Chapter

Prevention of Cesarean Scar Defects: What Is Possible?

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Abstract

Defect healing of the uterotomy at ceasarean section (CS) results in a morphological und probably functional disruption of the anterior uterine wall. Clinical sequelae concern subsequent pregnancies with a broad range of complications before and during pregnancy as well as at birth. In the following chapter, we provide an overview about the definition, diagnosis, symptoms and pathogenetical mechanisms of CS scar defects. Keeping in mind the pathogenesis allows to introduce preventative approaches.

Keywords: suture technique, peritoneum closure, contractions, immunology, tissue repair

1. Introduction

1.1 Definition of uterine scar defects

With the increasing rate of CS worldwide a meaningful long-term complication has been observed within the last two decades: the development of defects of the uterine scar. Previously, these defects were referred to as "pouch", "uterine/cesarean scar defect", "uterine diverticulum" or "sacculation" [1]. Nowadays, the terms "isthmocele" or "niche" are best established [2].

As niches occur almost exclusively after CS [3, 4], they are located within the uterine isthmus at the site of the former uterotomy [5]. There is still no international consensus about the exact definition of a niche or a standardized classification. Therefore, prevalence rates are of wide range [1]. Due to ongoing research, initial gaps in knowledge start to close [6]:

Most commonly, a niche is defined as any indentation of the myometrium at the location of the uterotomy with a depth of at least 2 mm [2]. The depth of a large niche either ranges between 50 and 80% of the myometrial thickness, or leaves a remaining myometrial thickness (RMT) thinner than 2.2 mm (measured by transvaginal ultrasound -TVUS-) or 2.5 mm (measured by contrast enhanced sonohysterography –SHG-), respectively [1]. Concerning the shape of the niche, the following subclassification was suggested: A simple niche (without any further branch), a simple niche with one branch, and a complex niche (with more than one branch) [2] (**Figures 1**–**3**). In most cases, the appearance of a niche is triangular in shape, but it can also be round [3]. A scar dehiscence is defined as a complete defect of the myometrium (**Figure 4**) [3].

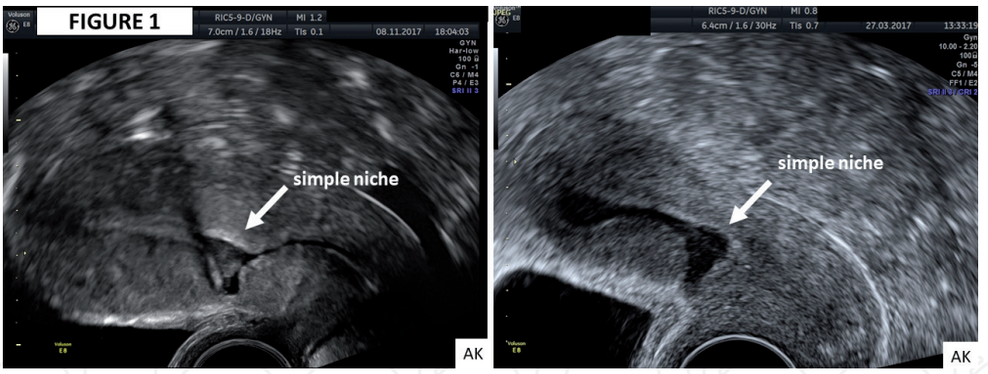

Figure 1.
Simple niches.

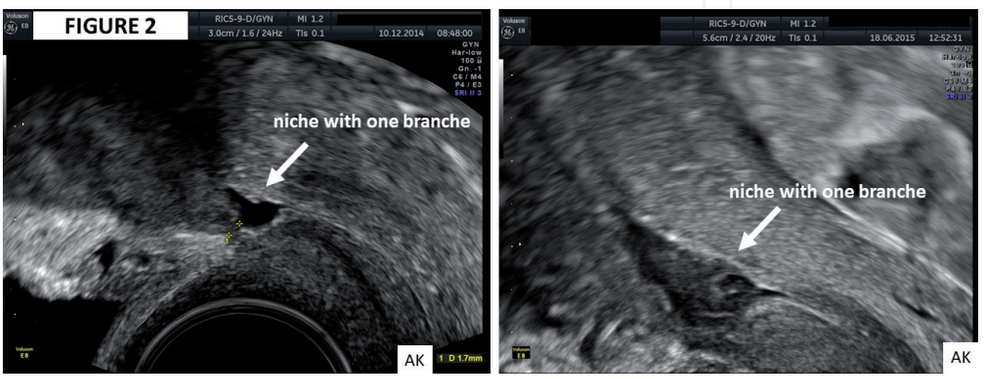

Figure 2.
Simple niches with branches.

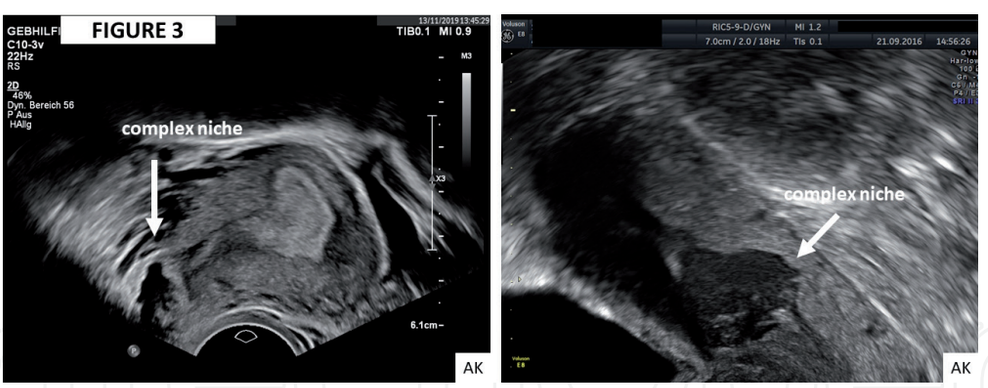

Figure 3.
Complex niches.

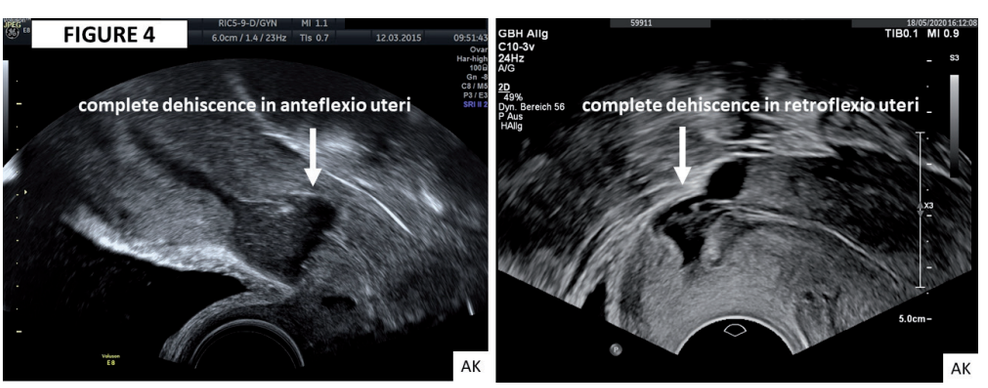

Figure 4.
Complete defect of the myometrium.

Several studies examined the prevalence of niches, resulting in a range from 22 to 84% of patients after CS [6, 7]. This rather wide range results from the different modes of assessment (TVUS or SHG) and the timing of the examination (several weeks up to 12 months after CS).

2. Niche diagnosis

2.1 Methods

Several methods exist to diagnose a niche: magnetic resonance imaging (MRI), hysteroscopy, two- or three-dimensional TVUS and SHG with the aid of saline or gel infusion.

By MRI, the thickness of the remaining myometrium can be measured quite exactly using T2 weighted views. As an advantage, the evaluation does not depend on the examiner's experience and consequently the measurements of RMT by MRI are more objective compared to those assessed by ultrasound [8]. On the other hand, MRI examinations are costly and not always available.

Hysteroscopy can simultaneously be used for diagnosis as well as for therapeutical interventions. As long as no mucus or residual blood obstruct the view, the potential defect can be visualized and treated in the same session. However, it is not possible to determine the RMT from inside the uterine cavity [9].

Ultrasound is widely available, harmless and rather unexpensive. However, diagnostic quality strongly depends on the examiner's experience. The exploration of a niche and the RMT can be facilitated by the use of saline or gel infusion enhancing the contrast. Several studies comparing ultrasound methods found that the use of contrast SHG is more sensitive and specific than simple TVUS for the identification of a niche [10]. In a prospective study of 371 patients, half of all myometrial defects remained undiagnosed with TVUS but could be seen with SHG, resulting in a higher prevalence of a niche using SHG (45,6% vs. 22,4%) [7] (**Figure 5**). A systematic review including 21 studies found a niche prevalence in up to 84% of women with a history of CS by using SHG for diagnosis [1]. SHG was considered as comparable to hysteroscopy in diagnosing defects of the myometrium with a sensitivity of 87%, specificity of 100%, a positive predictive value of 100%, a negative predictive value of 95% and an overall accuracy of 96% [1]. Because of the clear advantages of SHG, currently most authors consider it as a gold standard for diagnosing niches. If not available, simple TVUS with intrauterine fluid (e.g. blood during menstruation) to enhance the contrast [2, 7] constitutes a possible alternative.

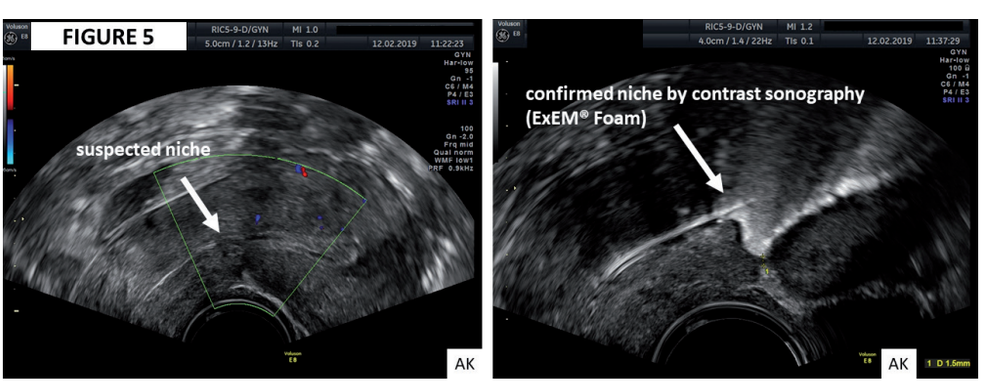

Figure 5.
Diagnosis of a niche without (left) and with (right) contrast enhanced sonohysterography.

2.2 Timing

For most exact results in measurement, optimal timing of the examination is necessary. This includes the day in the menstruation cycle as well as the interval to previous CS. Most authors agree that the best time for ultrasound is either during menstruation or in early follicular phase shortly after menstruation [2, 6]. The accumulation of blood in the isthmocele together with a thin endometrium facilitate the detection of the defect. Other authors prefer the time proximate to ovulation, when cervical mucus may distend a niche located within or near the cervix [11]. Using the follicular phase of menstrual cycle also is suitable to exclude the presence of an early pregnancy.

Unfortunately, data is limited concerning the best time interval to previous CS. The suggested time ranges from three to six months [2, 7]. Due to the fact that proper wound healing after CS takes up to six months [7], at least half a year interval before measuring the myometrial thickness is recommended.

2.3 Procedure

The assessment of the myometrium in search of a niche requires to follow a systematic workflow. A full bladder helps visualizing the lower uterine segment (LUS) but is not obligatory for the examination [2]. Variation in pressure with the probe is useful for an optimal image. Using doppler imaging, the differentiation between niche and myometrial vessels is possible. In 2019, Jordans et al. established a modified Delphi procedure for the sonographic examination of niches [2].

Briefly, the examination starts in the midsagittal plane including a proper visualization of the cervical canal. By panning the probe laterally left and right, the niche should become visible. Once the defect is identified measurements of length and depth are made. If the niche is complex with branches, both length and depth should be measured for every branch. Furthermore, the distance to the vesico-vaginal fold (VV) should be measured placing the caliper at the level where the residual myometrium is thinnest (**Figure 6**). Exactly at the same point measurement of the RMT is done. Next, adjacent myometrial thickness (AMT) is measured close to the niche. The last measurement in the midsagittal plane is the distance to the external os parallel to the cervical canal starting at the distal point of the niche (**Figure 7**).

Afterwards the niche is visualized in transverse plane by rotating the probe by 90 degree. Here, the niche's width can be measured. The transverse plane works best for detecting branches in case of complex niches.

Nevertheless, standardized cut off parameters for niche characterization, especially in the case of large niches, are not yet established. The following parameters

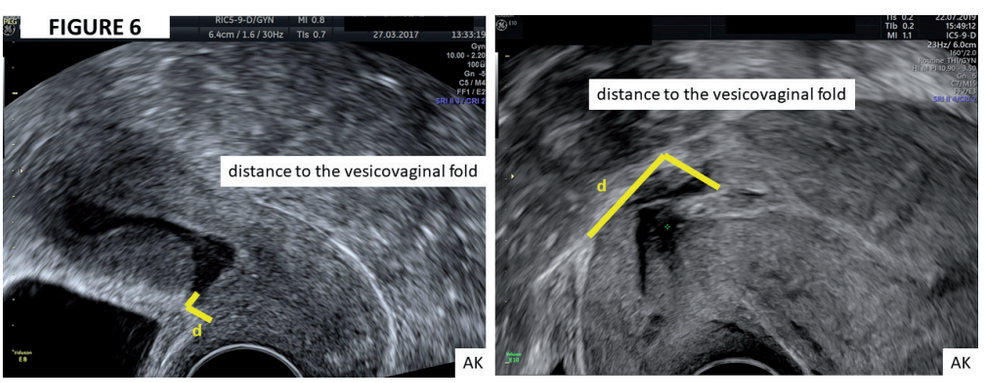

Figure 6.
Technique of niche measurement: distance between the niche and the vesicovaginal fold.

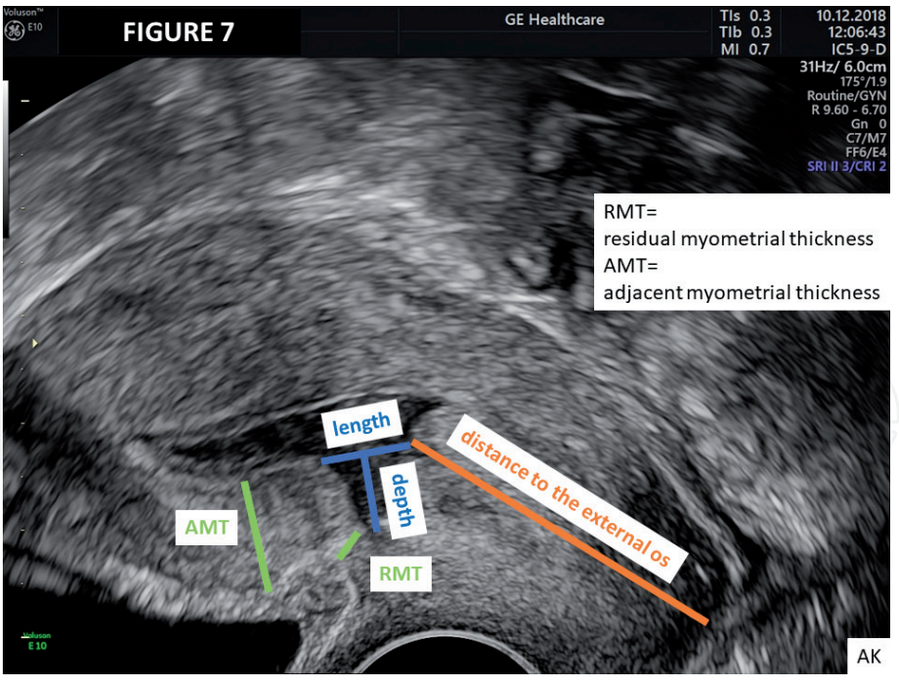

Figure 7.
Technique of niche measurement following the Delphi procedure [2].

seem to be suitable for clinical practice: the ratios RMT/AMT, depth/RMT, depth/AMT and RMT [1, 2, 7].

A further issue that needs to be considered in future studies is the clinical relevance of the size of the niche. To date, no study has clearly shown a direct correlation between the scar's thickness and the risk of e.g. uterine rupture [3, 5, 12, 13]. Therefore, further studies are needed to evaluate the association between a niche's size and clinical sequelae.

2.4 Niche symptoms

Although niches can also be asymptomatic [6], niche-associated problems differ between non-pregnant and pregnant women according to the symptoms and potential complications.

2.5 Non-pregnant women

Today there is international consensus that specific gynecological problems can be caused by a niche:

As the main symptom, abnormal uterine bleeding, e.g. postmenstrual spotting, results from a retention of menstruation blood in the indentation of the myometrium [14]. Nearly 30% of women with a niche report spotting compared to only 15% without a niche within 6–12 months after a CS [11]. An insufficient contractility of the myometrium seems to be the main reason [1]. Also the size of the niche is important since women with larger niches are reported to have more severe bleeding issues [2].

Several studies describe dysmenorrhea, dyspareunia or even chronic pelvic pain as further symptoms of a niche [6, 11]. The reason for pain during the menstruation bleeding might be found in the myometrium's distension caused by the accumulating blood.

Importantly, the presence of a niche may affect fertility: the accumulation of blood in the niche deteriorates the quality of cervical mucus, potentially inhibiting

sperm transport or referring to an impaired implantation of the embryo [15]. It has been shown that the repair of scar defects is able to restore fertility [15].

Therefore, a symptomatic niche can mimic frequent gynecological issues like endometriosis or pelvic inflammatory disease and should be considered as a differential diagnosis.

Addionally, an elevanted risk for intervention-related complications during a curettage oder device placement should be considered in the presence of a niche.

2.6 Pregnant women

In contrast to non life-threatening problems in non-pregnant women, the presence of a niche may derive in major complications during pregnancy. There is an important risk of a CS scar ectopic pregnancy (CSP) at the site of the niche [16] (**Figure 8**). CSP occur with an overall incidence of 1: 1800–1: 2216 pregnancies [17]. Even in early-pregnancy, CSP treatment can be associated with severe hemorrhage [18].

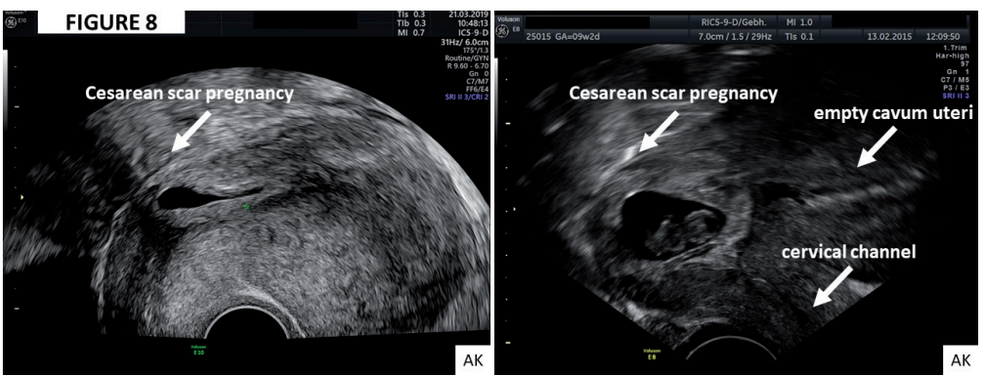

Figure 8.
Cesarean scar ectopic pregnancy.

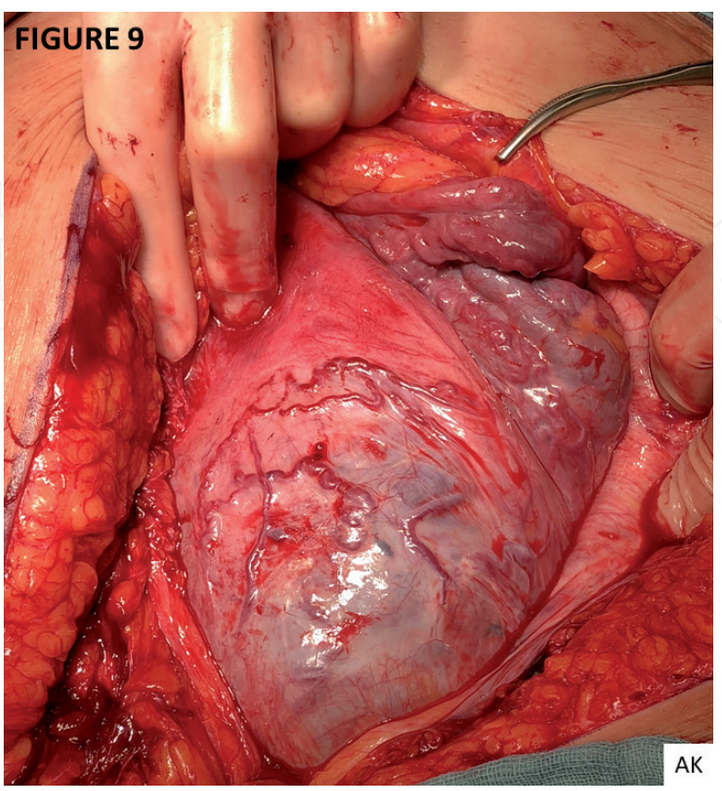

Figure 9.
Intraoperative demonstration of placenta percreta.

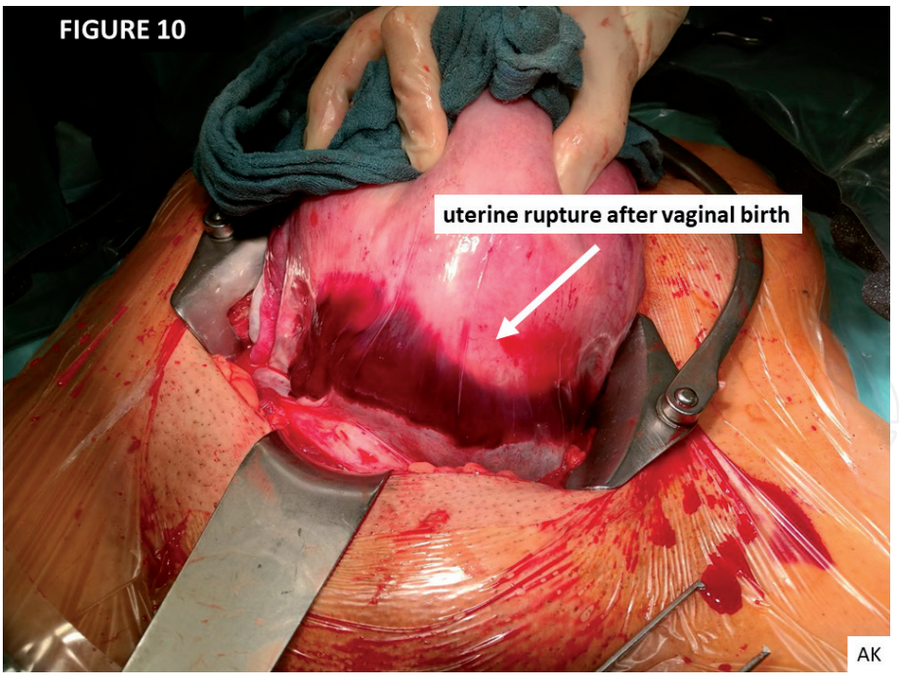

Figure 10.
Uterine rupture after vaginal delivery in a patient with a former Cesarean section.

In most cases, CSP results in morbidly-adhaerent placenta like placenta accreta, increta or percreta [19]. Short- and longterm complications can be detrimental [20] (**Figure 9**).

Uterine rupture during pregnancy and labour is a rare but life-threatening sequeleae both for the mother and the fetus [21] (**Figure 10**). It appears conclusive that a thinner myometrium increases the risk of a rupture. Unfortunately, no cut-off value of myometrial thickness was defined as a reliable predictor of uterine rupture. A RMT > 2.1–4.0 mm and LUS thickness between 3.1–5.1 mm were described as strong negative predictive values for uterine rupture. A RMT of 0.6–2.0 mm was considered as a positive predictive factor for uterine rupture [22].

Since the clinical consequences of niches can not be exactly predicted, the prevention of niches formation is crucial. Insights into the pathogenesis of niche development will allow the initiation of preventative approaches.

3. Pathogenesis of niches

Many studies focused on potential risk factors for developing niches after CS. The most promising considerations comprise problems in wound healing including a (reversible) retroflexio uteri, the number of previous CS and the location of the uterotomy. The latter is affected by the stage of labour and the dilation of the cervix when CS is done. For the surgeon the most important issue particularly might be the optimal technique for closure of the uterotomy.

3.1 (Reversible) Retroflexio uteri

In most women, the physiological direction of the uterus in the pelvic cavity is an anteflexion. A retroflexion is a non-pathologic alternative to the norm. In 2016, Ryo et al. reported that the uterus may change its flexion after delivery, shifting from ante- to retroflexion. Compared to vaginal delivery, a retroflexed uterus was observed significantly more frequently after CS, increasing with the number

of previous CS [23]. Other findings demonstrated a higher prevalence of niches in retroflexed uteri and notably large defects in cases of retroflexion [12, 13, 24]. Nowadays, it is widely accepted that there is a strong coincidence of niches and a retroflexion of the uterus [11–13, 25].

However, an important question remains: Does a retroflexion of the uterus facilitate the development of a niche or does a niche cause a (reversible) retroflexion? There are explanations for both hypotheses:

On the one hand, after CS, adhesions might cause mechanical tension on the anterior uterine wall leading to a retraction of the scar tissue with poor blood perfusion and resulting in an impaired wound healing. The retraction might be intensified if the uterus is already retroflexed [11]. This hypothesis is supported by the finding that the risk of developing a niche is more than twice higher, when the uterus is retroflexed [1].

On the other hand, the consideration of a niche causing a (reversible) retroflexion also seems plausible. Ryo et al. did not only examine the changes in uterine flexion after delivery but also provided a fairly logic objection to the above-mentioned pathogenesis: If a niche developed due to mechanical tension and retraction of the scar, the defect would be found at the outside of the anterior uterine wall [23]. In contrast, niches are generally found at the cavitary side of the myometrium. The uterine incision and the developing niche may compromise the contractility of the myometrium, leading to an imbalance between the anterior and posterior wall, causing traction backwards and resulting in a retroflexion.

Therefore, it seems more plausible that first a niche develops and second the uterus becomes retroflexed. Further studies are needed to better understand the role of a retroflexion in the pathogenesis of niches.

3.2 Number of previous Cesarean sections

Niches are almost solely diagnosed in women after CS. No studies report myometrial defects after vaginal birth. Osser et al. described a median myometrial thickness at the isthmus of 11.6 mm after vaginal delivery, compared to 8.3 mm/6.7 mm/4.7 mm after one/two/three or more CS [3]. Largely all studies report a positive correlation between the number of previous CS and increasing rates of niches [1, 3, 6, 23, 25]. The niche prevalence was found to be up to 63,1% after one, 76–81% after two and 88–100% after three CS, respectively [3, 7]. Not only the number of niches increase, but also the scar defect itself becomes larger the more CS found in the patient's history [3]. Total defects with no remaining RMT were more frequently found in women with multiple CS: 6%, 7% and 18% after one, two and ≥ three or more CS, respectively [1].

The possible explanation seems to be impaired wound healing: trauma to the uterine wall disrupts the physiological healing process due to a reduction of vascular perfusion [25].

Addionally, increasing CS rates correlate with higher prevalence of retroflexed uteri, underscoring the hypothesis about the association of retroflexed uteri with niches development [23].

Therefore, the careful evaluation of each CS in terms of its necessity seems to be the most promising step to reduce myometrial defects.

3.3 Position of the uterotomy and timing of the CS

The most common technique of uterotomy performance is a transversal incision of the isthmo-cervical region. During labour, the isthmo-cervical region undergoes continuous changes. First, the thinning and elongation, recognizable by a lifted

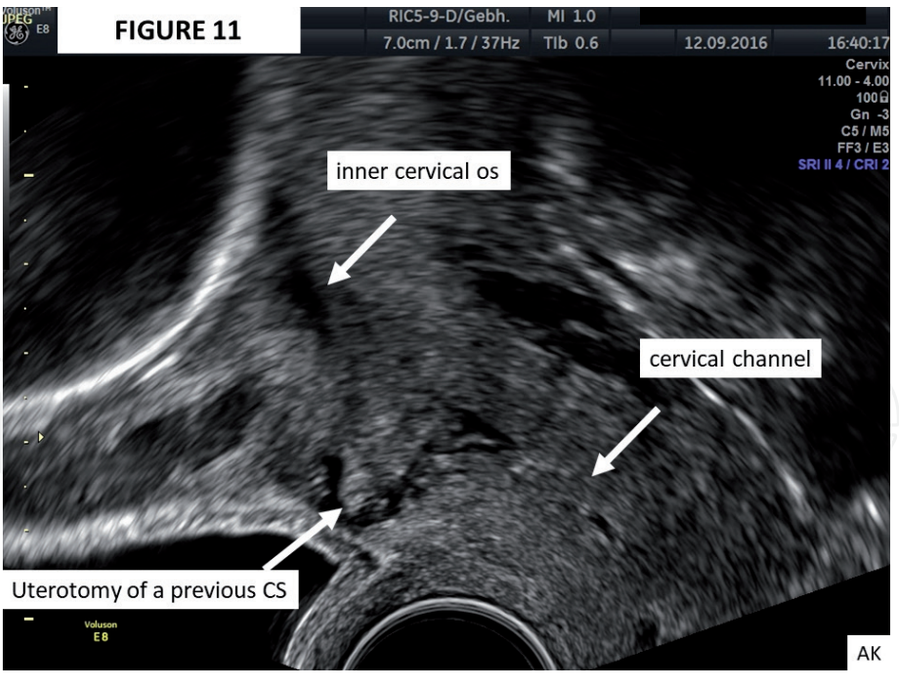

Figure 11.
Uterine incision of a former CS within the cervical channel.

urinary bladder or plica vesicouterina. Consecutively, also the inner cervical os with its mucous glands and only few muscular tissue moves upwards. Hence, if the surgeon incides the uterus at the same height in late labour as in an earlier stage of labour, the incision is placed either lower or even beneath the inner cervical os (**Figure 11**). The most likely explanation for distinct wound healing effects is found in the morphological difference between the region around the inner cervical os and the myometrium above. The mucus may dilate the sutured rims of the uterotomy or cause retention cysts, both leading to impaired wound healing [11, 26]. Furthermore, as a result of poor contraction in this area, wound edge adaptation may be insufficiently.

Therefore, CS at advanced stage of labor may provoke a lower incision including cervical tissue and resulting in more scar defects. On the other hand, contractions or rupture of membranes have already occurred in advanced stage of labor with a crucial and beneficial influence on the postoperative healing process of the uterine scar.

The following chapters discusses the effects of both of these opposite forces on scar healing:

On the one hand, CS performed before the onset of labour resulted in a thinner uterine wall in subsequent pregnancies than CS performed during labour [27, 28]. Jastrow et al. [29] showed significantly decreased LUS measurements depending on stage of labour prior to the CS (full LUS after CS in latent phase: 2.8 mm, in active phase: 3.1 mm and in CS prior to labour 2.4 mm, $p < 0.01$). Importantly, Park et al., were able to demonstrate no increased risk to develop a niche when CS was performed in situations with >8 cm dilated cervix [6].

A CS performed intrapartum reduces the probability to develop a placenta praevia in a following pregnancy [30] as well as the risk of uterine rupture in cases of vaginal birth after a CS [31], underlining the importance of contractions on wound healing. A case control study of 307 women showed a threefold increased risk to develop a morbidly adherent placenta after an elective CS compared to an emergency CS. In this study, the increasing severity of a morbidly adherent placenta (placenta accreta versus increta versus percreta) was associated with a

higher probability of a prior elective CS, respectively [32]. Hence, we hypothesize that uterine contractions and their immonological triggers may contribute to the postpartum tissue repair. To elucidate possible mechanisms, we shorthly discuss this topic on the end of this chapter.

On the other hand, several studies demonstrated, that the incidence of defect wound healing increased significantly when CS was performed in advanced labour [1, 6, 33].

It was shown that a prolonged labour beyond 5 hours or a CS performed during active labour with the cervix is dilated >5 cm, is associated with an increased risk to develop a niche (5–9 hours OR 13.0 (2.2–76.6), > 10 hours OR 33.1 (6.6–166.9); $p < 0.001$) [21].

Also, a higher percentage of RMT < 3 mm was observed in cases with advanced cervical dilatation at CS [7]. Park et al. showed a higher risk of niches in cases with a CS at a cervical dilatation of 5–7 cm compared to cases with CS at closed cervix [6].

But how can these conflicting results be explained?

The hypothesis to answer this question is that in cases of CS at advanced stage of labor, the uterotomy position is closer to the internal cervical os and wound healing is compromised in this area. This hypothesis can be confirmed by the following observations:

As shown by Vikhareva Osser, the uterotomy position was exactly positioned at the internal os in 97% of cases with a cervical dilatation >5 cm compared to 55% in cervical dilatation <5 cm [21].

Hanacek et al. demonstrated that if the CS is performed at full cervical dilatation, the resulting scars were closer to the external os and the RMT was markedly thinner [34]. These findings might be explained by the localization of the uterine incision, which is often overly caudal, due to cervical incorporation into the lower uterine part.

A very recently published prospective cohort study showed a higher prevalence of scar defects when the uterotomy was placed cranially of the internal os compared to a uterotomy placed caudally of the internal os in patients with a first CS [35]. Subgroup analysis, however, showed that in cases of a CS before the onset of labor, the uterotomy position was mostly cranial of the internal os whereas in cases with advanced labor, the position was rather caudal. Therefore, the beneficial effect of advanced labor was undermined by the more caudally position of the uterotomy.

In order to confirm the negative effects of a low uterine incision, a prospective randomized study published in 2019 compared the incidence of niches in patients with low and high incision (2 cm below vs. 2 cm above the plica vesicouterina) 6–9 months after an elective CS. Large scar defects occurred significantly more often in the low-incision group (41% vs. 7%) [33]. This leads to the conclusion, that the position of the uterotomy is one of the most important factors in the pathogenesis of niches.

In summary, CS performed under contractions in active stages of labour may elicit mechanisms that improve scar healing subsequently resulting in thicker RMT and in reduced development of niches. However, this benefit inverts when labour or cervical dilatation is too advanced and the uterotomy is localized overly caudal. In consequence, every obstetrician needs to consider the stage of labour and the cervical dilation for choosing the optimal position of uterine incision.

3.4 Closure of the uterotomy

Closure of the uterotomy is a crucial and very controversially discussed topic. Several studies addressed this important step in order to optimise scar integrity, endometrium rehabilitation, postoperative recovery and the reduction of risks in

subsequent pregnancies. The following section illustrates partially contrary strategies to close a uterotomy in order to prevent a niche.

3.5 Single versus double layer

Single vs. double layer sutures of the myometrium were discussed in a large number of studies and reviews. It is currently postulated that double layer is superior to single layer as it is associated with a thicker RMT (4.6 vs. 5.2 mm) [34, 36–38] and lower niche prevalence (4.2% vs. 1.3%, $p < 0.001$, RR 0.32, [28]).

These observations were confirmed in a large review including 20 randomised controlled trials or prospective cohort studies and more than 15000 women. Here, a double layer suture resulted in a thicker RMT (+ 1.26 mm double layer vs. single layer), a better healing ratio (=anterior wall thickness/anterior wall thickness + height of the wedge-shaped defect) and less dysmenorrhoea than single layer suture [39]. A 50% reduced risk of uterine rupture during subsequent pregnancy was also assumed following a double layer suture compared to a single layer [40]. Finally, Vachon-Marceau et al. demonstrated a significantly higher rate on scar dehiscence in the single- compared to double-layer group [28].

Of note, a number of studies pointed out that a proper single layer (unlocked) suture might not be inferior to double layer [36]. The RMT is commonly lower compared to double-layer suture, but interestingly the risk of uterine rupture in a subsequent pregnancy is influenced only marginally [38, 41, 42]. However, since the frequency of uterine rupture is very low in general, the sample size of most studies was too small to reach reliable data.

One large review including 9 randomised controlled trials (3969 patients) demonstrated a thinner RMT in the single layer suture group (mean difference – 2.19 mm), but no statistically significant differences regarding uterine scar defects, uterine dehiscence or uterine rupture. The authors acknowledged that even if uterine scar defects are associated with lower RMT, it remains questionable whether RMT alone is a proper marker for prospective uterine ruptures [38]. Jastrow et al. calculated that a cut-off value for myometrial layer tickness in third trimester below 1.4–2 mm and complete lower LUS of less than 2–3.5 mm correlates with a higher risk of niche incidence and therefore uterine rupture. Unfortunatly, the retrospective study design and small sample size limit the scope of these results [29].

A proper single layer suture was suggested to be helpful when the CS is performed during advanced labour and myometrial layers cannot be correctly identified [28]. One trial demonstrated that double layer suture results in a higher RMT than single layer suture only in elective CS but not in CS at advanced labor [43].

In summary, although there is no evidence for a higher uterine rupture rate following a single layer suture compared to a double-layer suture, RMT and therefore probably the integrity of the lower uterine segment is improved by the double-layer suture of the uterus, at least in cases with an elective CS.

3.6 Locked versus unlocked suture

Locking a suture was used for long time to reduce bleeding. However, there is some evidence that a locked suture may provoke defect scar healing.

One trial showed that only unlocked double-layer, but not locked double-layer suture was superior to locked single-layer in either RMT (3.8 ± 1.6 mm vs. 6.1 ± 2.2 mm) and healing ratio [36]. Higher rates of scar separation were described when a continuous suture was locked (OR 5.4, 95% CI 3.17–9.20, $p < 0.001$, [41]).

Stegwee et al. reviewed data from three randomized controlled trials and two prospective cohort studies to compare locked and unlocked suture. RMT decreased

significantly and niche prevalence was non-significantly higher when a locked suture was performed (RR 1.23, 95% CI 0.93–1.61, p = 0.14). Also one study including 48 women reported the healing ratio, which was lower in locked vs. unlocked sutures [39].

In summary: Locking a suture decreases healing due to the reduction in blood flow and consequently in oxygen supply to the scar, which is required for the healing process [44].

3.7 Single stitches versus continuous suture

A small number of studies is available comparing continuous suture with single stitches to close the uterine incision.

One case–control study (n = 98) analysed the effect of prior uterine closure on placenta location and placentation disorders. Half of the double-layer group had continuous suture of the inner layer, the others had interrupted sutures of the inner layer. Continuous suture of the inner layer of the myometrium was an independent risk factor for subsequent placenta accreta, total placenta praevia and anterior location. The risk for morbidly adherent placenta was 6-fold higher after continuous suture compared to interrupted stitches [45]. An additional prospective randomized study in primiparae with an elective CS demonstrated larger and more numerous niches in patients after locked continuous sutures compared to interrupted sutures (95% niches and 77% niches after 12 months, respectively). In this study, the decidua was excluded and a single layer suture without closure of the visceral peritoneum was performed [46].

Overall, conclusive evidence in this topic is limited by the small size of the studies. Currently, interrupted stitches of the inner layer of myometrial closure might favour the healing process.

3.8 Inclusion versus exclusion of the decidua in the suture

Including the decidua (endometrium) in the suture might lead directly to a worsened scar integrity and niche development. Roberge et al. observed, as mentioned before, that excluding the decidua in double-layer suture supports better scar healing than including it [36].

A recently published double-blind, randomised controlled study (2Close Trial) examined the presence of postmenstrual spotting after a single- versus a double- layer suture. In the double-layer group, the decidua was integrated in the scar, however, in the single-layer group, this integration was optional. Surprisingly, a significantly increased niche prevalence was found after double- compared to single-layer suture (73.6 versus 68.9%). The authors draw the conclusion that rather by the number of sutured layers this result was provoked by the integration of the decidua in the suture. In line with this, subgroup analysis of the single-layer group revealed a significantly lower niche incidence in cases of exclusion of the decidua (59.3 versus 71.8%) [47].

A retrospective cohort study showed no morbidly adherent placenta in a cohort of 109 patients with previous CS, although in 44% an anterior wall placentation was present. The authors concluded that the exclusion of the endometrium from the suture, which was a standard practice in the study center, chiefly contributed to the results. However, there was no control group and the study group was compared with historical cohorts [48].

A critical view on this approach raises the concern that less myometrium might be adapted if the endometrium is not included in the scar, probably contributing

to a defect healing. Yazicioglu et al. observed a higher incomplete healing ratio in sutures that excluded the endometrium compared to those including all layers [49]. However, the examination was performed 6 weeks after the CS, which is known to be rather early for a final assessment of wound healing. Furthermore, cervical dilatation was performed at a lower percentage in patients with incomplete healing, probably explaining the results. This study also was part of a meta-analysis pooling two studies recording niches after sutures including or excluding the decidua [39]. The second study, which was included in this meta-analysis, showed contrary results [50]: Three study groups were compared (group A: inclusion of all layers; group B: double-layer suture with inclusion of the decidua, group C: double-layer suture with a separate suture of the decidua and a separate suture of the myometrial layer). The group with the separate suture of the endometrium showed significantly lower niche rates (34%, 16% and 5.6% niches in group A, B and C, respectively).

In summary, the exclusion of the decidua from the suture seems favourable in preventing niches.

3.9 Closure of the peritoneum viscerale/parietale

The closure of the peritoneum reveals no advantages with regards to operation time, pain and bleeding amounts, as currently recommended the German Guideline Cesarean Section [51]. But does the closure of the peritoneum help to prevent a niche?

Verwoort et al. discussed several hypotheses on niche development. During laparoscopic scar repair surgery dense fibrotic adhesions attached on top of the niches were found [11]. One hypothesis is that adhesions pull the uterine scar towards the abdominal wall and induce scar development due to traction. One explanation for this adhesion between the anterior uterine and the abdominal wall might be the incision of the utero-vesical fold and subsequent dissection of the urinary bladder with the aim to keep the bladder out of the surgical area. This may create adhesions and provoke niche formation as well as a fixed retroflexio uteri [52].

Moreover, a systematic review including 249 patients evaluated whether the parietal peritoneum should be closed. This study showed that closure of the peritoneum prevents adhesions from abdominal to uterine wall [53].

In conclusion, further investigation is needed to be able to answer the question about the contribution of closure of the visceral and parietal peritoneum to niche prevention.

3.10 Dilatation of the cervix uteri

The rationale of dilating the cervix uteri during elective CS is to facilitate the proper drain of blood and "products of conception" postpartum. On the one hand, retained blood after CS is ought to impair scar healing and results in scar defects [54]. On the other hand, a risk of infection by a possible transmission and contamination from vaginal microorganisms to uterine or abdominal wounds is discussed [55]. A randomised trial analysed the different outcomes of CS after cervical dilatation (CD) was performed with Hegar dilator or not. 400 women with a singleton pregnancy were included and planned for elective CS at term. All patients received vaginal disinfection preoperatively with povidone iodine. No difference was observed regarding wound infection or endometritis between the groups. In the cervical dilatation group, indicators of better healing of the scar were found: Significantly higher scar width and depth, thicker RMT, and fewer scar defects were found together with better blood supply to the scar. In comparison, women without cervical dilatation were at higher risk for subinvolution of the uterus [54].

In another recently published trial (DONDI-Trial, prospective, open-label, randomized controlled trial), 447 women randomly received cervical dilation or not during CS. Women with current antibiotic therapy, chorioamnionitis, onset of labour with dilatation of the cervix and gestational age below 24 weeks were excluded. Dilatation of the cervix had no effect on infectious morbidity (puerperal fever, endometritis, wound infection and urinary tract infection), blood loss or even operating time. The only benefit observed in the dilatation group was a lower prevalence of patients that had retained products in the uterus cavity compared to the no-dilation group (0 vs. 6.2%, $p < 0.001$) [56]. Although scar healing was not examined in this study, retention of products may potentially disturb wound healing.

A recently published review underlined the following findings, too: performing or not CD at elective CS at term either with double gloved index or Hegar dilator caused no differences regarding postpartum haemorrhage, postoperative fever, endometritis or subinvolution. Cervical dilatation led to a slightly higher mean blood loss, thicker endometrial cavity, less retained products of conception, less distortion of uterine incision and better healing ratio. Operating time, wound infection, urinary tract infection and integrity of scar (defined as scar thickness less than 2.3 mm) were not affected [57].

In conclusion, dilatation of the cervix has positive effects on scar integrity, wound healing and RMT due to less retention of products in utero. It is safe regarding infections; however, vaginal disinfection should be considered before CS.

4. Add on: role of labor on post partum tissue repair

Since scar defects represent a kind of defect wound healing, we here focus on possible mechanisms which are involved in postpartum tissue repair. As shown in the section "Timing of the CS", there is evidence that an unplanned CS after the onset of labor has advantages concerning niche incidence and further pregnancy complications like uterine rupture and morbidly adherent placenta. Probably, immunological changes which only occur at the time of contractions, may have the potential to contribute to the clinical benefits of a CS after the onset of labor.

The human endometrial tissue holds the capacity to achieve complete regeneration after injures [58]. Particularly, childbirth and the detachment of the deeply invading placenta is generally followed by the restoration of the endometrial layer at the former implantation site. This regeneration is essential for successive pregnancies, as incomplete healing and repair results in endometrium fibrosis or scarring, with potential consequences on the uterine cavity shape or on the adhesiveness and invasiveness of the embryo [59–61]. Despite their relevance, the precise mechanisms of post partum tissue repair and the factors contributing to an impaired endometrial re-epithelialization e.g. after caesarean section remain still poorly described.

To date it is well known that labour entails a series of drastic changes that provoke uterine contractions and birth. This process is characterized by rapid fluctuations in maternal hormones, including the upregulation of glucocorticoids and oxytocin as well as the reduction in progesterone signalling [62, 63]. Simultaneously, there is a shift in the immune responses at the feto-maternal interface from the predominantly anti-inflammatory phenotype throughout pregnancy to a sterile inflammation-like response during labour [64]. This includes inflammasome activation, the release of cytokines and chemokines, and the further recruitment of leukocytes to the feto-maternal interface [65], as studied in detail in relevant animal models.

In line with this, it is tempting to hypothesize that the effects of labour and uterine contractions may surpass the birth and detachment of the placenta, conveying a central role to the labor-triggered recruitment of immune cells in the machinery of postpartum tissue regeneration. Indeed, the immune system critically orchestrates repair processes in multiple organisms and tissues. Danger signals prompted by tissue injure activate pattern recognition receptors to initiate an immune response [66, 67]. This dynamic response is characterized by the stepwise recruitment of granulocytes, monocytes/macrophages, and T cells [68]. Both recruited and tissue resident leukocytes play scavenger functions and secrete cytokines and growth factors that promote lympho- and angiogenesis, proliferation of tissue cells, and consequently repair [66, 69]. Recently, regulatory T cells have also emerged as important players that ensure regeneration of multiple tissues [70]. Particularly in the case of macrophages and T cells, the balance between inflammatory and anti-inflammatory responses may hold the capacity to tilt the repair process towards scarring or regeneration respectively [68].

Noteworthy, the specific features of the repair process are contingent on the particularities of the tissue affected and little is known about uterine wound healing and prevention of scarring in the postpartum period. In the rodent postpartum uterus, macrophages with an anti-inflammatory M2-like phenotype have been observed in the former implantation sites together with abundant expression of VEGF and its receptors in the uterine stroma and blood vessels that may jointly favour angiogenesis and healing [71, 72]. In contrast, accumulation of M1-like macrophages, neutrophils, and T cells was detected in the uterus of mice exhibiting dysfunctional postpartum uterine repair due to impaired Notch signalling [73]. These findings support that in the uterus, such as in other tissues, an anti-inflammatory milieu is required to prevent the formation of fibrosis upon wound healing. Despite this emerging evidence on the role of immune responses in postpartum tissue healing, further mechanisms and players remain still to be elucidated. In particular, it is still unknown whether labour-induced recruitment of immune cells under the regulatory influence of high levels of steroid hormones contribute to tissue healing, and whether the failure of such a recruitment, e.g. in caesarean deliveries without induction of labour, may hinder endometrial regeneration and result in scar formation.

5. Conclusion: how to perform a CS in 2021

Taken together all aspects which influence the risk of a defect scar healing, we advise to perform a CS as following:

1. CS after the onset of labour seems to be superior than an elective CS. Childbaering women should be encouraged to undergo vaginal birth whenever possible.

2. Uterotomy should be placed not overly caudal, avoiding an incorporation of the cervix or the region around the internal cervical os into the scar.

3. After delivery of the placenta, performing cervical dilatation is recommended in cases without cervical dilatation due to the absence of contractions.

4. The decidua should be excluded from the suture.

5. Double-layer-suture is recommended.

6. Single stitches (of the first layer) are superior to a continous suture.

7. Locked sutures (of the first layer) should be avoided.

   Personal opinion of the authors: We recommend to perform a double layer suture with single stitches of the first layer and a continuous unlocked second layer including the superficial muscle layer and the peritoneum viscerale.

8. Closure of the peritoneum parietale may be advantageous.

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