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Alternative technique of intrauterine myelomeningocele repair to decrease the incidence of unfavorable maternal and fetal outcomes

Short title: Alternative technique of intrauterine myelomeningocele repair

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ABSTRACT

Objectives: The aim of the study was to determine the effectiveness of an alternative method of open fetal surgery to prevent severe unfavorable prenatal events, both for the mother and the fetus.

Material and methods: In this study, the previously published results for a cohort of 46 patients, who had undergone intrauterine myelomeningocele repair (IUMR) at our Center by 2014, constituted the retrospective control group (CG). The MOMS protocol had been applied for hysterotomy, with an automatic uterine stapling device. The study group (SG) n = 57 was assembled during a prospective observation. IUMR was performed using an alternative method of hysterotomy, with the typical opening and closure of the uterus, without automatic stapling device, as described by Moron et al. Additionally, our single-center results were

compared with the post-MOMS findings of other centers: CHOP (Children's Hospital of Philadelphia) and VUMC (Vanderbilt University Medical Center).

Results: No cases of delivery before 30 weeks of gestation (0%, 0/55) were observed in the study group, which is a statistically significant difference ($p < 0.05$) as compared to controls (15/44). Statistically significantly lower incidence of chorioamniotic separation (5.4% (3/55) vs CHOP 22.9% (22/96), $p < 0.001$) and contractile activity resulting in preterm labor (16.3% (9/55) vs CHOP 37.5% (36/96), $p < 0.05$) was found in the study group. Premature rupture of the membranes was statistically significantly less common in the study group as compared to controls, CHOP and VUMC (SG 12.7% (7/55) vs CG 52.2% (24/46), $p < 0.001$; vs CHOP 32.3% (31/96), $p < 0.001$; vs VUMC 22% (9/43), $p < 0.01$, respectively).

Conclusions: The presented IUMR method is associated with improved perinatal outcomes, i.e., lower rates of preterm delivery at < 30 weeks of gestation, preterm premature rupture of membranes, and uterine contractility resulting in preterm delivery. That, in turn, results in lower prematurity rates and, consequently, more favorable neonatal outcomes.

Key words: myelomeningocele; fetal surgery; complications; alternative technique

INTRODUCTION

Open spina bifida (OSB) remains to be one of the most common congenital defects. Approximately 150 000 infants globally are born with myelomeningocele (MMC) every year, and the defect results in 44 000 deaths and is responsible for a substantial number of disabilities in the general population [1].

Until 1997, surgical management, implemented within the first 48 hours of neonatal life, has been the only therapeutic option of myelomeningocele repair. The results of the multi-center, randomized study of the MOMS (Management of Myelomeningocele Study) group heralded a new era of treating OSB, with long-term observational studies confirming the effectiveness of this approach [2–5]. Worldwide, a steadily growing number of centers undertake the task of treating fetal myelomeningocele (fMMC), and their findings continue to demonstrate improved maternal and fetal safety in prenatal MMC repair [6–11].

Currently, multilayered closure of fMMC using open fetal surgery (OFS), being one of the available therapeutic options, remains the gold standard for treating that defect. The management, regardless of its undeniable benefits, is associated with a considerable risk for

complications [3, 10–12], chief among them preterm labor (PTL) and the resulting prematurity, preterm premature rupture of membranes, (PPROM), as well as oligohydramnios or chorioamniotic separation (CAS) [3, 10–12]. Prenatal surgery is associated with maternal risk for pulmonary edema, hemorrhage which might require blood transfusion, and uterine scar dehiscence, including the risk of uterine rupture [12].

Fetoscopic procedures were introduced as an alternative approach, to lower the rate of maternal and perinatal complications associated with treating OSB using open fetal surgery. Fetoscopic surgery consists in covering the bifid part of the spinal cord with the fetal skin graft. Importantly, during fetoscopic procedures the tethered spinal cord is not released and the defect within the spinal column is not protected by a muscle layer, which increases the risk for secondary mechanical trauma to the spinal cord.

The search for alternative methods of surgery aims at lowering the complication rates and, consequently, improving maternal and fetal safety during the procedure.

Objectives

The opening and closure of the uterine muscle and the fetal membranes is a crucial stage of the intrauterine myelomeningocele repair. The MOMS protocol with an automatic uterine stapling device is used [2]. An alternative technique of hysterotomy (ATH) for myelomeningocele repair replaces the uterine stapling device with two DeBakey clamps. The uterine muscle between the two clamps is incised and later sutured to close [13].

The aim of the study was to determine the effectiveness of an alternative method of open fetal surgery to prevent severe unfavorable prenatal events, both maternal and fetal.

MATERIAL AND METHODS

Intrauterine myelomeningocele repairs have been conducted at the Department of Gynecology, Obstetrics and Gynecologic Oncology in Bytom, Medical University of Silesia, Katowice since 2005. Until January 2021, 136 IUMR surgeries have been performed.

The previously published results for a cohort of 46 patients, who by 2014 had undergone intrauterine myelomeningocele repair at our Center, served as a retrospective [6] control group (CG) n = 46 for this study. The MOMS protocol had been applied for hysterotomy, with an automatic uterine stapling device. The study group (SG) n = 57 was assembled during a prospective observation. IUMR was performed using an alternative technique of hysterotomy,

with the typical opening and closure of the uterus, without automatic stapling device, as described in the protocol by Moron et al. [13].

Differences between the hysterotomy using automatic uterine stapling device and the alternative technique used in our study are presented in Table 1. The stages of hysterotomy and ATH hysterorrhaphy are presented in Figure 1. Additionally, our single-center results were compared with the post-MOMS findings of other centers: CHOP (Children's Hospital of Philadelphia) [14] and VUMC (Vanderbilt University Medical Center) [15]. In our study, as well as the abovementioned cohorts, a uniform anesthesiologic maternal protocol was used, which combined general anesthesia (isoflurane) with simultaneous continuous epidural analgesia. Additionally, after fetal buttocks were visualized and position for hysterotomy, fetal anesthesia and muscle relaxation were achieved using intramuscular Fentanyl (20 μg/kg) and Vecuronium (0.2 mg/kg), respectively. During IUMR, magnesium sulfate was the first-line tocolytic in the control group, and 1–2 g/h was administered intravenously until complete uterine relaxation was achieved. In the study group, fluorinated methyl isopropyl ether in a 3.5% gas mixture was used to suppress uterine contractility. Magnesium sulfate was used sporadically, in cases when uterine muscle relaxation was questioned. After surgery, second-line tocolysis consisted in short-term (up to 48 hours) administration of the following: $beta_2$ adrenergic agonists, nitroglycerine, $COX^{1–2}$ inhibitor, and Atosiban, in accordance with the commonly used tocolytic protocol for open fetal surgery [16]. Oral nifedipine (30–40 mg/24 h) was used for long-term tocolysis, up to 36^{+6} weeks of gestation.

As far as eligibility is concerned, in our study we used the same inclusion and exclusion criteria as the three American centers (Children Hospital of Philadelphia; Vanderbilt University; University of California, San Francisco), published in the randomized MOMS trial [2].

Statistica 10 PL was used for statistical analysis. MS Excel 2007 was used to create the database. The values calculated for measurable variables are presented as arithmetical means with standard deviation (SD) or standard error of the mean (SEM). The Shapiro-Wilk test was used to check whether the variables were normally distributed and the Levene's test was used to verify homogeneity of variance.

RESULTS

A comparison of the clinical characteristics of the mothers and the fetuses with Chiari II at baseline, i.e., while checking eligibility for the myelomeningocele repair between 20^{+0}–25^{+6} weeks of gestation, is presented in Table 2. Unified eligibility criteria in all groups are indicative of similar demographic parameters among the mothers, except for ethnicity and parity.

A comparison of the fetal and neonatal results after IUMR in the following groups: SG vs CG vs CHOP vs VUMC is presented in Table 3. Originally, the study group comprised 57 patients, but the final analysis included 55 neonates due to two cases of fetal and neonatal death. The deaths occurred in the perioperative period: one intrauterine fetal demise (IUFD) during the initial incision of the uterine muscle and hemorrhage from the chorioamniotic space and one neonatal death (NND), 24h after IUMR, caused by placental ablation, probably due to later diagnosed thrombophilia. In the study group, the mortality rate reached 3.5% (2/57) and was not statistically significantly different as compared to the remaining groups (CG 3%, CHOP 6.1%, VUMV 5%). Mean gestational age at delivery in the study group was 35.0 ± 3.2 weeks of gestation ($24^{6/7}$–$38^{4/7}$) and was comparable to CHOP and VUMC (34.3 and 34.4, respectively). No cases of delivery before 30 weeks of gestation (0%; 0/55) after IUMR were noted in the study group, which was statistically significant ($p < 0.05$) as compared to controls (34.1%; 15/44).

Maternal results after IUMR, which are presented in Table 4, indicate lack of severe internal complications associated with surgery-related stress and the administered tocolysis. As far as favorable outcomes are concerned, statistically significantly lower rates of chorioamniotic separation (5.4% (3/55) vs CHOP 22.9% (22/96), $p < 0.001$), and contractile activity resulting in premature labor (16.3% (9/55) vs CHOP 37.5% (36/96), $p < 0.05$), were observed in the study group as compared to CHOP. Also, premature rupture of membranes was statistically significantly less common in the study group as compared to controls and the remaining groups (12.7% (7/55) vs controls 52.2% (24/46), $p < 0.001$; vs CHOP 32.3% (31/96), $p < 0.001$; vs VUMC 22% (9/43), $p < 0.01$). Statistically significantly lower ($p < 0001$) use of magnesium sulfate during IUMR in the study group as compared to controls and CHOP (5.3% (3/57) vs CG 50% (23/46) vs CHOP 100% (96/100) is another benefit of ATH. In the study group, evaluation of the hysterotomy/hysterorrhaphy site during cesarean section indicated a statistically significantly higher rate (76%) of uterine scar tightness and uncompromised

intactness as compared to CHOP (50.6%; $p < 0.05$), as well as statistically significantly lower (20%) rate of scar thinning as compared to CHOP (41.4%; $p < 0.05$).

DISCUSSION

Recent years have witnessed the development of prenatal repair methods, whose goal is to lower the complication rate, thus improving maternal and fetal safety. Preterm birth, and the consequent prematurity, is without question a serious complication of antenatal therapy. In our study group, mean gestational age at delivery was 35.0 ± 3.2 weeks (range: $24^{6/7}$–$38^{4/7}$). Importantly, no births at < 30 weeks of gestation were observed, and deliveries at < $36.^{+6}$ weeks of gestation constituted 44% of the study population.

The surgical protocol for our study group was modified as follows: the DeBakey clamps and anti-prostaglandin management with COX^{1-2} prostaglandin inhibitors and complete replacement of the amniotic fluid were used, which in turn significantly decreased the necessity of using magnesium sulfate as a first-line tocolytic, as compared to the cohort groups (SG 5.3% vs CG 50% vs CHOP 100%, $p < 0.001$). The risk of maternal pulmonary edema, which is a severe postoperative complication, was completely eliminated (0/57; 0%) if routine administration of magnesium sulfate during IUMR was abandoned.

The use of uterine stapling devices to widen the uterine opening in OFS, in numerous cohort studies and the randomized MOMS trial, has been extensively covered in the literature since 1998 [2, 6, 15]. The stapler method consists in a simultaneous grasp, automatic suture, and incision of all layers of the uterine muscle. Hysterorrhaphy consists in placing a continuous suture through all layers of the uterus as well as another suture or absorbable staples which join the external parts of the myometrium and the perimetrium. The primary benefit of that surgical approach is simultaneous suturing and opening of all layers of the uterine muscle, which shortens operative time (OFS 78.7–105 min.) [14]. However, the method has its limitations, especially in case of significant thickness of the uterine wall and inability to grasp all the layers, incomplete closure of the staples, higher blood loss and the necessity of surgical repair of the hysterotomy. Nevertheless, application of primary pressure to the layers of the uterine muscle, using a single DeBakey clamp even before using the stapler, is an effective way of preventing that complication [13]. CAS, PPROM and PTL, during IUMR or later during pregnancy, are the consequences of compromised intactness or an escape of the fetal membranes from under the stapler [17].

Classical surgical approach, as described by Moron et al. [13], offers an alternative to hysterotomy with uterine stapling device, and was used in our study. The operative time of IUMR [124.6 (110–143) minutes] was an anticipated limitation of the study [13]. The benefits include the following: full visualization and control of the uterine opening; placement of atraumatic, hemostatic DeBakey clamps which prevent CAS; protecting the chorion from inducing contractile activity after contact between PGs and the amniotic fluid, which is achieved by double-fixation of the amniotic membranes to the myometrium: first-line — externally to the DeBakey clamp, second-line — fetal membranes are attached to the lower segment of the uterine wall. Two-layered closure (continuous through the inner portion of the myometrium and external through the inner portion of the myometrium and the perimetrium) lowers the risk for amniotic fluid leakage. Anatomic proximity of the uterine layers initiates a physiologic process of tissue restoration. Carvalho et al. [18] presented histologic evidence of reparative activity in the fetal membranes after classical hysterotomy for IUMR. During histopathologic evaluation of the fetal membranes, these authors found areas of significant defragmentation of collagen fibers at the site of direct surgical intervention in patients after IUMR. Their findings also confirmed intensive reparative process consisting in intensified type 1–2 collagen production at the suture site as compared to sites not involved during surgical intervention (13.22 ± 2.84 vs 6.16 ± 1.09, $p < 0.0001$) [18]. The results of the study are indicative of a reparatory activity at the scar site to prevent amniotic fluid leakage, which lowers the risk of preterm delivery and prenatal complications [18].

Recent years have brought a dynamic development of minimally invasive therapies, including fMMC management. The primary goal of the methods in question is to limit the number of maternal adverse events (associated with the need of hysterotomy in case of open-surgery interventions) and fetal complications like PROM, PTL, and the consequent prematurity, while maintaining high effectiveness of the treatment. The initial findings of analyses from groups of over 200 fetuses undergoing fetoscopic MMC repair are conflicting [19–22]. Undoubtedly, the reasons include lack of uniform surgical protocol and unambiguous eligibility criteria, which makes it challenging to evaluate the therapy outcomes as well as compare the results to the outcomes of open fetal surgery repairs [23].

A recent analysis of 300 fetoscopic OSB repairs revealed that the clinical outcomes at 12 months of follow-up are comparable to open-surgery fetal results [9]. Also, natural vaginal delivery was possible in as many as one-third of the cases after fetoscopic procedures [9].

Still, fetoscopic interventions continue to be perceived as associated with an elevated risk for PPROM and PTL, irrespective of their confirmed neuroprotective effect [9, 24, 25].

Regardless of the timing of the surgical intervention, the release of the tethered cord is a vital stage of a MMC repair [26]. The ligament which connects the placode to the dura mater is observed in 90% of the fetuses undergoing surgery [26]. In case of fetoscopic surgeries, where OSB is merely covered with skin graft or biological material, the cord is not released, which constitutes a significant limitation of the surgical intervention.

Assessment of the uterine scar after an antenatal surgery, which is possible during a cesarean delivery, is also essential. In the MOMS study, scar thinning, partial scar dehiscence and uterine rupture were observed in 25%, 9% and 1% of the cases, respectively [2]. In our study, total scar healing, evaluated during cesarean section, was noted significantly more often in the study group as compared to CHOP (SG 42/55; 76% vs CHOP 44/87; 50.6), while scar thinning was found in 11/55 patients from the study group, which constituted 20% of the cases, and was statistically significantly less common ($p < 0.05$) as compared to CHOP (36/87; 41.4%). No severe surgery-related complications were observed during cesarean section.

In their meta-analysis, Kabagambe et al. [22] compared 11 FMMCR vs OFS cohort studies and reported higher rates of premature rupture of membranes (91 vs 36%, $p < 0.01$) and premature delivery (96 vs 81%, $p = 0.04$) for fetoscopic surgeries. These unexpected findings are consistent with the hypothesis by Pomini et al. [27] who demonstrated that even a small imperfection in the myometrial and amniotic barrier during FMMCR, with limited possibility of hermetic closure of the wound, results in leakage of the amniotic fluid with high concentration of prostaglandins (PGs) into the myometrium, inducing uterine contractility. Probably, the OFS method with the use of uterine stapling device while imbricating the second layer of the suture over all layers of the uterine muscle, chorion, and the amniotic membranes or the escape of the fetal membranes from the sewing mechanism of the uterine stapler, is the reasons why the intactness of the amniotic barrier is compromised and the amniotic fluid with high PGs concentration has contact with the myometrial cells. That hypothesis has been confirmed at our center by Zamłyński M et al. [28] who achieved mean gestational age of 34.4 ± 3.4 weeks of gestation in their study, with no deliveries at < 30 weeks of gestation, by applying anti-prostaglandin protocol with complete replacement of the amniotic fluid and the use of $COX^{1–2}$ prostaglandin inhibitors. Their protocol limited the use

of magnesium sulfate to 6%. Also, low incidence of complications such as CAS and PROM (6% and 15%, respectively) has been reported [28].

In our study, modification of the protocol, with the DeBakey clamps and anti-prostaglandin management with $COX^{1–2}$ prostaglandin inhibitors and complete replacement of the amniotic fluid, resulted in improved perinatal outcomes, i.e., significantly decreased rates of delivery at < 30 weeks of gestation, PROM, and uterine contractility leading to preterm birth. At the same time, ATH allowed to limit the use of tocolytics, which in turn resulted in lower maternal complication rates. Despite the positive trend, not all anticipated outcomes in our study reached statistical significance, which undoubtedly was the consequence of study limitations, i.e., no randomization and sample size. Another study limitation is lack of the follow-up and evaluation development of the prenatal operated children. Further research is necessary to verify the safety and effectiveness of antenatal OSB management, which might help establish a uniform surgical protocol both, for open fetal surgery as well as fetoscopic procedures.

CONCLUSIONS

ATH is a safe alternative technique of hysterotomy for myelomeningocele repair, which allows to limit tocolytic management, thus decreasing the incidence of maternal complications. That method of IUMR is associated with improved perinatal outcomes, i.e., lower rates of delivery at < 30 weeks of gestation, premature rupture of membranes and uterine contractility resulting in preterm labor, as well as lower prematurity rates and better neonatal outcomes. Least traumatic incision of the uterus and hermetic closure of the layers to restore the anatomic conditions allow for physiologic healing of the scar and maintaining its continuity, thus increasing the safety of the surgical procedure both, for the mother and the fetus.

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Table 1. Comparison of hysterotomy using automatic uterine stapling device and the alternative method.

Stage	**SG** n = 57 Moron [13]	**CG** n = 46 MOMS, CHOP [14, 15]
Incision of the uterine muscle	Two full-thickness stay sutures (polyfilament) are placed, 1cm initial incision of the uterine muscle is made using a monopolar electrode, fetal membranes are separated using Chaput Tissue Forceps and attached to the uterine muscle.	Ultrasound-guided placement of two full-thickness stay sutures (monofilament), initial opening of the uterus between the sutures.
Widening of the incision	Two DeBakey clamps are placed alongside the uterine midline and the uterine muscle	Placement of two staplers (Covidien Auto Suture, Norwalk CT) on the uterine muscle.

	between them is incised.	Ultrasound-guided placement of the sutures to exclude the presence of fetal tissue along the incision line. Widening of the uterine incision at 6–8 cm between the staplers.
Attachment of the fetal membranes	Hemostatic, continuous dual sutures, external to DeBakey Clamps are placed. Fetal membranes are sutured to half-thickness of the uterine muscle.	Stapler — encompassing the width of an automatic suture.
Amniotic fluid	Insertion of the catheter into the uterine cavity, total amniotic fluid replacement — 600 mL of 0.9% NaCl solution (heated).	Supplementation of the amniotic fluid.
Closure of the uterine muscle	First layer: half-thickness continuous intramucosal monofilament suture, with the fetal membranes.	First layer: a suture through the absorbable stapler and the chorioamniotic layers.
	Replacement of the amniotic fluid to baseline values (heated 0.9% NaCl), with simultaneous intra-amniotic administration of 1000 mg Cephazolin.	Supplementation of the amniotic fluid volume to baseline values (heated Ringer's solution), with simultaneous intra-amniotic administration of 500 mg Nafcillin or Vancomycin.
	Second layer: half-thickness polyfilament suture of the upper uterine muscle with the perimetrium.	Second layer: full-thickness continuous suture.

Table 2. Comparison of the clinical characteristics of the mothers and the fetuses with Chiari II at baseline, before for myelomeningocele repair at 20^{+0}–25^{+6} weeks of gestation in the following groups: SG vs CG vs CHOP vs VUMC

	SG **N = 57**	**CG** **N = 46**	**CHOP** **N = 100**	**VUMC** **N = 43**
Parity, n (%)				
Primiparas	**33 (57.9) ****	21 (45.6)	35 (35)	NA
Multiparas	**24 (42.1) ****	25 (54.5)	65 (65)	NA
Maternal age at screening, years, mean ± SD (range)	29.5 ± 4.2 (19–39)	29 ± 5	29.7 (18–41)	29.4 ± 5.5
Gestational age at screening, weeks/days, mean (range)	23.6 ± 1.6 (21 1/7–26 6/7)	23.4 ± 4.2 (22 1/7–26 0/7)	21 6/7 (18 1/7–25 4/7)	NA
Race, n (%)				
Caucasian	**57 (100)** *	46 (100)	88 (88)	41 (95)
Other	0	0	12 (12)	2 (5)
BMI, kg/m^2, mean ± SD (range)	25.8 ± 4.3 (16–37)	24.1 ± 3.2	26.3 (18.7–35)	25 ± 5.1

*p < 0.05; **p < 0.01 vs CHOP; NA — not analyzed

Table 3. Comparison of fetal and neonatal results after IUMR in the following groups: SG vs CG vs CHOP vs VUMC

	SG **N = 55**	**CG** **N = 46**	**CHOP** **N = 100**	**VUMC** **N = 43**
Fetal results				
Mean gestational age at delivery w/d, mean ± SD	35.0 ± 3.2 ($24^{6/7}$–$38^{4/7}$)	NA	34.3 ($22^{1/7}$–$37^{4/7}$)	34.4 ± 6.6
Gestational age at delivery, n (%)				
< 30 weeks	**0***	15/44 (34.1)	9/96 (9)	2/41 (4)
30^{+0}–34^{+6} weeks	21 (38)	11/44 (25)	35/96 (36)	12/41 (29)
35^{+0}–36^{+6} weeks	10 (18)	10/44 (22.7)	26/96 (27)	11/41 (27)
> 36^{+6} weeks	24 (44)	8/44 (18.2)	26/96 (27)	16/41 (39)
Mortality, n (%)	2/57 (3,5) 1 IUFD,	2 (3)	6/98 (6.1) 2 IUFD,	2/43 (5)

	1 NND		4 NND	
Neonatal results				
Birth weight, g mean ± SD (range)	2389 ± 886 (780–3870)	NA	2415 (501–3636)	2487 ± 631
Apgar score at 1/5 min. (points) mean ± SD (range)	7.4 (1–10) /8.0 (2–10)	NA	7.5 (1–10) /8.4 (3–10)	NA
Apgar scale n (%)				
0–3	NA	4 (16.7)	NA	NA
4–7		7 (29.2)		
8–10		13 (54.2)		
Evolution of hindbrain herniation (HH), n (%)				
Complete reversal of HH	**41 (74)** ## 30–31 w.g. MRI	10/28 (35.7) 30–31 w.g. MRI	59/83 (71.1) 12 m MRI	**15 (36)** *** on USG
Partial reversal of HH	6 (11) 30–31 w.g. MRI	13/28 (46.4) 30–31 w.g. MRI	13/83 (15.7) 12 m MRI	NA

*p < 0.05; ***p < 0.001 vs CHOP; ##p < 0.01 vs CG and VUMC. NA — not analyzed; IUFD — intrauterine fetal demise; NND — neonatal death within 24 h after IUMR

Table 4. Comparison of maternal results after IUMR in the following groups: SG vs CG vs CHOP vs VUMC

	SG N = 57	**CG N = 46**	**CHOP N = 100**	**VUMC N = 43**
Maternal outcomes, n (%)				
Pulmonary edema	0	1 (2.2)	2 (2)	0
Pre-eclampsia/hypertension	0	2 (4.3)	NA	NA
Gestational diabetes	0	1 (2.2)		
Blood transfusion	1 (1.7)	3 (6.5)	1 (1)	
Peritonitis	0	1 (2.2)	0	
Chorioamniotic separation	3/55 (5.4) ***	8 (17,3)	**22/96 (22.9)** ###	0

Oligohydramnios (AFI < 5 cm)	7/55 (12.7)	4 (8.7)	6/96 (6.3)	**10 (24)** **
Preterm premature rupture of the membranes (PPROM)	7/55 (12.7) ^ ***##	24 (52.2)	31/96 (32.3)	9 (22)
Contractile activity resulting in preterm labor (< 37^{+0} weeks)	**9/55 (16.3)** *	8/44 (18.2)	36/96 (37.5)	10 (24)
Tocolytics				
Magnesium sulfate	**3 (5.3)** *** ###	23 (50)	96 (100)	NA
$Beta_2$ adrenergic agonists	1 (1.7)	40 (87)	0	
Nifedipine	57 (100)	46 (100)	96 (100)	
Atosiban	2 (3.5)	NA	NA	
Total operative time, min	91.5 (80–112)	NA	78.5 (54–106)	NA
Length of hospitalization, days, mean (range)	**7.5 (4-8)** *		4.2 (3–8)	5
Estimated blood loss during labor, ml, mean (range)	690 (420–1.270)		754 (400–2.000)	NA
Blood transfusion during labor	2/57 (3.5)		3/89 (3.4)	0
Condition of the hysterotomy scar evaluated during the cesarean delivery				
Complete scar healing	**42/55 (76)** *	34 (73.9)	44/87 (50.6)	36 (88)
Scar thinning	**11/55 (20)** *	0	**36/87 (41.4)** ###	2 (4)
Partial scar dehiscence	2/55 (4)	3 (6.5)	6/87 (6.9)	3 (7)
Total scar dehiscence	0	2 (4.3)	1/87 (1.1)	0
Delivery into the abdominal cavity	0	1 (2.2)	NA	NA

*p < 0.05; **p < 0.01; ***p < 0.001 vs CHOP; #p < 0.05; ##p < 0.01; ### p < 0.001 vs VUMC; ^p < 0.001 vs CG. NA – not analyzed

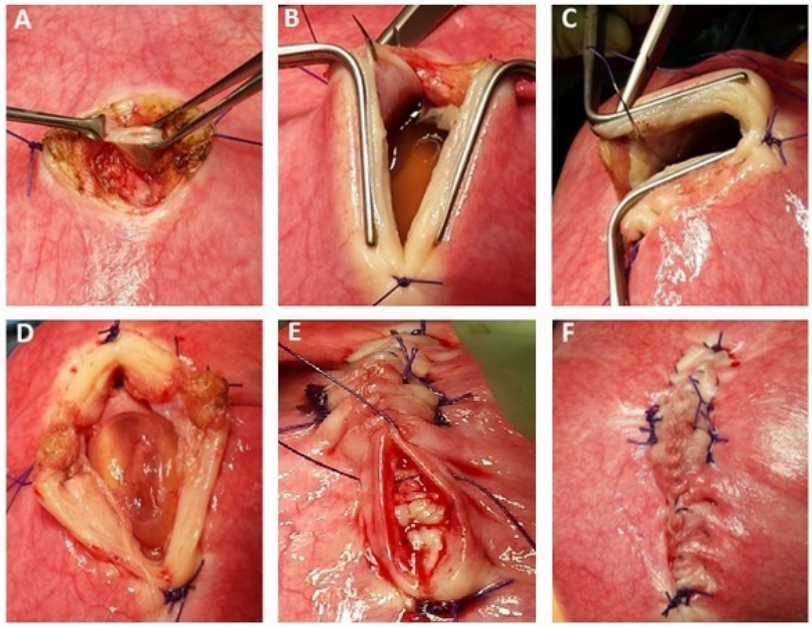

Figure 1. Stages of hysterotomy and hysterorrhaphy (own photos). **A**. Opening of the uterus and grasping of the fetal membranes after two stay sutures had been placed; **B**. Widening of the hysterotomy using the DeBakey clamps; **C**. Suturing of the wound edges and attachment of the fetal membranes; **D**. Final hysterotomy effect with visible fetal MMC; **E**. Hysterorrhaphy — half-thickness continuous suture through the myometrium and the perimetrium; **F**. Final hysterorrhaphy effect