery, at 28 weeks and again at 30 weeks. Half of the patients had preterm premature rupture of membranes (PPROM) and in two of these cases, labor started soon after.

There were three cases of uterine scar dehiscence (two complete and one partial). Both cases of complete dehiscence had oligohydramnios, but no fetal parts were protruding through the myometrial scar at cesarean section. All deliveries were through cesarean section, without any immediate complications. In several cases, upon opening the abdominal cavity, the surgeons noticed red stains and burgundy stripes diffusely spread over the uterus, up to the tubes. These areas were thought to be a possible inflammatory reaction to the prothrombin glue used during fetal surgery. Despite this aspect, in all cases there was adequate uterine contraction after placental removal. The postpartum period was uneventful, all patients had normal bleeding and none required additional medication for pain or any other complications.

Neonatal outcomes

All neonates were adequate for gestational age and mean birth weight was 1,942 g, (range 1,385–2,525 g) (Table 1). There were three infants with low Apgar scores (<7): two at 1 min and one at 5 min. Three infants needed to be intubated soon after delivery due to respiratory distress syndrome. They remained intubated for an average of 5 days (ranging from 1 to 9 days) and were then treated with CPAP (continuous positive airway pressure).

Two infants needed to have cerebrospinal fluid shunts placed. The first child had an atrial diameter of 16 mm previous to fetal surgery and received the shunt on the third day of life. The second child was born without any clinical signs of intracranial hypertension, confirmed on neonatal tomography which indicated only ventricular dilation. This infant was discharged home and received a shunt on the 66th day of life, when she presented signs of cranial hypertension.

There was one case of late sepsis which responded to antibiotics. This same child also had thrombocytopenia (30,000 platelets), which reverted after the antibiotic course ended. One neonate had a urinary infection due to *Klebsiella*, which also responded to antibiotics. None of the infants had sonographic signs of urinary tract abnormalities on immediate postnatal ultrasounds. There were no instances of pulmonary or central nervous system infections. All infants survived and were discharged home between 4 and 81 days after birth (mean 30.8 days). After discharge of hospital, these children were to origin cities and the obstetrics and neurosurgery teams did not have more contact with them, until 3.5 years when these children were invited to go to São Paulo to realize the orthopedic, urologic and neurology tests.

Outcome at 3.5 years of age

All children were alive at their last follow-up visit and continue to come for periodical check-ups at UNIFESP. After discharge, only one of the six cases had pulmonary morbidity. This child was born at 28+5 weeks and required supplementary oxygen on a regular basis at home during almost 1 year and was diagnosed with bronchopulmonary dysplasia. This child continues to have frequent episodes of bronchial spasms, without pulmonary infections. The child who had a late shunt placement needed a revision surgery at the age of 1 year, without further complications. This same child also had surgery for a foot deformity.

Results of the CMMS test are presented on Table 2. Five of the children had normal cognitive function, including the two infants with cerebrospinal fluid shunting surgeries. One child with neurodevelopment delay had difficulties interpreting figures and therefore could not be assessed through the CMMS test. This child had been delivered at 28 weeks of pregnancy, 11 days after fetal surgery. She was assessed using the Denver II test. She had spontaneous speech, could recognize objects in her surroundings, had normal visual movements, her gaze followed objects and people, and she had good arms and hands coordination. However, due to the anatomical or radiographic level (first defective vertebral level) of her spinal cord lesion, she had poor lower limb motor function. These limitations did not allow assessment of neuromotor abilities, such as her capacity to stand upright or to keep seated. Additionally, she had difficulties in manipulating small objects with her hands. Part of this delay was attributed to her extreme prematurity which probably affected basic cognitive and motor areas of her brain.

Table 1 Neonatal outcomes

Case	1	2	3	4	5	6
GA at delivery (weeks+days)	28+5	34+5	34+4	33+3	32+1	32+3
GA at fetal surgery (weeks)	27	26	26	25	26	26
Birth weight (g)	1385	2525	1830	2360	1860	1695
Apgar scores	9/9	8/9	4/6/9	8/9	8/10	1/9
Orotracheal intubation	Yes	No	Yes	No	No	Yes
Duration of intubation (days)	9	–	1	–	–	5
Need for CPAP	Yes	–	Yes	–	Yes	Yes
Duration of hospital stay (days)	81	4	33	9	35	23
Neonatal infection	No	No	Late sepsis	No	UTI (*Klebsiella*)	No
Other complications	Apnea	–	Apnea Thrombocytopenia	–	–	–
Need for postnatal shunt placement	No	No	No	Yes	Yes	No
Sonographic ventricular index	0.40	0.4	0.50	>0.50	0.53	0.30
Renal ultrasound	Normal	Normal	Normal	Normal	Normal	Normal
Foot deformity	No	No	Equinovarus	Equinovarus	Não	Não

GA gestational age, *UTI* urinary tract infection, *CPAP* continuous positive airway pressure

Table 2 Results of the Columbia Mental Maturity Scale for cognitive function

Case	Chronological age	Percentile	Gestational age at delivery (weeks)
1[a]	4 years and 5 months	–	28+5
2	4 years and 2 months	92	34+5
3	3 years and 9 months	88	34+4
4	3 years and 11 months	75	33+3
5	3 years and 11 months	99	32+1
6	3 years and 10 months	87	32+3

Chronological age is presented in the left column

[a] Case 1 could not be assessed through this test

Table 3 presents the distribution of the anatomical and lower extremity function functional levels of the lesions. Two children with anatomical spinal cord lesions at the level of L4–L5 had normal leg movements. They were classified community ambulators, not needing any type of equipment to walk and were categorized as having a sacral functional level. Three children had upper lumbar anatomical level lesions and one had a lower thoracic anatomical level lesion. These four children need orthoses, braces and wheelchairs for mobility. One of them had an L1–L2 spinal cord lesion and a high lumbar functional level lesion; she is a non-ambulator and is wheelchair-bound. Another child with a lesion in the same anatomical level has a lower lumbar functional level. This child uses braces and was classified as a household ambulator. Case 3 is also a household ambulator; she had a T12 anatomical lesion and a high lumbar level functional lesion. Case 4 had an anatomical lesion at L2–L3, a lower lumbar level functional lesion and despite the use of orthoseses, was classified as a community deambulant. In all cases, the functional level was lower than the original anatomical level of the lesion.

Obstetric ultrasound was effective in identifying the anatomical topography of the lesion within one vertebra. This assessment was important to exclude cases with higher or more extensive lesions, whose inclusion in the fetal surgery protocol could have been questionable.

All children had complications associated with neurogenic bladder. All children had urinary tract infections or needed to use intermittent bladder catheters or medications for these complications. Each child had at least three urinary tract infections up to the third month of life. There was one case of grade 5 vesicoureteral reflux. This child (case 1) had five urinary tract infections and was admitted to the hospital twice for treatment of these episodes.

Discussion

Until 1997, couples with a fetus affected by MMC had three choices: pregnancy interruption, expectant management until delivery for postnatal correction or elective preterm delivery, in cases of progressive hydrocephaly. The first option is not legal in many countries, including Brazil. After the pioneer studies performed at Vanderbilt University Medical Center and Children's Hospital of Philadelphia, a fourth option became available: antenatal correction of MMC. However, this option involves maternal and fetal risks.

Johnson et al. [10] reported that all cases who undertook this procedure were delivered preterm at a mean gestational age of 33.2 weeks, 11.8% before 30 weeks. According to these investigators, three factors were associated with preterm delivery in these cases: preterm labor (50%), PPROM (28%) and oligohydramnios (48%). Perinatal mortality in these cases (4–5%) is also associated with preterm delivery [11]. In the MOMS study, 21% and 13% of the cases were delivered after 37 and <30 weeks, respectively. In the same study, PPROM was reported in 46% of the cases and spontaneous contractions occurred in 38%. Our incidence of spontaneous preterm labor was 83.3% and 50% of our cases had PPROM, resulting in a 100% rate of preterm birth, with a mean gestational age at delivery of 32+4 weeks.

Table 3 Anatomical, functional levels and ambulatory classification

Case	1	2	3	4	5	6
Anatomical level	L1–L2	L4–L5	T12–L1	L2–L3	L2–L3	L4–L5
Anatomical level on antenatal US	L3–L4	L5–S1	L1–L2	L2–L3	L2–L3	L4–L5
Functional level	Low lumbar	Sacral	High lumbar	Low lumbar	Low lumbar	Sacral
	L4–L5	S1–S2	L1–L2	L4–L5	L4–L5	S1–S2
Ambulation category	Non-ambulator (wheelchair-bound)	Community ambulator	Household ambulator	Community ambulator	Household ambulator	Community ambulator
Equipment needed for mobility	Wheelchair	None	Othosis and short brace	Orthosis and long brace	Othosis and short brace	None

Comparison with anatomical level on antenatal ultrasound

US ultrasound

Half of our patients had oligohydramnios following fetal surgery, a number similar to that reported by Vanderbilt University Medical Center [10], but higher than the 21% reported in the MOMS study [8]. Oligohydramnios is attributed to small amniotic–peritoneal fistulae that may be invisible to the naked eye but cause chronic leakage of amniotic fluid into the maternal abdomen. Two of our cases had uterine scar dehiscence and both went into spontaneous preterm labor. Dehiscence is probably caused by scar healing defects or uterine contractions leading to rupture of the wound scar. There was only one case of scar rupture in the MOMS study [8].

The greatest impact of fetal surgery for MMC was the reduction and even elimination of hindbrain herniation through the foramen magnum. This led to a smaller number of cerebrospinal fluid shunting surgeries in these patients, compared to historical controls. Intrauterine MMC correction can increase spinal liquor pressure and push herniated structures back into the fetal skull [12–14].

Bruner et al. [15] reported a reduction in hindbrain herniation in 29 patients submitted in fetal surgery. Only 38% of the cases in the fetal surgery group had some degree of hindbrain herniation, compared to 95% in the control group. Additionally, while 91% of the control infants needed to have cerebrospinal fluid shunting surgery soon after birth, only 59% of those in the fetal surgery group needed this intervention and in most cases, surgery was performed when the child was older.

In our study, only two cases (33%) needed shunting surgeries. Both of these children had ventricular dilation of at least 14 mm and a spinal lesion above L3. Tulipan et al. [16] reported that 84% of their cases with ventricular dilation over 14 mm needed to have shunting surgeries and 79% of those with lesions above L3. The best cases for fetal MMC correction seem to be those with gestational age below 25 weeks, ventricular dilation up to 14 mm and a spinal defect below L3. Only 25% of the fetuses with these characteristics needed to have cerebrospinal fluid shunt placement after delivery.

In the MOMS [8] study, the need for placement of a cerebrospinal fluid shunt by the age of 12 months was 40% and 80% in the antenatal versus postnatal MMC surgery groups, respectively. Additionally, the proportion of children without brain herniation was significantly higher in the fetal surgery group than in the postnatal correction group (36% versus 4%). Similarly, there was a lower rate of moderate to severe herniation in infants undergoing antenatal compared to postnatal MMC correction (25% versus 67%, $p<0.001$).

Experimental and clinical evidence indicate that neurological tissue can regenerate when aggression occurs before myelination. Therefore, the ideal gestational age for MMC surgery would be before 24 weeks, when the spinal cord, with the exception of the corticospinal tract, is not yet completely myelinated. The effects of fetal MMC correction on motor function are questionable [17]. Investigators at Vanderbilt University Medical Center compared 37 cases submitted to fetal surgery between 20 and 28 weeks with 40 cases operated postnatally and reported no significant differences in motor function [17]. On the other hand, 57% of the cases with thoracic or lumbar defects submitted to fetal surgery before 26 weeks at the Children's Hospital of Philadelphia had improved motor function. The discrepancy in these results may in part be attributed to different selection criteria used in the two centers. While the Vanderbilt team included older fetuses with club feet and absent limb movements, the Philadelphia team included only fetuses with normal feet and limb movements and performed the surgery at an earlier gestational age [18].

Two of our cases were able to walk without the need for any equipment, indicating sacral functional level lesions, while their anatomical lesion was at L4. At the other extreme, we have two wheelchair-bound children. The first had a thoracic anatomical lesion and a high lumbar functional level lesion. The other child had an anatomical lesion located in the upper lumbar region and a functional lesion corresponding to a lower lumbar level. The other two children need equipments to walk and also had a lower functional level than their anatomical level. These results suggest that fetal surgery possibly improved motor function, since all cases had a functional level lower than their anatomical level. Danzer et al. [19] examined 54 children submitted to antenatal MMC correction at a mean age of 66 months. Approximately 80% of these children were able to walk without any equipment, 24% needed braces or orthoses and 7% were wheelchair-bound. In the MOMS study [8], significantly more children operated during the antenatal period than in the postnatal period had a difference of two vertebrae between the anatomical and functional levels (32% versus 12%; $p=0.005$). Children in the first group were also less likely than those in the second group to need orthoses or other equipment to deambulate (42% versus 21%, $p=0.01$).

Neurological development of the children submitted to fetal MMC surgery was also assessed in the two American studies. The first 29 children operated at Vanderbilt University had a mean score of 100 in the Bayley test (ranging from 80 to 118) [15]. The first 30 cases operated in Philadelphia obtained a mean score of 90.8 (ranging from 73 to 103). Neurological development was considered normal in 67% of the cases, slightly deficient in 20% and severely deficient in 13%. Children with low birth weight and who needed shunt placements had the lowest test scores [20].

Five of our cases had normal cognition according to the CMMS, a test used in older children and validated in Brazil. Only one child, who had difficulties in understanding figures, could not be evaluated through this test. According to the Denver II test, which also assesses motor function, this child had neuropsychomotor delay. Her birth at 28 weeks and the

high anatomical level of her spinal defect could have contributed to her reduced cognition. Her mother was instructed and trained on the importance of stimulation to help this child´s development. She is scheduled for a follow-up visit within a few months. According to the MOMS [8] study, fetal surgery was associated with higher scores in the Bayley and Peabody motor scale.

The benefits of antenatal correction of MMC on urinary tract function seem to be limited. Holzbeierlein et al. [21] reported less urethral reflux and fewer urinary infections in children submitted to this fetal surgery. Our patients had neurogenic bladders and some needed intermittent catheterization, along with medication. One of our children needed to have a vesicostomy in an attempt to reduce progressive kidney dilation.

In Brazil, where interruption of pregnancy is not legal, fetal surgery for MMC can be a valid option. It can help to reduce future long term sequels and the financial burden imposed by these children especially for low-income families, which account for a substantial proportion of our population.

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