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Risk Factors for Preterm Birth following Open Fetal Myelomeningocele Repair: Results from a Prospective Cohort

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Open fetal myelomeningocele repair · Preterm birth · Risk factors

Abstract
Background: Fetal myelomeningocele (fMMC) repair is a therapeutic option in selected cases. This study aimed to identify risk factors for preterm birth (PTB) following open fMMC repair. ***Methods:*** Sixty-seven women underwent fMMC repair and delivered a baby between 2010 and 2018 at our center. Demographic, surgical, and pregnancy complications, including potential risk factors for PTB such as preterm premature rupture of membranes (PPROM), chorioamniotic membrane separation (CMS), and placental abruption were evaluated. ***Results:*** Maternal body mass index, maternal age, parity, previous uterine surgery, gestational age at fetal surgery, total surgery duration, surgical subcutaneous hematoma, oligohydramnios, and amniotic fluid leakage were not identified as risk factors for PTB. CMS ($p = 0.028$, 92 vs. 52%) and PPROM ($p = 0.001$, 95 vs. 52%) were highly associated with PTB. Placental abruption was found more often in women after fMMC repair than in a general obstetrical population (12 vs. 1%) and ended in premature birth in all cases ($p = 0.024$, 100 vs. 60%). However, the majority of women delivered at a gestational age >35 weeks. ***Conclusions:*** In our study cohort, risk factors for PTB were PPROM, CMS, and placental abruption, whereas surgery duration did not influence outcome. We conclude that the surgery technique should aim to minimize CMS and amniotic fluid leakage.

Introduction

Spina bifida, namely myelomeningocele (MMC) as its most common form, remains an important and relatively frequent congenital defect compatible with life despite the possible prevention of about 70% of cases by preconceptional folic acid supplementation [1, 2]. Infants with MMC suffer from significant morbidity (with a mortality of 1% per year) which can partly be attributed to an associated Chiari type II malformation. The latter comprises hindbrain herniation, abnormalities in the brain stem

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and venous sinuses, and a small posterior fossa resulting in hydrocephalus. As a consequence, placement of ventriculoperitoneal shunts is needed in a high percentage of patients (>80%). Patients are confronted with various degrees of lower extremity paralysis and neuropathic bladder dysfunction [2, 3].

The assumption of a 2-hit pathogenesis of MMC, firstly the failure of neural tube formation and secondly the consecutive destruction of the exposed neural tissue within the in utero environment, led to the development of fetal MMC (fMMC) repair [4]. Superiority of fMMC repair was demonstrated by the Management of Myelomeningocele Study (MOMS) comparing the outcomes of fMMC repair with standard postnatal MMC repair in a randomized controlled trial [3].

However, in MOMS, fetal surgery was associated with higher rates of obstetrical complications, such as oligohydramnios, preterm premature rupture of membranes (PPROM), chorioamniotic membrane separation (CMS), and consequently preterm birth (PTB) [3, 5]. PTB itself poses the neonate at a higher risk for admission to the neonatal intensive care unit, respiratory morbidities, necrotizing enterocolitis, and neurological morbidities [6]. The underlying study aims to identify risk factors for PTB in the first 67 cases of open fMMC repair at the Zurich Center for Fetal Diagnosis and Therapy.

Materials and Methods

Patient Population and Study Design

Sixty-seven pregnant women with a fetus diagnosed with MMC at a gestational age (GA) of 22 3/7 to 26 1/7 weeks received fMMC repair between 2010 and 2018 at the Zurich Center for Fetal Diagnosis and Therapy. Eligibility was mainly determined by the MOMS enrollment criteria [3]. Pregnant women were admitted to the prenatal ward before fetal surgery in order to complete fetal lung maturation and neuroprotection in fetuses ≥24 weeks GA prior to fMMC repair. Patients received 2 intramuscular injections of 16 mg dexamethasone within an interval of 24 h for fetal lung maturation, and neuroprotection was achieved by intravenous application of 25 mL magnesium sulfate per hour over 24 h. During the admission examination, cervical length was routinely measured via transvaginal ultrasound. Tocolytics were initiated on the day of fMMC repair and tapered off after surgery, adapted to the women's clinic as described previously by Ochsenbein-Kölble et al. [7]. After fMMC repair, all women were monitored in an intensive care unit (ICU) for 2 days to assure adequate monitoring and were then transferred to our prenatal ward. On the ICU, ultrasound examinations (amniotic fluid index, fetal umbilical and middle cerebral artery Doppler, exclusion of CMS, and postsurgical membrane hematoma) were performed 2–3 times/day and thereafter once weekly. Further, a fetal MRI was performed 2–4 weeks after the operation to confirm the ultrasound findings. Once the women were stable and did not require any intravenous medication, they were discharged into the ambulatory setting, usually 2–4 weeks after surgery. Regarding the anticipated risk for preterm labor and postsurgical complications such as CMS, oligohydramnios (defined as an amniotic fluid index <5 cm), and membrane hematomas, follow-up was scheduled once per week during pregnancy for close surveillance of the women in the ambulatory setting (including ultrasound examination and CTG) . In case of tocolysis (palpable contractions confirmed by CTG), PPROM, CMS, or other health-related reasons, women were monitored on our prenatal ward until delivery to ensure optimal management of the high-risk pregnancy. On-ward routine monitoring included 2 CTGs per day as well as 1 ultrasound examination per week. The latter comprised monitoring of the following fetal and maternal parameters: fetal growth, fetal position, head circumference, ventricular size, development/reversal of hindbrain herniation, cerebellum size, fetal movements, fetal kidneys, amniotic fluid index, uterine scar thickness, uterine leakage, hematoma/seroma, and CMS. In uncomplicated cases, delivery was planned via elective cesarean section at 37 weeks GA. Preterm cesarean section was performed in cases of premature labor, signs of chorioamnionitis, placental abruption, or other indications requiring immediate delivery of the fetus; no rescue corticosteroids were given.

Statistical Analysis

We evaluated risk factors for the outcomes of PTB, PPROM, and CMS. In line with clinical knowledge and previous studies [3, 5], we included the following demographic and obstetric risk factors: maternal age, race/ethnicity, BMI, parity, previous uterine surgeries, cervical length before fMMC repair, GA at surgery, duration of surgery, preeclampsia/gestational hypertension, oligohydramnios, MRI-confirmed amniotic fluid leakage, hematoma, placental abruption, vaginal bleeding, uterine rupture, CMS, and PPROM.

Demographic and clinical variables were analyzed using standard statistical tests: nominal variables were compared by χ^2 test, and serial variables were tested for normal distribution using the Kolmogorov-Smirnov test followed by the independent t test or Mann-Whitney U test, as appropriate. Stratification was conducted based on 2 PTB categories (GA <37 and ≤34 weeks). Odds ratios (OR) and 95% confidence intervals were calculated. Data are presented as medians (interquartile ranges) or *n* (%). A p value <0.05 was accepted as significant. Statistical analyses and data processing were conducted with SPSS (version 24; IBM, USA).

Results

Demographics and baseline characteristics of the study cohort are shown in Table 1. Table 2 reveals pregnancy complications and outcomes.

Risk factors for preterm delivery <37 weeks (n = 43; 64.2%) and ≤34 weeks (n = 12; 17.9%) are shown in Tables 3 and 4, respectively. Maternal BMI, maternal age, parity, previous uterine surgery, GA at intrauterine surgery, surgical subcutaneous hematoma, oligohydramni-

Table 1. Demographic and clinical variables (n = 67)

Maternal age, years	31 [26–35]
Fetal gender, *n* of females (%)	37 (55.2%)
GA at surgery, weeks	25.0 [24.4–25.4]
Race/ethnicity, *n* (%)	
White	63 (94%)
African American	2 (3%)
Hispanic	1 (1.5%)
Other	1 (1.5%)
Maternal BMI	25.8 [23.1–29.7]
Current smokers, *n* (%)	1 (1.5%)
Primipara, *n* (%)	29 (43.3%)
Previous uterine surgeries, *n* (%)	8 (11.9%)
Cervical length before fMMC repair, mm	40.0 [31.8–43.3]
Anterior placenta, *n* (%)	33 (49.3%)
Fetal lesion ≤L3, *n* (%)	52 (77.6%)
Fetal clubfoot, *n* (%)	10 (14.9%)

n (%) or medians [interquartile ranges]. fMMC, fetal myelomeningocele.

Table 2. Pregnancy complications and outcomes (n = 67)

Hematoma	4 (6%)
Subcutaneous seroma	20 (29.9%)
Pulmonary edema	2 (3%)
Preeclampsia/gestational hypertension	2 (3%)
Oligohydramnios	8 (11.9%)
MRI-confirmed amniotic fluid leakage	4 (6.0%)
CMS	12 (17.9%)
GA at CMS, weeks	27.5 [25.9–29.7]
Placental abruption	8 (11.9%)
Vaginal bleeding	7 (10.4%)
Gestational diabetes	18 (26.9%)
PPROM	19 (28.4%)
GA at PPROM, weeks	33.7 [31.6–35.1]
Uterine rupture	1 (1.5%)
Pulmonary embolism	1 (1.5%)
Perinatal death	1 (1.5%)
Preterm labor	31 (46.3%)
GA at birth, weeks	36.3 [34.7–37.0]
GA at birth, *n* of women	
<30 0/7 weeks	1 (1.5%)
30 0/7 to 34 6/7 weeks	23 (34.3%)
35 0/7 to 36 6/7 weeks	20 (29.9%)
≥37 0/7 weeks	23 (34.3%)
Birth weight, g	2,710 [2,400–2,910]
5-min Apgar score	9 [8–9]
Umbilical artery pH	7.3 [7.3–7.4]

n (%) or medians [interquartile ranges]. CMS, chorioamniotic membrane separation; PPROM, preterm premature rupture of membranes.

os, and amniotic fluid leakage were not identified as risk factors for PTB. Surgery duration did not pose any risk to PTB within our study cohort.

In women experiencing PTB <37 weeks as well as in the subcohort of women with a PTB ≤34 weeks, we found an association with PPROM (p = 0.001, OR 16.6 [2.0–134.1], and p = 0.011, OR 5.0 [1.3–18.7], respectively) and placental abruption (p = 0.024, OR 1.2 [1.1–1.4], and p = 0.029, OR 6.4 [1.3–30.8], respectively). PTB <37 weeks was also associated with CMS (p = 0.028, OR 7.9 [1.0–65.6]).

Further, we analyzed risk factors for PPROM ≤34 weeks and found a significant association with CMS (p = 0.001, OR 8.2 [2.0–33.6]; Table 5). CMS itself occurred less often in nullipara (p = 0.018, OR 0.1 [0.01–0.834]; Table 6) but was associated with a lower GA at the time of fMMC repair (p = 0.040, 24.7 [24.4–25.3], vs. 25.2 [24.4–25.6] weeks GA; Table 6).

In total, 19 women (28.4%) exhibited PPROM. Nine (47%) of them delivered on the same day while 7 women (90%) delivered within 5 days after PPROM. The longest time from PPROM to delivery was 7 days (n = 1; 5%). The median duration from the diagnosis of PPROM until delivery was 0.1 [0–1.7] days.

Twelve women (17.9%) had CMS, and 7 (58.3%) of them had PPROM in the following course of pregnancy. The median duration from CMS diagnosis until PPROM was 25.7 [22.7–28.6] days. The sequence of gravidae going into PPROM is visualized in Figure 1.

Discussion

We found PPROM, CMS, and placental abruption to be the main risk factors for PTB in our cohort. Further, this study depicts the characteristics of our 67 initial fMMC cases, as well as major pregnancy outcomes and complications.

Preterm Birth

PTB still represents a major complication of fetal surgery. Looking at the MOMS outcome parameters, our data are at least comparable, since 54% of women reached a GA of 35 weeks (in our cohort 64.2%) and 21% reached a GA ≥37 weeks (in our cohort 34.3%) in MOMS [3]. In the post-MOMS period in the Children's Hospital of Philadelphia (CHOP), 27% of women reached a delivery at term [8].

The Fetal Center at Vanderbilt reported a mean GA of 34.4 ± 3.1 weeks when comparing the MOMS cohort to their post-MOMS cohort [9]. A clinical center in Poland recently published data on their fMMC repair outcomes:

Table 3. Preterm birth <37 weeks stratified by risk factor

	Delivery		*p* value	Odds ratio [95% CI]
	<37 weeks GA (*n* = 43)	≥37 weeks GA (*n* = 24)		
Maternal age, years	31 [27–35]	31 [25–36]	0.551	
Race/ethnicity			0.728	
White	40 (93.0%)	23 (95.8%)		
African American	1 (2.3%)	1 (4.2%)		
Hispanic	1 (2.3%)	–		
Other	1 (2.3%)	–		
Body mass index	25.5 [23.1–27.8]	26.1 [23.0–31.4]	0.480	
Cervical length before fMMC repair, mm	40.0 [31.0–44.0]	40.0 [34.3–42.8]	0.941	
Parity			0.077	
Primipara	15 (34.9%)	14 (58.3%)		
Multipara	28 (65.1%)	10 (41.7%)		
Previous uterine surgery			0.496	
Yes	6 (14%)	2 (8.3%)		
No	37 (86%)	22 (91.7%)		
Anterior placenta			0.267	
Yes (posterior hysterotomy)	19 (44.2%)	14 (58.3%)		
No (anterior hysterotomy)	22 (55.8%)	10 (41.7%)		
Gestational age at surgery, weeks	24.9 [24.6–25.4]	25.2 [24.3–25.6]	0.573	
Duration of surgery, min				
Total	136 [123–162]	137 [121–159]	0.937	
Uterine	92 [75–100]	88 [77–91]	0.256	
Preeclampsia/gestational hypertension			0.283	
Yes	2 (4.7%)	–		
No	41 (95.3%)	24 (100%)		
Oligohydramnios			0.916	
Yes	5 (11.6%)	3 (12.5%)		
No	38 (88.4%)	21 (87.5%)		
MRI-confirmed amniotic fluid leakage			0.123	
Yes	4 (9.3%)	–		
No	39 (90.7%)	24 (100%)		
Subcutaneous hematoma			0.614	
Yes	2 (4.7%)	2 (8.3%)		
No	41 (95.3%)	22 (91.7%)		
Placental abruption			**0.024**	**1.2 [1.1–1.4]**
Yes	8 (18.6%)	–		
No	35 (81.4%)	24 (100%)		
Vaginal bleeding			0.713	
Yes	5 (11.6%)	2 (8.3%)		
No	38 (88.4%)	22 (91.7%)		
Uterine rupture			0.452	
Yes	1 (2.3%)	–		
No	42 (97.7%)	24 (100%)		
Chorioamniotic membrane separation			**0.028**	**7.9 [1.0–65.6]**
Yes	11 (25.6%)	–		
No	32 (74.4%)	24 (100%)		
Preterm premature rupture of membranes			**0.001**	**16.6 [2.0–134.1]**
Yes	18 (41.9%)	1 (4.2%)		
No	25 (58.1%)	24 (95.8%)		

n (%) or medians [interquartile ranges]. CI, confidence interval; fMMC, fetal myelomeningocele.

Table 4. Preterm birth ≤34 weeks stratified by risk factor

	Delivery		*p* value	Odds ratio [95% CI]
	≤34 weeks GA (*n* = 12)	>34 weeks GA (*n* = 55)		
Maternal age, years	33 [29–35]	31 [26–35]	0.441	
Race/ethnicity			0.095	
White	10 (83.3%)	53 (96.4%)		
African American	1 (8.3%)	1 (1.8%)		
Hispanic	1 (8.3%)	–		
Other	–	1 (1.8%)		
Body mass index	25.4 [21.9–28.3]	25.8 [23.1–30.0]	0.545	
Cervical length before fMMC repair, mm	41.5 [31.3–47.3]	40.0 [33.3–34.0]	0.405	
Parity			0.901	
Primipara	5 (41.7%)	24 (43.6%)		
Multipara	7 (58.3%)	31 (56.4%)		
Previous uterine surgery			0.671	
Yes	1 (8.3%)	7 (12.7%)		
No	11 (91.7%)	48 (87.3%)		
Anterior placenta			0.562	
Yes (posterior hysterotomy)	5 (41.7%)	28 (50.9%)		
No (anterior hysterotomy)	7 (58.3%)	27 (49.1%)		
Gestational age at surgery, weeks	25.2 [24.2–25.3]	25.0 [24.4–25.6]	0.623	
Duration of surgery, min				
Total	136 [124–152]	137 [122–163]	0.653	
Uterine	93 [71–98]	88 [77–99]	0.531	
Preeclampsia/gestational hypertension			0.230	
Yes	1 (8.3%)	1 (1.8%)		
No	11 (91.7%)	54 (98.2%)		
Oligohydramnios			0.577	
Yes	2 (16.7%)	6 (10.9%)		
No	10 (83.3%)	49 (89.1%)		
MRI-confirmed amniotic fluid leakage			0.703	
Yes	1 (8.3%)	3 (5.5%)		
No	11 (91.7%)	52 (94.5%)		
Subcutaneous hematoma			0.335	
Yes	–	4 (7.3%)		
No	12 (100%)	51 (92.7%)		
Placental abruption			**0.029**	**6.4 [1.3–30.8]**
Yes	4 (33.3%)	4 (7.3%)		
No	8 (66.7%)	51 (92.7%)		
Vaginal bleeding			0.763	
Yes	1 (8.3%)	6 (10.9%)		
No	11 (91.7%)	49 (89.1%)		
Uterine rupture			0.638	
Yes	–	1 (1.8%)		
No	12 (100%)	54 (98.2%)		
Chorioamniotic membrane separation			0.205	
Yes	4 (32.3%)	8 (14.5%)		
No	8 (66.7%)	47 (85.5%)		
Preterm premature rupture of membranes			**0.011**	**5.0 [1.3–18.7]**
Yes	7 (58.3%)	12 (21.8%)		
No	5 (41.7%)	43 (78.2%)		

n (%) or medians [interquartile ranges]. CI, confidence interval; fMMC, fetal myelomeningocele.

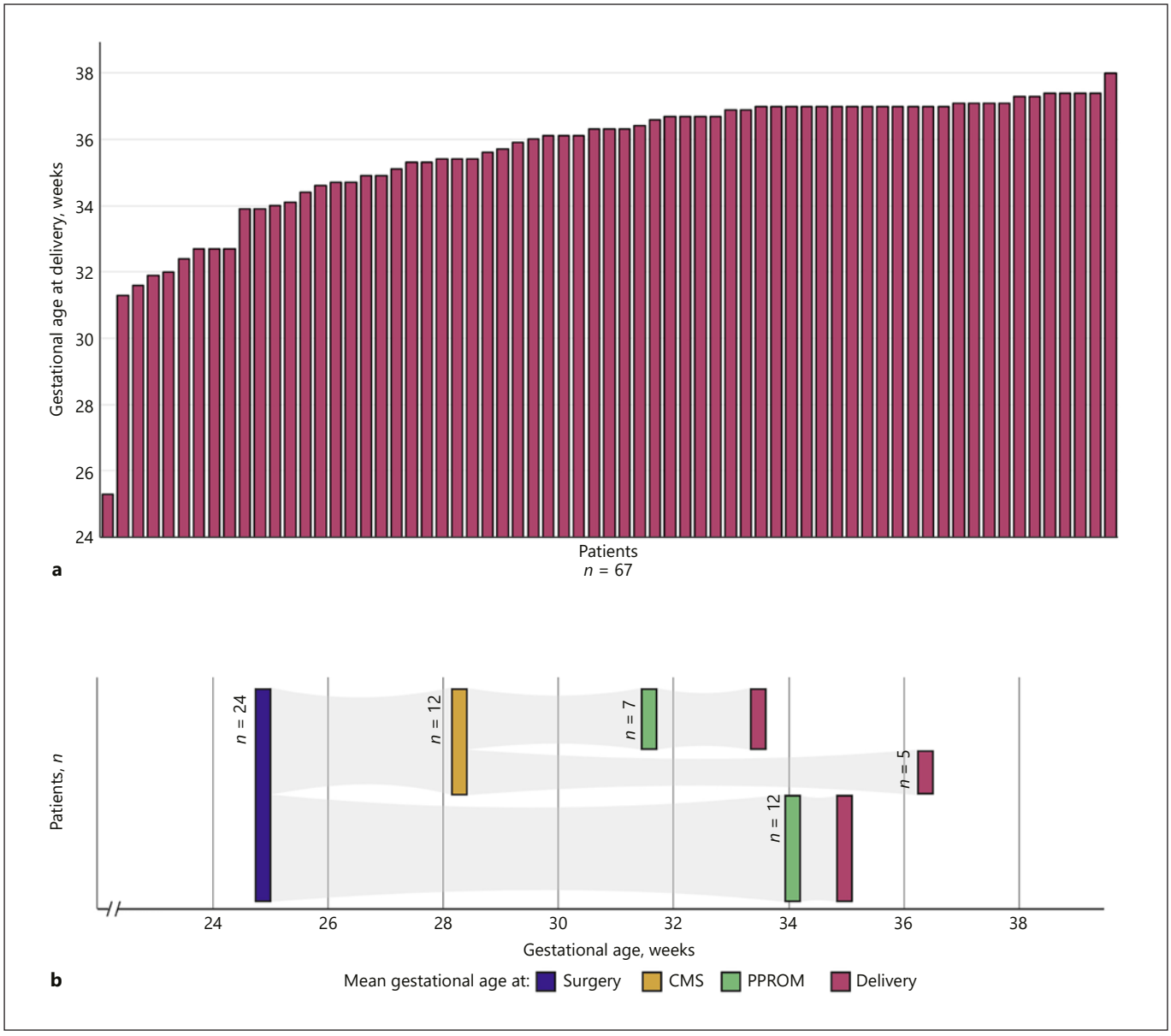

Fig. 1. a GA at delivery (n = 67; from lowest to highest GA; mean GA 35.6 ± 2.1 weeks). **b** Sequence of CMS, PPROM, and PTB. Of the 12 (50%) women with CMS, 7 (58%) had PPROM and subsequent PTB. Twelve (50%) women developed PPROM without preceding CMS, which also led to PTB in all cases.

18.3% of their cases reached a GA of 37 weeks (vs. 35.8% in our study population) [10].

Overall, we report a median GA of 36.3 [34.7–37.0] weeks at delivery. The majority of our women (64 %) delivered after 35 completed gestational weeks, and 34% reached a GA ≥37 weeks. Further, Zamora et al. [11] showed a mean GA at delivery of 35.5 ± 1.8 weeks following open fetal surgery, which is similar to the median GA at delivery of 36.3 weeks in our study.

Preterm Premature Rupture of Membranes

Research has shown that PPROM is a major risk factor for preterm delivery, in particular following fetal surgery. Apart from MOMs, there are only limited data available on PPROM rates following fetal surgery, particularly after fMMC repair.

PPROM occurred in 46% of women in the MOMs cohort (vs. 8% in women with postnatal MMC repair). PPROM rates in post-MOM fMMC repair at large fetal

Table 5. Preterm premature rupture of membranes (PPROM) ≤34 weeks stratified by risk factor

	PPROM (n = 12)	No PPROM ≤34 weeks (n = 55)	p value	Odds ratio [95% CI]
Maternal age, years	32 [28–35]	31 [26–35]	0.658	
Body mass index	26.4 [22.1–28.3]	25.5 [23.1–30.0]	0.980	
Cervical length before fMMC repair, mm	40.0 [31.0–48.0]	40.0 [32.0–43.0]	0.523	
Parity			0.207	
Primipara	3 (25%)	26 (47.3%)		
Multipara	9 (75%)	29 (52.7%)		
Previous uterine surgery			0.671	
Yes	1 (8.3%)	7 (12.7%)		
No	11 (91.7%)	48 (87.3%)		
Anterior placenta			0.954	
Yes (posterior hysterotomy)	6 (50%)	27 (49.1%)		
No (anterior hysterotomy)	6 (50%)	28 (50.9%)		
Gestational age at surgery, weeks	24.7 [24.6–25.3]	25.1 [24.4–25.6]	0.394	
Duration of surgery, min				
Total	135 [125–155]	136 [122–163]	0.844	
Uterine	89 [71–98]	90 [77–99]	0.702	
Oligohydramnios before PPROM			0.124	
Yes	3 (25%)	5 (9.1%)		
No	9 (75%)	50 (90.9%)		
Chorioamniotic membrane separation before PPROM			**0.001**	**8 .2 [2.0–33.6]**
Yes	6 (50%)	6 (10.9%)		
No	6 (50%)	49 (89.1%)		

n (%) or medians [interquartile ranges]. CI, confidence interval; fMMC, fetal myelomeningocele.

Table 6. Chorioamniotic membrane separation (CMS) ≤34 weeks stratified by risk factor

	CMS (n = 11)	No CMS ≤34 weeks (n = 56)	p value	Odds ratio [95% CI]
Maternal age, years	34 [28–35]	31 [26–34]	0.575	
Body mass index	27.0 [23.6–30.8]	25.7 [23.0–29.0]	0.441	
Cervical length before fMMC repair, mm	43.0 [40.0–48.0]	39.0 [31.0–43.0]	**0.034**	
Parity			**0.018**	**0.1 [0.01–0.834]**
Primipara	1 (9.1%)	28 (50%)		
Multipara	10 (90.9%)	28 (50%)		
Previous uterine surgery			0.335	
Yes	–	8 (14.3%)		
No	11 (100%)	48 (85.7%)		
Anterior placenta			0.783	
Yes (posterior hysterotomy)	5 (45.5%)	28 (50%)		
No (anterior hysterotomy)	6 (54.5%)	28 (50%)		
Gestational age at surgery, weeks	24.7 [24.4–25.3]	25.2 [24.4–25.6]	**0.040**	
Duration of surgery, min				
Total	140 [130–163]	135 [122–160]	0.703	
Uterine	95 [75–105]	88 [77–95]	0.175	

n (%) or medians [interquartile ranges]. CI, confidence interval; fMMC, fetal myelomeningocele.

surgery centers remain high (52.2% [24/46], 28.0% [25/89], and 30.7% [27/88]) [3, 5, 8, 10] and are comparable to our PPROM prevalence (28.4% [19/67]). In our cohort, 28.4% of gravidae exhibited PPROM. If PPROM occurred, 90% of our women delivered within 5 days after PPROM.

In 2013, Perrini et al. [12] showed that contractions are likely to increase the risk of PPROM.

Tocolysis after PPROM has not yet been proven to improve neonatal or obstetric outcome [13], but in the case of PPROM following fMMC repair, tocolysis might be beneficial or at least not harmful if there is no evidence for chorioamnionitis.

Chorioamniotic Membrane Separation

Eighteen percent of our gravidae exhibited CMS (vs. 26% in MOM and 23% in post-MOM women) [3, 5, 8]. In accordance with previous studies, women developing CMS received fMMC surgery at a lower GA (24.7 [24.4–25.3] weeks GA vs. 25.2 [24.4–25.6] weeks GA; $p = 0.04$) [8, 14, 15]. Congruently, studies on CMS following fetoscopic laser photocoagulation revealed a higher risk for CMS with earlier timing of surgery [16, 17]. It has been hypothesized that the pathogenesis lies in the weaker adherence of the amniotic and chorionic membranes during early gestation [17]. Johnson et al. [5] as well as Wilson et al. [14] reported an association between CMS and PPROM, which is in line with our data.

Accordingly, CMS was found to be a risk factor for PPROM leading to a lower GA at delivery in this study. Additionally, a lower GA at the time of surgery was shown to be a risk factor for CMS with PTB ≤34 weeks GA.

Placental Abruption

Another clinically logical finding of this study is an association of placental abruption (12% in MOMs; 6 and 2% in the CHOP post-MOM cohort) with PTB in the context of fMMC repair, holding true for both PTB categories (<37 and ≤34 weeks GA) [3, 8].

PPROM was associated with placental abruption ($p = 0.022$), but other common risk factors for placental abruption, such as patient age, duration of surgery, or preeclampsia, were not associated. There was a tendency towards a higher prevalence of placental abruption in patients with an anterior placenta (6 cases of anterior placenta vs. 2 cases of posterior placenta) but without reaching a level of significance. Anterior placentas might lead to more intraoperative manipulation and fetal positioning, which might pose an additional risk for placental abruption.

Miscellaneous Risk Factors

Various clinical characteristics, such as maternal BMI, maternal age, parity, previous uterine surgery, GA at intrauterine surgery, and surgical subcutaneous hematoma, were not identified as risk factors for PTB, which is in line with a study by Johnson et al. [5].

In contrast to expectations and to the latter-mentioned study, oligohydramnios and amniotic fluid leakage were neither associated with PPROM nor with preterm delivery in our gravidae. Further, it is questionable whether surgery duration had a major impact on PTB following fMMC repair, as surgery duration did not pose any additional risk for PTB within our study cohort as it had in a previous study [5]. This finding stands in contrast to those of Johnson et al. [5], who showed a correlation between longer surgery duration and PPROM and PTB <34 weeks GA. It has to be taken into account that prolonged surgery duration can also be a surrogate for intraoperative complications which may lead to PPROM and PTB postoperatively.

There are several limitations to this study. First, the number women (67) enrolled during the study period limits the power of statistical analyses. Contrariwise, our patient collective presents one of the largest cohorts treated with fMMC repair within Europe. Further, the tocolytic management was changed after the first 15 women from magnesium sulfate to atosiban due to the apparent superiority of the latter within our own study cohort [7]. Additionally, we see a strength in our concept of tight follow-up and return for delivery as well as for subsequent pregnancy counseling.

Conclusion

The knowledge of major risk factors for PTB within our cohort (PPROM, CMS, and placental abruption) enables us to take early and direct clinical measures aiming at the prevention of PTB or at least at the prolongation of gestation after fMMC repair. Such measures can comprise minimal manipulation at the uterus during fMMC repair for prevention of CMS and PPROM or placental abruption, or the initiation of intravenous tocolytics for (I) the prevention of CMS and PPROM directly following fMMC repair in the presence of contractions and (II) after PPROM without signs of chorioamnionitis or CMS in case of premature contractions. Additionally, optimal surveillance after CMS diagnosis in terms of a prolonged hospital admission is a possible consequence. We conclude that frequent examinations aiming to identify risk

factors for PTB is appropriate. Future surgery techniques need to adress minimization of CMS to reduce the risk for PPROM and consequently preterm delivery of the fetus.

Statement of Ethics

Subjects have given their written informed consent. This study protocol has been approved by the research institute's committee on human research named "Kantonale Ethikkommission Zürich" (Cantonal Ethics Review Board of Zurich).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.K. Kahr wrote the manuscript. The initial study outline was designed by N. Ochsenbein-Kölble and M.K. Kahr. F. Winder, L. Vonzun, and M.K. Kahr collected data and performed data quality control. M.K. Kahr performed data analysis. All authors participated in the drafting and/or revising of the manuscript and contributed to its intellectual content. The final version of the manuscript was approved by all authors prior to publication.

References

1 Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, et al.; National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008 Jul;82(7):527–32.

2 Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, Sutton LN, Whitehead AS. Spina bifida. Lancet. 2004 Nov;364(9448):1885–95.

3 Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al.; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011 Mar;364(11):993–1004.

4 Meuli M, Moehrlen U. Fetal surgery for myelomeningocele is effective: a critical look at the whys. Pediatr Surg Int. 2014 Jul;30(7):689–97.

5 Johnson MP, Bennett KA, Rand L, Burrows PK, Thom EA, Howell LJ, et al; Management of Myelomeningocele Study Investigators. The Management of Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery. Am J Obstet Gynecol. 2016 Dec;215(6):778e1–778e9.

6 Cheng YW, Kaimal AJ, Bruckner TA, Halloran DR, Caughey AB. Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. BJOG. 2011 Nov;118(12):1446–54.

7 Ochsenbein-Kölble N, Krähenmann F, Hüsler M, Meuli M, Moehrlen U, Mazzone L, et al. Tocolysis for in utero Surgery: Atosiban Performs Distinctly Better than Magnesium Sulfate. Fetal Diagn Ther. 2018;44(1):59–64.

8 Moldenhauer JS, Soni S, Rintoul NE, Spinner SS, Khalek N, Martinez-Poyer J, et al. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther. 2015;37(3):235–40.

9 Bennett KA, Carroll MA, Shannon CN, Braun SA, Dabrowiak ME, Crum AK, et al. Reducing perinatal complications and preterm delivery for patients undergoing in utero closure of fetal myelomeningocele: further modifications to the multidisciplinary surgical technique. J Neurosurg Pediatr. 2014 Jul;14(1):108–14.

10 Zamłyński J, Horzelska E, Zamłyński M, Olszak-Wąsik K, Nowak L, Bodzek P, et al. Current views on fetal surgical treatment of myelomeningocele - the Management of Myelomeningocele Study (MOMS) trial and Polish clinical experience. Ginekol Pol. 2017;88(1):31–5.

11 Zamora IJ, Ethun CG, Evans LM, Olutoye OO, Ivey RT, Haeri S, et al. Maternal morbidity and reproductive outcomes related to fetal surgery. J Pediatr Surg. 2013 May;48(5):951–5.

12 Perrini M, Bürzle W, Haller C, Ochsenbein-Kölble N, Deprest J, Zimmermann R, et al. Contractions, a risk for premature rupture of fetal membranes: a new protocol with cyclic biaxial tension. Med Eng Phys. 2013 Jun;35(6):846–51.

13 Lorthe E, Goffinet F, Marret S, Vayssiere C, Flamant C, Quere M, Benhammou V, Ancel PY, Kayem G: Tocolysis after preterm premature rupture of membranes and neonatal outcome: a propensity-score analysis. Am J Obstet Gynecol. 2017 Aug;217(2):212.e1–212.e12.

14 Wilson RD, Johnson MP, Crombleholme TM, Flake AW, Hedrick HL, King M, et al. Chorioamniotic membrane separation following open fetal surgery: pregnancy outcome. Fetal Diagn Ther. 2003 Sep-Oct;18(5):314–20.

15 Soni S, Moldenhauer JS, Spinner SS, Rendon N, Khalek N, Martinez-Poyer J, et al. Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele repair. Am J Obstet Gynecol. 2016 May;214(5):647 e1-7.

16 Takano M, Nakata M, Murata S, Sumie M, Morita M. Chorioamniotic Membrane Separation after Fetoscopic Laser Photocoagulation. Fetal Diagn Ther. 2018;43(1):40–4.

17 Ortiz JU, Eixarch E, Peguero A, Lobmaier SM, Bennasar M, Martinez JM, et al. Chorioamniotic membrane separation after fetoscopy in monochorionic twin pregnancy: incidence and impact on perinatal outcome. Ultrasound Obstet Gynecol. 2016 Mar;47(3):345–9.