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Maternal Complications following Open Fetal Myelomeningocele Repair at the Zurich Center for Fetal Diagnosis and Therapy

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Fetal surgery · Maternal complications · Neural tube defect · Intrauterine surgery · Myelomeningocele · Clavien-Dindo classification

Abstract
Introduction: Despite undoubtable benefits of open fetal myelomeningocele (fMMC) repair, there are considerable maternal risks. The aim of this study was to evaluate and systematically categorize maternal complications after open fMMC repair. ***Methods:*** We analyzed data of 40 fMMC repairs performed at the Zurich Center for Fetal Diagnosis and Therapy. Maternal complications were classified according to a 5-level grading system based on a classification of surgical complications proposed by Clavien and Dindo. ***Results:*** We observed no grade 5 complication (death of a patient). Five (12.5%) women demonstrated severe grade 4 complications: 1 case of uterine rupture in a nullipara at 36 gestational weeks (GW), a third-degree atrioventricular block which needed short mechanical resuscitation, a bilateral lung embolism requiring intensive care unit (ICU) management due to low-output syndrome, and chorioamnionitis and urosepsis both requiring ICU management at 31 GW. Twenty-six (65%) women had minor (grade 1–3) complications. ***Conclusions:*** Only one grade 4 complication (uterine rupture, 2.5%) was a clear-cut direct consequence of fetal surgery. The other four grade 4 complications (10%) occurred in the context of, but cannot unequivocally be attributed to, fetal surgery, since they may occur also in other circumstances. The classification system used is a tenable step towards stringent documentation of maternal complications.

Introduction

Spina bifida aperta is one of the most severe congenital anomalies. A large prospective, randomized study, the Management of Myelomeningocele Study (MOMS trial), has demonstrated that prenatal surgery for fetal myelomeningocele (fMMC) improved neurofunctional outcomes, including the ability to walk at 30 months of age, and decreased the need for postnatal placement of a ven-

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triculoperitoneal shunt. Therefore, fMMC repair has become a therapeutic option for selected candidates [1, 2].

In order to reduce maternal morbidity by avoiding hysterotomy, there have been several attempts towards a fetoscopic and therefore minimally invasive approach. Although this strategy theoretically offers the potential of decreased maternal complications, there are still challenges associated with fetoscopic fMMC repair, including unsolved trocar entry site issues, inadequate surgical closure of the spina bifida lesion, and unacceptable prematurity rates [1, 3, 4].

Compared to postnatal repair, open fetal surgery and subsequent delivery by cesarean section pose considerable maternal risks to the otherwise unaffected mother. The objective of the present study was to describe, evaluate, and categorize maternal complications after fMMC repair.

Methods

In this prospective nonrandomized cohort study, we evaluated 40 prenatal fMMC repair cases performed consecutively between December 2010 and July 2016 at the Zurich Center for Fetal Diagnosis and Therapy (www.swissfetus.ch) for maternal complications. We collected data on maternal demographics, prenatal diagnostic criteria, fetal surgery, delivery, and neonatal as well as maternal outcomes. The Ethics Committee of the Canton of Zurich approved the study (KEK-ZH.Nr. 2015-0172).

The key inclusion criteria for this study were a singleton pregnancy, MMC with the upper level located between T1 and S1, evidence of hindbrain herniation, a gestational age (GA) of 19–25.9 weeks, a normal karyotype, and maternal age of at least 18 years. These criteria are consistent with the MOMS trial protocol published in *The New England Journal of Medicine* in 2011 [5], except for US residency and body mass index (BMI; MOMS trial <35 kg/m^2). Major exclusion criteria were additional severe fetal malformations unrelated to MMC, severe kyphosis of >30°, short cervix, previous preterm birth, placenta praevia, former placental abruption, maternal HIV or hepatitis B/C positivity, uterine abnormality (large or multiple fibroids), previous hysterotomy in the active uterine segment, or any other contraindication for major surgery. Data on excluded cases are published separately [6].

We evaluated women carrying a fetus with fMMC referred to our center in a standardized way by sonography and fetal magnetic resonance imaging (MRI) prior to comprehensive prenatal counseling. In case the patient qualified for fMMC repair, written informed consent was obtained, and the fetal operation was scheduled to occur between 22 and 26 gestational weeks (GW).

The fMMC repair was performed by fetal surgeons according to standardized operative techniques and perioperative management as reported in the MOMS trial [5]. After fMMC repair, all women were monitored in an intensive care unit (ICU) for 2 days. Analgesic management included an epidural analgesia for 3–5 days, paracetamol, and tramadol. During ICU surveillance, uterine contractions were continuously registered by tocography, and fetal heart rate was checked by Doppler fetal monitor (<24 GW) or cardiotocography (≥24 GW) 3 times per day. We performed ultrasonography at least twice a day. After transfer to our prenatal unit, contractions were monitored by tocography (<24 GW) or cardiotocography (≥24 GW) twice a day. Postoperatively, tocolysis was maintained with intravenous magnesium sulfate in the first 15 cases. Thereafter, we used atosiban (Tractocile, infusion of 37.5 mg/5 mL; Ferring AG), and, if necessary, hexoprenaline infusion (Gynipral, infusion of 10 μg/2 mL; Takeda Pharma AG) with transition to oral nifedipine (Adalat CR, retard tablets of 60 mg; Bayer AG). The more detailed protocol was previously described by Ochsenbein-Kölble et al. [7]. In case a patient remained stable without complication for 2–4 weeks, we managed the patient on an outpatient basis with weekly ultrasound and clinical evaluation until rehospitalization at 34 GW for closer observation and elective cesarean delivery at 37 GW.

As primary outcome, we evaluated the maternal complications during and after fMMC repair with classification according to a 5-level severity grading based on a therapy-oriented classification of surgical complications by Dindo et al. [8] (Clavien-Dindo classification). Grade 1 indicates minor complications defined as events not requiring any pharmacological treatment or surgical intervention (with exception of analgesic, antipyretic, and antiemetic drugs). Grade 2 complications call for pharmacological treatment other than allowed for grade 1, and grade 3 complications require surgical intervention. Grade 4 complications are major events which are life-threatening and require IC/ICU management. Grade 5 is death of the patient [8].

We performed statistical analysis using the statistical software package SPSS version 22.0 (IBM, SPSS Inc., USA). Quantitative data are presented as means ± standard deviations or medians with minimum and maximum values. The results of categorical variables are provided as percentages.

Results

Maternal and gestational characteristics are presented in Table 1. The maternal BMI before surgery ranged from 20.0 to 41.3 with an average of 27.2. Three women had previous cesarean sections. Thirty-nine of the 40 patients delivered at the University Hospital of Zurich. The average GA at delivery was 35.5 ± 2.3 GW; 2.5% delivered at <30 GW, and 35% delivered at 37 GW or more. The average birthweight was 2,631.5 ± 535 g. The mean GA at the time of fMMC repair was 24.7 ± 0.84 GW. The total operative time from maternal skin incision to closure was on average 139.1 ± 24.1 min.

We observed 5 (12.5%) women with severe grade 4 complications (Table 2). One woman demonstrated a uterine rupture. She was a nullipara who presented with abdominal pain at 36.9 GW and had never been operated on her uterus before except for the fMMC repair. Caesarean section was promptly performed and revealed a rupture of the previous hysterotomy site which could be excised and sutured without any difficulty. The postoperative course was uneventful.

Table 1. Study group characteristics (40 patients)

Maternal age, years	29.9±4.9
Nulliparous	21 (52.2)
Race/ethnicity	
White	37 (92.5)
Black	1 (2.5)
Hispanic	1 (2.5)
Other	1 (2.5)
Body mass index	27.2±5.4
Currently smoking	0
Previous uterine surgeries, including cesarean	3 (7.5)
Gestational age at fetal surgery, weeks	24.7±0.84
Gestational age at birth, weeks	35.5±2.3
Gestational age at birth	
<30 weeks	1 (2.5)
30 weeks 0 days to 34 weeks 6 days	10 (25)
35 weeks 0 days to 36 weeks 6 days	15 (37.5)
≥37 weeks	14 (35)
Fetal birthweight, g	2,631.5±535

Values are means ± standard deviations or *n* (%).

Table 2. Operative/pregnancy complications (40 patients)

Grade 1 – minor complications not requiring any pharmacological treatment or surgical intervention (with exception of analgesic, antipyretic, and antiemetic drugs)	
Chorioamniotic membrane separation	12 (30)
Seroma	10 (25)
Gestational diabetes (nutritional therapy)	6 (15)
Amniotic fluid leakage	4 (10)
Hematoma	3 (7.5)
Wound dehiscence (skin)	2 (5)
Symptomatic cholecystolithiasis (analgesics only)	1 (2.5)
Grade 2 – complications requiring pharmacological treatment	
PPROM	14 (35)
Gestational diabetes (pharmacological therapy)	2 (5)
Cholestasis of pregnancy	1 (2.5)
Pulmonary edema (no intubation)	0
Blood transfusion	0
Grade 3 – complications requiring surgical intervention	
Placental abruption	4 (10)
Seroma (requiring surgical intervention)	2 (5)
Symptomatic cholecystolithiasis (requiring surgical intervention)	1 (2.5)
Incisional hernia	1 (2.5)
Preeclampsia	1 (2.5)
Chorioamnionitis (not requiring IC/ICU management)	1 (2.5)
Major bleeding (extragenital)	1 (2.5)
Bartholin's cyst	1 (2.5)
Grade 4 – life-threatening complications requiring IC/ICU management	
Chorioamnionitis	1 (2.5)
Third-degree AV block with mechanical reanimation	1 (2.5)
Uterine rupture	1 (2.5)
Lung embolism	1 (2.5)
Urosepsis	1 (2.5)
Pulmonary edema (with intubation)	0
Grade 5 – death	
Maternal death	0

Values are *n* (%). PPROM, preterm premature rupture of membranes; ICU, intensive care unit; AV, atrioventricular.

Another patient presented with bilateral central lung embolism on the second day after fMMC repair requiring ICU management due to low-output syndrome. The patient recovered with anticoagulation treatment without the need for mechanical ventilation, and the remainder of the pregnancy was without complications. No thrombosis in the lower part of the body was found as a source of the embolism, and a hereditary thrombophilia was excluded after pregnancy.

One patient exhibited a third-degree atrioventricular (AV) block 11 h after fMMC repair, which needed short mechanical resuscitation. Magnesium sulfate infusion – as tocolytic agent prescribed by the former protocol (MOMS) – was suspected as the etiology of the heart block, and once magnesium sulfate was stopped, the patient had no further episodes of an AV block. After pregnancy, the cardiac checkup showed no pathologies and no signs of long-term consequences resulting from the resuscitation.

One woman had to be transferred to the ICU for observation because she suffered from severe urosepsis. From the beginning of the pregnancy, she had received several times antibiotics due to recurrent urinary infections. In her 31st GW, she presented with temperatures up to 39.1 °C, symptoms of shock, and positive urine and blood cultures. Intravenous antibiotics and ICU management led to a full recovery of the patient without any consequences for the pregnancy.

Finally, 1 woman was diagnosed with severe and potentially life-threatening chorioamnionitis at 31 GW. Following emergency caesarian section, she required ICU management without any long-term consequences for her and her child.

A total of 26 women (65%) had at least 1, but often more than 1, minor (grade 1–3) complication (Table 2). More than half of these complications are categorized as a direct consequence of fMMC repair, including 15 cases (37.5%) with a hematoma/seroma at the abdominal incision and 14 cases (35%) with preterm premature rupture of membranes (PPROM). In 2 (5%) cases, fine-needle as-

piration of a seroma was necessary (grade 3 complications). One woman (2.5%) presented with a hernia at the maternal incision site after a T-incision of the fascia 3 years after repair. She will require surgery to repair this hernia.

We saw 4 (10%) placental abruptions (one during fMMC repair and the others between 31 and 36 GW) in which an emergency caesarian section was performed. Blood loss was <1,000 mL in all cases, and the women did not need an IC/ICU management. Therefore, these complications were classified as grade 3. We further documented 1 woman with significant extragenital bleeding after an endoscopic retrograde cholangiopancreatography (at 31 GW) and 1 woman with preeclampsia (at 35 GW), leading to an earlier than planned caesarian section (grade 3).

By postoperative ultrasound and/or MRI, we detected 12 (30%) cases with chorioamniotic membrane separation and 3 (7.5%) cases with amniotic fluid leakage both classified as grade 1 since there was no specific treatment needed. Between fMMC repair and delivery, we observed minor complications not directly linked to fetal surgery, including gestational diabetes and cholestasis.

The average BMI of our 40 patients was 27.2. Four women had a BMI of >35. The women with the highest BMI (41.3) in our study had three grade 3 complications (symptomatic cholecystolithiasis, endoscopic retrograde cholangiopancreatography with major bleeding, and seroma requiring surgical intervention). Two of the 4 patients had a gestational diabetes (grade 1 and 2), and 1 of them additionally developed PPROM (grade 2). The forth women suffered from symptomatic cholecystolithiasis not requiring surgical intervention (grade 1).

There were no grade 5 complications. No patient suffered from pulmonary edema (grade 4), and no patient required blood transfusions (grade 2). Finally, we have not observed any significant maternal long-term consequences of fMMC repair.

Discussion

This is a study looking at maternal complications in the context of open maternal fetal surgery for spina bifida. In order to obtain a structured global picture over all recorded complications, the Clavien-Dindo classification was applied to categorize complications into well-defined severity grades.

Overall, complications were identified in 31 out of 40 women analyzed (78%). Generally speaking, mild complications were much more frequent than severe complications, while, fortunately, fatal complications were absent. A number of aspects deserve a detailed comment.

First, and most importantly, we did not observe maternal death (complication grade 5) which would, doubtlessly, be the worst catastrophe to be experienced in a fetal surgery program. This still holds true up to date with actually 70 cases operated. In the literature, as well, no maternal death as a direct consequence of fetal surgery has been reported.

Yet, severe maternal complications (grade 4) occurred in 5 (12.5%) patients. The 1 case with uterine rupture (2.5%) is definitely a direct consequence of fetal surgery. The other 4 (10%) cases (lung embolism, AV block, urosepsis, and chorioamnionitis) were possibly, and maybe even likely, caused by fetal surgery; however, they may also occur as pregnancy complications without there being a previous prenatal intervention [9–11].

One patient presented with a uterine rupture very late in gestation, which was fixed during emergency caesarean section without any further problems. Johnson et al. [12] reported on 2 out of 88 patients (2.3%) showing complete dehiscence of the hysterotomy. Of note, we documented a higher number of nulliparous women (52 vs. 40.7%) and, therefore, fewer patients with previous uterine surgeries (7.5 vs.13.2% [12]). The risk of uterine rupture, especially for women with previous caesarean deliveries, should be part of prenatal counseling prior to fMMC repair.

Lung embolism is a well-known surgical complication [13, 14], but it was never reported in previous studies on fMMC repair [15, 16]. In our case, thrombosis in the lower part of the body as well as hereditary thrombophilia were excluded. Possibly, the thrombus or even thrombi formed intraoperatively during fMMC repair and then travelled to cause bilateral central pulmonary embolisms. Clearly, in this context, good patient monitoring and short total operative time are paramount [17, 18].

The 1 case of a third-degree AV block in our study which required short mechanical resuscitation at the ICU was attributed to marked electrolyte imbalance caused by the initially used high-dose magnesium sulfate tocolysis [7]. Therefore, magnesium was substituted by Atosiban, which basically eliminates this risk [7].

The other grade 4 complications may not be interpreted as a direct consequence of fetal surgery. Chorioamnionitis, for example, has an incidence of 3–5% in normal pregnancies [9]. Therefore, the 2 cases (5%) in our study – one grade 3 and one grade 4 – are still in a statistical range of usual pregnancy complications.

We saw a dramatic intraoperative placental abruption probably due to a combination of polyhydramnios, uter-

ine manipulation, and fast loss of amniotic fluid volume during fMMC repair. The other 3 placental abruptions occurred more than 5 weeks postoperatively, 1 even at 36 GW. Therefore, it is difficult to conclusively determine whether these complications were a consequence of prenatal surgery. We could not detect, but nevertheless included, severe pulmonary edema and blood transfusion in our list, since these 2 complications are frequently documented in other studies [5, 16].

In the literature, there are hardly any data on maternal complications during or following fetal surgery with a standardized classification. In the MOMS trial [5], 6% of patients with pulmonary edema, 6% with placental abruption, 3% with chorioamnionitis, and 1% with uterine rupture are described. Comparable rates have been published by Zamłyński et al. [16]. They describe 6.5% of cases with uterine rupture, 4.3% with chorioamnionitis, 4.3% with placental abruption, and 2.2% with pulmonary edema. In these studies, however, it is not specified whether these women needed IC/ICU management afterwards, which is the essential information to classify these complications as either grade 4 or less. Thus, it is not possible to really compare these rates with our results. Nevertheless, all studies show that fMMC repair may cause severe complications (grade 4), highlighting the importance of having an experienced team for optimal patient safety and best possible management of complications.

Our total operative time was on average 38 min shorter than in a recently published study by Elbabaa et al. [15] but still longer than in comparable other studies [4, 12, 19]. This may be due to a time-consuming 4-layer closure of the fetal lesion. It consists of a tubularization of the neural placode (whenever possible), covered by an additional 3-layer closure. In order to avoid prosthetic material, we sometimes use transposition flaps for skin closure [20]. These operative steps differ slightly from the surgical technique used in the MOMS trial [5]. Although Johnson et al. [12] describe surgery duration as a risk factor for PPROM, we had a very similar PPROM rate of 35% compared to 32% published by Moldenhauer et al. [19], while we had a considerably longer total operative time (139.1 vs. 78.5 min [19]). Unfortunately, the study by Elbabaa et al. [15] with an even longer operation time than in our study did not report on their PPROM rate.

The patients' inclusion and exclusion criteria in our study are consistent with the MOMS trial selection protocol [5], except for US residency and BMI. Patients where referred to our center from all over Europe with the majority being Caucasian (92%). It was an interdisciplinary decision to include 4 women in our study with a BMI of 36–41 that exceeded the recommended and published 35 kg/m^2 of the MOMS trial [5]. As a consequence, the average BMI of our 40 patients is higher than in comparable studies [5, 12]. We did not observe technical problems in our obese cases. Except for seroma and PPROM, none of the complications in this subgroup can be directly assigned to fetal surgery. Higher numbers of patients with a BMI >35 are needed for more conclusive statements in this matter.

A few studies with minimally invasive fetoscopic strategies for fMMC repair [3, 21] hint at the potential of decreased maternal complications. However, as Araujo Júnior et al. [4] demonstrated in their review that there is inconsistency with regard to both techniques and results. Due to the small numbers of patients and the lack of a randomized trial or soundly documented long-term outcomes, the published data on fetoscopic fMMC repair must be interpreted with caution. Additionally, the absence of documentation standards makes it hard to compare the actual maternal outcomes of the different techniques and highlights the need for a classification system as proposed in this study. Moreover, fetoscopic approaches are still associated with serious fetal complications, including high numbers of inadequate back closure as well as high rates of preterm delivery (<34 GW) and PPROM up to 100% [4, 22] following endoscopic surgery [3, 4, 23]. Another important challenge for the fetoscopic technique is to lower the actually very long operative times (up to 450 min) [23]. Of note, there is a correlation between duration of an operation and the risk for complications, such as deep venous thrombosis, pulmonary embolism, or need for blood transfusion [17, 18].

To optimize the safety and outcome of our patients, we suggest to not only standardize patient selection and procedure protocols as it has been rigorously done in the MOMS trial, but also to document complications in a standardized manner. This strategy would allow for a sound quality assessment and a true comparison between different centers.

In this study, we used the well-established Clavien-Dindo classification [8]. This system has been widely adopted for quality assessment of a large number of surgical procedures in multiple surgical disciplines [24, 25]. We, therefore, believe that it also represents a suitable tool to categorize maternal complications following prenatal surgery, and, definitely, it would also allow a credible comparison of results between centers.

In summary, this study analyzed maternal complications after open fetal surgery for spina bifida according to the Clavien-Dindo classification. The key finding is that

5 out of 40 women (12.5%) had serious (grade 4) complications, yet only 1 of these (2.5%) was a clear-cut direct consequence of surgery. Adequate diagnostic workup and management led to favorable outcomes without any long-term consequences in all of these patients. Clearly, centers performing innovative high-end fetal surgery have a professional, medical, as well as ethical obligation to carefully document, study, and publish all sorts of problems, including, but not limited to, complications.

Statement of Ethics

The Ethics Committee of the Canton of Zurich approved the study (KEK-ZH.Nr. 2015-0172). Written informed consent was obtained from the patients.

Disclosure Statement

All authors declare no conflicts of interest.

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