

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

ISTHMOCELE:

Definition, prevalence, risk factors and symptoms

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➤ Over the last few decades, the cesarean section rate and the number of women undergoing multiple cesarean sections have nearly doubled .*

➤ Cesarean section rate has been increasing despite the World Health Organization's recommendation of a maximum 15%, with some countries reaching rates as high as 50%.

➤ This has been followed by an increased complication rate ** and the appearance of a new clinical pathology, the cesarean scar defect, known as isthmocele or niche.***

- *Gibbons L, No. 30. WorldHealth Report Background Paper; 2010.
- **Bij de Vaate AJ: systematic review. Ultrasound Obstet Gynecol. 2014.
- ***Uppal T,. J ObstetGynaecol. 2011

- Uterine niche, also described as **uterine isthmocele**, **caesarean scar defect** and **diverticulum**, is an iatrogenic defect in the myometrium at the site of previous caesarean scar due to defective tissue healing.

An isthmocele is an anatomical uterine defect, defined as a reservoir-like pouch in the isthmus of the anterior uterine wall, at the site of the CS scar.

A niche is formally defined by the European Niche Taskforce as an indentation of the uterine myometrium of at least 2 mm at the site of the Caesarean scar, assessed by transvaginal ultrasound.

(Jordans et al., 2019)

In 1995, Morris was the first to describe the caesarean scar defect.

He examined the uterus of women who had undergone hysterectomy due to AUB symptoms in the absence of any identifiable cause and did

not respond to hormonal therapy.

All women had at least one previous CS.

He found that most of these women presented distortion and widening of the lower uterine segment

as well as inflammatory changes in this site.



- It was proposed that menstrual blood accumulates in the isthmocele and delay menstrual bleeding, causing PAUB .
Not only the anatomical defect is responsible for the spotting, but also other mechanisms such as, in situ production of blood and decreased contractility of the myometrium in this area were suggested to contribute to blood accumulation.

Prevalence

Uterine niche occurs in up to 70% women with previous caesarean of whom 30% are symptomatic (Naji O, *Ultrasound Obstet Gynecol.* 2012; van der Voet, *BJOG.* 2014)

Reported prevalence varies based on diagnostic method used : 24–70% with transvaginal sonography (TVS) and 56–84% with gel/saline instillation sonohysterography (SHG) .

Prevalence of 45.6% was reported in a prospective observational study (n = 371) where sonohysterography was done six months post-caesarean

- (Antila-Långsjö RM, *Am J ObstetGynecol.* 2018)

Prevalence increases with increasing number of previous caesareans.

➤ Current data suggest the development of isthmocele in approximately 60% of patients after a primary cesarean section (CS) and 100% after 3 CSs .

van der Voet LF, Vervoort AJ, Veersema S, BijdeVaate AJ, BrölmannHA, Huirne JA. Minimally invasive therapy for gynaecological symptoms related to a niche in the caesarean scar: a systematic review. *BJOG*. 2014;

Pathology, Etiology

The pathogenesis comes from an alteration of two major processes:

- the inadequate healing of the caesarean suture line , probably secondary to reduced vascular perfusion in this area
- the reduction of the residual thickness of the overlying myometrium.

Nazik, H, Nazik E. A new problem arising after cesarean, cesarean scar defect (Isthmocele) a case report. *Obstet Gynecol Int J* 2017, 7(5): 00264.

Morris was the first to analyze macro and microscopical changes within the scar tissue of the Isthmocele, finding fibrosis, old blood, mucus, debris and inflammatory cells.

Morris H. Surgical pathology of the lower uterine segment cesarean segment scar: is the scar a source of clinical symptoms?. Its J Gynecol Pathol.1995; 14: 16-20.

The clear etiology is unknown, but arises from the scar of previous CS. It appears that the major factor is an inadequate surgical management of the hysterotomy closure, including the suture material and technique , numbers of layers closed, among others.

- Darwish A. Fertility-oriented Female Reproductive Surgery , Microsurgical Cesarean Section 5. January 18th 2017.

Hypothesis 1: Cervical location of the uterine incision induces impaired wound healing

- first hypothesis is that low incisions through cervical tissue, containing mucus-producing glands, hampers wound healing.

Local mucus formation may induce dehiscence of the approximated myometrium layers. In addition, local mucus accumulation in communicating spaces may induce the formation of large 'retention cysts' or may increase the size of a niche over time.

A.J.M.W. Vervoort, Human Reproduction, 2015



Laparoscopic view on a mucus-containing large niche that is located in the lower cervix. Mucus is expelled during a laparoscopic niche resection after dissection of the bladder and opening of the niche.

This hypothesis is in line with the results of two prospective cohort studies. One study reported very low uterine incisions to be **an independent risk factor for the development of large niches.**

(Osseret al., 2010).

Others reported a CS performed in active labour, after the cervix has effaced and has become part of the uterine wall, to be associated with a higher prevalence of niches **(Zimmer et al., 2004).**

Hypothesis 2: Incomplete closure of the uterine wall

The second hypothesis is that **partial closure** of the uterine wall during CS, due to unintentional omission of closing the deeper muscular layer, may subsequently lead to a disrupted myometrium and thus niche development.

A.J.M.W. Vervoort, Human Reproduction, 2015

Potential causes include superficial closure due to non-perpendicular sutures and endometrial saving Techniques

- **double-layer closure versus single-layer closure**
- no differences (Roberge et al., 2014)
- not significant differences (Yasmin,et al., 2011)
- double-layer closure could reduce the risk of uterine rupture (Bujold et al., 2002, 2010; Durnwald and Mercer, 2003).

double-layer closure of the uterus, compared with single-layer, reduces the risk of uterine rupture in a future pregnancy by half (Bujold et al., 2010).

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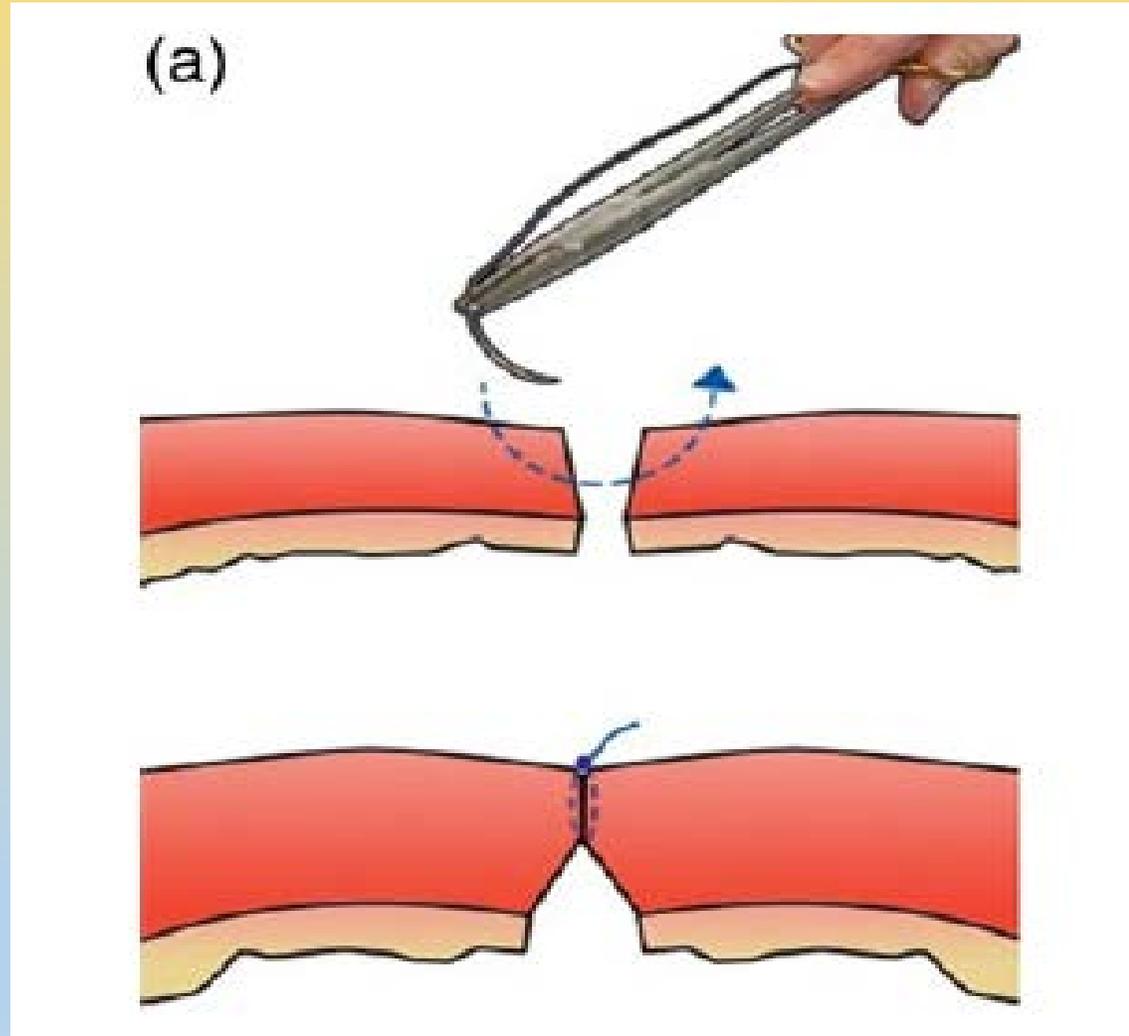
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- Fewer niches were reported in this study after single full thickness uterine closure compared to split thickness uterine closure, which excluded the endometrium
- (Yazicioglu et al., 2006)
- Two meta-analyses reported low-to-moderate evidence that single and double-layer closure of the uterine incision is associated on ultrasound with similar incidences of niches (Di Spiezio Sardo, 2017; Stegwee et al., 2018).

Single-layer closure of the uterus may increase niche formation due to greater risk of incomplete closure



- **locked versus unlocked sutures.**
- locked modification of a single-layer suture may increase the risk of uterine rupture due to an increase in tissue hypoxia and subsequent deficient healing (Roberge et al., 2011).
- decreased myometrial thickness (60 patients; mean difference, 22.5; 95% CI, 23.2 to 21.8; P , 0.001)) with locking of the first layer. (Yasmin et al., 2011)
- no difference in terms of proportion of scar defect at ultrasound 6–12 the CS (55 patients; RR, 1.16; 95% CI, 0.97–1.40; P ¼ 0.11), using continuous locked single-layer compared with interrupted, unlocked, single-layer suture. However, continuous, locked, single-layer closure was coupled with a larger scar defect (P , 0.001) on sonographic evaluation. (Ceci et al., 2012).

- **Double-layer uterine closure** using **non-locking** sutures may result in a thicker residual myometrium and potentially a lower prevalence of niches.

A.J.M.W. Vervoort, Human Reproduction, 2015

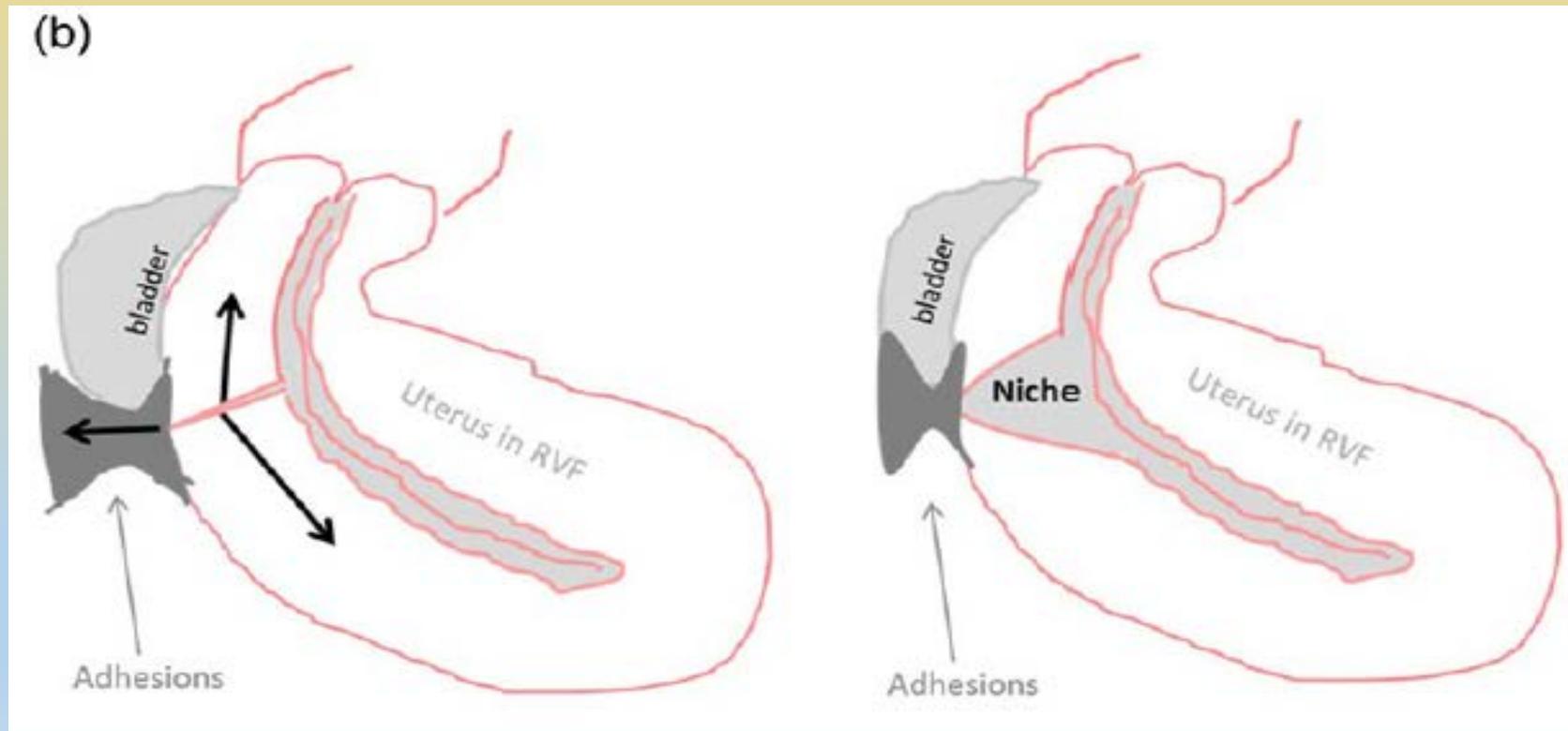
optimal closing technique in terms of the prevention of niches:
requires additional studies, preferably RCTs with long-term follow-up

Hypothesis 3: Surgical activities that may induce adhesion formation and as a consequence induce impaired wound healing due to counteracting forces on the uterine scar

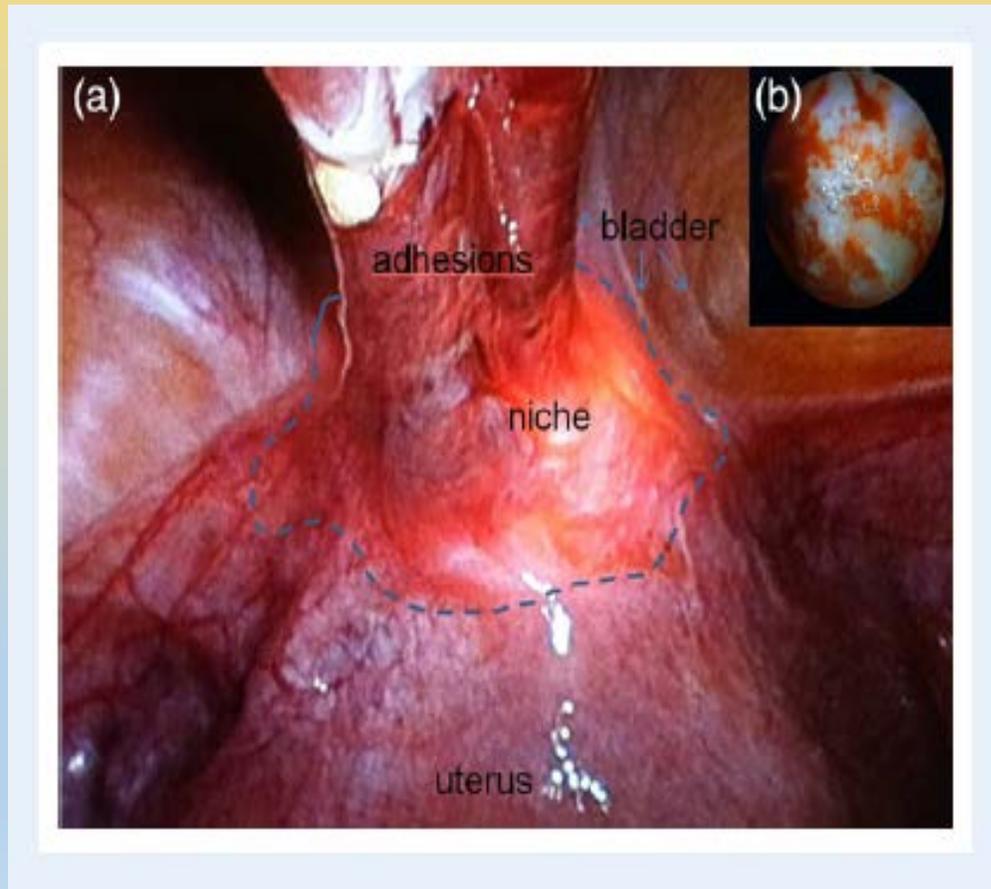
- The reported prevalence of adhesions in women during their second CS is 12–46% and 26–75% during their third CS (Makoha et al., 2004; Morales et al., 2007; Tulandi et al., 2009; Walfisch et al., 2014).
- hypothesis is that adhesions may induce niche development due to retraction of the scar tissue, which pulls on the uterine scar towards the abdominal wall. This force is opposite to the direction of the retracting tissue in the uterine scar itself, that is required for optimal approximation of the myometrium layers and healing.

These counteracting forces may even be increased by gravity on the corpus in a retroflexed uterus.

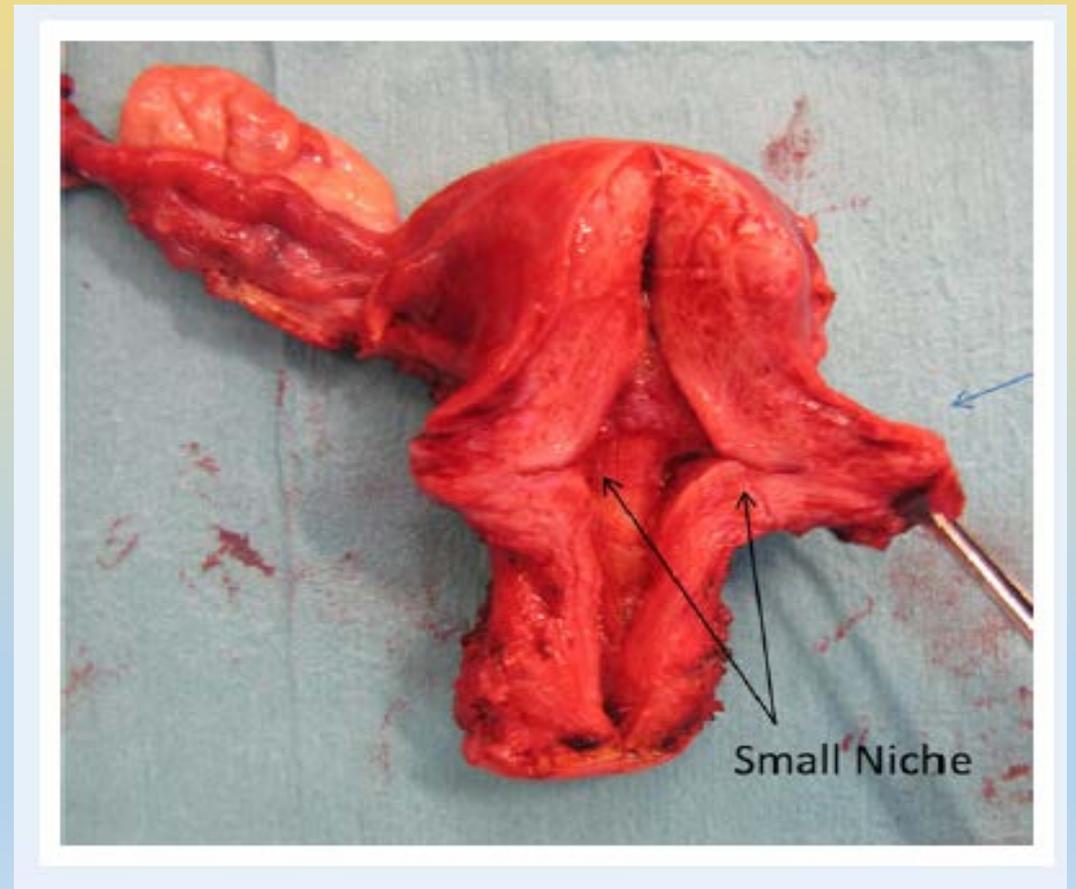
Counteracting forces on the Caesarean section uterine scar, due to retraction of adhesions between the uterine scar and the abdominal wall in a retroflected uterus, may impair wound healing and increase the formation of niches



Adhesions between the niche and the abdominal wall seen during laparoscopy



Macroscopic image of a uterus with, a niche, adhesions are located at the deepest point of niche



Hypothesis 4: Patient or disease related factors that impair wound healing

In an animal model it has been demonstrated that genetic predisposition may affect histological and biomechanical wound healing of artificial myometrial defects (Buhimschi et al., 2010).

- BMI, preeclampsia or hypertension (Osser et al., 2009)
- (may affect haemostasis, inflammation and related adhesion formation)
- A.J.M.W. Vervoort, Human Reproduction, 2015

Potential Risk Factors

Niche forms due to poor healing of caesarean scar. Risk factors may be ***surgery related*** or ***patient related*** .

Factors Affecting Lower Uterine Segment

- Cervical dilatation of > 5 cm, > 5 h duration of labour and advanced foetal station predispose to large niche due to thinner or lesser vascularized myometrium resulting in inadequate healing .
- . Vikhareva O *Ultrasound Obstet Gynecol.* 2010.
- . Bij de Vaate AJ, : systematic review. *Ultrasound Obstet Gynecol.* 2014

Level Of Uterine Incision

- Lower uterine incision towards the cervix results in poor healing, as mucus secreted by cervical glands interferes with myometrial approximation. Mucus gradually increases the niche size also .
- Caesarean done in advanced labour after cervical effacement and also creation of uterovesical fold of peritoneum influence the level of uterine incision.
- . Vikhareva Osser O *Ultrasound Obstet Gynecol.* 2010.
- . Vervoort AJ, *Why do niches develop in Caesarean uterine scars? Hypotheses on the aetiology of niche development.* Hum Reprod. 2015

Uterine Closure Techniques

- ***Single-layer, decidua sparing closure technique*** predisposes to incomplete closure, compared to single full thickness closure.

Almost 95% patients with niches had single-layer closure without closing peritoneum.

A strong myometrial scar with proper anatomical approximation without tissue strangulation minimizes risk of niches.

- Vervoort AJ, Van der Voet LF, Witmer M, et al. The HysNiche trial: hysteroscopic resection of uterine caesarean scar defect (niche) in patients with abnormal bleeding, a randomised controlled trial. *BMC Womens Health*. 2015;15:103
- . Bij de Vaate AJ, Broilmann HA, van der Voet LF, et al. Ultrasound evaluation of the cesarean scar: relation between a niche and postmenstrual spotting. *Ultrasound Obstet Gynecol*. 2011;37:93–9.

- If muscular edges are thick, they are best approximated by including deeper part in the first layer and the remaining superficial cut edges in the second layer.
- Non-perpendicular sutures leading to an irregular myometrium closure, locking sutures or very tight second layer leading to ischemic necrosis result in poorly healed scar predisposing to niche formation.

Vidushi Kulshrestha¹ · Nutan Agarwal^{1,2} · Garima Kachhawa¹ Post-caesarean Niche (Isthmocele) in Uterine Scar: An Update The Journal of Obstetrics and Gynecology of India, August 2020

- The CORONIS trial on the cesarean section surgical techniques compared the chromic catgut and polyglactin-910 for uterine closure. A 3 year follow up there was no evidence of a difference in the main comparisons for adverse pregnancy outcomes in subsequent pregnancy, such as uterine rupture. (CORONIS collaborative group, randomized controlled trial. Lancet. 2016)
- RCT: Closure of the uterine scar with synthetic absorbable monofilament suture has a positive effect on scar healing and increases RMT thickness in comparison of multifilament sutures.
- (Alper Baspug, J invwetigative surgery, 2019)
- Cohort : Vicryl sutures were associated with a lower risk of CSD formation in comparison with catgut sutures. (Hosseini et al ; J Gynecol Obstet Hum Reprod. 2021)

- Thus, double-layer uterine closure using non-locking sutures is the optimal closure technique that results in thicker residual myometrium and hence potentially lower risk of niches.
- Suboptimal surgical techniques: Inadequate haemostasis, tissue ischemia, devascularization and excessive tissue manipulation contribute to poor scar healing and adhesions, consequently forming niche.

- Thus, double-layer uterine closure using non-locking sutures is the optimal closure technique that results in thicker residual myometrium and hence potentially lower risk of niches.

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Adhesions

- Adhesion formation with abdominal wall pulls the uterine scar towards abdominal wall, exerting counteracting force opposite to the direction of retracting uterine scar tissue and causing impaired wound healing.

- . Vervoort AJ, Uittenbogaard LB, Hehenkamp WJ, et al. Why do niches develop in Caesarean uterine scars? Hypotheses on the aetiology of niche development. Hum Reprod. 2015.

Retroflexed Uterus

- Effect of gravity on uterine corpus also increases counteracting forces. Large niches are mostly found with retroflexed uterus .
- *. Bij de Vaate AJ., Prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following Cesarean section: systematic review. *Ultrasound Obstet Gynecol.* 2014;43(4):372–82.
- ** Vervoort AJ,, et al. on the aetiology of niche development. *Hum Reprod.* Why do niches develop in Caesarean uterine scars? *Hypotheses* 2015;30(12):2695–702
- ***Vervoort AJ et al. Why do niches develop in Caesarean uterine scars? Hypotheses on the aetiology of niche development. *Hum Reprod.* 2015;30(12):2695–702.

Patient Factors

- **Genetic predisposition** contributes to impaired healing, poor haemostasis, inflammation, or adhesion formation, post-operative infection.

- [. Vervoort AJ, Hum Reprod. 2015](#)

- **Gestational diabetes** (odds ratio, 1.73), previous caesarean (OR, 3.14) and advanced body mass index (OR, 1.06) are independent risk factors.

Risk increases by 6% for every additional unit increase in body mass index.

Longer active labour prior to emergency caesarean also increases risk (OR, 1.06).

However, there is no difference between elective and emergency caesarean.

- [. Antila-Långsjö RM, Am J ObstetGynecol. 2018.](#)

Clinical Presentation

- **most women may remain asymptomatic**
- **Post-menstrual Spotting**
- **Prolonged Bleeding**
- **Intermittent Spotting**
- **Pain**{dysmenorrhea(40–50%), chronic pelvic pain (35%), dyspareunia (18%), suprapubic pain}
- **Midcycle Intrauterine Fluid Accumulation**
- **Caesarean Scar Ectopic Pregnancy**
- **Secondary Infertility**

- **worsens ART outcomes in fresh or frozen cycles**(unfavorable impact on the implantation process, increase the risk of early pregnancy loss) (in embryo transfers)
- **failed implantation**
- **Bladder Dysfunction**
- **Obstetric Complications in Future Pregnancy, early pregnancy**
- loss, cesarean section scar pregnancy, placenta
- accreta/percreta, uterine rupture, preterm delivery, and prematurity.
- **Scar Abscess**
- **Complications during some gynaecological procedures** such as curettages, hysteroscopy, intrauterine device insertion

Post-menstrual Spotting

It is defined as ≥ 2 days of intermenstrual spotting, or ≥ 2 days of brownish discharge after the end of menstruation if bleeding duration exceeds 7 days (discharge is considered normal if bleeding duration is < 7 days) .

- 30–55% at 6–12 months post-caesarean
- 20% after 1 year of caesarean
- Collected menstrual blood (obstruction of flow of menstrual blood by anterior edge of niche , poor contractility of surrounding fibrosed muscle) .

Postmenstrual spotting is correlated to niche volume and inversely correlated to residual myometrium thickness ([van der Voet et al., 2014a](#); [Bij de Vaate et al., 2014b](#)).

Intermittent Spotting

In situ blood formation in the niche, evidenced by free erythrocytes in scar, may lead to intermenstrual spotting.

Pain

Women with niche may present with dysmenorrhea (40–50%), chronic pelvic pain (35%), dyspareunia (18%) or suprapubic pain. Pain could be due to abnormal myocontraction to empty niche contents .

Secondary Infertility

- One of the largest systematic reviews on caesarean section scar-associated secondary infertility showed a correlation between caesarean delivery and increased odds of subfertility when compared to vaginal delivery (1.6 95% CI 1.45-1.76, $p < 0.00001$)
- (OE Keag, Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. PLoS Med. 2018)

A meta-analysis reported that a Caesarean section reduces the probability of subsequent pregnancy **by 10%** [relative risk (RR) 0.91; 95% 0.87–0.95] on average, compared with a previous vaginal delivery. Most of the 16 included studies found reduced fertility after a Caesarean section.

The size of the effect depended on the type and indication for caesarean section.

However, none of the studies included in the meta-analysis evaluated the relation between subsequent fertility and the presence of a niche.

(Gurol-Urganci et al., 2013)

Various explanations for the cause of post-Caesarean subfertility have been proposed, ranging from placental bed disruption and pelvic adhesions influencing tubal oocyte pick-up to women's reproductive choices.

(Murphy et al., 2002)

(Porter et al., 2003; Oral and Elter, 2007)

- Study: In 45.7% the isthmocele was isolated as the primary cause of infertility after excluding all the other causes of secondary infertility. (Stefano Calzolari, MD, *Ochsner Journal*, 2019)

some retrospective studies showed a detrimental effect of a Caesarean section on implantation.

Retrospective study: the live birth rate in women who had an IVF or ICSI treatment at the IVF Centre, Amsterdam, the Netherlands, between 2006 and 2016 with one previous delivery. In total, 1317 women were included, of whom 334 had a previous caesarean section and 983 had previously delivered vaginally.

Results showed impaired pregnancy outcomes. Live birth rates were lower in women with a previous Caesarean section, at 15.9% versus 23.3% for women with a previous vaginal delivery (odds ratio 0.63 95% CI 0.45–0.87). Of the women in the study, 77% received a single embryo transfer and the quality of embryos did not differ between the two groups.

- Vissers et al., Reduced pregnancy and live birth rates after in vitro fertilization in women with previous Caesarean section: a retrospective cohort study. Hum Reprod 2020

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Retrospective study on 310 IVF patients reported a lower clinical pregnancy rate in women with a previous Caesarean section (40.3%), especially if a post-Caesarean scar defect (niche) in combination with endometrial fluid (12.5%) was present, compared to women with a previous vaginal delivery (54.8%) (P 0.05).

- Wang et al., Reproductive outcomes in women with prior cesarean section undergoing in vitro fertilization: a retrospective case-control study. J Huazhong Univ Sci Technolog Med Sci 2017

- There is growing evidence that IVF success rates are lower in patients who deliver via caesarean section when using embryos from the same cohort, suggesting a possible impact of embryo implantation.
- (MK Hayes, et al. Repeat in vitro fertilisation success rates are lower in patients who deliver via caesarean section when using embryos from the same cohort. Fertil Steril. 2016)

The lower clinical pregnancy rate per embryo transfer indicates that implantation is particularly hampered after a Caesarean section.

In theory, intrauterine accumulation of either blood or fluid may cause a hostile environment for implantation.

Some authors have postulated that accumulation of blood may lead to degradation of haemoglobin in the uterine cavity, resulting in a higher iron exposure, which is known to be embryotoxic (Van Langendonck et al., 2002; Lousse et al., 2009).

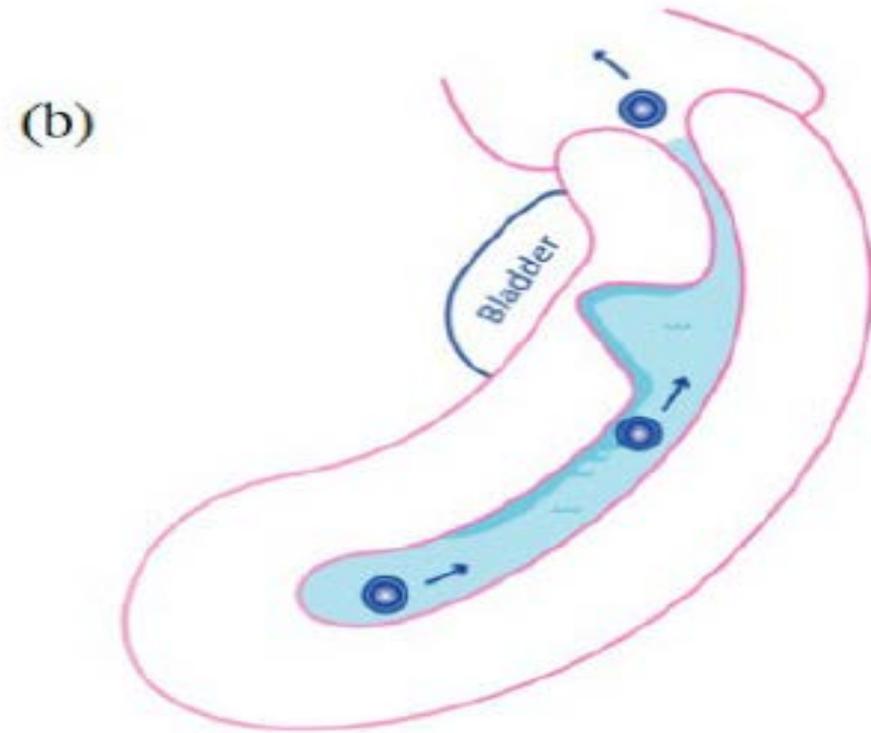
- Accumulation of fluid is seen in approximately 42% of patients with a large niche (Vissers et al., 2020). This may impair pregnancy outcomes due to reduced implantation yet may also be Embryotoxic & or continuous flow of intrauterine fluid.
- Future studies are needed to assess the effect on implantation of intrauterine fluid related to a niche and the possible embryotoxicity of the intrauterine fluid, as well as the additional value of surgical interventions on fertility outcomes.

Intrauterine fluid accumulation in the uterus and the niche

High fluid accumulation in the uterus and the large niche



Schematic figure of an embryo that is separated from the endometrium on a film of fluid.



It appears that a niche is not a favourable site for implantation.

A prospective cohort study evaluating the site of implantation using transvaginal ultrasound during early pregnancy in 380 women after a Caesarean section concluded that the site of implantation is affected by the presence of a niche. The distance between implantation site and scar was related to the risk of spontaneous miscarriage. Implantation very close to or in the niche resulted in miscarriage in seven out of eight pregnancies.

(Naji et al., 2013).

distorted contractility of the uterus

The non-pregnant uterus shows myometrial contractile activity throughout the menstrual cycle. These contractions originate in the subendometrial myometrium and are controlled by steroids. throughout the menstrual cycle endometrial wave like activity patterns of the uterus with adequate wave patterns appear to be related to successful reproduction in natural cycles and assisted reproduction (Bulletti and de Ziegler, 2006).

- transverse uterine incision may lead to poor contractility of the uterine muscle around the scar (Thurmond et al., 1999)
- reduced thickness of the residual myometrium (Bij de Vaate et al., 2011; van der Voet et al., 2014a; Bij de Vaate et al., 2014b)

Sometimes a niche in combination with a strongly retroflexed uterus and/or a complex niche may hamper the insertion of an insemination or embryo transfer catheter.

In rare cases even under ultrasound guidance, it is, impossible to enter the uterine cavity. In such cases, a laparoscopic niche resection to restore the anatomy for embryo transfer could be Considered. (Vervoort et al., 2018)

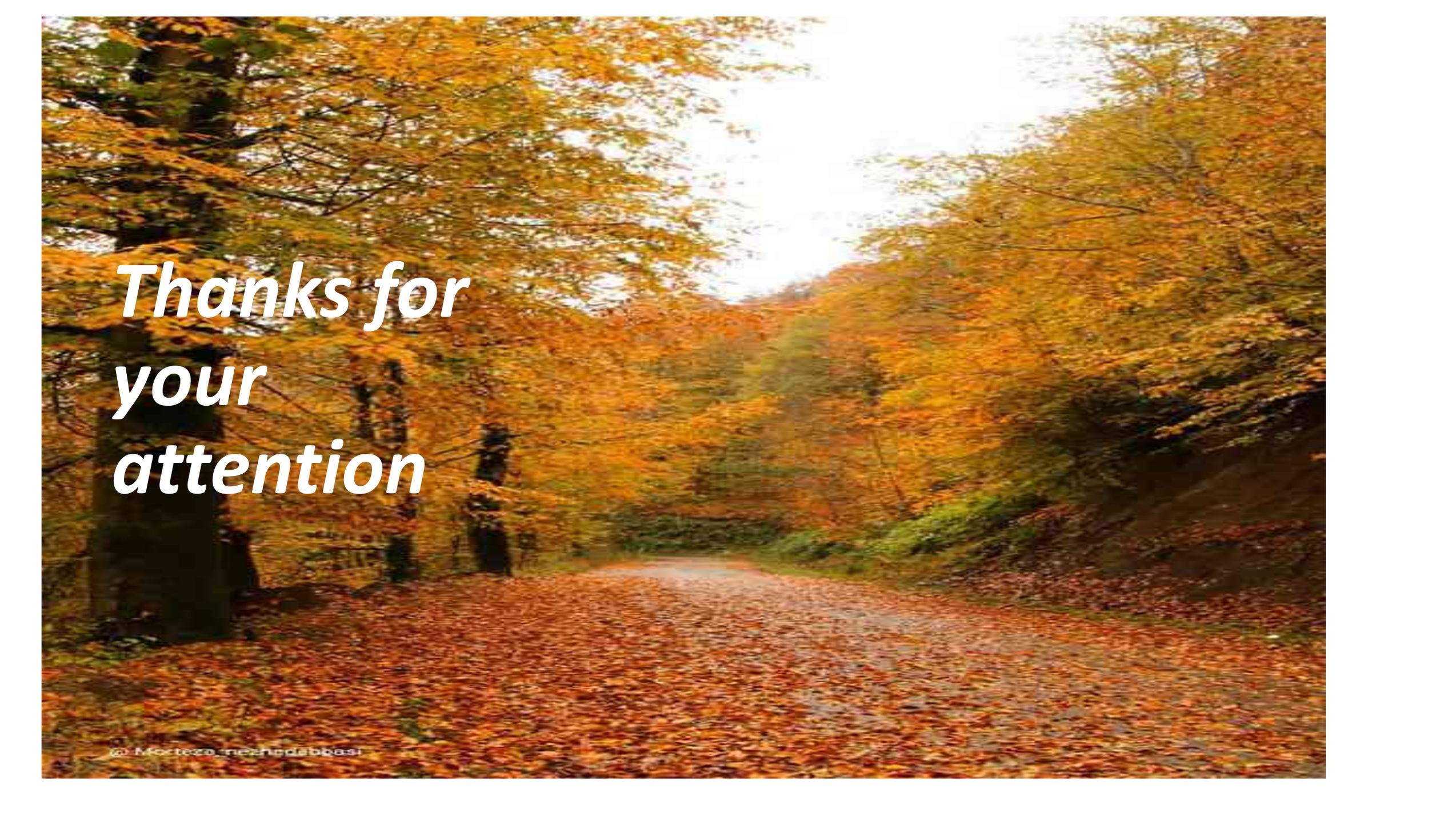
- The failure to become pregnant was associated
- with a higher BMI, a higher isthmocele grade, and a higher number of c-sections.
- .(Stefano Calzolari, MD, *Ochsner Journal*, 2019)

- Isthmocele is similar to a small hollow that can trap blood into it, which may cause
 - poor quality of cervical mucus,
 - impaired sperm transport
 - chronic endometritis.
- Isthmocele may function as a reservoir for menstrual blood or fluid , and the accumulated content can possibly flow through the uterine cavity.
- The excess of iron after hemoglobin degradation in the uterine cavity may be toxic to the embryos or impair the implantation potential of embryos owing to the disturbed endometrial receptivity or uterine microbiota .

(Moreno I, FertilSteril.2018)

- Altered immunobiology and/or increased inflammation when a niche is present
- Distorted contractility of the uterus caused by fibrosis or interruption of the myometrial layer at the site of the niche
- . A large niche in combination with a strongly retroflexed uterus impairs accessibility for an eventual embryo transfer due to a distorted anatomy

The lower fertility reported after Caesarean section may have various causes. Studies suggest that a niche in the uterine scar may play an intermediate role.



*Thanks for
your
attention*