Fetal Myelomeningocele Repair through a Mini-Hysterotomy

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Key Words

Fetal myelomeningocele · Fetal surgery · Myelomeningocele repair · Neural tube defect · Open fetal surgery · Spinal dysraphism

Abstract

Objective: To present the feasibility of fetal myelomeningocele (MMC) repair through a mini-hysterotomy and to describe the perinatal results from our initial experience. **Methods:** A descriptive study of cases of fetal MMC correction via mini-hysterotomy performed between 2014 and 2016. **Results:** Forty-five women underwent fetal surgery and 87% (39/45) delivered. A complete multilayer correction of the MMC was possible in all cases. There were no maternal, fetal or neonatal deaths. No maternal or fetal complications occurred from fetal MMC correction until maternal hospital discharge. The average gestational age (GA) at surgery was 24.5 weeks (standard deviation, SD: 1.7; range: 20.7–26.9). The median hysterotomy length was 3.05 cm (SD: 0.39; range:

2.50–3.50). One patient (1/39; 2.6%) experienced chorioamniotic separation. Nine patients (9/39; 23.1%) had premature preterm rupture of membranes at a median GA of 34.1 weeks (range: 31.1–36.0). The average GA at delivery was 35.3 weeks (SD: 2.2; range: 27.9–39.1). Ninety-five percent (37/39) of our patients had an intact hysterotomy site at delivery. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates. **Conclusion:** Fetal MMC repair is feasible through a mini-hysterotomy. This approach appears to be associated with reduced risks of very preterm delivery and maternal, fetal and neonatal complications.

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Introduction

Recent studies have demonstrated that infants who undergo an in utero repair of a myelomeningocele (MMC) through an open surgery have better neurological outcomes than those who are treated after birth [1]. The fe-

tal operation significantly reduces the need for postnatal ventriculoperitoneal shunting and improves infants' global and motor neurological scores [1]. Maternal morbidity is nonnegligible in the fetal treatment group, as observed by the high rates of premature preterm rupture of membranes (PPROM), preterm labor, chorioamniotic separation, dehiscence of the hysterotomy and the need for maternal transfusion at delivery [1].

Classically, open surgery for fetal MMC is performed through a 6.0- to 8.0-cm hysterotomy to allow for the multilayer correction of the neural tube defect (NTD) as would be performed postnatally [1–6]. With the purpose of minimizing access to the fetus and decreasing maternal morbidity, some research groups have tested an endoscopic approach [7–12]. However, the neurological outcomes after these apparently less invasive procedures are not well known, and the rates of PPRM, preterm delivery and dehiscence of fetal/neonatal scars requiring postnatal reoperation are still very high.

We describe a modification of the classic open surgery for fetal MMC in which the same multilayer correction of the spinal defect is performed through a 2.5- to 3.5-cm hysterotomy. The main purposes of this study were to present the feasibility and technical details of this approach and to describe the perinatal results from our initial experience.

Material and Methods

This is a descriptive study of consecutive cases of fetal MMC correction via mini-hysterotomies performed at The Heart Hospital, São Paulo, Brazil, between October 2014 and April 2016. All women that were eligible for fetal surgery were thoroughly educated about the benefits and disadvantages of both fetal and neonatal corrections of the MMC. The patients who opted for the fetal treatment were aware of the technical modifications proposed by our multidisciplinary team and signed a specific informed consent form before the surgery. The ethics committee for medical research at The Heart Hospital approved this study.

The inclusion criteria for fetal surgery were as follows: (1) singleton pregnancy; (2) gestational age (GA) from 18⁺⁰ to 26⁺⁶ weeks; (3) MMC with an upper anatomical level from T1 to S1 and the presence of a Chiari II malformation; (4) no chromosomal abnormality or fetal anatomical defect other than the MMC and associated alterations; (5) no previous history of prematurity or a short cervix of less than 25 mm in size during the current pregnancy; (6) no fetal scoliosis of more than 30°; (7) easy access to the tertiary referring center for follow-up and/or emergency assistance after fetal surgery; (8) no serious maternal disease that could significantly increase the surgical risk, and (9) no positive maternal serology for HIV or hepatitis B and C.

All of the surgeries were performed by the same multidisciplinary team (R.D.B., V.I., K.J.R.C., R.R.J., A.A.F.S. and C.F.A.P.)

according to the following steps: (1) Maternal anesthesia was induced by thiopental, fentanyl and rocuronium. (2) A Pfannestiel incision was performed, and the uterus was partially exteriorized from the abdominal cavity. (3) The fetus was gently moved by external manipulation guided by ultrasound so that the spinal defect was located against the uterine wall free of the placenta; until adequate fetal positioning was achieved, low doses of midazolam and remifentanyl were used to maintain the uterine tone and maternal-fetal anesthesia. (4) A 2.5- to 3.5-cm hysterotomy was performed with an electric blade at least 2 cm away from the border of the placenta, above the fetal defect (fig. 1). The membranes were sutured to the inner layer of the myometrium, and a neonatal Ankeney™ retractor (Schobell Industrial, Rio Claro, SP, Brazil) was used to hold the hysterotomy walls (fig. 1). At this stage, midazolam was replaced by inhaled sevoflurane, and the remifentanyl infusion was readjusted. Uterine relaxation was optimized by the use of nitroglycerin, and from this moment, maternal hemodynamics were carefully controlled by the fluid infusion and the use of inotropic agents. Fetal heart rate was continuously monitored by ultrasound, and an umbilical artery Doppler was checked throughout the procedure. (5) Two neurosurgeons operated on the fetus using a microscope while one of the fetal medicine specialists carefully held and manipulated the fetus to properly expose the MMC. Because the size of the MMC was often larger than the hysterotomy orifice, the fetus had to be constantly and carefully moved so that a specific portion of the lesion could be observed by the neurosurgeons. During these gentle movements, the Ankeney™ retractor was pulled away from the neural placode and the edges of the NTD. While the MMC was being repaired and while fetal manipulation was not necessary, the Ankeney™ retractor was steadily held by a Leyla Retraction System (Integra™; LifeSciences Corporation, USA) in order to minimize any extra pressure on the NTD (fig. 1). (6) The neural placode was dissected, and the defect was closed in separate layers (fig. 2). (7) Uterine suturing was performed in two layers, and before the last stitch was tightened, the physiological solution was returned to the amniotic cavity until the amount of fluid was considered normal according to the ultrasound images. (8) After the surgery, the patient was kept in the intensive care unit for at least 12 h and was then transferred to a common infirmary, where she was kept under observation for at least 3 days. (9) Nifedipine (20 mg t.i.d.) and vaginal progesterone (200 mg) were used from the end of the surgery until delivery.

After hospital discharge, the patient was maintained in close proximity to the institution where delivery was planned to occur, and the patient was evaluated every 2 weeks by a maternal-fetal medicine specialist until the end of the pregnancy.

The following variables were evaluated: maternal and fetal characteristics at the time of surgery, such as maternal and GAs; previous history of NTDs; parity; body mass index; upper level position of the MMC; presence of ventriculomegaly, inferior limb deformity and normal movements (subjective evaluation); size of the lateral ventricle, and placental position. Perioperative variables included hysterotomy length (incision size); total operative time (maternal skin-to-skin); duration of the fetal surgery; occurrence of maternal and/or fetal complications during and/or after the surgery, and total length of stay in the hospital. Variables evaluated from the time of maternal hospital discharge after fetal surgery until delivery included changes in the fetal ventricle size; the reversal of the Chiari II malformation; the presence

Fig. 1. **a** Exposure of the chorioamniotic membranes (arrow) through the mini-hysterotomy. **b** Suture of the chorioamniotic membranes to the inner layer of the myometrium (arrow). **c** Placement of the neonatal Ankeney™ retractor in the mini-hysterotomy. **d** Ankeney™ retractor (white arrow) attached to the Leyla Retraction System (yellow arrow; colors refer to the online version only).

Fig. 2. **a** Microscope view of the fetal MMC (white arrow: central spinal canal; yellow arrow: neural placode; colors refer to the online version only). S = Skin; AM = arachnoid mater. **b** Drawing of a transverse view of the MMC (by Dr. Dennis Malkasian, MD, PhD). **c** Closed neural placode (arrows). **d** Closure of the dura mater. **e** Closure of the skin.

of fetal inferior limb deformities and movements (subjective evaluation); the occurrence of chorioamniotic separation, fetal death and PPRM; the GA at PPRM, and the time intervals between fetal surgery and birth and between PPRM and delivery. Peripartum variables included the GA at the time of delivery; the occurrence of maternal and/or fetal complications during the caesarean section; the condition of the hysterotomy site, and the

neonatal Apgar scores and weight. Neonatal variables recorded until hospital discharge included the condition of the scar at the MMC repair site; the results of the transfontanelar ultrasound and/or brain MRI scans; the need for ventriculoperitoneal shunting; global and motor neurological status; the occurrence of neonatal death or any other complication, and the total length of stay in the hospital.

Table 1. Maternal and fetal characteristics at the time of myelomeningocele repair

	All cases (n = 45)	Delivered (n = 39; 86.6%)
<i>Maternal characteristics</i>		
Age, average (SD); range, years	29.6 (5.7); 18.2–43.0	30.1 (5.7); 18.7–43.0
BMI, average (SD); range	26.6 (4.5); 19.5–36.4	26.8 (4.7); 19.5–36.4
Parity, n (%)		
Multiparous	32 (71.1)	29 (74.4)
Nulliparous	13 (28.9)	10 (25.6)
GA, average (SD); range, weeks	24.5 (1.7); 20.7–26.9	24.5 (1.8); 20.7–26.9
<i>Fetal and placental characteristics</i>		
MMC upper anatomical level, n (%)		
T10/T12	3 (6.7)	3 (7.6)
L1/L2	14 (31.1)	12 (30.7)
L3/L4	17 (37.8)	17 (43.5)
L5/S1	11 (24.4)	7 (17.9)
Presence of ventriculomegaly, n (%)	32 (71.1)	26 (66.6)
Lateral ventricle diameter, average (SD); range, mm	11.4 (3.1); 4.0–20.0	11.3 (3.2); 4.0–20.0
Presence of inferior limb deformity, n (%)	19 (42.2)	15 (38.5)
Presence of inferior limb movements, n (%)	35 (77.8)	30 (76.9)
Placental position, n (%)		
Anterior	20 (44.4)	18 (46.2)
Posterior	22 (48.9)	20 (51.3)
Other	3 (6.7)	1 (2.6)

Fetal ventriculomegaly was diagnosed when the width of the lateral ventricle at the level of the parieto-occipital fissure was greater than 10 mm. The largest measurement between the two sides was considered for analysis. During the follow-up after fetal surgery, a significant change was defined as a difference of more than 1 mm in the lateral ventricle diameter from the time of surgery to the last ultrasound evaluation before delivery.

A complete reversal of the fetal Chiari II malformation after MMC repair was recorded when both normal anatomy and measurements of the cerebellum (transverse cerebellar diameter and craniocaudal diameter of the vermis) were obtained by ultrasound. In addition, the cerebellum and the pons were required to be located completely above the foramen magnum in a midsagittal view of the brain, and the cisterna magna had to be measurable in a standard suboccipital view. A partial reversal of the Chiari II malformation was defined when the cerebellum fastigium was visible above the foramen magnum in a midsagittal view by ultrasound, but when portions of the cerebellum could still be observed below the level of the foramen magnum. In addition, improved visualization of the transverse cerebellum anatomy in relation to the preoperative image was required. The cisterna magna was obliterated and was not measurable.

Continuous variables were described using averages and standard deviations (SD) or medians and ranges when appropriate, and categorical data were described using absolute and relative frequencies. The Statistical Package for the Social Sciences (SPSS, Chicago, Ill., USA), version 21.0, was used for the analyses.

Results

During the study period, 45 women underwent fetal surgery for MMC through a mini-hysterotomy. A complete multilayer correction of the fetal defect was possible in all of the cases. No maternal or fetal complications occurred during or after fetal MMC correction until maternal hospital discharge, apart from 1 case (1/45; 2.2%) of pneumonia that was most likely acquired prior to maternal admission. Two patients (2/45; 4.4%) reported having a previous sibling with NTD. At the time of this analysis, 39 women (39/4; 86.6%) had delivered. The perioperative variables were similar in all of the patients and in those who had delivered (table 1). The median hysterotomy length was 3.05 cm (SD: 0.39; range: 2.50–3.50). The total operative time and time taken to perform the MMC repair were 3.44 h (SD: 0.71; range: 1.50–4.57) and 1.90 h (SD: 0.72; range: 0.50–3.50), respectively. The average maternal length of stay in the hospital was 3.55 days (SD: 1.56; range: 4–11).

The variables that were evaluated from the time of maternal hospital discharge after fetal surgery to the time of delivery are presented in table 2. There were no fetal deaths, and only 1 patient (1/39; 2.6%) experienced cho-

Table 2. Variables evaluated from fetal MMC repair until delivery (n = 39)

Change in fetal cerebral lateral ventricle size, n (%)	
Increased	17 (43.6)
Decreased	6 (15.4)
Stabilized	16 (41.0)
Reversal of the Chiari II malformation, n (%)	
Complete	10 (25.6)
Partial	24 (61.5)
None	5 (12.8)
Presence of inferior limb deformity, n (%)	14 (35.9)
Presence of inferior limb movements, n (%)	28 (71.8)
Interval between fetal surgery and delivery, average (SD); range, weeks	10.9 (2.3); 5.7–17.9
PPROM, n (%)	9 (23.1)

Table 3. Peripartum variables

GA at delivery, average (SD); range, weeks	35.3 (2.2); 27.9–39.1
>36 ⁺⁶ weeks, n (%)	9 (23.1)
34 ⁺⁰ to 36 ⁺⁶ weeks, n (%)	23 (59.1)
32 ⁺⁰ to 33 ⁺⁶ weeks, n (%)	5 (12.8)
<32 ⁺⁰ weeks, n (%)	2 (5.1)
Hysterotomy site, n (%)	
Intact	37 (94.9)
Complete dehiscence	0
Partial dehiscence	2 (5.1)
Thinning	0
Neonatal Apgar scores	
1st min, median (range)	8 (7–10)
5th min, median (range)	9 (8–10)
Neonatal weight, average (SD); range, g	2,493 (531); 1,100–3,740

Table 4. Neonatal variables until hospital discharge (n = 39)

Reversal of the Chiari II malformation on MRI, n (%)	
Complete	13 (33.3)
Partial	17 (43.6)
None	5 (12.8)
Not imaged	4 (10.3)
Ventriculoperitoneal shunting, n (%)	3 (7.7)
Presence of clubfoot, n (%)	22 (56.4)
Inferior limb movements, n (%)	
Normal	18 (46.2)
Reduced	16 (41.0)
None	5 (12.8)
Other complications, n (%)	
Neurogenic bladder	5 (12.8)
Peri-intraventricular hemorrhage	1 (2.6)
Necrotizing enterocolitis	1 (2.6)

rioamniotic separation, which was not followed by oligohydramnios. There was a decrease or stabilization in the fetal cerebral lateral ventricle size in 22 cases (22/39; 56.4%), and 34 fetuses (34/39; 87.1%) exhibited a complete or partial reversal of the Chiari II malformation. Nine patients (9/39; 23.1%) experienced PPRM at a median GA of 34.1 weeks (range: 31.1–36.0). No patients delivered more than 1 week after the rupture of the membranes.

Peripartum variables are presented in table 3. All women delivered by caesarean section, and the indications for delivery included signs of labor and/or rupture of membranes in 36 patients (36/39; 92.3%), severe pre-eclampsia in 2 patients (2/39; 5.2%) and placental abruption in 1 patient (1/39; 2.6%). There were no fetal or neonatal deaths, and no cases of maternal bleeding requiring transfusion.

The neonatal variables until hospital discharge are displayed in table 4. All neonates survived, and the median

length of stay in the hospital was 5 days (range: 2–75). Two neonates (2/39; 5.1%) exhibited partial skin dehiscence at the repair site with no fluid leakage; 1 neonate required complementary repair. Thirty-seven neonates (37/39; 94.9%) underwent transfontanellar ultrasound and/or MRI scans. Information about the Chiari II malformation obtained by MRI was available for 35 neonates. Complete and partial reversal of the Chiari II malformation was observed in 33.3% (13/39) and 43.6% (17/39) of cases, respectively. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates.

Discussion

This study demonstrated that fetal MMC repair through a mini-hysterotomy is feasible and safe for the mother, the fetus and the neonate. It must be clarified that

despite the fact that the technique for fetal access was labeled as a mini-hysterotomy, the procedure is not minimally invasive, but is rather a modification of the traditional open surgery for fetal spina bifida.

The assumption that fetal MMC correction could improve postnatal neurological outcomes compared to neonatal surgery was confirmed by the results of the MOMs trial (Management of Myelomeningocele Study) [1]. Despite the presence of favorable outcomes for the children, prenatal surgery was associated with a higher maternal morbidity, evidenced by the rates of PPROM (46%), preterm labor (38%), complete or partial dehiscence of the hysterotomy site (30%), chorioamniotic separation (26%), need for maternal blood transfusion at delivery (9%) and acute pulmonary edema (6%).

Focusing mainly on the reduction of maternal morbidity, we aimed to minimize the size of the hysterotomy so that the NTD could be repaired as was performed in the MOMs trial. The main differences in fetal access were the size of the hysterotomy (present study: 2.5–3.5 cm; MOMs trial: 6.0–8.0 cm) and the fact that we did not use staples to secure the borders of the hysterotomy. Instead, after the myometrium was incised using an electric blade, the membranes were attached to the inner third of the incised tissue using a running suture. Another feature of our technique was the use of an AnkeneyTM retractor to hold the borders of the hysterotomy and to expose the NTD. It could be argued that this approach could cause extra damage to the neural tissues, especially during fetal manipulation for the exposure of the MMC. However, as mentioned before, the AnkeneyTM retractor was pulled away from the NTD during fetal manipulation, and when no manipulation was needed, the device was held by a Leyla Retraction System to avoid excessive pressure on the fetus. The very low incidence of neonatal scar dehiscence in our study indicates that little or no additional damage is caused to the neural tissue or to the surrounding skin while the MMC correction is performed with this approach. In parallel to our clinical experience, our team currently participates in a collaborative experimental study in the Centre for Surgical Technologies at the Faculty of Medicine of the Katholieke Universiteit (KU) of Leuven. It is a feasibility and efficacy study in a sheep model to evaluate the results of fetal MMC repair via traditional open surgery (6.0- to 8.0-cm hysterotomy) and via mini-hysterotomy (2.5- to 3.5-cm hysterotomy). Preliminary results show that fetal MMC repair via mini-hysterotomy is feasible and the complete analysis of spinal and cerebral structural and functional assessments will be the subject of further publication.

We concentrated on the comparison of our data (39 cases with neonatal results) with data from the post-MOMs experience, which focused on the perinatal results rather than on a longer-term follow-up of the infants [13]. Our inclusion criteria for fetal MMC repair were comparable, as were most of the maternal and fetal characteristics at the time of fetal surgery, which are summarized as follows (present series $\times$ post-MOMs experience): average GA at surgery (24.5×23.3 weeks); most frequent upper level of the MMC (L1–L4: $74.2 \times 87.0\%$); average size of the larger lateral cerebral ventricle (11.3×10.6 mm), and presence of talipes ($38.5 \times 15.0\%$).

In terms of perioperative variables, there were differences in the total operative time (3.44×1.31 h), the frequency of patch use ($0.0 \times 20\%$) and the need for fetal resuscitation ($0.0 \times 5.0\%$). Most likely, the longer operative time in the current study reflected our decision not to use staples and patches. This decision supports our aim to demonstrate that fetal MMC correction is feasible through a smaller hysterotomy, even for more challenging (larger) defects. Despite the longer operation time, our surgery-to-delivery interval was the same as that described in the post-MOMs experience. This could be explained by the hysterotomy size itself and by the way in which the membranes are attached to the myometrium in our cases. These two aspects could help to prolong the latency to delivery even after a longer operation time. The same arguments could be used to explain why the rates of PPROM ($23.1 \times 32.3\%$) and chorioamniotic separation ($2.6 \times 22.9\%$) were lower in the current study.

Despite a similar average GA at delivery (35.3×34.3 weeks), the distribution of deliveries according to GA intervals was different. The rate of late preterm deliveries (after 34 complete weeks) was higher in the current study ($82.2 \times 54.2\%$), and only 5.1% (2/39) of our patients delivered before 32 weeks (1 delivered at 27.9 weeks, and the other delivered at 31.9 weeks). In the post-MOMs evaluation, there were 4 (4/96; 4.2%) extreme preterm deliveries that occurred 2 weeks after the fetal MMC repair. Despite the fact that both studies had a similar average time interval between fetal surgery and birth (approximately 11 weeks), none of our patients delivered less than 5.7 weeks after the MMC repair.

Two other aspects that deserve recognition are the perinatal mortality and dehiscence at the hysterotomy site that were observed at delivery. In the current study, there were no perinatal deaths (vs. 6.1% in the post-MOMs experience) and 94.9% (37/39) of our patients had an intact hysterotomy site at delivery (vs. 50.6 in the post-

MOMs experience). The impact of the lower incidence of uterine scar dehiscence on future pregnancies is unknown.

The only important difference in the neonatal variables was the rate of ventriculoperitoneal shunt placement prior to hospital discharge, which was higher in the current study than in the post-MOMs evaluation ($7.7 \times 2.4\%$). Interestingly, the rates of complete or partial reversal of the Chiari II malformation on the MRI scans in both studies were similar ($76.9 \times 79.5\%$). One explanation could be that in the present study, the neonates were followed by different neurology teams using different criteria for the indication of ventriculoperitoneal shunting. The values in the current study are still within an acceptable shunt rate, and the results will be reevaluated within 30 months to determine if the values approach the results that were reported in the MOMs trial.

The frequency of major adverse events, such as the maternal pulmonary edema, the need for maternal transfusion at the time of fetal surgery or delivery, the need for fetal resuscitation, or the incidence of fetal or neonatal death, was 17 among 100 cases in the post-MOMs experience, whereas only 1 (1/39; 2.6%) of our patients experienced placental abruption close to the time of delivery.

The main weaknesses of our study are the small number of patients, the short follow-up period and the uneven criteria for ventriculoperitoneal shunting. However, all the children are undergoing formal neurological evaluations, and these data will be presented soon.

In conclusion, we propose that fetal MMC repair is feasible through a mini-hysterotomy. This approach appears to be associated with reduced risks of very preterm delivery and maternal, fetal and neonatal complications when compared to the classical hysterotomy procedure for fetal MMC repair.

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