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Keywords
Fetal surgery · Fetal myelomeningocele repair · Spina bifida · Histology · Hysterotomy · Wound healing · Fetal membrane · Myometrium

Abstract
Introduction: Among the risks associated with open fetal surgery, myometrium and fetal membrane issues are vexing problems since they may lead to uterine dehiscence or preterm premature rupture of membranes resulting in uterine rupture or preterm birth or both. The aim of this study was to examine whether stapled and sutured hysterotomy scars demonstrate partial or complete healing. ***Methods:*** Hysterotomy sites after open fetal surgery were clinically evaluated in 36 women during Caesarean section, classified into the categories intact, thin, and partially or completely dehiscent, then completely excised and histologically analyzed in 25 cases. The histological examination focused on wound healing of myometrium and fetal membranes. ***Results:*** The myometrium was intact, thin, and partially or completely dehiscent in 33, 58, and 9%, respectively. The interval between myelomeningocele repair and delivery did not correlate with the healing process. The myometrium showed a reparative zone (scar) with adjacent avital myometrium tissue, fibrosis, and inflammation with foreign body reaction. The intact myometrium was below 1 mm thickness in 56%. All fetal membranes showed complete dehiscence; in 41% they were completely avital. ***Conclusion:*** Our study provides evidence that the myometrium shows scarring with substantial thinning or dehiscence. Fetal membranes do not heal spontaneously. In order to prevent uterine rupture in subsequent pregnancies, we recommend the hysterotomy site to be completely excised after birth.

Introduction

Open fetal surgery for myelomeningocele (MMC) repair is nowadays a valid therapeutic option for selected cases [1]. A main risk after open fetal surgery is the 14% dehiscence and 14% rupture rate of the previous hyster-

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otomy in a subsequent pregnancy [2], which might end up in a life-threatening situation for mother and child. How the scar of the primary hysterotomy looks like is scarcely known. Furthermore, preterm birth remains a major complication after open fetal surgery, occurring in about 70–80% [1, 3] with or without iatrogenic premature preterm rupture of the fetal membranes (iPPROM). Known risk factors for iPPROM and/or earlier gestational age at birth include chorioamniotic membrane separation (CMS) [4, 5] and the occurrence of oligohydramnios after open fetal surgery [4]. Thus, the fetal membranes, which have to be handled with care during the fetal operation, play an important role for the fetal outcome. Although open fetal surgery is inherently connected with iatrogenic opening of the amniotic cavity, obvious postoperative loss of amniotic fluid is only reported in 32–46% after open fetal MMC repair [1, 3]. The fact that in 54–68% of the cases a watertight closure can be achieved until delivery can be explained either by the suture technique (use of staplers, fixating the fetal membranes tightly to the decidua and myometrium, in combination with an imbricating suture technique and long-lasting polydioxanone [PDS] sutures) [6] or a primary healing of the membrane defect. The latter explanation is still controversially discussed [7–11]. In vitro studies showed that amnion-derived cells were able to repair defects in up to 80% after 24 h [10] with a complete repair of epithelial cultures within 40 h [12]. Mesenchymal cell proliferation and lesion repair, however, are dependent on gestational age, with preterm cells being more active than term cells [12].

The objective of this study, therefore, was to evaluate the hysterotomy site after open fetal MMC repair including myometrium and fetal membranes in order to answer the question whether the standard method of hysterotomy for MMC repair shows features of partial or complete healing during the remaining months until delivery by Caesarean section (C-section). We clinically assessed how many hysterotomies were well healed, thinned out, showed an area of dehiscence, or were completely dehiscent and histologically evaluated how the repair of the myometrium looks like and whether fetal membranes healed in a waterproof way.

A better insight into the reparative mechanisms of both, myometrium and fetal membranes, following open fetal surgery could help to eventually modify both surgical closure technique as well as devices and materials used to prevent iPPROM, preterm birth, and uterine dehiscence.

Material and Methods

From December 2010 till May 2016, 37 fetal MMC repairs and C-sections were performed at our center according to our protocol. This protocol is basically analogous to the MOMS trial protocol [1] (with a few modifications deemed irrelevant regarding the scope of the present study), and it was institutionally approved (EK-ZH-Nr. 2015-0172). Beside compiling the usual patient stem data, we specifically focused on the aspects listed below.

Hysterotomy and Hysterotomy Closure

Two monofilament traction sutures were placed through the full-thickness uterine wall under ultrasound guidance and the initial opening of the uterus was performed by electrocautery between the sutures. The uterine stapling device (loaded with absorbable polyglycolic acid staples, Covidien Auto Suture, Norwalk, CT, USA) was then slid into the uterine cavity. By activating two staplers, a 5.5–11 cm uterine incision was performed. If necessary, additional stay sutures were placed at the corners of the incision. After fetal MMC repair, the uterus was closed in the same standardized way as in the MOMS trial [1] with two layers using PDS sutures. The first layer incorporated the absorbable staples and uterine membranes by a continuous suture. The second layer consisted of a series of interrupted full-myometrium thickness retention sutures placed every 1–2 cm. Afterwards an omentum patch was placed over the hysterotomy.

Clinical Assessment and Surgical Management of Repair Site at Delivery

Thirty-six women delivered at our hospital. During C-section, the previous hysterotomy site was clinically evaluated in these cases by the same team of feto-maternal specialists. It was classified into the same categories as in the MOMS trial [1]: intact/well healed (I), very thin (II), area of dehiscence (III), and complete dehiscence (IV). Because groups III ($n = 2$) and IV ($n = 1$) were so small, the latter 3 cases were combined with group III as "abnormal" hysterotomy site group for statistical analysis.

In cases in which the previous hysterotomy seemed well healed, the scar was only excised in 3 cases, because stapler material was still palpable. In all other cases of thinning, the previous hysterotomy was excised, except for 2 cases. One case of a placental abruption occurred during fetal surgery at 25.3 gestational weeks (GW) leading to immediate delivery of the baby. Therefore, this case was excluded from the classification and the histological examination.

Histological Evaluation of Resected Repair Sites

All 25 excised specimens were fixed on cork and sent for histopathological evaluation (Fig. 1). The pathologists were blinded to the clinical hysterotomy classification. The hysterotomy specimens were formalin fixed and paraffin embedded. Routinely, hematoxylin and eosin (HE) and Elastica-van-Gieson (EvG) staining of the slides of transmural cut sections were histologically assessed for the following parameters: reparative/regenerative changes, fibrosis, granulation tissue, inflammatory cells, hemosiderin deposition, hemorrhage, stapler material/foreign body reaction, amniotic fluid components, appearance of the fetal membranes, and adherence of adipose tissue on the serosal part. The diameter of the area with reparative changes (= reparative zone; scar) and of the remaining intact uterine wall (= intact zone) was

Table 1. Characteristics of the 37 women who underwent fetal MMC repair in Zurich, grouped into a normal hysterotomy group (= intact, well healed [I]) and an abnormal hysterotomy group (= very thin [II], an area of dehiscence [III], or complete dehiscence [IV]) after clinical assessment of the previous hysterotomy site during C-section

	All 37 cases	Normal hysterotomy $n = 12$	Abnormal hysterotomy $n = 24$
GA at fetal surgery, weeks	24.7±0.9	24.4±0.9	24.8±0.9
Maternal age, years	29.6±4.7	29.9±4.9	29.5±4.8
Nulliparous, *n* (%)	20 (54)	7 (58)	12 (50)
Ethnicity, *n* (%)			
Caucasian	34 (92)	11 (92)	22 (92)
Black	1 (2.7)	0	1 (4)
Hispanic	1 (2.7)	0	1 (4)
Others	1 (2.7)	1 (8)	0
Body mass index	27.1±5.2	26.3±6.1	27.2±4.6
Current smoker, *n* (%)	0	0	0
Married or living with partner, *n* (%)	36 (97)	12 (100)	23 (96)
Previous uterine surgery, *n* (%)	2 (5)	1 (8)	1 (4)
Cervical length, mm	42±5	42±6	42±5
Anterior placenta, *n* (%)	21 (57)	7 (58)	13 (54)

There was one case of an abruption of the placenta during fetal surgery at 25.3 gestational weeks, which was excluded. There were no significant differences between the normal and abnormal hysterotomy group. GA, gestational age.

measured in millimeters. Additional immunohistochemical stainings to highlight macrophages (CD68, DAKO) and myometrium (desmin, DAKO) were performed on an automated staining platform (Ventana).

Statistical analysis was performed using the statistical software package SPSS version 25.0 (IBM, SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD). The data were first tested for normal distribution with the Kolmogorov-Smirnov test. For comparison of means of 2 groups, an independent test or Mann-Whitney U test where appropriate. To compare proportions between groups, Pearson χ^2 test was applied. Statistical significance was given at $p < 0.05$.

Results

Maternal characteristics of the whole study population and the clinically normal and abnormal hysterotomy groups are presented in Table 1. There were no significant differences between the two hysterotomy groups.

After open fetal MMC repair, oligohydramnios, CMS, or iPPROM occurred in 22% ($n = 8$), 27% ($n = 10$), and 32% ($n = 12$), respectively. The average gestational age (GA) at delivery was nearly 36 GW (35.4 ± 2.1 GW). Seventy-three percent (27 of 37) of fetuses were delivered after 35 GW.

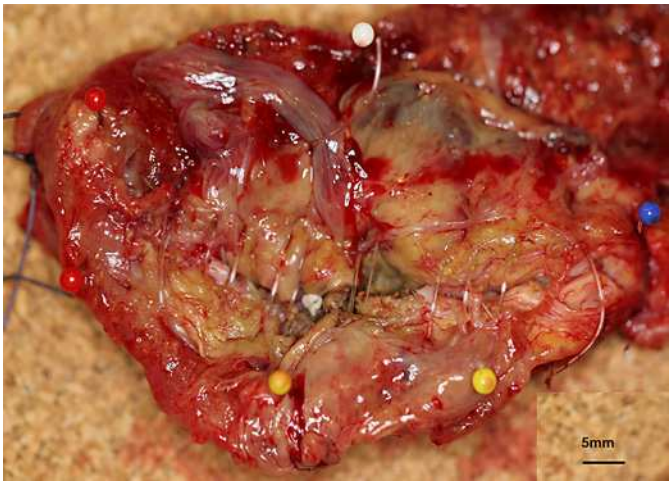

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Fig. 1. Example of an affixed native specimen of an excised previous hysterotomy. View of the inner side of the uterus with the non-healed fetal membranes.

Clinical Assessment of Repair Site at Delivery

The previous hysterotomy site at delivery was intact and well healed (I) in 33.3% ($n = 12$) of women. In 58.3% ($n = 21$), the previous hysterotomy was thin (II), and in 8.4%, an area ($n = 2$) (III) or a complete ($n = 1$) (IV) de-

hiscence was found. Outcome data of the clinically normal and abnormal hysterotomy groups are presented in Table 2. No significant differences were found between the 2 categories.

Two of three women with a leakage of amniotic fluid into the maternal abdomen, diagnosed by MRI, showed an area of dehiscence at C-section. In the third woman, a thin previous hysterotomy was diagnosed at C-section. The woman with a complete dehiscence presented with a uterine rupture at 36.9 GW.

Table 2. Outcome data of the clinically normal and abnormal hysterotomy groups

	Normal hysterotomy $n = 12$	Abnormal hysterotomy $n = 24$
GA at delivery, weeks	35.4±2.1	36±1.2
Seroma, *n* (%)	3 (25)	7 (29)
Hematoma, *n* (%)	0	3 (13)
Oligohydramnios, *n* (%)	1 (8)	7 (29)
CMS, *n* (%)	3 (25)	7 (29)
PPROM, *n* (%)	4 (33)	8 (33)
Spontaneous labor, *n* (%)	6 (50)	14 (58)

One case with an abruption of the placenta during fetal surgery at 25.3 gestational weeks was excluded. No significant differences were found between the 2 categories. GA, gestational age; CMS, chorioamniotic membrane separation; PPROM, premature preterm rupture of the fetal membranes.

Histological Evaluation of Resected Repair Sites

Histological findings are presented in Table 3. Reparative changes in the inner part towards the uterine cavity were found in all cases (Fig. 2a, b). In the central scar, smooth muscle was replaced by collagen (Fig. 3a–d). These changes consisted of areas with granulation tissue and of densely collagenized fibrotic areas with a mild to moderate amount of predominantly chronic inflammatory cells and hemosiderin deposits. The diameter of the reparative zone ranged between 4 and 21 mm and the underlying intact muscular uterine wall measured 0.5–6 mm. Distribution of the reparative ($p = 0.53$) and intact ($p = 0.41$) zone of the myometrium was the same among the different hysterotomy categories. The intact layer of the myometrium was below 1 mm thickness in 56% ($n = 14$) of cases. Some of them showed adherence to adipose tissue, corresponding to pieces of the detached omentum patch. The maximal measured thickness of an intact zone of the myometrium was 6 mm. Hemorrhage in the myometrium was just found in one case with uterine rupture. Mostly in central areas of the scar, foreign material (Fig. 4a, b) was present with surrounding giant cell reaction. The

Table 3. Histological findings of the excised previous hysterotomy sites ($n = 25$)

		Status of hysterotomy at delivery			
		intact, well healed	very thin	area of dehiscence	complete dehiscence
Fetal membranes					
Partially avital, *n* (%)	13/22 (59)	3 (100)	10 (62.5)		
Completely avital, *n* (%)	9/22 (41)		6 (37.5)	2 (100)	1 (100)
Missing, *n* (%)	3/25 (12)				
Myometrium	$n = 25$	$n = 3$	$n = 19$	$n = 2$	$n = 1$
Reparative zone, mm	11±3.8	14.7±5.5	10.3±3.5	12±4.2	12
Intact zone, mm	1.3±0.6	1.3±0.6	1.3±1.5	1.3±1.1	0.5
Fibrosis, *n* (%)	25 (100)	3 (100)	19 (100)	2 (100)	1 (100)
Inflammation					
Mild, *n* (%)	20 (80)	2 (67)	16 (84)	2 (100)	
Severe, *n* (%)	5 (20)	1 (33)	3 (16)		1 (100)
Foreign material/giant cell reaction, *n* (%)	25 (100)	3 (100)	16 (100)	2 (100)	1 (100)
Stapler present, *n* (%)	25 (100)				
Hemorrhage present, *n* (%)	1 (4)	0	0	0	1 (100)
Adipose tissue or adhesions on serosal area, *n* (%)	24 (96)	2 (67)	16 (100)	2 (100)	1 (100)

foreign material was partly reabsorbed and partly showed birefringence under polarized light. All fetal membranes showed complete dehiscence; in 41%, they were completely avital (Table 3). In all cases, smaller parts of fetal membranes were present in the luminal area, mostly with denuded or avital amniotic epithelium (Fig. 4c) and without an intact decidual layer, predominantly in the central parts of the samples. Towards the edges, there were some intact amniotic epithelial cells with underlying decidua. Components of amniotic fluid like squamous material was observed in all cases, sometimes towards the cavity but also located in deeper parts of the uterine wall.

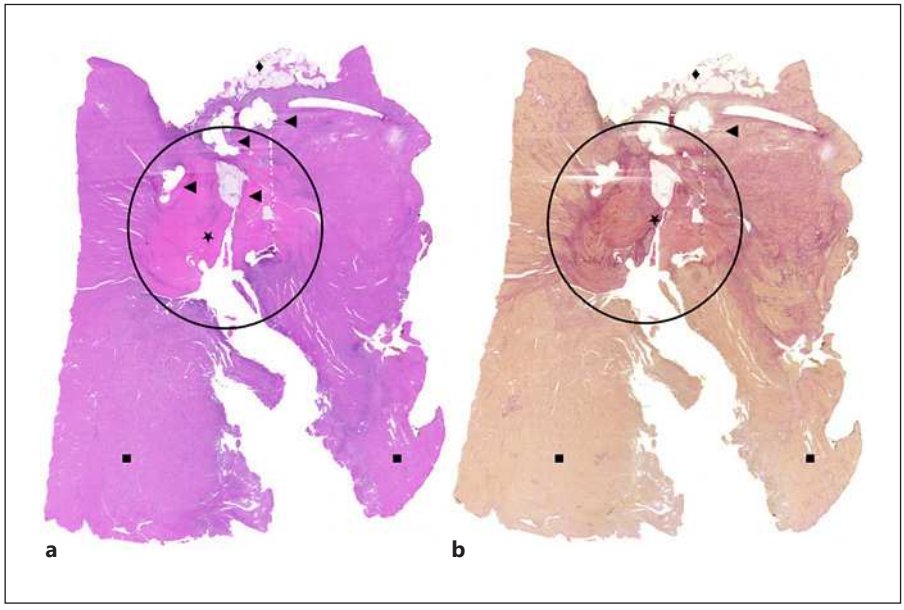

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Fig. 2. Overview of a cross-section of the uterine wall in areas of prior surgery: decidua overlying normal-appearing myometrium on the edges of the specimen (■). Central scar where smooth muscle is replaced by collagen (★). Partially reabsorbed foreign material (▶). Adherent adipose tissue on the outer peritoneal side in areas of scarring (♦). **a** H and E. **b** Elastica van Gieson. The circles indicate the hysterotomy scar.

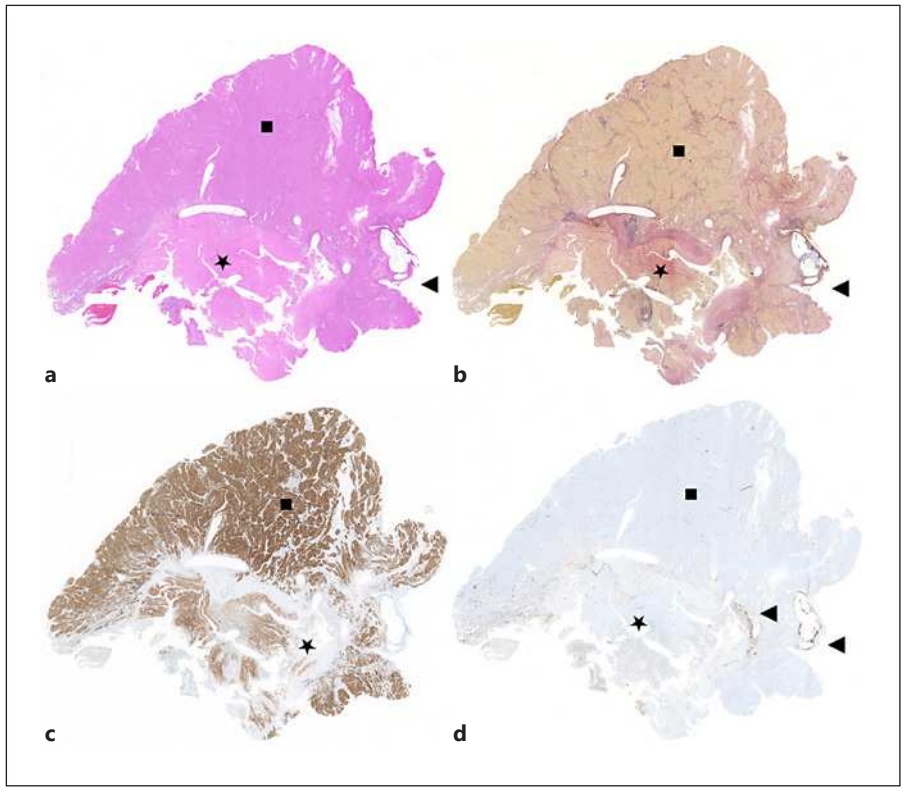

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Fig. 3. Overview of a cross-section of the uterine wall in areas of prior surgery. **a** H and E. **b** Elastica van Gieson. Regular-appearing myometrium (■) and central scar area where smooth muscle is replaced by collagen (★), highlighted in an immunohistochemical stain for smooth muscle marker desmin (**c**). Immunohistochemistry for CD68 (**d**) shows many macrophages in areas of scarring and around partially reabsorbed foreign material (▶) but not in normal-appearing myometrium (■).

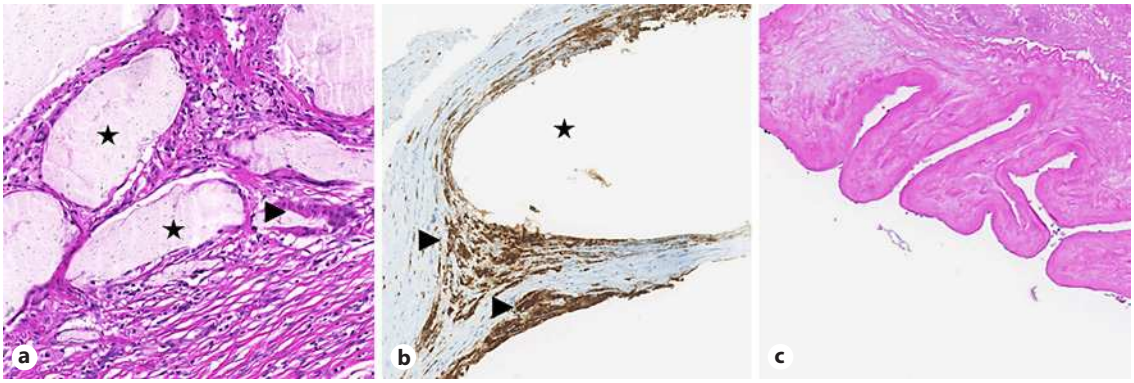

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Fig. 4. Partially reabsorbed foreign material in areas of prior surgery (★) with surrounding giant cell reaction and macrophages (▶). **a** H and E, original magnification 100×. **b** Immunohistochemistry for macrophages (CD68), original magnification 100×. **c** Avital fetal membranes in areas of scarring. H and E, original magnification 100×.

Discussion

The main finding of our study is that the myometrium does heal after open fetal MMC repair, but shows an incomplete wound healing with substantial thinning or dehiscence in a significant number of cases. We confirmed that human fetal membranes do not heal spontaneously after surgical hysterotomy closure using staples and sutures. The following aspects deserve a detailed consideration.

Healing of the Myometrium, Risk of Uterine Rupture, and Surgical Technique for Uterine Closure

As our histological examinations of the hysterotomy sites showed substantial thinning or dehiscence in 67%, these regions are weak points with an increased risk for a uterine dehiscence or rupture during further course of pregnancy or in a subsequent pregnancy. Previous studies reported a 10% dehiscence rate of the previous hysterotomy at C-section (partial in 9 and total in 1%) [1], which is comparable to the 9% rate of our study. Interestingly, the 3 cases in our series, which were clinically classified as "well healed," showed also substantial thinning in the histological examinations. In order to prevent uterine rupture in subsequent pregnancies, we recommend complete excision of the MMC repair hysterotomy site after delivering the baby.

But how high is the risk of uterine rupture in a subsequent pregnancy after an operation at the uterus? Landon and Lynch [13] reported a 1–12% risk of rupture after C-section with classical incision and a 0.5–0.7% risk after myomectomy. After open fetal surgery, uterine rupture in subsequent pregnancies occurred in up to 14% [2, 4]. That the surgical technique for uterine closure influences uterine scar healing seems obvious, but there is still no consensus about optimal uterine closure during C-section. Di Spiezio Sardo et al. [14] performed a systematic review and meta-analysis of randomized controlled trials on single- versus double-layer closure of the uterus and the risk of uterine scar defects. They included 9 randomized controlled trials (3,696 women) in their meta-analysis: women who received single-layer closure had a similar incidence of uterine scar defects (25.5 vs. 43.0%; RR 0.77; 95% CI 0.36 to 1.64) compared with women who received double-layer closure [14]. Myometrial thickness on ultrasound was thinner in single-layer sutures compared with double-layer sutures (–2.19 mm, 95% CI –2.80 to –1.57), but no differences were found in the incidence of uterine dehiscence (0.4 vs. 0.2%; RR 1.34, 95% CI 0.24 to 4.82) or uterine rupture in the subsequent pregnancy (0.1 vs. 0.1%; RR 0.52, 95% CI 0.05 to 5.53) [14].

Recently, Zaretsky and colleagues [6] published their modified hysterotomy closure technique for open fetal surgery. After placement of a series of interrupted full-myometrium-thickness #0 PDS retention sutures placed every 2–3 cm, a running #0 PDS suture to re-approximate the stapled myometrium edges was placed followed by a third imbricating layer. Interrupted #0 PDS U-stitches were performed resulting in serosal-to-serosal apposition above the underlying closure. Only 23% (n = 10) of their patients delivered at their center. In 88% (43 of 49), they received operative reports. They reported a rate of completely healed hysterotomies of 95.4%. In only 4.6% (2 cases) was a thinning or partial dehiscence observed. However, their average GA at delivery was 31.7 ± 3.8 GW. The authors stated that they do not believe that the lower GA at delivery accounts for the dramatic reduction in hyster-

otomy complications nor that the third layer results in a reduction in GA at delivery [6]. Whether any healing or even more necrosis was present in fetal membranes or myometrium after a third layer was not examined.

Bennett et al. [15] described another modified approach to uterine entry. After opening of the fetal membranes, a full-thickness running locked suture was used to secure the membrane to the uterine wall. Surgical staplers were used at one time to enlarge the hysterotomy. For the uterine closure, a full-thickness running locked 0 PDS suture, supplemented at intervals with full-thickness figure-of-eight interrupted sutures, was applied. They reported an intact hysterotomy status at delivery of 88% and a uterine complication rate of 12%, with 2 cases of thinning and 3 cases with an area of dehiscence in a cohort of 41 women [15]. Unfortunately, they also did not provide any histological information on the previous hysterotomy site.

Fetal Membrane Healing

Our study on the reparative activity of fetal membranes after open fetal MMC repair revealed that the fetal membranes do not heal spontaneously after surgical closure of the uterotomy using staples and stitches based on the histological findings of necrosis. This is in accordance with findings after fetoscopic procedures [8, 11], although increased levels of metalloproteinases in the amniotic fluid of sheep after fetoscopies suggested an active fetal membrane remodeling process [16] as it is found in the wound healing process of skin or cornea [17, 18]. Interestingly, mesenchymal progenitor cells from the amnion can be mobilized, proliferate, and maintain their native extracellular matrix production by use of engineered matrices containing migration- and proliferation-inducing factors, such as platelet-derived growth factor, basic fibroblast growth factor, or epidermal growth factor [19]. These results suggest that production of tissue components with defined mechanical and biochemical properties and the ability to present migration- and proliferation-inducing factors could be a clue in sorting out the clinical problem of fetal membrane wound healing.

An aspect for the absent membrane healing after open fetal surgery could be their adherence to the polyglycolic acid staples. These staplers are indeed absorbable, but polyglycolic acid sutures depolymerize only about 5–6 weeks after application [20]. In monkey uteri, these staplers virtually dissolved completely by 40 days with a minimal inflammatory response in the myometrium [21]. How the fetal membranes in the primates reacted is not mentioned [21]. Interestingly, our study found also an inflammatory reaction with giant cells around residual stapler material in all myometrium sections. The myometrium of all samples showed that healing was accompanied by dense fibrosis and some inflammation. However, the advantage of these absorbable staplers is that they achieve excellent hemostasis within the hysterotomy even when varicosis is present during C-section [22]. They are visible on ultrasonography throughout the postpartum period [23], but no previous study on these absorbable uterine staplers during C-section reported on wound healing after their application [22–24].

Whether another operation technique without staples shows less tissue damage is not proven. In Brazil, the staplers are not accredited by the government agency. Therefore, the fetal membranes are sutured to the myometrium using a continuous monocryl 4–0 [25]. Botelho et al. [25] reported their outcome after fetal MMC repair through a mini-hysterotomy, as follows: CMS rate of 2.6% (1 of 39 women), PPROM rate of 23% (n = 9), rate of an intact hysterotomy site at delivery of 95% (n = 37), and a 5% rate of partial uterine dehiscence. Unfortunately, they did not provide any histological information on the myometrium or fetal membranes of the previous hysterotomy.

An advantage of our study is the combination of a clinical hysterotomy classification with the histological evaluation of the hysterotomy site after open fetal surgery including myometrium and fetal membranes with a considerable number of cases. Other strengths of our study are that 97% of all women delivered at our center and that always the same team of 4 fetomaternal specialists performed the C-sections and evaluation of the previous hysterotomies in these cases. Furthermore, the pathologists were blinded to the clinical findings. A certain limitation of this study is that only 25% of the intact, well-healed hysterotomy cases were excised and no histological statement can be made on the others.

In conclusion, our study demonstrates that the myometrium does heal, but shows an incomplete wound healing with substantial thinning or dehiscence in a significant number of cases. In contrast, human fetal membranes do not heal spontaneously after surgical hysterotomy closure using staples and sutures. Therefore, we recommend completely excising the former hysterotomy site at delivery in order to prevent potentially dangerous uterine dehiscence or even rupture in subsequent pregnancies.

Disclosure Statement

All authors declare no conflicts of interest.

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