Open Intrauterine Fetal Myelomeningocele Repair: Changes in the Surgical Procedure and Perinatal Complications during the First 8 Years of Experience at a Single Center

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Abstract: INTRODUCTION Open fetal myelomeningocele (fMMC) repair is nowadays a therapeutic option in selected cases. We aimed to evaluate changes in maternal and fetal outcome after fMMC repair during the first 8 years of experience at a tertiary referral fetal medicine center in Switzerland. -Materials and Methods: Between 2010 and 2018, fMMC repair and delivery of the neonate via planned cesarean section was performed in 67 cases. Cases were retrospectively stratified into 2 groups: a "training phase" (TP) with supervision from an external surgeon during 11 operations (2010-2014, 15 cases) followed by an "experienced phase" (EP, 2014-2018, 52 cases); each phase lasted about 4 years. Both phases were compared with regard to various maternal and fetal outcome parameters. RESULTS Analyses did not reveal differences between TP and EP in major outcome parameters such as gestational age at delivery, chorionic membrane separation, or the incidence of placental abruption. Although more complex surgical techniques were applied in EP (e.g., dermal closure using a rotational flap), surgery time was not different from TP. At the same time, surgical complications such as oligohydramnios (27 vs. 8%, p = 0.046) with MRI-confirmed leakage (13 vs. 4%, nonsignificant) and subchorionic hematoma (20 vs. 2%, p = 0.009) were less common in EP than TP. CONCLUSIONS This study shows that the level of competence at our center with regard to major perinatal outcome parameters was already high in the first years of fMMC repair. However, more complex surgical techniques and significantly less minor complications were observed during the most recent years.

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Open Intrauterine Fetal Myelomeningocele Repair: Changes in the Surgical Procedure and Perinatal Complications during the First 8 Years of Experience at a Single Center

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Congenital malformations · Fetal surgery · Intrauterine surgery · Myelomeningocele · Spina bifida

Abstract
Introduction: Open fetal myelomeningocele (fMMC) repair is nowadays a therapeutic option in selected cases. We aimed to evaluate changes in maternal and fetal outcome after fMMC repair during the first 8 years of experience at a tertiary referral fetal medicine center in Switzerland. ***Materials and Methods:*** Between 2010 and 2018, fMMC repair and delivery of the neonate via planned cesarean section was performed in 67 cases. Cases were retrospectively stratified into 2 groups: a "training phase" (TP) with supervision from an external surgeon during 11 operations (2010–2014, 15 cases) followed by an "experienced phase" (EP, 2014–2018, 52 cases); each phase lasted about 4 years. Both phases were compared with regard to various maternal and fetal outcome parameters. ***Results:*** Analyses did not reveal differences between TP and EP in major outcome parameters such as gestational age at delivery, chorionic membrane separation, or the incidence of placental abruption. Although more complex surgical techniques were applied in EP (e.g., dermal closure using a rotational flap), surgery time was not different from TP. At the same time, surgical complications such as oligohydramnios (27 vs. 8%, $p = 0.046$) with MRI-confirmed leakage (13 vs. 4%, nonsignificant) and subchorionic hematoma (20 vs. 2%, $p = 0.009$) were less common in EP than TP. ***Conclusions:*** This study shows that the level of competence at our center with regard to major perinatal outcome parameters was already high in the first years of fMMC repair. However, more complex surgical techniques and significantly less minor complications were observed during the most recent years.

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Introduction

Open in utero treatment of myelomeningocele (MMC) has become an optional treatment in large fetal surgery centers worldwide. The Management of Myelomeningocele study (MOMS) has shown the benefits of open fetal MMC (fMMC) repair versus standard postnatal MMC repair for qualifying cases [1]. In the "post-MOMS era," centers have been working on surgical optimization as well as improved perioperative management with the aim to overcome associated perinatal complications and risk factors [2–5].

Various studies have shown an association of intrauterine surgery with obstetrical complications such as chorioamniotic membrane separation (CMS), oligohydramnios, preterm premature rupture of membranes (PPROM), and subsequent preterm birth with its well-known sequelae for the premature neonate [2, 6–9].

This study aimed to compare outcome parameters in 2 phases of surgery as well as obstetrical experience at the Zurich Center for Fetal Diagnosis and Therapy between 2010 and 2018.

Materials and Methods

Patient Population

In the study interval from 12/2010 to 02/2018, a total of 67 patients underwent fMMC repair and were delivered via cesarean section. Indication for fMMC repair was based on MOMS enrollment criteria [1]. All patients undergoing fMMC repair were included in this study, and data collection was performed prospectively.

The protocol of patient admission and surgery preparation at our center required a timely on-ward administration of the gravidae for fetal neuroprotection and lung maturation in fetuses ≥24 weeks of gestational age (GA) before the actual fMMC repair. A postoperative MRI was conducted about 2 weeks after surgery to identify potential unfavorable fMMC repair complications. With regard to the analysis presented here, the following maternal aspects were evaluated: surgical hematomas and seromas, amniotic fluid leakage from the uterotomy, and CMS [10]. Amniotic fluid leakage on MRI was defined as a continuous fluid signal through the myometrium.

Once clinically stable after fMMC repair, patients were discharged into the ambulatory setting, including weekly follow-up exams (ultrasound exam and CTG). Fetuses were delivered via elective cesarean section ideally at 37 weeks GA. Delivery was planned in uncomplicated cases via elective cesarean section at 37 weeks GA. Cesarean section was preponed in cases of chorioamnionitis, placental abruption, and in cases of premature labor or in any other existent indication for immediate delivery.

Definition of "Training Phase" and "Experienced Phase"

While all surgeons involved had long-standing experience in postnatal MMC repair prior to starting fMMC repair, the initial 11 fMMC cases were supervised by an external surgeon from the Children's Hospital of Philadelphia. Prior to fMMC repair, the local obstetrical experience in periprocedural management of fetal interventions was mainly based on placenta laser surgery in cases of twin-to-twin transfusion syndrome, along with the long-standing experience in managing preterm gravidae. The most significant change in obstetrical management during the study period concerned a change from magnesium sulfate to atosiban for peri-/postoperative tocolysis after the occurrence of a third-degree atrioventricular block (case 15). At the same time, about 4 years after the first repair at our center, the frequency of fMMC repair increased considerably for various reasons (e.g., higher rate of international referral). Reflecting on these aspects, we retrospectively defined the first 4 years of fMMC repair at our center as the "training phase" (TP, up to case 15). The most recent 4 years, including 52 cases, were defined as "experienced phase" (EP).

Statistical Analysis

We evaluated patient characteristics, pregnancy outcomes, and complications during TP and EP at our center. Demographic and clinical variables for each phase were included: maternal age, fetal gender, GA at surgery, race/ethnicity, BMI, smoking status, parity, previous uterine surgeries, placenta location, height of fetal lesion, and fetal club feet. Further pregnancy complications and outcomes were stratified by TP and EP: subchorionic hematoma, subcutaneous seroma, pulmonary edema, preeclampsia/gestational hypertension, oligohydramnios, MRI-confirmed amniotic fluid leakage from uterotomy, CMS, GA at CMS, placental abruption, gestational diabetes, PPROM, GA at PPROM, uterine rupture, pulmonary embolism, perinatal death, preterm labor, GA at birth, birth weight, APGAR score, umbilical artery pH, and duration of surgery (total and uterine). Data processing and statistical analyses were performed with SPSS (version 25; IBM, USA).

Data were stratified by TP and EP and presented as medians (interquartile ranges, IQR) or *n* (%). The χ^2 test and Fisher's exact test were applied as applicable for the comparison of nominal variables. Since all continuous variables did not match the criteria required for normal distribution based on the Shapiro-Wilkinson test, the Mann-Whitney U test was used to compare groups. A p value <0.05 was accepted as significant.

Results

Presurgical Parameters

Table 1 provides an overview of the demographics and important clinical variables of the patient population. Except for a later timing of surgery in EP versus TP (GA at the time of surgery 24.1 [23.7–24.7] vs. 25.3 [24.6–25.6] weeks in TP and EP, respectively), demographic parameters and general clinical variables did not differ between both phases. Maternal age, fetal gender, race/ethnicity, BMI, smoking status, parity, previous uterine surgeries, placenta location, fetal lesion height, and fetal club feet were not different between groups.

Table 1. Demographic and clinical variables

	Training phase (n = 15)	Experienced phase (n = 52)	p value
Maternal age, years	29 [26–33]	32 [26–35]	0.327
Fetal gender female	9 (60%)	28 (54%)	0.673
Gestational age at surgery, weeks	24.1 [23.7–24.7]	25.3 [24.6–25.6]	**0.001**
Race/ethnicity			0.192
White	13 (86.7%)	50 (96.2%)	
African American	1 (6.7%)	0 (0%)	
Hispanic	1 (6.7%)	1 (1.9%)	
Others	0 (0%)	1 (1.9%)	
Maternal BMI, kg/m^2	25.4 [22.7–28.4]	26.1 [23.1–30.6]	0.775
Current smokers	0 (0%)	1 (1.9%)	0.776
Primipara	9 (60%)	20 (38.5%)	0.138
Previous uterine surgeries	1 (6.7%)	7 (13.5%)	0.423
Anterior placenta	8 (53.3%)	25 (48.1%)	0.474
Fetal lesion ≤L3	13 (86.7%)	39 (75%)	0.490
Fetal club foot	1 (6.7%)	9 (17.3%)	0.436

Data are presented as n (%) or medians [interquartile ranges].

Table 2. Surgical details

	Training phase (n = 15)	Experienced phase (n = 52)	p value
Fetal dura closure	9 (60%)	50 (96.2%)	**0.003**
Fetal skin closure	11 (73.3%)	49 (94.2%)	**0.020**
Skin rotation flap	0 (0%)	12 (23.1%)	**0.040**
Fetal myofascial flap	11 (73.3%)	48 (92.3%)	0.093
Patches	4 (26.7%)	23 (45.1%)	0.202
Total surgery time, min	123 [110–137]	141 [124–165]	**0.014**
Fetal surgery time, min	37 [30–48]	42 [33–53]	0.132

Data are presented as n (%) or medians [interquartile ranges].

Surgical Procedure

The total surgery time was significantly shorter in TP than EP (123 [110–137] vs. 141 [124–165] min; p = 0.014; Table 2), while we did not observe a difference in fetal surgery time between TP and EP (37 [30–48] vs. 42 [33–53] min; nonsignificant). The placenta location did not have an impact on the operation time (137 min [125–163] and 135 min [120–155] for anterior placenta localization, p = 0.319). Fetal dura closure (60.0 vs. 96.2%, p = 0.003), fetal skin closure (73.3 vs. 94.2%, p = 0.020), and skin rotation flaps (0 vs. 23.1% [n = 12], p = 0.040) were significantly more commonly applied in EP cases than in the initial 15 TP patients (Fig. 1a). At the same time, no difference in the incidence of fetal myofascial flaps and patches was noted (Table 2).

Postsurgical Complications and Perinatal Outcome

Major surgical and pregnancy complications and perinatal outcomes are summarized in Table 3. We found statistically significant differences in hematoma and oligohydramnios incidence rates in TP and EP. In the TP group, 3 women developed a subchorionic hematoma (20%) compared to only 1 case in the EP group (1.9%, p = 0.009; Fig. 1b). Similarly, there were significantly more cases of oligohydramnios during TP than EP (26.7 vs. 7.7%, p = 0.046; Fig. 1c). The incidence of MRI-confirmed amniotic fluid leakage in the presence of oligohydramnios demonstrated a nonsignificant trend towards a lower frequency in EP than TP (13.3 vs. 3.8%, nonsignificant). While there was 1 perinatal death (case 2, postnatal death after cesarean section at 37 weeks GA with un-

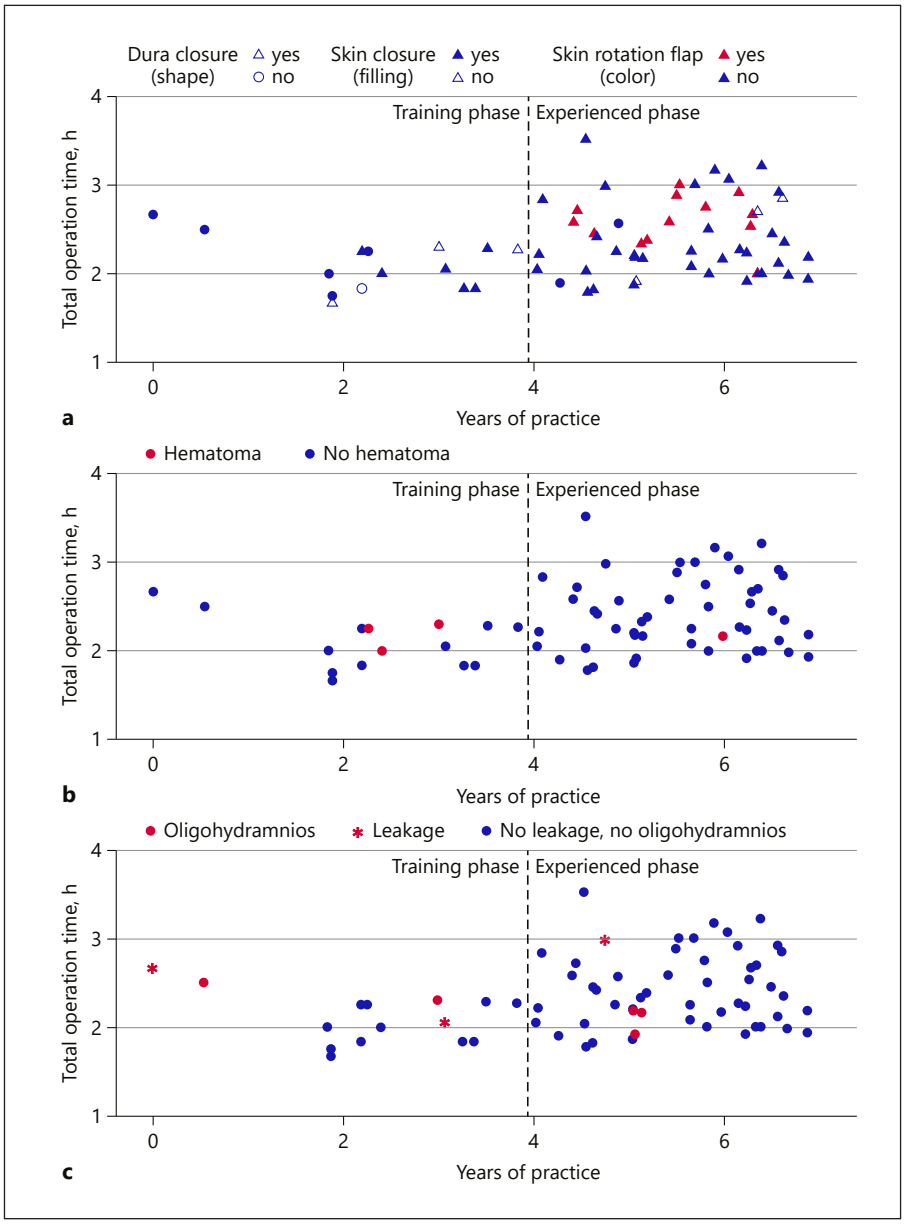

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Fig. 1. Complications after open fetal myelomeningocele repair by years of practice in 67 patients. During the training phase, 15 patients were treated (equivalent to 4 years). Each dot represents 1 case. **a** While total operation time increased, and fetal operation time did not differ between both phases, fetal defect closure by dura closure, skin closure, and skin rotation flaps was significantly more common in the experienced phase. **b** Surgical hematomas (red dots) were more commonly encountered in the learning phase (20 vs. 2%, $p = 0.009$). **c** Oligohydramnios (red dots) were significantly more common in the training phase (27 vs. 8% of cases, $p < 0.045$). This is in line with a tendency to a higher prevalence of MRI-confirmed leakage of amniotic fluid (asterisk) in the learning phase (13 vs. 4%, nonsignificant).

clear etiology) in TP, EP was mortality free (p = 0.065). We did not observe a difference in GA at delivery between groups (36.1 [34.9–37.1] vs. 36.3 [34.6–37.0] weeks, $p = 0.556$), but a nonsignificant trend towards a lower rate of premature labor in EP (66.7 vs. 40.4%, $p = 0.072$).

Discussion

Main Findings

The underlying study enrolled the initial 67 patients undergoing fMMC repair in Zurich, Switzerland. Overall, main outcome parameters such as GA, PPROM, CMS, or placental abruption did not differ between the initial TP and the following EP. However, with more experience, other surgical complications, such as surgical hematomas and oligohydramnios, became significantly fewer. While the duration of fetal surgery was not different between both phases, the complexity of fMMC closure techniques increased. Of note, our main outcome parameters are comparable with those of the MOMS and post-MOMS reports by other renowned institutes [2, 7, 11].

Table 3. Pregnancy complications and outcomes

	Training phase (n = 15)	Experienced phase (n = 52)	p value
Direct/indirect surgical complications			
Subchorionic hematoma	3 (20%)	1 (1.9%)	**0.009**
Subcutaneous seroma	4 (26.7%)	16 (30.8%)	0.760
Uterine rupture	0 (0%)	1 (1.9%)	0.588
Oligohydramnios	4 (26.7%)	4 (7.7%)	**0.046**
With MRI-confirmed amniotic fluid leakage	2 (13.3%)	2 (3.8%)	0.172
Chorioamniotic membrane separation	3 (20.0%)	9 (17.3%)	0.811
PPROM	5 (33.3%)	14 (26.9%)	0.628
Gestational age at PPROM, weeks	34.9 [33.3; 35.3]	32.5 [30.5; 35.0]	0.151
Preterm labor	10 (66.7%)	21 (40.4%)	0.072
Placental abruption	0 (0%)	8 (15.4%)	0.105
Pulmonary edema	0 (0%)	2 (3.8%)	0.441
Pulmonary embolism	0 (0%)	1 (1.9%)	0.588
Prenatal death	1 (6.7%)	0 (0%)	0.061
Miscellaneous pregnancy complications			
Preeclampsia/gestational hypertension	0 (0%)	2 (3.8%)	0.441
Gestational diabetes	3 (20.0%)	15 (28.8%)	0.496
Perinatal outcome parameters			
Gestational age at birth, weeks	36.1 [34.9; 37.1]	36.3 [34.6; 37.0]	0.556
Gestational age at birth			
≤34 0/7 weeks	2 (13.3%)	9 (17.3%)	0.714
≥37 0/7 weeks	6 (40.0%)	18 (34.6%)	0.702
Birth weight, g	2,860 [2,300; 2,950]	2,690 [2,405; 2,869]	0.250
5-min Apgar score	8 [8; 9]	9 [8; 9]	0.074
Umbilical artery pH	7.3 [7.3; 7.4]	7.3 [7.3; 7.4]	0.311

Data are presented as n (%) or medians [interquartile ranges]. PPROM, preterm premature rupture of membranes.

Interpretations

GA at delivery was comparable to previous studies as 34% of our women reached GA ≥37 weeks (21% in MOMS and 27% in the post-MOMS period at the Children's Hospital of Philadelphia) [1, 2], while the median GA at birth was not significantly higher in EP than TP. PPROM rates did not significantly decline in EP (33.3 vs. 26.9%, nonsignificant), but the overall PPROM percentage of 28.4% of gravidae in our cohort is rather low compared to PPROM rates in the MOMS cohort (46%, [1]) or in the post-MOMS cohorts (lowest PPROM rate of 26.7%, which was reported by Moron et al. [2, 4, 7, 12]), but comparable to PPROM rates in fetoscopic laser coagulation for twin-to-twin transfusion syndrome [13]. Overall 18% of our women (20% in TP vs. 17.3% in the EP) exhibited CMS (versus 26% in MOMS and 21–23% in post-MOMS women [1, 2, 12]), and the incidence was not reduced with more operative and postoperative experience. Of note, the CMS incidence after fetoscopy in monochorionic twin pregnancy widely ranges from 7 to around 21%, as previous studies have shown [14, 15].

Surprisingly, total surgery time was longer with more experience (Table 2; Fig. 1). Interestingly, fetal operation time was not significantly different between TP and EP although the type of fetal defect closure became more complex over time (i.e., more time-consuming skin rotation flaps were introduced in EP).

Strengths and Limitations

This study represents one of the largest European case series of open fMMC repair, not only providing this type of surgical intervention to Swiss women, but also to women from a variety of other European countries. The initial 11 open fMMC repairs were performed under the supervision of an external surgeon from an experienced hospital in the USA aiming at a high-quality surgical procedure from the first case on and further seeking adequate training of our permanent multidisciplinary team. We assume

that this strategy led to the sound results from the beginning of fMMC surgery.

Further, a tight follow-up after surgery, return to our institution for delivery, and subsequent neonatal treatment, as well as subsequent pregnancy counseling is a strength of our setting. Pregnancy complications and outcomes were comparable to prior studies, including those with a higher case load [2, 7, 12]. A limitation of this study was the number of women (n = 67) that were enrolled during the study period, as this generally limits the power of statistical analyses. Moreover, studies examining the learning curve for fetoscopic laser surgery revealed that at least 60 procedures are required to improve the overall outcome [13, 16].

Conclusion

In summary, we attribute the rather similar outcomes of TP and EP to an already high standard of surgical performance from the beginning on due to the support by the Children's Hospital of Philadelphia. However, the reduction in surgical subchorionic hematomas and oligohydramnios did show a trend towards better quality of uterine closure with more experience. Further, more complex fetal defect closure techniques in EP did not prolong the fetal surgery time. Women opting for open fMMC repair should be counseled regarding the risks emanating from this surgical procedure, which persist despite increasing intra- and perioperative experience worldwide.

Statement of Ethics

The study was approved by the local ethics committee (KEK 2015-0172), and written informed consent was given by all participants.

Disclosure Statement

The authors declare no conflicts of interest.

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