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MATERNAL-FETAL MEDICINE

Open fetal myelomeningocele repair at a university hospital: surgery and pregnancy outcomes

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Abstract

Purpose Myelomeningocele (MMC) is an open neural tube defect that causes great morbidity. Prenatal open repair is the standard treatment; however, there are many complications related to the procedure. This study reports preliminary findings of open in utero repair of MMC in a public tertiary hospital in Brazil and describes factors that could be associated with increased surgical morbidity.

Methods Thirty-nine patients underwent open in utero repair of MMC from October 2015 to August 2019. The Clavien–Dindo classification of surgical complications and a classification system with the preterm definitions of the World Health Organization were used, respectively, for maternal and fetal complications.

Results A total of 28 mothers (71.8%) and 31 fetuses (79.5%) experienced at least one minor to major complication. Three mothers (7.7%) had a severe grade 4 complication. Fetal complications grades 3 to 5 occurred in 13 fetuses (33.3%). Gestational age at surgery and at birth were 24.88 ± 1.16 weeks and 33.23 ± 3.68 weeks, respectively. Preterm delivery occurred in 30 patients (76.9%), membrane rupture in 18 patients (46.2%) and chorioamnionitis in 13 patients (33.3%).

Conclusion Open fetal surgery for MMC was performed at a Brazilian public tertiary care center, resulting in three grade 4 maternal complications. Relevant fetal complications were also present. The use of a standard classification system for complications renders studies more comparable and data more useful for counseling patients. Adjustments of perioperative procedures and long-term follow-up are needed to determine the real benefit of open in utero repair of MMC at our hospital.

Keywords Myelomeningocele · Spina bifida · Open neural tube defect · Fetal surgery

Introduction

Myelomeningocele (MMC), the most common malformation of the central nervous system (CNS), occurs due to failed closure of the neural tube around the fourth postconceptual week of gestation [1]. It is a form of spinal dysraphism, thus belonging to the group of neural tube defects (NTD) [2]. Medical problems of the disease include paralysis, hydrocephalus, Arnold-Chiari type II malformation, deformations of the limbs and spine, bladder/bowel/sexual dysfunction, and learning disabilities [3].

The treatment of MMC until the late 1990s consisted of surgical closure of the spinal canal right after birth [4]. As neurological deficits are mostly permanent and irreversible, the main objectives of surgical repair included preservation of the viable nervous tissue, anatomical reconstitution, and prevention of infection [5]. The "two-hit" hypothesis is a

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theory that emerged from several observational and experimental studies resulting in an important change of perspective for the treatment of MMC [6]. According to this theory, the first hit would be the existence of the congenital defect and the second hit would be related to mechanical and chemical traumas inflicted on the continuously exposed neural structures in the uterine environment. This hypothesis predicted that in utero repair would arrest the process of neural tissue destruction and rescue neurological function at birth.

In 2011, a randomized multicenter prospective study known as the Management of Myelomeningocele Study (MOMS) [7] compared outcomes of open in utero repair of myelomeningocele with postnatal repair. Its main findings were that the group of patients who underwent fetal surgery had significant reduction in the need for ventriculoperitoneal shunt at 12 months, increased frequency of independent walking at 30 months, more reversals of hindbrain herniation, and improved functional level. The same trial also showed that, despite all of the benefits, important maternal–fetal complications, such as postoperative pulmonary edema, chorioamniotic membrane separation (CMS), oligohydramnios, preterm premature rupture of membranes (PPROM), preterm birth (PTB), excessive bleeding, and uterine scar dehiscence, were common in patients who underwent prenatal repair [7].

Following the lead of the MOMS trial, many fetal medicine centers around the world [8, 9] and in Brazil [10, 11] adopted in utero repair as the standard treatment. This study proposes to report the preliminary findings regarding open in utero repair of MMC in a public tertiary hospital in Brazil, to compare these results with those of other centers of excellence, and to describe factors that could be associated with the increase in surgical morbidity for mothers and fetuses undergoing the procedure.

Materials and methods

This is a cross-sectional observational study with a prospective collection of data from 39 consecutive patients who underwent open in utero repair of MMC between October 2015 and August 2019. This figure includes all patients from the beginning of the program until data analysis for publication. They were operated on by a consistent multidisciplinary team of the same obstetricians, neurosurgeons, and anesthesiologists at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP). The patients were prospectively followed from the moment they accepted the treatment until childbirth and discharge from the hospital. The study protocol was approved by the hospital's research ethics committee (CAAE 93020218.7.0000.0068) and all patients signed an informed consent statement before surgery.

The inclusion criteria were the same as those of the MOMS [7] except for the upper limit of gestational age (GA) at surgery, which was extended from 25 6/7 weeks to 26 6/7 weeks. This change was made to allow a greater number of patients to benefit from surgery, since diagnosis of complex malformations and referral to tertiary specialized centers often occur later in the second trimester for patients who depend on the Brazilian public health system. The main exclusion criteria were also the same as those used in the MOMS.

At the fetal unit, all patients underwent a sonographic fetal evaluation, including a morphological assessment, and an echocardiogram. Amniotic fluid for fetal karyotype was collected during surgery in every case. Once eligible for surgery, the patients were given explanations about risks and benefits and a written informed consent statement was obtained. Surgery followed as soon as possible.

The surgical procedure was performed by the multidisciplinary team in the obstetric surgical center at the HCFMUSP. The surgical technique used was the mini-hysterotomy proposed by Botelho et al. [11]. The main departures from the MOMS procedure were the smaller size of the hysterotomy, a uterine incision without use of a stapling device, attachment of the membranes to the myometrium, and the use of the Ankeney™ retractor to hold the hysterotomy walls during surgery.

Perioperative management included the use of prophylactic antibiotics and tocolytics; no changes were made in the protocol during the study period. Antibiotics included preoperative use of cephazolin (2000 mg) and postoperative use of cephalexin (2000 mg daily) for 7 days. Atosiban was started at the beginning of the procedure and continued for the first 24 h after surgery to prevent uterine contractions. Intraoperative magnesium sulfate was administered after uterine closure and continued postoperatively for 5 h. Vaginal progesterone (400 mg daily) and nifedipine (80 mg daily) were maintained until delivery.

Mothers were usually discharged 6 days after surgery following ultrasound confirmation of normal fetal heartbeat rate and normal amniotic fluid volume. They were strongly counseled to stay in the city of São Paulo until delivery. Ultrasound assessments were scheduled every 2 weeks after surgery, and routine prenatal appointments were scheduled following institutional protocol. Delivery was scheduled to be performed via cesarean section (C-section) at 37 weeks' gestation in the same obstetrical surgery center where prenatal repair was performed. Preterm C-section was performed in situations of preterm labor with the risk of uterine rupture, signs of clinical chorioamnionitis, placental abruption, and other fetal/maternal situations that would require the baby's delivery. If the mother experienced PPROM, she was admitted to the hospital and managed expectantly until 36 weeks GA, at which time she was delivered. If PPROM occurred

at 36 weeks or more, a C-section was performed immediately. Follow-up at our institution was guaranteed for both the mother and the child.

Demographic and pregnancy data, such as operative characteristics and maternal/fetal outcomes, are reported. Maternal complications were evaluated according to the classification of surgical complications by Clavien and Dindo, a 5-level therapy-oriented severity grading system [12]. Fetal complications were assessed based on the terminology of Adverse Events of the Medical Dictionary for Regulatory Activities (MedDRA) including the World Health Organization (WHO) definitions of preterm delivery [13–15]. The following risk factors were investigated in search of an association with preterm birth (PTB) before 34 weeks: maternal age; ethnic group classified as black/white/brown; nulliparity; placental position classified as anterior/posterior/lateral; CMS; oligohydramnios (defined as maximum vertical pocket < 2 cm or amniotic fluid index < 5 cm); placental abruption; PPROM; chorioamnionitis; GA at surgery; duration of surgery (fetal and total time); cervical length; and duration of hospital stay after surgery. The same risk factors were investigated for PPROM before 34 weeks. In the analysis of chorioamnionitis, both the clinical and/or the histological situations were considered positive cases.

Data regarding maternal, fetal, surgical, perinatal, and postnatal outcomes were collected and transferred to an EXCEL spreadsheet (Microsoft Corporations, Redmond, WA, USA) and analyzed using the Statistical Package for Social Sciences program (SPSS, version 20.0, SPSS Incorporated, Chicago, Illinois, USA). Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Parametric variables were reported as mean and standard deviation (SD), nonparametric data were expressed as median and range, and categorical variables were displayed as absolute numbers and percentages. The comparison between continuous and categorical variables was made with the Student *t* test and the Mann–Whitney test when appropriate. Categorical variables were compared by the χ^2 test or the Fisher exact test when indicated. Univariate logistic regression was used to estimate the odds ratio (OR) and the 95% confidence interval (95% CI). A p value < 0.05 was considered statistically significant.

Results

Patients (Fig. 1)

One hundred and twenty-one patients were referred to the Fetal Medicine Unit of HCFMUSP between October 2015 and August 2019 to be evaluated regarding a previous fetal diagnosis of open spinal dysraphism. Of these 121 patients, 79 did not fulfill the inclusion criteria and three declined surgery. The remaining 39 patients underwent open in utero repair during the period mentioned above.

Baseline and perioperative characteristics (Tables 1 and 2)

Fetal lesion was L3 or below in 29 patients (74.4%). The lesions were classified as myelomeningocele and myeloschisis in 74.4% and 25.6% of the patients, respectively. Ventriculomegaly was present in 76.9% of the cases and clubfoot in almost half of them (46.1%). Mean GA at surgery was 24.88 ± 1.16 weeks. Total operative time was 229.7 ± 30.02 min. Primary fetal skin closure was not possible in 12 fetuses (30.8%), thus skin relaxing incisions (8 cases) and collagen patches (4 cases) had to be used. It was more difficult to successfully perform a primary skin closure in fetuses with myeloschisis than in fetuses with myelomeningocele (70% vs. 17.2%, p = 0.004, OR 11.20 [2.13–58.94]). The duration of surgery on fetuses with myeloschisis was longer, but the time difference was not statistically significant: fetal operative time and total operative

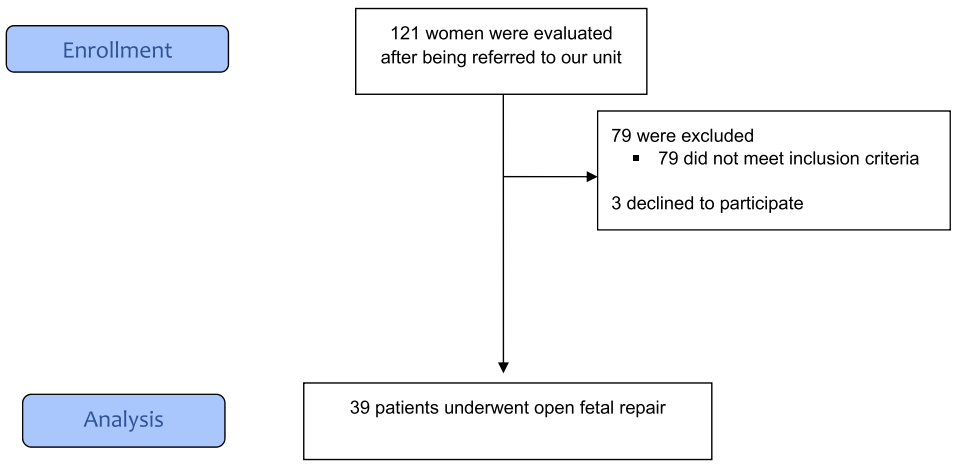

Fig. 1 Enrollment

Table 1 Baseline characteristics of the study population ($N=39$)

Maternal age at surgery—years	29.41 ± 5.92
Ethnic group—No. (%)	
White	21 (53.8)
Black	8 (20.5)
Brown	10 (25.6)
Schooling—No. (%)	
Primary education	3 (7.7)
Secondary education	23 (59)
University	13 (33.3)
Married or living with a partner—No. (%)	29 (74.4)
Nullipara—No. (%)	17 (43.6)
Previous uterine surgery—No. (%)	7 (18)
Fetal sex—No. (%)	
Female	26 (66.7)
Male	13 (33.3)
Placenta position—No. (%)	
Anterior	21 (53.8)
Posterior	17 (43.6)
Lateral	1 (2.6)
Lesion level on ultrasonography—No. (%)	
Thoracic	2 (5.1)
L1–L2	8 (20.5)
L3–L4	18 (46.2)
L5–S1	11 (28.2)
Lesion level L3 or lower	29 (74.4)
Type of lesion on ultrasonography—No. (%)	
Myelomeningocele	29 (74.4)
Myeloschisis	10 (25.6)
Ventriculomegaly—No. (%)	30 (76.9)
Ventricle measurement before surgery (largest)—mm	12.29 ± 3.55
Clubfoot on ultrasonography	18 (46.1)

Values are presented as mean ± SD or No. (%)

Table 2 Operative characteristics and general outcomes ($N=39$)

Operative characteristics	
Gestational age at surgery—week	24.88 ± 1.16
Hysterotomy length—cm ($n=36$)	3.56 ± 0.33
Total operative time—min ($n=33$)	229.7 ± 30.02
Fetal operative time—min ($n=36$)	87.69 [55–155]
Requirement of skin relaxing incisions/patch—No. (%)	12 (30.8)
Skin relaxing incision	8 (20.5)
Patch	4 (10.3)
Postoperative length of stay—days	6.92 [4–17]
Maternal–Fetal Outcomes	
Gestational age at PPROM – week	31.48 ± 2.78
PPROM—No. (%)	18 (46.2)
< 30 week	4 (22.2)
30–33 6/7 week	10 (55.6)
34–36 6/7 week	4 (22.2)
Spontaneous labor—No. (%)	20 (51.3)
Gestational age at birth— week	33.23 ± 3.68
Gestational age at birth—No. (%)	
< 28 week	4 (10.3)
28–31 6/7 week	8 (20.5)
32–33 6/7	10 (25.6)
34–36 6/7 week	8 (20.5)
≥ 37 week	9 (23.1)
Birth weight—g	2056.26 ± 700.6
Interval between surgery and delivery—days	58.97 ± 26.94
Cases with PPROM	55.17 ± 21.21
Cases without PPROM	62.24 ± 31.18
Hysterotomy site at delivery—No. (%)	
Intact	35 (89.7)
Dehiscence	4 (10.3)

Values are presented as mean ± SD, median [range], or No. (%)

time were 98.8 ± 28.65 and 235.3 ± 27.93 min for fetuses with myeloschisis vs. 83.42 ± 22.74 and 227.17 ± 31.14 min for fetuses with myelomeningocele ($p=0.100$ and $p=0.473$ respectively).

General outcomes (Table 2)

Most of our patients (33, 84.6%) delivered at HCFMUSP. Data from the six patients who delivered at other hospitals were obtained by contacting medical care professionals from those institutions. The mean GA at birth was 33.23 ± 3.68 weeks. A PTB occurred in 30 patients (76.9%). A PPROM occurred in 18 patients (46.2%) at a mean GA of 31.48 ± 2.78 weeks. All 18 PPROM cases led to a PTB and the median time between the PPROM and birth was 1 day (0–28). The mean interval between surgery and delivery was 58.97 ± 26.94 days, shorter in the PPROM cases than in those without PPROM (55.17 ± 21.21 days *vs.* 62.24 ± 31.18 days, respectively). However, the difference was not statistically significant ($p=0.421$).

Maternal complications (Table 3)

A total of 28 mothers (71.8%) had at least one minor to major complication. There were no maternal deaths (grade 5 complication); however, three patients (7.7%) experienced a severe grade 4 complication. The very first patient who underwent prenatal MMC repair had a PPROM at 28 4/7 weeks and developed clinical signs of chorioamnionitis two weeks later. She had a postpartum hysterectomy secondary to uterine atony not responsive to pharmacological therapy. Blood transfusion was required. She was multiparous with nine previous pregnancies and

Table 3 Maternal complications ($N=39$)

Grade 1 – Minor complications not requiring any pharmacological treatment or surgical intervention	
Gestational diabetes	7 (17.9)
Oligohydramnios	7 17.9)
Chorioamniotic membrane separation	1 (2.6)
Chorioamnionitis (histologically only)	6 (15.4)
Grade 2 – Complications requiring pharmacological treatment	
PPROM	18 (46.2)
Pulmonary edema	2 (5.1)
Blood transfusion	5 (12.8)
Uterine atony	2 (2.6)
Grade 3 – Complications requiring surgical intervention	
Oligohydramnios	2 (5.1)
Placental abruption	2 (5.1)
Chorioamnionitis	7 (17.9)
Uterine atony	1 (2.6)
Grade 4 – Life-threatening complications requiring IC/ICU management	
Postpartum hysterectomy	1 (2.6)
Seizure due to central venous thrombosis	1 (2.6)
Peritonitis due to bowel lesion during surgery	1 (2.6)
Grade 5 – Death	0

Values are presented as No. (%)

had an uneventful recovery after a short stay in the intensive care unit (ICU). Another patient presented with seizure 6 days after surgery. Investigation led to a diagnosis of central venous thrombosis (CVT). After management in the ICU, including appropriate anticoagulant treatment, the patient had a full recovery without any permanent damage. In the investigation, no specific risk factors for CVT were found. At 30 6/7 weeks she had a PPROM and at 32 6/7 weeks she developed clinical signs of chorioamnionitis, prompting a preterm cesarean delivery. Finally, one woman exhibited clinical signs of peritonitis at 25 4/7 weeks, 6 days after fetal MMC (fMMC) repair. A laparotomy was performed and evidenced an accidental bowel injury that had occurred during fetal surgery. She was managed in the ICU after surgical repair and no long-term consequences occurred.

Eleven patients (28.2%) had at least one grade 3 complication. Most noteworthy were the two cases (5.1%) of placental abruption at 32 5/7 weeks and 33 3/7 weeks; one case (2.6%) of uterine atony during cesarean section, which required a B-Lynch suture, and seven cases (17.9%) of chorioamnionitis. A grade 2 complication occurred in 23 patients (58.9%), and a grade 1 complication in 15 women (38.5%). All 7 cases (17.9%) of chorioamnionitis classified as grade 3 were in the PPROM group. Six other patients had a histological diagnosis of chorioamnionitis without clinical signs, which was classified as a grade 1 complication. Hence, there were 13 patients (33.3%) with chorioamniotic infection among the histological and clinical cases. Patients who developed chorioamnionitis had lower mean GA at birth (30.90 ± 2.96 vs. 34.93 ± 3.64 weeks [$p=0.002$]) and lower neonatal birth weight (1633.46 ± 597.55 vs. 2384.95 ± 681.96 g [$p=0.003$]) than those who did not. The hysterotomy site at delivery showed an area of dehiscence in four patients (10.3%).

Fetal complications (Table 4)

Thirty-one fetuses (79.5%) experienced complications. There were three (7.7%) perinatal deaths, therefore classified as grade 5 complications. One was intrauterine and the other two occurred in the neonatal period. In the former case, the fetus presented with persistent bradycardia during fMMC repair and required pharmacological resuscitation procedures, to which it responded, and surgery could be finished. However, it died 6 h later. Since autopsy was not allowed, the death cause could not be confirmed. One of the neonatal deaths, of a baby born at 25 4/7 weeks, occurred 3 days postpartum in consequence of a bowel lesion during fMMC repair, which caused maternal peritonitis. The second neonatal death occurred two weeks after birth due to respiratory failure unresponsive to treatment. It was born at 33 weeks' gestation because of persistent oligohydramnios; a uterine scar dehiscence was seen during the cesarean section.

Four fetuses (10.3%) were severe preterm (grade 4 complications): two of them were born spontaneously; another was

Table 4 Fetal complications ($N = 39$)

Grade 1 – Minor complications	
Late preterm (34—36 6/7 week)	8 (20.5)
Grade 2 – Moderate complications	
Bradycardia during surgery	1 (2.6)
Moderate preterm (32—33 6/7 week)	10 (25.6)
Grade 3 – Severe complications	
Bradycardia during surgery (pharmacological therapy)	1 (2.6)
Very preterm (28–31 6/7 week)	8 (20.5)
Grade 4 – Life-threatening complications	
Severe preterm (< 28 week)	4 (10.3)
Grade 5 – Death	
Fetal (bradycardia during surgery with pharmacological therapy; death 6 h after surgery)	1 (2.6)
Neonatal (birth at 25 4/7 week due to maternal bowel lesion; death 3 d later / Birth at 33 w due to persistent oligohydramnios; death 2 week later)	2 (5.1)

Values are presented as No. (%)

born due to the aforementioned maternal bowel lesion and the fourth case was the fetus that died in utero 6 h after surgery. There were nine (23.1%) fetuses with grade 3 complications: one presented persistent bradycardia during fMMC repair and required pharmacological resuscitation procedures; the other eight fetuses with grade 3 complications had very preterm births. The most common reasons for these premature births were a PPROM followed by preterm labor and clinical signs of chorioamnionitis. A grade 2 complication occurred in 11 fetuses (28.2%): one had bradycardia during surgery with spontaneous remission, and ten had a moderate preterm birth. Finally, 8 fetuses (20.5%) presented a grade 1 complication; all of them had late preterm births.

Factors associated with PTB under 34 weeks and PPROM under 34 weeks (Tables 5 and 6)

For women experiencing a PTB and/or a PPROM before 34 weeks, the only associated risk factor was chorioamnionitis ($p = 0.012$, OR 7.50 [1.38–40.88] and $p < 0.001$, OR 18.33 [3.44–97.70], respectively) (Tables 5 and 6). None of the factors under analysis were found associated with chorioamnionitis: maternal age at surgery, GA at surgery, type of lesion, nulliparity, placental position, duration of surgery (total and fetal), length of hospital stay after surgery, and the need for fetal skin closure procedures.

Discussion

General aspects

This prospective study presents surgical, maternal, and fetal outcomes of the first cases of open fetal MMC repair performed between October 2015 and August 2019 at the Hospital das Clínicas, São Paulo University, a public tertiary hospital in São Paulo, Brazil, and compares the results with other centers of excellence in maternal–fetal medicine.

The technique we adopted was the mini-hysterotomy first described in 2017 by Botelho and colleagues [11]. It is a modification of the classic open surgery consisting of a smaller uterine incision and the nonuse of staplers. The technique has been demonstrated to be feasible and comparable to that of the MOMS in terms of maternal–fetal outcomes. We chose to perform open in utero repair of MMC through a mini-hysterotomy because of their first results, which were promising. Therefore, we invited the fetal expert who created the technique to operate on the first 10 cases and help with our learning process.

Complications directly or not directly related to the fMMC repair occurred in 71.8% of mothers and 79.5% of fetuses, all of whom experienced at least one minor to major complication. Most of the complications were minor to moderate, but there was a higher-than-expected rate of major complications, which deserve being discussed.

Table 5 Preterm birth before 34 weeks stratified by risk factor

	Preterm birth < 34 weeks (n=22)	Birth ≥ 34 weeks (n = 17)	p value	OR [95% CI]
Maternal age	29.6 ± 5.7	29.1 ± 6.3	0.790	1.01 [0.91–1.13]
Ethnicity			0.080*	
Black	4 (50)	4 (50)		0.43 [0.06–2.97]
Brown	3 (30)	7 (70)		2.50 [0.47–13.39]
White	15 (71.4)	6 (28.6)		1.0
Nulliparity			1.0	
Yes	10 (58.8)	7 (41.2)		1.19 [0.33–4.28]
No	12 (54.5)	10 (45.5)		
Placental position			0.613*	
Anterior	13 (61.9)	8 (38.9)		1.0
Posterior	9 (52.9)	8 (47.1)		0.69 [0.19–2.53]
Lateral	0	1 (100)		Not calculated
Chorioamniotic separation			0.436*	
Yes	0	1 (100)		Not calculated
No	22 (57.9)	16 (42.1)		
Oligohydramnios			0.709*	
Yes	4 (50)	4 (50)		0.72 [0.15–3.43]
No	18 (58.1)	13 (41.9)		
Placental abruption			0.495*	
Yes	2 (100)	0		*Not calculated*
No	20 (54.1)	17 (45.9)		
Preterm premature rupture of membranes			0.334	
Yes	12 (66.7)	6 (33.3)		2.20 [0.60–8.08]
No	10 (47.6)	11 (52.4)		
Chorioamnionitis			0.012	
Yes	11 (84.6)	2 (15.4)		7.50 [1.38–40.88]
No	11 (42.3)	15 (57.7)		
Gestational age at surgery— week	24.6 ± 1.15	24.6 ± 1.18	0.939	1.02 [0.59–1.78]
Duration of surgery—min				
Total	229.7 ± 32.7	229.6 ± 27	0.993	1.0 [0.98–1.02]
Fetal	79 (55–155)	90 (60–140)	0.760	1.0 [0.97–1.03]
Cervical length—mm	34.9 (4.8)	35.2 (6.7)	0.871	0.99 [0.86–1.13]
Length of hospital stay—d	6 (4–17)	6 (4–10)	0.884	1.19 [0.85–1.67]

Values are presented as mean ± SD, median [range], or No. (%)

Maternal complications

Grades 4–5 complications

There were three (7.7%) life-threatening complications requiring intensive care (IC/ICU) management (grade 4 complication). Using the same classification as in other studies, the severe maternal complications were less frequent than those in Winder et al. (12.5%) [16] and approximately as frequent as those in Vonzun et al. (6.4%) [17]. As with other complex surgeries, complications are expected to occur, and patients about to undergo the procedure need to be counseled regarding the risks. Even though these were serious cases requiring intensive care, they did not cause permanent damage to the patients. More importantly, there were no maternal deaths (grade 5 complication).

PTB, PPROM and chorioamnionitis

The most frequent complications related to open fetal surgery for MMC in our study were PTB (76.9%), PPROM (46.2%), and chorioamnionitis (33.3%). Numbers for premature births and for rupture of membranes were very similar

Table 6 Preterm premature rupture of membranes before 34 weeks stratified by risk factor

	With PPROM < 34 weeks ($n=14$)	Without PPROM < 34 weeks ($n=25$)	p value	OR [95% CI]
Maternal age	28.44 ± 6.76	31.14 ± 3.57	0.174	1.09 [0.96–1.24]
Ethnicity			0.739*	
Black	2 (25)	6 (75)		0.44 [0.72–2.74]
Brown	3 (30)	7 (70)		0.57 [0.11–2.84]
White	9 (42.9)	12 (57.1)		1.0
Nulliparity			0.738	
Yes	7 (41.2)	10 (58.8)		1.50 [0.40–5.60]
No	7 (31.8)	15 (68.2)		
Placental position			0.833*	
Anterior	7 (33.3)	14 (66.7)		1.0
Posterior	7 (41.2)	10 (58.8)		1.40 [0.37–5.27]
Lateral	0	1 (100)		Not calculated
Chorioamniotic separation			1.0*	
Yes	0	1 (100)		Not calculated
No	14 (36.8)	24 (63.2)		
Oligohydramnios			0.686*	
Yes	2 (25)	6 (75)		0.53 [0.09–3.05]
No	12 (38.7)	19 (61.3)		
Placental abruption			1.000*	
Yes	1 (50)	1 (50)		1.85 [0.11–32.00]
No	13 (35.1)	24 (64.9)		
Chorioamnionitis			< 0.001*	
Yes	10 (76.9)	3 (23.1)		18.33 [3.44–97.70]
No	4 (15.4)	22 (84.6)		
Gestational age at surgery— week	24.82 ± 1.07	24.43 ± 1.29	0.319	0.74 [0.41–1.33]
Duration of surgery—min				
Total	225.65 ± 28.12	239 ± 33.66	0.247	1.02 [0.99–1.04]
Fetal	85 [60–155]	79.50 [55–140]	0.355	1.01 [0.99–1.04]
Cervical length—mm	36.03 ± 6.60	33.75 ± 3.52	0.286	0.92 [0.79–1.07]
Length of hospital stay—d	6 [6–17]	6 [4–17]	0.814	1.12 [0.87–1.44]

Values are presented as mean ± SD, median [range], or No. (%)

*Fisher's exact test

to those of the MOMS trial (79% and 46%, respectively) [7]; however, the chorioamniotic infection rate was higher. Our overall PTB rate was also similar to that of a study by Peralta et al. [18] (76.4%), but they had nearly half the cases of PTB below 32 weeks (15.6% vs. 30.8%) and lower rates of PPROM (28.3%). Chorioamnionitis was the only risk factor associated with either PPROM or PTB before 34 weeks in our cohort. However, we did not find risk factors associated with chorioamnionitis in our work.

We do not believe perioperative management was the cause of the higher rate of infection because we followed the same protocol of the studies by Botelho et al. [11] and Peralta et al. [18], who did not mention having cases of chorioamnionitis. Furthermore, the protocol of fMMC repair at our institution included antibiotic prophylaxis during surgery and postoperatively for 7 days. One explanation for our higher infection rate is the fact that we considered both the clinical and/or the histological situations as positive cases of chorioamnionitis, while most studies usually take into account only clinically diagnosed cases [7, 19]. Two studies reported their histological and clinical chorioamnionitis cases separately, thus elevating their total infection rate when compared to other studies: 22.2% in Soni et al. [20] and 13% in Vonzun et al. [17]. Nonetheless, it was still lower than ours. We believe that one of the main causes for the higher rate of infection and therefore of PTB in the present work is related to the lower socioeconomic status of the population assisted at our institution. Specific aspects of the population being treated in public hospitals in Brazil, such as low educational levels and bad living conditions,

may have helped increase the infection rate. It could also be hypothesized that prevalence was overestimated since we used strict diagnostic criteria that combined both clinical signs and laboratory tests [21].

Uterine scar dehiscence

The 10.3% rate of uterine scar dehiscence in our cohort was the same as that of the MOMS (10%) [7], but higher than what was seen in the other two mini-hysterotomy studies (5.1% and 3.5%) [11, 18]. We believe that our result may have been overestimated owing to technical difficulties in defining the presence of uterine dehiscence and its degrees. There is no measurable parameter, which makes the evaluation of the hysterotomy site at delivery subjective, therefore dependent on the surgeon's impression. Cases evaluated as dehiscent might have been only cases of thinned scars since none of the patients presented symptoms of dehiscence. None of the four patients exhibiting an area of dehiscence at the hysterotomy site at delivery had undergone previous uterine surgeries and three of them were nulliparous. Johnson et al. [22] also found nulliparous women were at a higher risk for nonintact hysterotomies, but the reason for this is not clear. In addition, there was not enough time to follow-up the patients until novel pregnancies occurred; hence, the present study cannot draw conclusions regarding the effect of the uterine incision on future pregnancies.

Chorioamniotic membrane separation (CMS)

Several studies have shown that CMS is very frequent in patients who undergo open in utero repair of MMC [7, 23]. The study by Johnson and colleagues [22] with the complete MOMS cohort found that CMS was a risk factor for spontaneous rupture of the membranes at any GA. Soni et al. [20] reported higher prevalence of PPROM and earlier GA at delivery in patients with CMS. In the present study, there was only one case of CMS (2.6%), the same number reported by Botelho et al. [11] (one case, 2.6%); a study by Bennet et al. did not mention any cases of membrane separation [24]. These three studies have a technical feature in common, and that is the inclusion of a running suture around the borders of the hysterotomy to better attach the membranes to the myometrium. This could help explain the lower rates of CMS found in the present work and in the other two as argued by Botelho et al. [11]. Consequently, CMS was not considered a risk factor for the occurrence of PPROM and PTB in our cohort.

GA at surgery and PPROM

The study of Soni and colleagues [20] at the Children's Hospital of Philadelphia reported that patients who underwent surgery before 23 weeks were at a higher risk for PPROM. Since that publication, only patients at or over 23 weeks' gestation have been allowed for surgery at that institution. In our population, GA at fetal surgery has not been associated with PPROM, which is in line with the findings of Peralta et al. [18]. However, our median GA at surgery was higher than that of the study by Soni et al. and only two patients underwent surgery before 23 weeks' gestation, thus precluding an analysis of the effects of earlier surgeries on our population. Nevertheless, further discussion of the matter is needed before a decision can be made to change the inclusion criteria.

Fetal complications

The study by Vonzun et al. [17] used the same classification for fetal complications we did and had 2% of deaths. By contrast, our 7.7% rate of perinatal deaths (grade 5 complication), one intrauterine and two neonatal, may seem alarming. However, other studies have reported rates that approximate ours: 5% in Bennet et al. [24] and 5.7% in Soni et al. [20]. Also of note were the 10.3% rate of severe preterm births (grade 4 complication) and the 20.5% rate of very preterm births (grade 3 complication).

Technical aspects

Learning curve

Time and experience are required to achieve competency in complex surgeries [25]. According to a meta-analysis by Joyeux et al. [26], the number of procedures to complete the learning curve (LC) of open fMMC closure varies depending on the surgical technique, with standard hysterotomy having the shortest LC (35 cases), while 57 or more consecutive cases are predicted as necessary to achieve competency in mini-hysterotomy. Such findings place our study within the process of progressive mastering, given that we are reporting the first 39 cases of open fetal MMC surgeries.

A recent publication by Kahr et al. [27] compared outcomes between what they called a training phase and an experienced phase. The training phase comprised the first 11 surgeries they performed with the supervision of an experienced fetal surgeon from the Children's Hospital of Philadelphia. The experienced phase included the 52 subsequent cases. They did not find significant differences in outcomes such as gestational age at delivery, occurrence of CMS and placental abruption between the two phases,

which they attributed to an already high standard of surgical performance since the beginning due to the presence of the mentioned expert in the first phase. But they did find that minor complications such as oligohydramnios and subchorionic hematoma were less common in the experienced phase, thus showing a trend towards better quality of uterine closure with gain of experience.

Duration of surgery

Most European and American maternal–fetal specialists perform open in utero repair of myelomeningocele with 6-to-8-cm-long uterine incisions made with a stapling device [7, 19]. With staplers, the uterine incision is completed at the same time as the chorioamniotic membranes are attached to the myometrium and hemostasis is accomplished. Brazilian fetal surgeons more commonly perform hysterotomy and hemostasis of the uterine wall in open surgeries with alternative techniques not involving the use of staplers [10, 11, 18]. Manual and smaller hysterotomies seem to extend the duration of the procedure because the incision is harder to perform manually and manipulation of the lesion during surgery is more difficult within a smaller surgical field. In the present study, it was deemed important to adhere rigorously to the surgical technique described by Botelho et al. [11] in all cases. However, in future cases, we may choose to have larger hysterotomies to facilitate surgical repair and reduce duration of surgery.

Moldenhauer et al., using the classic technique, had a mean total operative time of 1.31 h [8]. With a smaller (4–6 cm) but manual uterine incision, Moron et al. [11] took 2 h on average to complete the procedure. Botelho et al. [11] with the mini-hysterotomy technique took an even longer time to finish surgery (3.44 h). Although their operative time was longer than that reported by Moldenhauer and colleagues, Botelho et al. had a similar surgery-to-delivery interval, lower rates of CMS and PPROM, and a higher rate of deliveries after 34 weeks. Our total operative time was 3.83 h, longer than what was reported by Botelho and colleagues; however, duration of surgery was neither associated with PPROM nor with PTB before 34 weeks in our cohort. A subsequent study with the same MOMS population by Johnson et al. [22] found that surgical duration was not associated with either CMS, PPROM, or PTB under 34 weeks in the multivariable logistic regression analysis, even though there was an association of longer surgical time with PPROM and PTB before 34 weeks in the univariable analysis of risk factors. These findings suggest that surgical duration has no influence on the main complications of open fetal surgery for MMC, such as CMS, PPROM, and PTB.

Type of lesion

Although myeloschises accounted for only a quarter of the total fetal lesions, they posed a greater challenge at primary fetal skin closure than MMC. In several studies mentioning difficulties achieving primary fetal skin closure, attempts were made with different techniques to overcome them [28–30]. A myeloschisis is a flat lesion without enough loose skin around the borders, thus causing greater tension in the suture line and making it more difficult to approximate the borders. In our work, we used skin relief incisions on one or both sides of the defect or a collagen patch over the lesion. All eight cases of skin relaxing incisions closed a few weeks after birth and did not require interventions. Cases in which a collagen patch is used often appear incompletely epithelialized at birth, but complete covering of the patch occurs within a few weeks. Inexperience with such an appearance can lead to unnecessary interventions. For example, the first of the four patients in whom we used a collagen patch underwent a skin flap after birth. However, there was no sign of dehiscence and later the team agreed that the skin flap procedure had been unnecessary because the skin would have covered the patch in a few weeks.

Conclusion

This study presents the results of the first cases of fetal myelomeningocele surgery performed with an open technique at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, a Brazilian teaching hospital dedicated solely to public health service. A few complication rates were comparable to those of the MOMS and to other studies that followed. However, there were higher-than-expected rates of undesired outcomes. Improvements in our surgical and perinatal results will require completion of the learning curve, adjustments to the perioperative procedures (e.g., increase in hysterotomy size), revision of the definition and management of chorioamnionitis, and analysis in future publications of the long-term follow-up of children who underwent the procedure. Such measures will help determine the real benefit of open in utero repair of myelomeningocele at our center. In addition, the use of a standard classification of maternal–fetal complications, such as the Clavien–Dindo system, may render studies more comparable and may help with the process of prenatal counseling, so important in centers offering fetal myelomeningocele repair.

Authors' contributions LSNR—Data collection, Data analysis, Manuscript writing. VB—Protocol development, Manuscript editing, Participation in surgeries. AGAF—Protocol development, Manuscript editing, Participation in surgeries. DDC—Participation in surgeries. HM—Participation in surgeries. HSF—Participation in

surgeries. FSN—Participation in surgeries. RPVF—Manuscript editing. MHBC—Protocol development, Data analysis, Manuscript editing, Participation in surgeries.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval/Consent to participate All subjects gave their written informed consent to participate and the study protocol was approved by the hospital's research ethics committee (CAAE 93020218.7.0000.0068).

Consent for publication All subjects gave their informed consent for publication of information related to the findings of the study.

Availability of data and material Data are available.

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