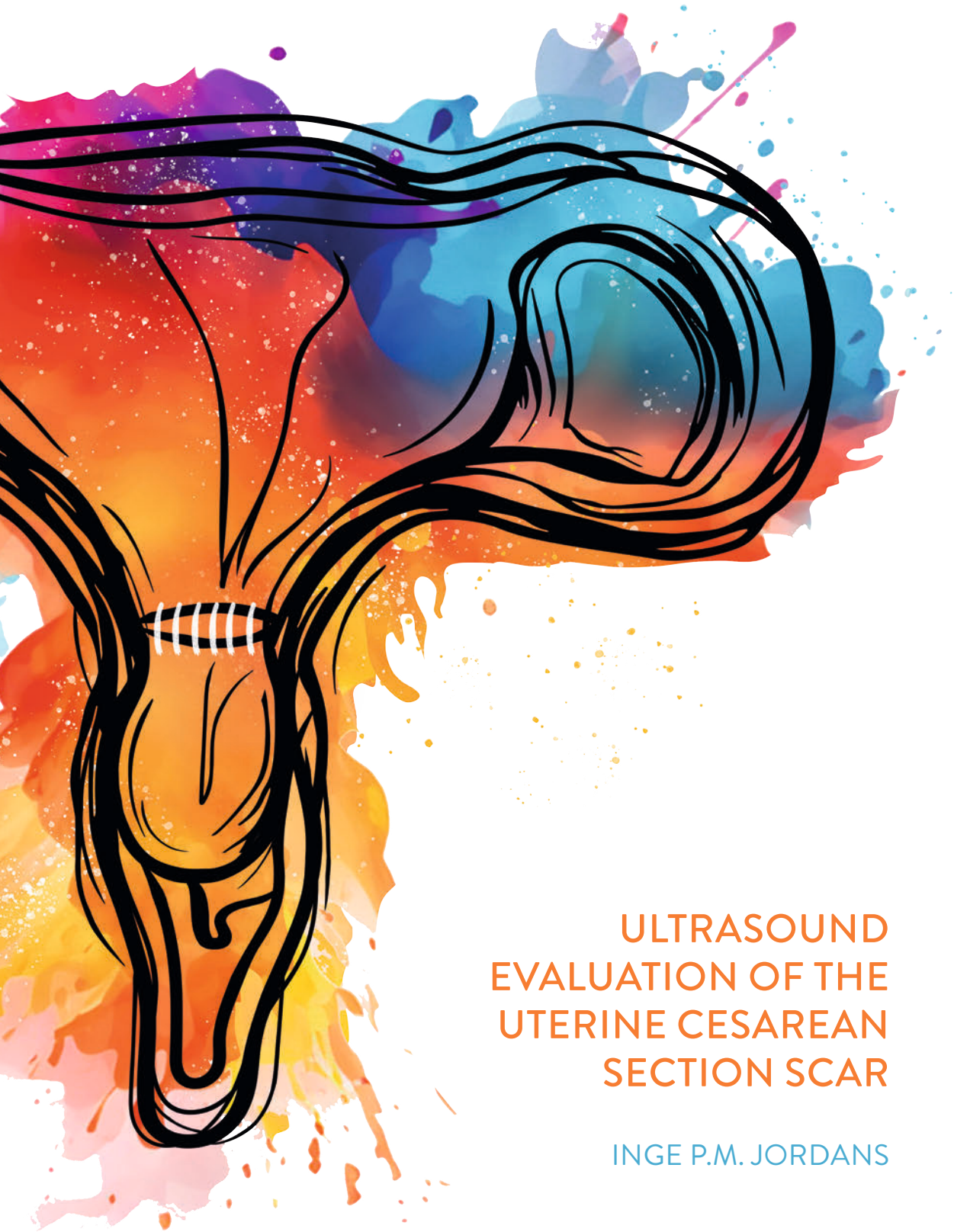

ULTRASOUND EVALUATION OF THE UTERINE CESAREAN SECTION SCAR

INGE P.M. JORDANS

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Inge Petronella Maria Jordans

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

The history of the cesarean section (CS) has been documented for well over four centuries. In the 16th century it was mainly a post mortem procedure in the hope of saving a child's life after the mother's death. [1] Later, in the 17th and 18th century, CSs were performed on living women resulting in live births, but with a high maternal mortality rate (52-100%).[1] The introduction of antibiotics during CSs and an improved selection of eligible patients resulted in a decrease in maternal mortality rate to nearly 1% in the 1920s, and to an increase in fetal survival rate as well. [1] However, at this time the first cases of complications after CS were reported including uterine rupture of the cesarean scar. [2, 3]

Nowadays, the CS is one of the most common surgeries performed in the world with an average rate of 21% globally, ranging from 5% in sub-Saharan Africa to 43% in Latin America and the Caribbean, and is in the latter area's often performed without medical indication. [4] Projections suggest that the CS rate will be 29% in 2030 (38 million CSs annually) due to multiple factors, including women's preferences, health professional's views and beliefs, convenience and remuneration. [4] However, there is no evidence that a CS rate above 10% improves mortality rates[5]; the risk of maternal and perinatal mortality and morbidity increases. [6, 7] In addition, the number of patients with long-term gynecological and obstetrical complications after CS is increasing due to the rising CS rate, with the presence of a uterine CS scar defect or "niche" being of concern and often underreported or neglected. [8-12]

WHAT IS A NICHE?

In 1959, a niche was first described as a 'thinned area with both external and internal depression, consisting entirely of fibrous tissue in the uterus at the site of the previous CS'. This definition was based on histopathological assessment and evaluation by using hysterosalpingography, in the absence of ultrasound. [13] Since then, different definitions of a niche have been postulated, but a uniform definition is lacking. The most commonly used description is 'a triangular anechoic area at the site of the CS scar'[14], illustrated in Figure 1A. A niche is observed in 24-70% of women after CS, evaluated by using transvaginal ultrasound (TVUS), see Figure 1B. [11, 15]

The exact etiology of niche development is unknown, but it is hypothesized that surgery- and patient-related factors may negatively affect wound healing and related angiogenesis. [16] In absence of a uniform technique for performing a CS, a potential

surgery-related factor is an inadequate suturing technique during closure of the uterine wall. Uterine closure techniques, including single versus double-layer closure of the uterine wall, vary per clinic and it is still unresolved what is best in relation to adverse outcomes. Patient- or disease-related factors include genetic disposition, body mass index (BMI), preeclampsia or hypertension, and perioperative infection. [17-20]

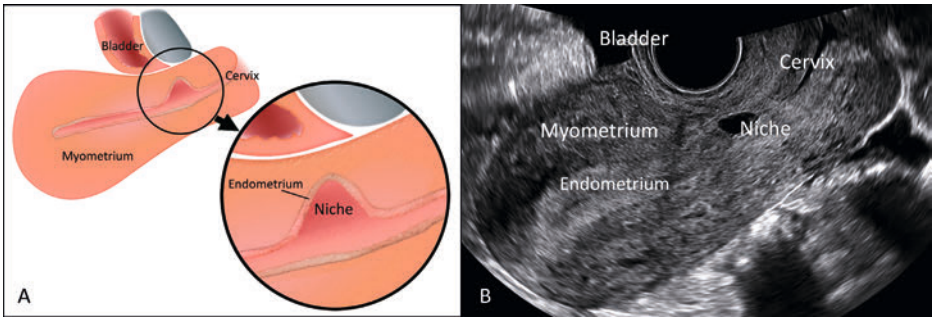

Figure 1. A) Illustration of a niche. B) Example of a niche made visible by transvaginal ultrasound in sagittal plane.

NICHE IMAGING

Different diagnostic tools can determine the presence of a niche, including TVUS, with or without saline or gel contrast, hysteroscopy and Magnetic Resonance Imaging (MRI). [10, 21-24] Most niche studies use TVUS which seems to be the golden standard. [15] However, niche evaluation can be difficult, taking into account variations that occur in scar morphology. This has led to different methods of niche evaluation in reported studies, making a comparison of results more difficult, if not impossible. The timing of CS scar evaluation after CS is important in determining its presence and performing accurate niche measurements, useful for research, the clinical assessment of gynecological symptoms and the planning of possible surgical treatment. [25, 26] In most studies the CS scar is evaluated once between three to twelve months after a CS, but the optimal moment after CS has never been explored. [27]

Furthermore, little is known about the best timing and method of evaluation of the CS scar in a subsequent pregnancy. Niche studies with pregnant women use either transabdominal ultrasound or TVUS, and the timing is often in the third trimester of pregnancy or during labor. The residual myometrial thickness (RMT) measured in the third trimester of pregnancy has been reported as an associated factor in the risk of uterine rupture or dehiscence. [28, 29] However, RMT, and also niche size, change during pregnancy. [30] Therefore, it is important to gain insight into niche changes during pregnancy to predict the risk of complications during pregnancy.

CLINICAL IMPLICATIONS AND TREATMENT

In the consulting room, and probably also in an acute setting in the delivery room, when the indication for a CS is made, all short-term risks of the procedure are usually discussed with the woman involved, including infection, bleeding, and damaging the bladder or bowels. However, the long-term risk, including niche presence after CS and its possible clinical symptoms and consequences, is never discussed. Why not? More and more is known about the clinical implications due to an increasing number of niche studies in the last two decades.

It has been demonstrated that the presence of a niche is associated with gynecological symptoms, subfertility, and obstetric complications in subsequent pregnancies. [8-12, 25, 31] Abnormal bleeding (i.e. post menstrual spotting), as one of the gynecological symptoms, is reported in 34-83% of the women with a niche. [15] Dysmenorrhea and chronic pelvic pain, also related to the niche, are seen in 53% and 37%, respectively. [15] Furthermore, lower implantation and pregnancy rates after a CS compared to a previous vaginal delivery are reported, where the niche is considered as the underlying factor. [31-34] These symptoms have a major impact on the quality of life; it hinders women in daily life activities and work capacity, and it negatively influences their self-esteem and sexual activity. [35] For this reason alone it is important to assess whether it is possible to prevent women from developing a niche after CS.

But also, pregnancies after CS may be considered high-risk for cesarean scar pregnancy (CSP), placenta adherence complications, and uterine dehiscence or rupture in the second or third trimester of pregnancy. [8, 12, 36, 37] In case of a CSP the pregnancy implants on the uterine scar or in the niche, see Figure 2A and B. [38] Because of a high risk of hemorrhage and placental problems, recognition and evaluation in early pregnancy is crucial, but a standardized guideline on how to locate the pregnancy in relation to the CS scar by using ultrasound is lacking. Also, accurate evaluation of the RMT to determine a cutoff value to predict the chance of uterine rupture in a subsequent pregnancy is not yet standardized.

Treatment

If treatment is desired, women with gynecological symptoms in the presence of a niche are usually offered hormonal medication or a levonorgestrel intrauterine device (IUD) as first choice. For women who wish to conceive, a hysteroscopic or laparoscopic niche resection can be proposed. During a hysteroscopic niche resection the distal rim of the niche is dissected hysteroscopically; during a laparoscopic niche resection the niche is completely resected laparoscopically and the uterotomy wound is sutured. Both

procedures have been reported to reduce post menstrual bleeding days[39-41], but little is known about the effect on obstetric outcomes.

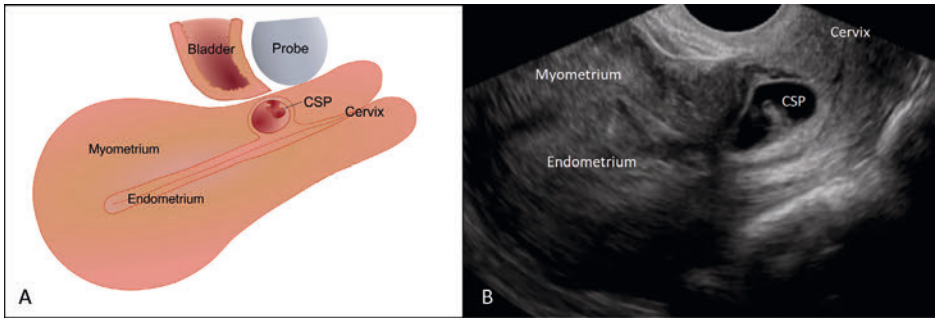

Figure 2. A) Illustration of a cesarean scar pregnancy (CSP). B) Example of a CSP made visible by transvaginal ultrasound in sagittal plane (adapted from: Timor-Tritsch et al. 2012).

PHYSIOLOGICAL UTERINE PERISTALSIS AFTER CS

Just as peristalsis can be observed in smooth muscles of other organs of the human body (i.e. in the gastrointestinal tract, urinary tract, or lymphatic tract), it is also seen in the uterine muscle. Uterine peristalsis can be made visible to the naked eye by TVUS, as long as you keep the transvaginal probe still and you take your time. Objective evaluation of uterine peristalsis can be determined by speckle tracking, a technique widely used as cardiac diagnostic tool to assess myocardial function[42-44], and it has proven to be valid and effective for gynecological purposes.[45, 46]

During the menstrual cycle different patterns of uterine peristalsis, originating in the subendometrial layer, see Figure 3, are found; from fundus to cervix during the menstruation phase to expel endometrium and blood from the uterine cavity, and from cervix to fundus just before and during ovulation.[47] Myometrial disorders are reported to affect uterine peristalsis.[48-50] It is hypothesized that postmenstrual spotting in presence of a niche and lower implantation rates after CS is caused by dysfunctional contractililty due to discontinuity of the myometium.[32, 51] However, the presence of a niche after CS as probable underlaying cause of disturbed uterine peristalsis has never been investigated.

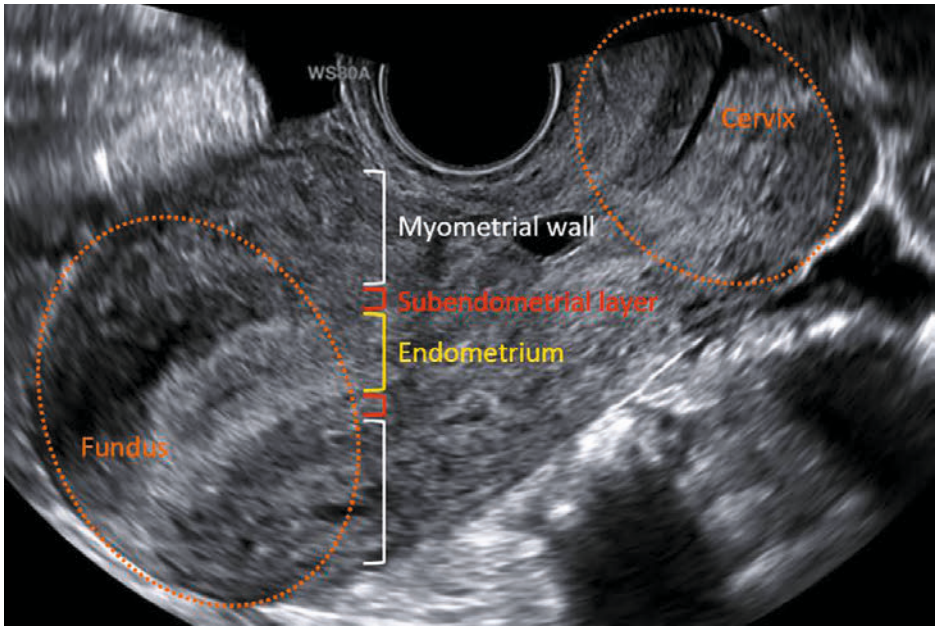

Figure 3. Transvaginal ultrasound of the uterus, presenting the subendometrial layer (in red)

AIM OF THIS THESIS AND RESEARCH QUESTIONS

In summary, it is known that niche presence after previous CS can cause gynecological symptoms that affect the quality of life. Women are offered different treatment options, but proper research assessing the cost-effectiveness of these treatments is lacking because there is no uniform definition of a niche. Also, the prevalence of obstetric outcomes, including CSP, is not entirely clear due to the lack of definition and uniform reporting systems. Therefore, these definitions should be determined first.

Furthermore, if we treat women with niche-related symptoms, it is important to evaluate its long-term outcomes including obstetric outcomes in order to be able to properly inform women about possible risks. Finally, the ultimate goal is to assess whether niche development can be prevented.

The general aim of this thesis was to evaluate the uterine scar after previous CS and during subsequent pregnancy by using ultrasound. In this thesis the following research questions are addressed:

1. How should the uterine cesarean scar be defined and evaluated in non-pregnant women by using ultrasound?

2. What is the influence of a niche in the CS scar on the physiological subendometrial peristalsis of a non-pregnant uterus?
3. How should the uterine cesarean scar be evaluated in the first trimester of pregnancy after previous CS by using ultrasound, regarding assessment of possible CSP?
4. What moment after CS is optimal to visualize and evaluate the uterine cesarean scar by using ultrasound?
5. What is the influence of laparoscopic niche resection on niche presence during subsequent pregnancy after previous CS?
6. Does the uterine closure technique influence niche development?

OUTLINE OF THIS THESIS

The first part of this thesis focuses on ultrasound evaluation of the uterine niche after CS in non-pregnant and pregnant women.

Chapter 2 presents recommendations on the method of niche ultrasound evaluation in non-pregnant women following a modified Delphi procedure amongst international niche experts.

In **chapter 3**, the results of evaluation of subendometrial peristalsis in women with a niche compared to women without a niche by using ultrasound speckle tracking are described.

Recommendations on the method of ultrasound evaluation and classification of a CSP in first trimester, that followed from a modified Delphi study amongst international gynecological and obstetrical niche experts, are presented in **chapter 4**.

The focus of the second part of the thesis is on niche development after previous CS including the moment of development.

Chapter 5 presents the results of a proof-of-concept study in which changes of the uterine scar during the first year after CS were evaluated.

In **chapter 6**, the results of a systematic review are described in which niche presence and changes of niche features were studied in non-pregnant and pregnant women after previous CS aiming to determine the best moment after CS to evaluate the uterine scar.

Chapter 7 describes the results of a cohort study evaluating niche changes during pregnancy in women after previous laparoscopic niche repair compared to controls without niche surgery.

The third part of the thesis focuses on the possible influence of uterine closure technique that was used during previous CS on niche development.

The results of a systematic review on uterine closure techniques that affect ultrasound findings, including niche prevalence, are described in **chapter 8**.

In **chapter 9**, the study protocol of a randomized controlled trial evaluating two uterine closure techniques (single layer versus double layer) in comparison to post menstrual spotting is described. Niche prevalence was included as secondary outcome in this study.

In **chapter 10**, the main findings of this thesis are outlined and discussed, and future perspectives are presented.

Finally, a summary of this thesis in English and Dutch is provided in **chapter 11**.

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PART 1

SONOGRAPHIC NICHE EVALUATION

CHAPTER 2

SONOGRAPHIC EXAMINATION OF UTERINE NICHE IN NON-PREGNANT WOMEN: A MODIFIED DELPHI PROCEDURE

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ABSTRACT

Objective

To generate guidance for detailed uterine niche evaluation by ultrasonography in the non-pregnant woman, using a modified Delphi procedure amongst European experts.

Methods

Twenty gynecological experts were approached through their membership of the European Niche Taskforce. All experts were physicians with extensive experience in niche evaluation in clinical practice and/or authors of niche publications. By means of a modified Delphi procedure, relevant items for niche measurement were determined based on the results of a literature search and recommendations of a focus group of six Dutch experts. It was predetermined that at least three Delphi rounds would be performed (two online questionnaires completed by the expert panel and one group meeting). For it to be declared that consensus had been reached, a consensus rate for each item of at least 70% was predefined.

Results

Fifteen experts participated in the Delphi procedure. Consensus was reached for all 42 items on niche evaluation, including definitions, relevance, method of measurement and tips for visualization of the niche. A niche was defined as an indentation at the site of a Cesarean section with a depth of at least 2 mm. Basic measurements, including niche length and depth, residual and adjacent myometrial thickness in the sagittal plane, and niche width in the transverse plane, were considered to be essential. If present, branches should be reported and additional measurements should be made. The use of gel or saline contrast sonography was preferred over standard transvaginal sonography but was not considered mandatory if intrauterine fluid was present. Variation in pressure generated by the transvaginal probe can facilitate imaging, and Doppler imaging can be used to differentiate between a niche and other uterine abnormalities, but neither was considered mandatory.

Conclusion

Consensus between niche experts was achieved regarding ultrasonographic niche evaluation.

INTRODUCTION

Cesarean section (CS) rates are increasing worldwide, with a corresponding increase in associated complications. The CS scar defect or 'niche' has been reported as an important feature that is associated with future complications. Recently, it has been demonstrated that niches may be the causative factor for abnormal uterine bleeding, dysmenorrhea, obstetric complications in subsequent pregnancies and, possibly, subfertility.[1–6] The relationship between various niche features and symptoms has not been elucidated fully, although both niche volume and the 'healing ratio' (residual myometrial thickness (RMT)/adjacent myometrial thickness (AMT)) have been reported to be associated with abnormal uterine bleeding.[3,4] Therefore, the accurate measurement and description of a niche is becoming increasingly important, for research, for the clinical assessment of gynecological symptoms and for the planning of possible surgical treatment.[6,7]

Although many studies have evaluated the development of niches and associated symptoms, there is no standardized guideline for their examination, measurement or description.[8] A niche can be examined using two- (2D) or three- (3D) dimensional transvaginal sonography (TVS), with or without saline or gel contrast, magnetic resonance imaging and hysteroscopy.[4,9–12] Naji *et al.*[13] proposed a standardized approach for niche description using ultrasonography in non-pregnant women, based on definitions and methods described in the literature. However, their proposed approach to document the size of a niche did not take into account variations that occur in scar morphology.

Having identified the need for more detailed practical guidance for clinicians, we decided to develop this, focusing on non-pregnant women. (It should be borne in mind that there is a considerable difference between measuring a niche in a pregnant woman and doing so in a non-pregnant one.) We considered a Delphi method to be the most suitable means, as this could achieve consensus amongst international experts in a structured way. This technique has been used widely in healthcare research, in particular within the field of education and training, and in developing clinical practice.[14,15] The aim of this study was to generate guidance for detailed uterine niche evaluation using ultrasonography in the non-pregnant woman, by means of a modified Delphi procedure amongst European experts.

METHODS

Design of a modified Delphi study

To achieve consensus, we followed a modified Delphi procedure (Figure 1). We carried out a systematic literature search and formed a focus group of Dutch experts to identify relevant items for niche assessment and design a questionnaire on niche measurement, which would be answered online anonymously by the experts participating in the Delphi study. A modified Delphi procedure was applied, with repeated rounds of the questionnaire, to enable the participating experts to reflect on the results of each previous questionnaire round in a structured manner. Thus, in each round, after analysis of the collective opinion of the group, the results of one round were used as the basis for formulating the next. It was predetermined that the process would include at least three rounds (two online questionnaire rounds and one face-to-face meeting) and additional rounds if required until data saturation was achieved. The data were collected between May and October 2016.

Literature search to collect data for first Delphi round

A systematic search of the literature up to October 2015 was performed in PubMed and EMBASE databases, with the assistance of a clinical librarian. We searched for all possible methodological items describing ultrasonographic evaluation of uterine scar in non-pregnant women (see Appendix S1 for search strategy). Duplicate articles were excluded. We included any English or Dutch article that reported on niche measurement by ultrasound and reported on one or more of a set of questions that was predetermined by J.H., R.L. and I.J. The questions concerned: (1) the optimal timing for measuring a niche following CS; (2) the best infusion fluid (gel or saline); (3) whether 2D or 3D ultrasonography should be used; (4) what features of the niche should be measured; (5) the best time in the menstrual cycle for measurement; (6) the relevance of pressure from the transvaginal probe; (7) the relevance of Doppler ultrasound; and (8) the relevance of measuring the distance between the vesicovaginal (VV) fold and the internal os. From all reviewed papers, we extracted all items that could possibly be relevant in a concept questionnaire for the Delphi procedure, and these were presented to the focus group for final selection.

Focus group and development of questionnaire used in first Delphi round

The focus group contained six Dutch experts who had participated previously in the Dutch HYSNICHE trial[16] (Hysteroscopic resection of uterine Cesaran scar defect (niche) in patients with abnormal bleeding, a randomized controlled trial) and SCAR[4] (Sonohysterographic evaluation of Cesarean scar defects and determination of risk factors) or SECURE[3] (Scar Evaluation after Cesarean by Ultrasound Registry) studies. In

a face-to-face meeting, a proposal for the Delphi questionnaire that included the items that we had identified as being potentially relevant for niche measurement (illustrated by ultrasonographic images) was discussed to determine internal validity. We recorded and analyzed all comments and recommendations discussed in this meeting. A summary of the results was sent to the members of the focus group for feedback. Based on these results, an online questionnaire for the first round of the Delphi procedure was designed.

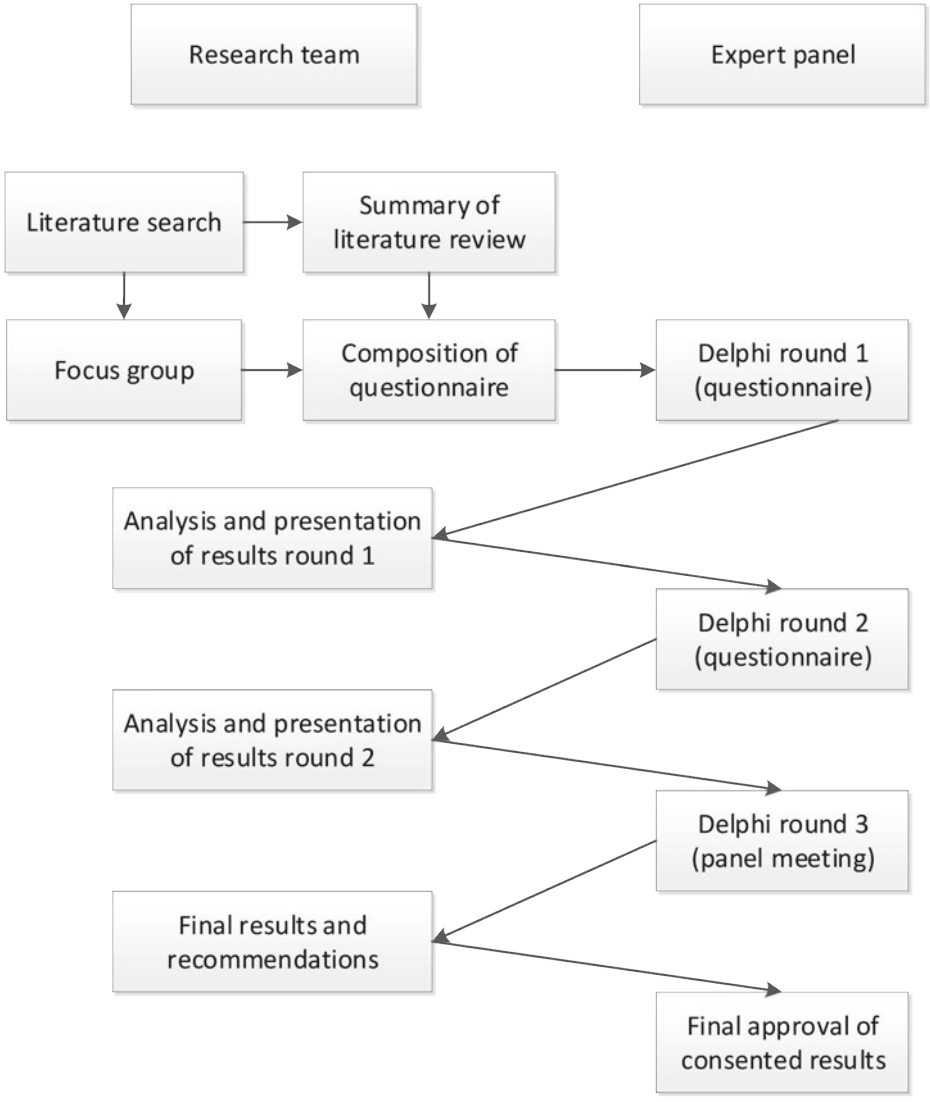


Figure 1. Study design: stepwise modified Delphi method used to reach consensus on uterine niche definition and sonographic evaluation.

Expert panel recruitment

In order to form an expert panel comprising members with sufficient experience in niche measurement, members of the European Niche Taskforce were invited to participate in the Delphi procedure. These experts were each asked to invite one colleague, from the same institute, who was known to have sufficient experience in the field. For the purpose of this Delphi procedure, an 'expert' was predefined as a gynecologist or resident who performed more than 30 niche evaluations a year, or who had published at least one article on niches in a peer-reviewed journal or given at least one presentation concerning ultrasound and niches at an appropriate conference. In total, 20 experts were invited. After confirmation of their participation, the experts each received an email containing a unique link to the online questionnaire. In the first questionnaire, the experts confirmed the items selected by the focus group.

Delphi rounds and structural consensus method

The answers from all experts were analyzed for each question. Consensus was predefined as a rate of agreement (RoA)>70%, where RoA = (agreement – disagreement)/(agreement + disagreement + indifferent)×100%; this is a commonly used cut-off value for consensus.[14,17,18] If no consensus was reached, the question was transferred to the second round and the results of the first round were fed back anonymously, including the reasoning of the respondents. Additional questions seeking clarification were added as appropriate. Non-responders in the first round were not invited to participate in the following rounds. Based on the results of the second round, a draft set of recommendations was designed. These results were presented in a face-to-face meeting at the European Society for Gynecological Endoscopy world congress in Brussels, in October 2016, and the items without consensus were discussed. We recorded all comments and recommendations made in this meeting. The experts could reflect on their reasoning and, if necessary, reconsider their opinion. The final results of the agreed items were sent to all experts who had participated in the first round for final approval.

RESULTS

Literature search

The literature search resulted in 1034 papers after removal of duplicates (Appendix S1). All titles and abstracts were reviewed by two of the authors (I.J. and R.L.) and 908 articles were excluded because their subject was not related to niche measurement. After assessing the full text of the remaining 126 articles, we identified 10 papers that reported on our predefined research questions. The main results of the search are presented in Table 1. In total, six papers reported higher detection rates of niches using saline or gel

contrast rather than standard TVS.[3–5,10,19,20] Two papers assessed the value of 3D-TVS[21,22] and two proposed methodology for niche measurement[5,13]. Fabres *et al.*[23] reported that the best time during the menstrual cycle to evaluate a niche is during menstruation. No literature was available to address our other research questions. Based on these 10 studies, we formulated 11 main topics and 19 subtopics as being potentially relevant for niche measurement and presented these for discussion to the focus group (Appendix S2). The most relevant and illustrative results of our literature search were also presented to the experts in an evidence table scored according to the GRADE method[24] (Appendix S3).

Table 1. Results of literature search which identified 10 papers[3–5,10,13,19–23] reporting on predefined research questions regarding sonographic measurement of uterine niche

Predefined research question	Study	Study type	Results
Optimal timing after CS to measure niche	None		
Best method (TVS or with contrast) for measurement	Allison (2010)[19]	Overview of literature	Saline contrast is a useful adjunct to TVS, especially for evaluation of endometrium and adjacent lesions.
	Baranov (2016)[10]	Cohort study	Scar defects in 46.4% of cases seen by both observers on TVS; scar defects in 69.1% of cases seen by both observers on saline contrast.
	Vikhareva Osser (2009)[20]	Cohort study	53 scar defects seen on saline contrast; 42 scar defects seen on TVS.
	Tower (2013)[5]	Overview of literature	Saline contrast has higher sensitivity and specificity for detection of CS scar defects than does TVS. Recommendation based on literature: if CS defect is suspected, evaluation using saline contrast is recommended unless this is unacceptable or contraindicated in the patient, in which case TVS can be used.
	Bij de Vaate (2011)[3]	Observational prospective cohort study	Prevalence of niche on TVS = 24%; prevalence of niche using gel infusion = 56%.
	Van der Voet (2014)[4]	Prospective cohort study	Prevalence of niche on TVS = 49.6%; prevalence of niche on gel infusion = 64.5%.

Table 1. (Continued)

Predefined research question	Study	Study type	Results
Best method (3D- or 2D-TVS) to use for measurement	Bij de Vaate (2015)[21]	Prospective cohort study	3D is a reproducible tool for niche measurement (size and RMT) in sagittal plane.
	Giral (2015)[22]	Retrospective study	Prevalence of niche on 3D-TVS = 50%; prevalence of niche on 2D saline contrast sonography = 86%.
Niche measurements	Naji (2012)[13]	Overview of literature	Length, width, depth of niche and RMT should be measured in both sagittal and transverse planes; see illustration in their paper.
	Tower (2013)[5]	Overview of literature	RMT is measured from apex of defect to outer edge of myometrium.
Best time in menstrual cycle to measure niche	Fabres (2003)[21]	Retrospective review	Best time during cycle to identify CS defect with sonography is during bleeding episode, usually a few days after menses.
Relevance of pressure from transvaginal probe	None		
Relevance of Doppler ultrasound	None		
Relevance of measurement between VV fold and internal os	None		

Only first author of each study is given. CS, Cesarean section; RMT, residual myometrial thickness; TVS, unenhanced transvaginal sonography; VV, vesicovaginal.

Focus group participation and Delphi procedure

The focus group discussion took place on 10 January 2016. It was recorded and transcribed, resulting in an analysis of 50 keywords using Atlas.ti.software[25]. Analyzing these keywords, 40 relevant items comprising 79 questions emerged for inclusion in the first online questionnaire. These questions could be categorized as: definitions and methods of measurement and their relevance, general ultrasound methods (including machine settings), additional tools (including Doppler ultrasound) and the use of gel or saline contrast. Appendix S4 gives an overview of questions of both questionnaires and subjects discussed during the face-to-face meeting.

During successive rounds of the procedure, a further two items were added. A total of 15 experts were involved in the first round of the Delphi procedure and completed

the first online questionnaire. Of these, 12 (80%) also completed the second round and nine were able to participate in the face-to-face meeting. All 15 participants of the first round agreed on the final results, and consensus was reached for all 42 items (Figure 2). Table S1 presents the mean consensus achieved per item in each round of the Delphi procedure.

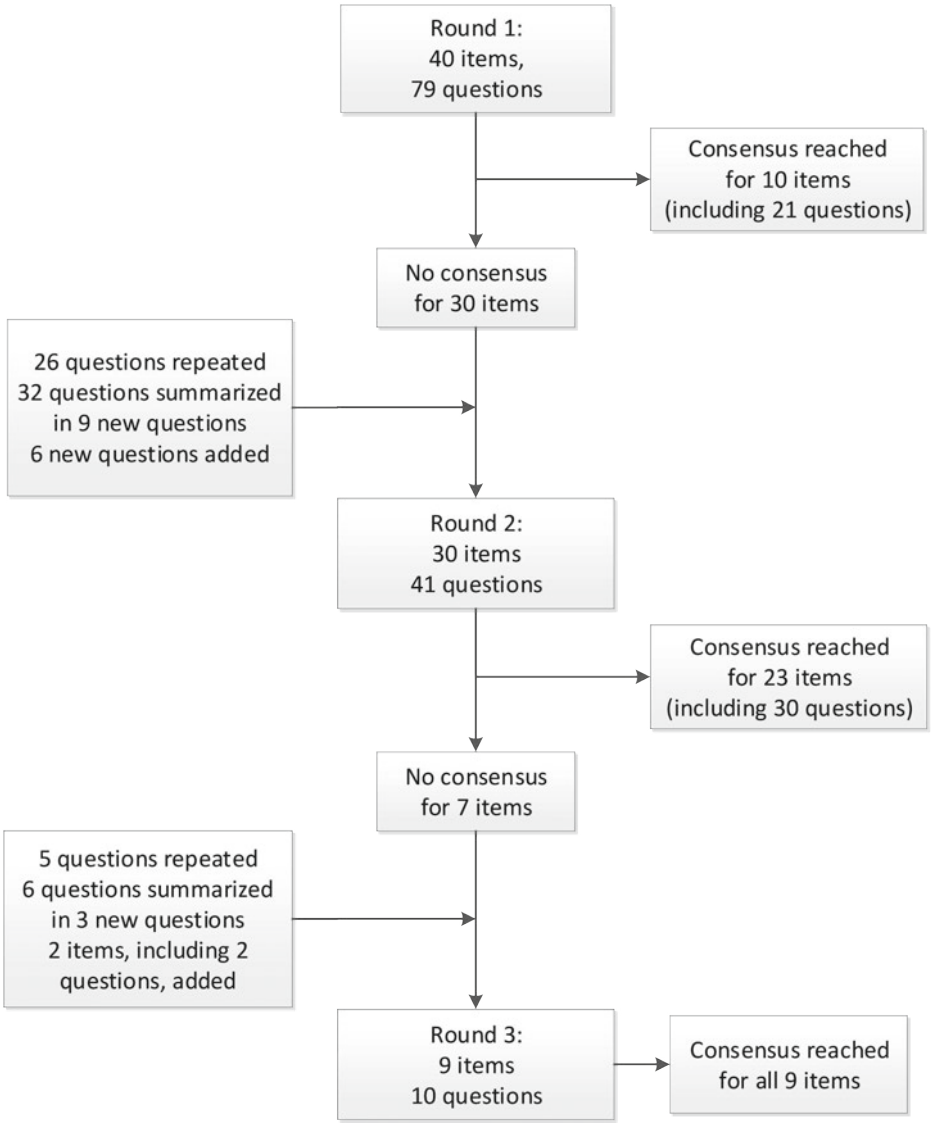


Figure 2. Flow diagram summarizing agreement with or rejection of items during Delphi procedure. Items were accepted if consensus agreement of at least 70% was reached.

Agreed recommendations and statements

Definitions and relevance

Most (83%) experts agreed that a niche should be defined as an indentation at the site of the CS scar with a depth of at least 2 mm. A niche can be subclassified as follows: (1) simple niche; (2) simple niche with one branch; (3) complex niche (with more than one branch). A branch was agreed to be a thinner part of the main niche, which is directed towards the serosa and has a width smaller than that of the main niche (86% agreement), and should always be recorded. The main niche is illustrated as the green and red area in Figure 3; the blue area illustrates a branch.

The VV fold is a triangular-shaped fold between the bladder, the vagina and the cervix, created by placing the transvaginal probe in the anterior vaginal fornix (Figure 3). The distances between the niche and the VV fold, and the niche and the external os were considered to provide additional value for planning future surgical strategies and for research but not for basic niche evaluation (92% and 75% agreement, respectively). Measurement of the AMT was agreed to be relevant in clinical practice (92% agreement). The internal os was defined as a slight narrowing in the lower uterine segment, between the uterine corpus and the cervix at the lower boundary of the urinary bladder (73% agreement); however, the distance was considered to be irrelevant both in clinical practice and in the research setting (75% agreement).[13]

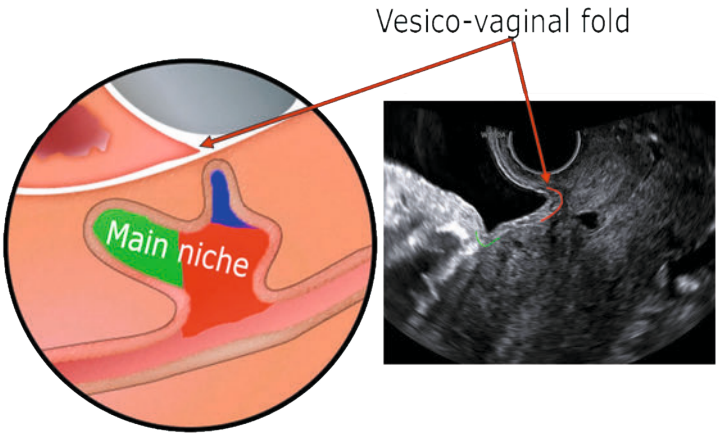


Figure 3. Main niche and vesicovaginal fold. (a) Red and green areas represent main niche and blue area represents branch. (b) Green line indicates plica vesicouterina or uterovesical fold, while red line indicates vesicovaginal fold.

Methods of measurement

The best method to obtain the correct sagittal and transverse planes for niche measurement is described in Table 2. Clinically relevant measurements of the niche include: length, depth, RMT, width, AMT, distance between the niche and the VV fold, and distance between the niche and the external os. It was agreed that the length, depth and RMT should be measured in the sagittal plane (100% agreement). The transverse plane was considered relevant only for measurement of the width of a niche and to identify branches; it was not recommended to repeat depth and RMT measurements in this plane (100% agreement). The length, depth and width of the niche should each be measured in the plane in which it is largest (92–100% agreement); RMT should be measured in the sagittal plane in which the main niche has the smallest RMT (83% agreement). For simple niches, therefore, all measurements can be done in a single plane, while, for complex niches, more than one plane may be necessary, with length and depth being measured in the same sagittal plane, and one or two different sagittal planes being required to measure the thinnest RMT of the main niche and the thinnest RMT of the branch.

Table 2. Summary of agreed statements after three Delphi rounds, regarding methods of uterine niche measurement

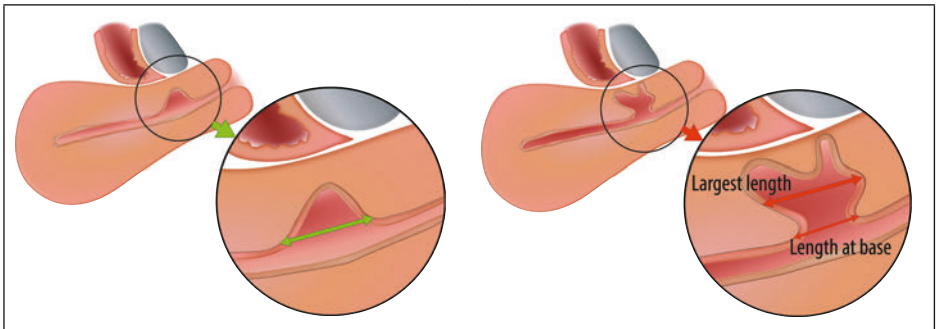
Methods of measurement
Endometrium should be ignored; niche measurements are based only on myometrium
Correct sagittal plane to perform niche measurement depends on the measurement itself (length, depth or RMT) in case of niches with one or more branches (i.e. thinnest RMT including branch may be found in a sagittal plane other than the plane in which the main niche has its largest length and depth and thinnest RMT)
Transverse plane is used only for third dimension of the niche (width), not for depth or RMT.
General ultrasound methods to be used
Best method to obtain correct sagittal plane for niche measurement is by starting in midsagittal plane, with good visualization of cervical canal, then moving transvaginal probe laterally to both sides
Best method to visualize niche in transverse plane is by starting in sagittal plane, keeping good visualization of niche while rotating transvaginal probe from sagittal to transverse plane
Best method to detect possible branches is in transverse plane, screening entire lower uterine segment from cervix to corpus
To measure uterine niche, there should be good visualization of lower uterine segment only; this applies to all uterine positions (anteversion, retroversion or stretched)
Position of transvaginal probe (in anterior or posterior fornix) affects correct plane for niche measurement
Value of additional tools
It is useful to vary pressure with transvaginal probe in order to achieve best plane for niche measurement

Table 2. (Continued)

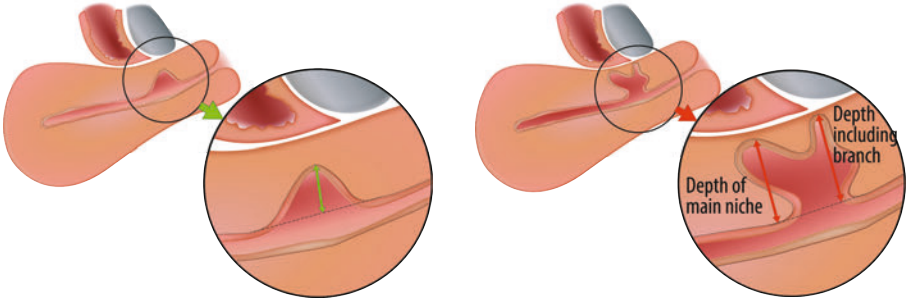
Use of Doppler imaging is not mandatory in standard niche measurement, but can be useful to differentiate between uterine niche and, for example, hematomas, adenomyomas, adenomyosis, fibrotic tissue
Gel/saline contrast sonography
Contrast sonography has added value in patients with uterine niche
There is no preference for either gel or saline
There is no preference for catheter used in contrast sonography
Best location of catheter used in contrast sonography is just in front of niche (caudal to its most distal part) or, if possible, cranial to its most proximal part, at start of gel/saline contrast infusion, then pulling catheter slowly backwards towards base of niche
While performing ultrasound with saline infusion, catheter can be left in front of niche
While performing ultrasound with gel infusion, there is no preference whether to remove catheter or leave it in front of niche
In case of intrauterine fluid accumulation, gel or saline infusion is not of additional value.

RMT, residual myometrial thickness.

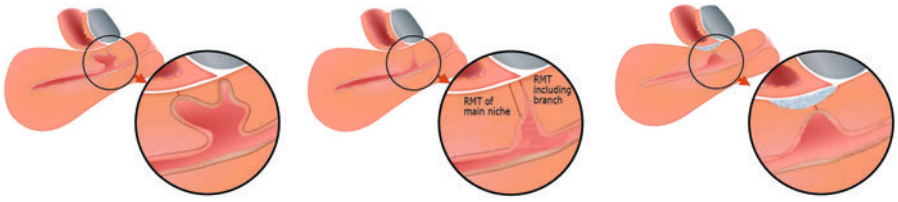
Figures 4 and 5 illustrate the various measurements, showing what should be measured and how the calipers should be positioned. According to all of the experts, if the length or the width of the main niche is larger at any point other than the niche base, two different measurements should be performed: at the base of the niche and at the point of the largest length (Figure 4a) or width (Figure 5). If visible, branches should be measured; measurements of the depth (Figure 4b) and the RMT (Figure 4c) should be made separately for the main niche and including any branch. All experts agreed that documenting features of the endometrium was not relevant to niche measurement; thus, the calipers should be placed on the border of the myometrium (for example, see Figure 4a).



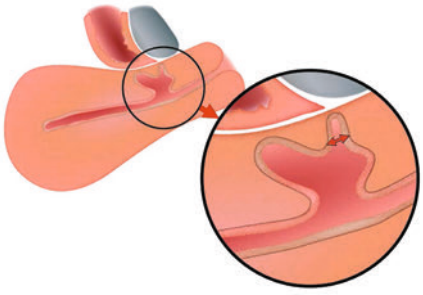
(a) Niche length. Both largest length and length at niche base should be measured.



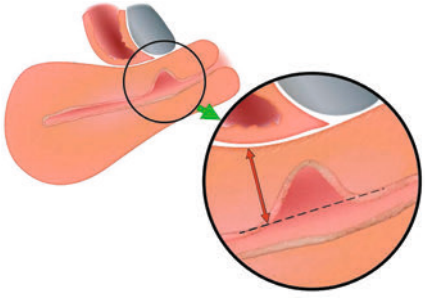
(b) Niche depth. Largest depth should be measured, both of main niche and including deepest branch if branches are present.



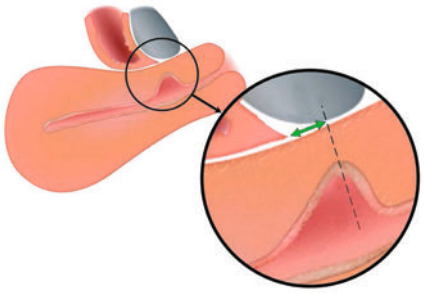
(c) Residual myometrial thickness (RMT). Thinnest point of RMT should be measured, regardless of direction (measured perpendicular to serosa but not necessarily to uterine cavity), both from main niche and, if there are any branches, from branch with thinnest RMT. Fibrosis is not included in RMT measurement.



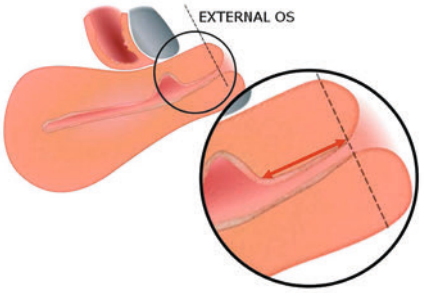
(d) Branches. Width of any branch should be measured.



(e) Adjacent myometrial thickness (AMT). AMT should be measured close to niche, where myometrium is thickest.



(f) Distance between niche and vesicovaginal (VV) fold. Niche–VV fold distance should be measured from level of top of main niche (where residual myometrial thickness is smallest (dotted line)) to VV fold.



(g) Distance between niche and external os. Niche–external os distance should be measured parallel to cervical canal, from most distal point of niche to external os.

Figure 4. Position of calipers for different sonographic measurements of uterine niche in the sagittal plane.

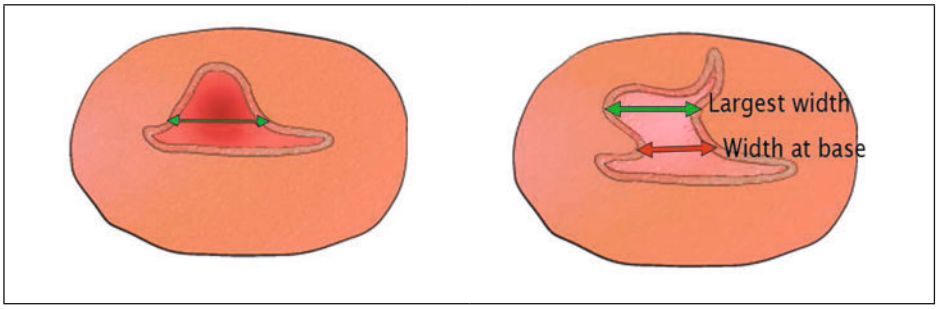


Figure 5. Position of calipers for sonographic measurement of width of uterine niche in transverse plane. Both largest width and width at niche base should be measured.

Tips for the visualization of niches

During the Delphi procedure, various tips and tricks to improve visualization of the niche were proposed by individual experts and were added to the questions over the course of the process. It is important to have good visualization of the lower uterine segment (80% agreement). One expert tip was that the operator should be aware that TVS is a dynamic process, in which variation of the position of the probe (anterior or posterior fornix) and application of pressure using the probe can affect (either positively or negatively) visualization of the niche. Visualization of a niche that is located more proximal within the uterus in general requires more pressure, while less pressure is needed for good visualization of niches located more distally or for visualization of the VV fold. A full bladder is not obligatory for visualization of the VV fold. Doppler imaging was felt to be

useful to differentiate between a niche and other uterine abnormalities (e.g. hematomas, myomas or adenomyosis), but was not considered mandatory for niche measurement.

Most (75%) experts agreed that niche evaluation with either gel or saline infusion is of additional value compared with using standard 2D ultrasonography, but no preference was expressed of one over the other. The expert panel also concluded that there need be no preference for the type of catheter used for contrast sonography, apart from one catheter for gel infusion that was considered unsuitable since it impairs visualization of the niche due to a thicker intracervical component (the 'GIS-Kit'). It was also considered that, if fluid is present in the uterine cavity, there is no need for additional gel or saline instillation (100% agreement).

DISCUSSION

Main findings

The modified Delphi procedure used in this study included two questionnaire rounds and one face-to-face meeting, resulting in consensus amongst experts for all items concerning the definition and evaluation with ultrasonography of a uterine niche. Based on the consensus findings, we formulated a definition for uterine niche and produced guidance for its various measurements, keeping these as simple and consistent as possible to facilitate their use in daily clinical practice. Only basic measurements, including niche length and depth, RMT and AMT in the sagittal plane, and niche width in the transverse plane, are considered to be essential. If there are branches, these should be reported and additional measurements are recommended. The use of gel or saline infusion is preferred over standard TVS but is not mandatory if intrauterine fluid is present. Variation in pressure generated with the transvaginal probe can optimize imaging, and Doppler imaging can be used to differentiate between a niche and other uterine abnormalities, but neither is considered mandatory.

The current consensus focused on the basic evaluation, which can be used in daily clinical practice; additional items that may be relevant for presurgical assessment or research purposes were not included.

Comparison with other studies

Although the number of published studies on uterine niche has increased over the last few years, there is no uniform, internationally recognized definition and guideline for niche evaluation. In their proposed standardized method for identifying a niche with ultrasonography, Naji *et al.*[13] suggested classifying the appearance of a niche based on its

clinical value (mild, moderate or severe scar defect) and performing measurements in three dimensions (length, width and depth) as well as measuring RMT; measurements were not further defined or specified for different niche shapes, for example in the presence of a branch or fibrotic tissue at the site of the uterine scar. Tower *et al.*[5] proposed a classification of niches based on RMT and the RMT/AMT ratio as the only ultrasonographic features. Our literature search confirmed a lack of detailed guidelines for niche measurement. In most previous niche studies, measurements were not described clearly and reasons for their use were not given for the types of measurement used. Given the lack of studies evaluating the accuracy and validity of various niche measurements, we decided to use a structured consensus method to produce the current recommendations. The usefulness and accuracy of our recommendations need to be confirmed in future studies.

Strengths and limitations

The use of a modified Delphi method is a strength of our study. This procedure allows experts to maintain anonymity during questionnaire rounds, preventing domination by any individual, and to revise their opinion during successive rounds. Furthermore, we composed a focus group prior to commencing the Delphi procedure, in order to optimize the validity of the questionnaire to be used in the first round. The items selected by the focus group were additionally confirmed by the expert panel. Additionally, members of the expert panel were gynecologists from all over Europe potentially with different viewpoints due to their different education and experience.

It is a limitation that the response rate in the second round decreased to 80% and only nine (60%) experts were present during the group meeting. However, consensus on the content of all 42 items concerning niche measurement was achieved in three Delphi rounds, and these items were then approved by all 15 experts who participated in the first round. Validity of the construction and accuracy of the item list used should be determined in future studies.

Future perspectives

These recommendations on detailed uterine niche evaluation are intended as a basic practical guideline for gynecologists, ultrasound examiners and researchers, with the aim of standardizing niche measurement in non-pregnant women. In order to facilitate its use, we have designed an e-learning module including these recommendations on which consensus was reached. The value of this e-learning program (the eNiche study) is being assessed and these findings will be published in the future. During our Delphi procedure we identified several knowledge gaps concerning niche measurement that require future research. These include: the optimal cut-off value for the depth of a niche to be used in defining different sizes of niche; the optimal cut-off values of RMT

and ratios of RMT/AMT or depth/RMT to define the clinical relevance of a niche; and the relevance of certain measurements that include a branch, the distance between niche and external os and the measurements of width and length if the niche base is not the largest part. The relevance of these parameters in terms of related symptoms, subfertility or problems during fertility treatment, prediction of obstetric complications in a subsequent pregnancy and prediction of treatment risks and success, needs to be elucidated. To determine the optimal timing for niche measurement after a CS, future studies are needed as data are limited. An ongoing trial with this aim is registered in the trial register (NTR6921). A previous study reported a difference in niche measurements using saline contrast sonohysterography between those made at 6–12 weeks and those at 12 months following CS.[26] Based on the expected duration of the scar healing process, and until future data become available, we advise evaluating a niche at least 3 months after CS. This is in line with a large ongoing study in 2290 patients (NTR5480), in which niches are measured at 3 months follow-up after double or single-layer closure of a uterine CS scar. Also, the best timing for niche measurement during a menstrual cycle needs to be elucidated. Since intrauterine fluid is seen most frequently during the midfollicular phase, possibly under the influence of increased estradiol levels[27], niche evaluation between cycle days 7 and 14 may prevent the need for any additional infusion of gel or saline. Furthermore, this allows evaluation of the existence of intrauterine fluid during this phase, which may be relevant in women who want to conceive, since this may affect implantation.[28,29]

Conclusion

We have developed and describe here a uniform definition and recommendations for evaluating uterine niche in the non-pregnant woman. Consensus was achieved, using a modified Delphi procedure, amongst European experts for all 42 items regarded as relevant for ultrasonographic niche evaluation. The relationship between the morphological characteristics and measurements of a niche with clinical outcome has yet to be described.

Acknowledgements

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Disclosure of interests

J.H., I.J. and S.S. declare their involvement in the Dutch 2Close study, 'The cost effectiveness of double layer closure of the cesarean (uterine) scar in the prevention of gynecological symptoms in relation to niche development'. This is a randomized controlled trial funded by ZonMw, an organization for health research and development in The Netherlands.

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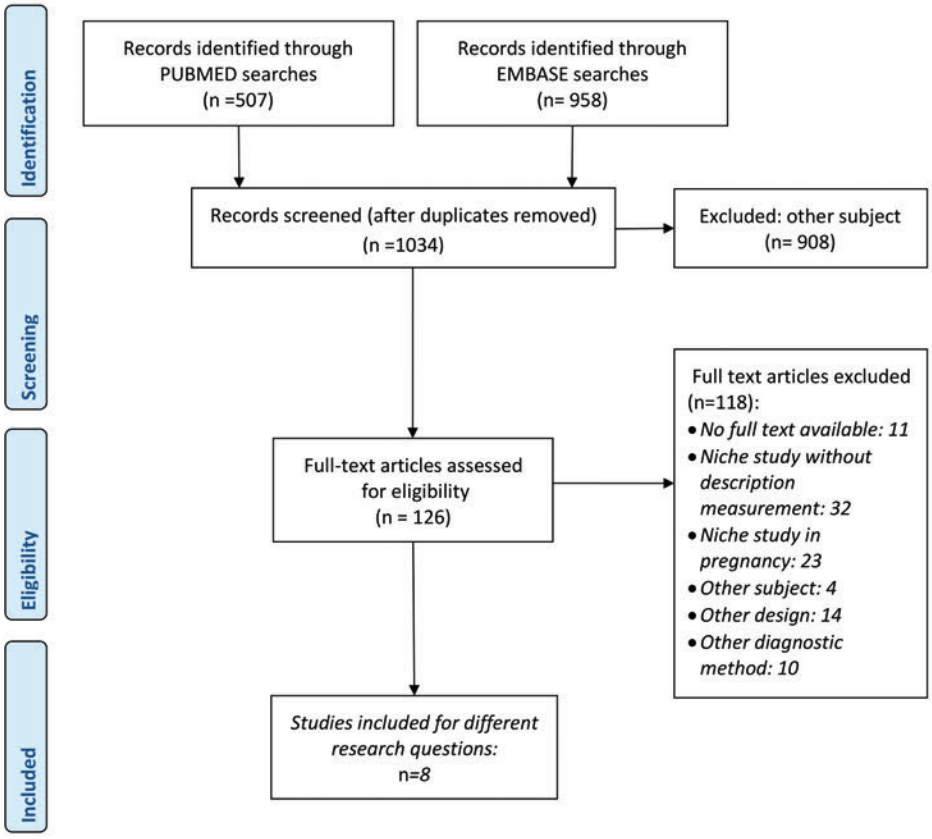
APPENDICES

Appendix S1. Method of literature search



Search strategy for Pubmed (December 8th, 2015)

Search	Query	Items found
#6	#4 AND #5	507
#5	"Ultrasonography"[Mesh] OR ultraso* [tiab] OR sonohysterograph*[tiab] OR sonograph*[tiab] OR hysterosonograph*[tiab] OR hysteroscop*[tiab] OR echograph*[tiab]	467,314
#4	#1 AND #2 AND #3	1,741
#3	"Cesarean Section"[Mesh] OR cesarea*[tiab] OR caesarea*[tiab] OR "c section"[tiab] OR "c sections"[tiab] OR (abdominal[tiab] AND deliver*[tiab]) OR postcesarea*[tiab] OR postcaesaria*[tiab]	63,609
#2	"Uterus"[Mesh] OR "Uterine Diseases"[Mesh] OR uterus[tiab] OR uterine[tiab] OR myometri*[tiab] OR endometri*[tiab] OR endomyometri*[tiab] OR myoendometri*[tiab]	298,204
#1	"Cicatrix"[Mesh] OR cicatr*[tiab] OR scar[tiab] OR scars[tiab] OR scarring[tiab] OR isthmocele*[tiab] OR niche[tiab] OR niches[tiab] OR anechoic[tiab] OR pouch*[tiab] OR diverticul*[tiab]	143,746

[Mesh], Medical subject headings (MeSH); [Mesh:NoExp], Medical subject headings (MeSH) without explosion; [tiab], words in title or abstract

Search strategy for Embase.com (December 8th, 2015)

Search	Query	Items found
#6	#4 AND #5	958
#5	'echography'/exp OR 'color ultrasound flowmetry'/exp OR ultraso*:ab,ti OR sonograph*:ab,ti OR echograph*:ab,ti OR echotomograph*:ab,ti OR sonohysterograph*:ab,ti OR hysterosonograph*:ab,ti OR hysteroscop*:ab,ti	780,187
#4	#1 AND #2 AND #3	2,542
#3	'cesarean section'/exp OR cesarea*:ab,ti OR caesarea*:ab,ti OR 'c section':ab,ti OR 'c sections':ab,ti OR (abdominal:ab,ti AND deliver*:ab,ti) OR postcesarea*:ab,ti OR postcaesarea*:ab,ti	92,028
#2	'uterus'/exp OR 'uterus disease'/exp OR uterus:ab,ti OR uterine:ab,ti OR myometri*:ab,ti OR endometri*:ab,ti OR endomyometri*:ab,ti OR myoendometri*:ab,ti	388,002
#1	'wound dehiscence'/exp OR 'scar formation'/exp OR 'scar'/exp OR cicatr*:ab,ti OR scar:ab,ti OR scars:ab,ti OR scarring:ab,ti OR isthmocele*:ab,ti OR niche:ab,ti OR niches:ab,ti OR anechoic:ab,ti OR pouch*:ab,ti OR diverticul*:ab,ti	190,455

/exp, EMtree keyword with explosion; :ab,ti, words in title or abstract

Appendix S2. Topics presented for discussion to the focus group

Main topics		Subtopics	
1	Fullness of the bladder		
2	Positioning of the transvaginal probe		
3	Region of interest	3a	Imaging of the cervix
		3b	Imaging of the bladder
		3c	Imaging of the uterus
4	Settings of the ultrasound machine	4a	The use of the zoom function
		4b	The use of the focus function
5	Pressure of the transvaginal probe		
6	Best method (TVS or SCSH/GIS)		
7	Relevance of Doppler ultrasound		
8	How to obtain the best measurement	8a	In the sagittal plane
		8b	In the transversal plane
9	Which measurements to be performed		*Sagittal plane*
		9a	Length of a niche
		9b	Depth of a niche
		9c	RMT
		9d	AMT
		9e	Distance niche-VV fold
		9f	Distance niche-external os
			Transversal plane
		9g	Width of a niche
		9h	Depth of a niche
		9i	Branches
		9j	RMT
		9k	AMT
		9l	Shape of a niche
10	Best moment after CS to evaluate a niche		
11	Best moment in the menstrual cycle to evaluate a niche		

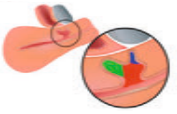
AMT, adjacent myometrial thickness; CS, cesarean section; GIS, gel infusion sonography; RMT, residual myometrial thickness; SCSH, saline contrast sonohysterography; TVS, transvaginal sonography; VV fold, vesicovaginal fold

Appendix S3. Transvaginal sonography (TVS) *vs* saline contrast sonohysterography (SCSH) / gel infusion sonography (GIS) in uterine niche measurement; GRADE level of evidence[24]

Reference	Study design	Characteristics	Intervention	Control	Outcome	Results	Study quality	Level of evidence
Baranov, 2015	Cohort study	56 women with one previous CS at ≥37 weeks GA and no previous surgery on the uterus other than CS 2 observers	SCSH 6-9 months after CS	TVS 6-9 months after CS	Visibility of scar defect and interobserver agreement	Scar defects in 46,4% seen by both observers by TVS Scar defects in 69,1% seen by both observers by SCSH	Low	B
Bij de Vaate, 2011	Observational prospective cohort study	225 women with a previous CS Exclusion: PID, cervical cancer, pregnancy	GIS 6-12 months after CS	TVS 6-12 months after CS	Primary: prevalence of postmenstrual spotting Secondary: niche classification	Prevalence of niche on TVS was 24%, prevalence of niche on GIS was 56%	Low to moderate	B
Vikhareva Osser, 2010	Cohort study	108 women with one or more previous CSs Exclusion: previous surgery on the uterus other than CS, pregnancy, unclear information about previous uterine surgery	SCSH 6-9 months after CS	TVS 6-9 months after CS	To determine agreement between TVS and SCSH and objective measurements of defect size	53 scar defects seen on SCSH; 42 scar defects seen on TVS	Low to moderate	B
Van der Voet, 2013	Prospective cohort study	197 women with a previous CS Exclusion: twin pregnancies, known uterine abnormalities, uterine infection	GIS 6-12 weeks after CS	TVS 6-12 weeks after CS	Prevalence of niche measured by TVS and GIS	Prevalence of niche on TVS was 49,6%, prevalence of niche on GIS was 64,5%	Low to moderate	B

CS, cesarean section; GA, gestational age; PID, pelvic inflammatory disease

Appendix S4. Overview of the questions and subject used in the Delphi procedure

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Definitions	*Niche*	How would you define a niche?	53	Given the reasons described above what should be the definition in your opinion?	67	NA	
				If the definition should be "at least 2 mm, could you agree with that?	83		
	Main niche	What part of the niche do you call "main niche"?* 	60	Do you agree to call the red and green areas in figure 2a the "main niche", with a branch (blue area)?	100	NA	
	Branch	How would you define a branch of a niche?	86	NA		NA	
	UV fold	Do you agree that the green marked line expressing the fold between the bladder and the uterus should be called the plica vesico-uterina or uterovesical fold (UV fold)?	100	NA		NA	
	VV fold	During TV ultrasound the vaginal probe is often placed in the fornix anterior inducing an artificial triangular shaped fold between the bladder, the vagina and the cervix (marked with the red line), how would you call this fold?	86	NA		NA	

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Definitions	*Internal os*	Do you agree with the definition of the internal os described as "a slight narrowing in the lower uterine segment (LUS), between the uterine corpus and the cervix at the lower boundary of the urinary bladder (Naji 2012)"?	73	NA		NA	
	Distance internal os-niche	Do you agree to report the distance of the internal os – niche as a negative number if the direction of measurement is towards the cavity? Do you agree to report the distance of the internal os – niche as a positive number if the direction of measurement is as towards the external os?	73 73	NA		NA	
	Length and width of niche	How should length and width of a niche be defined? (width in sagittal plane and length in transversal plane or visa versa)	53	Do you agree that it is desirable for niche measurement to measure width and length in ultrasonography and in hysteroscopy following the same method? How should width and length of a niche in ultrasonography be defined?	92 67	Measurement of the length of a niche in the sagittal plane; measurement of the width of a niche in the transversal plane	100

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Definitions	*Niche classification*	Do you agree on our proposed niche classification (simple niche without branches; simple niche with one branch; and complex niche with more than one branch) in order to add recommendations for niche measurement in the future?	53	Given the arguments described above can you agree with the classification mentioned above to be used in future studies to assess its clinical relevance?	92	NA	
Method of measurements	*In- or exclusion of endometrium*	Which arrow would you define as the "base" of the niche? (line with border endometrium-myometrium, or in line with border endometrium-cervical canal?)	53	Do you agree to base all niche measurements on the myometrium only and that we do not take the endometrial tissue into account?	100	NA	
		To measure the width of a niche; where would you position the calipers? (endometrium in- or excluded?)	67				
		To measure the depth of a niche; where would you position the calipers? (endometrium in- or excluded?)	67				
		To measure the residual myometrium; where would you position the calipers? (endometrium in- or excluded?)	100				
		To measure the length of a niche; where would you position the calipers? (endometrium in- or excluded?)	67				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Method of measurements		To measure the depth of a niche; where would you position the calipers? (endometrium in- or excluded?)	60				
	Length and width of niche; two measurements	To measure the width of a niche; where would you position the calipers? (widest part; in line with endometrium; or both?)	47	Do you agree to perform 2 measurements for the width and length; the widest part of the niche (green arrow) and the width and length in line with the endometrium (red arrow)?	67	Measurement of both the largest length and largest width of a niche, as the length and width at the base of the niche	100
		To measure the width of a niche; where would you position the calipers? (widest part & parallel to cervical canal; or in line with endometrium, widest part whatever the position or direction; or multiple widths?)	47				
		To measure the length of a niche; where would you position the calipers? (longest part of the niche; or in line with the endometrium; or both distances?)	60				
		To measure the length of a niche; where would you position the calipers? (longest part of the niche, but parallel to the cervical canal; or in line with the endometrium; or longest distance, whatever the direction?)	60				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Method of measurements	*Depth of niche*	To measure the depth of a niche; where would you position the calipers? (widest depth of main niche; or depth in midline main niche; or widest depth including branch; or widest depth whatever the position or direction; or multiple depths)	53	Do you agree to perform a second measurement for depth besides the largest depth including a branch?	100	NA	
		To measure the depth of a niche; where would you position the calipers? (longest distance of the niche, including a branch; or longest distance of the niche, branch not included; or distance in the center of the niche; or multiple distances?)	60	Besides the orange arrow, which arrow should we measure additionally in case of a complex niche?	92		
	RMT	To measure the residual myometrium; where would you position the calipers? (distance from main niche; or thinnest part including branches; or distance from midline main niche; or multiple RMTs?)	73	Although previously consented we would like to ask again (to define final % of agreement) if you agree to measure if a branch is in case of a niche with a branch both the RMT of the branch and the niche?	92	NA	
		To measure the RMT; where would you position the calipers? (shortest RM you can find; or shortest RM in a vertical line to ventral?)	93	In this complex niche, how would you measure the RM of the main niche apart from the RM of the branch? (thinnest RMT of the main niche; or at the middle of the main niche)	92		

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Method of measurements		To measure the RMT; where would you position the calipers? (shortest RM, including a branch; or shortest RM in a vertical line to ventral; or shortest RM, branch not included; or multiple distances?)	60	To measure the RMT of the main niche in addition to an eventual RM of a branch in the transversal plane; where would you position the calipers? (thinnest RMT of the main niche (perpendicular to the serosa); or at the middle of the main niche; or thinnest RMT (perpendicular to the serosa AND to the uterine cavity)	83		
	RMT and fibrotic tissue	To measure the residual myometrium; where would you position the calipers? (fibrotic tissue in- or excluded?)	93	NA		NA	
		To measure the residual myometrium; where would you position the calipers? (fibrotic tissue in- or excluded?)	87				
	Depth and RMT; measurement of main niche and branch	Is it necessary to measure and report depth and residual myometrium (RMT) of the main niche as well as depth and RMT of the branch?	73	NA		NA	

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Method of measurements	*Measurement of branch*	What do you consider to be more clinically relevant for a branch?	40	Do you agree to register the width of a branch in mm only?	100	NA	
	AMT	To measure the adjacent myometrium; where would you position the calipers? (at the border of niche base; or at some distance from the niche base border?)	67	To measure the adjacent endometrium; can you agree to measure it at the location of the red arrow?	100	NA	
	1. Distance VV fold-niche	To measure the distance VV-fold – niche, do you agree to position the calipers as showed in the illustration?†	80	To measure the distance niche – VV fold; where would you position the calipers? (starting from the middle of the main niche; or starting at the top of the main niche)	58	Measurement of the distance between niche and VV fold on top of the main niche	100
	1. Distance VV fold-niche	To measure the distance VV-fold – niche, where would we place the calipers in this situation?	47	To measure the distance between niche - VV fold / internal os / external os; where would you start your measurement? (starting from the most distal niche point; or starting from the distal part at the base of the niche)	50	Measurement of the distance between niche and VV fold from the most distal niche point to VV fold.	100
	2. Distance internal os-niche	To measure the distance VV-fold – niche, where would you position the calipers?	40			Measurement of the distance between niche and external os; from the most distal niche point to external os.	
	3. Distance external os-niche	To measure the distance niche – internal os; where would you position the calipers?	73			The additional value of the distance between niche and internal os for surgical strategy and research.	
		To measure the distance niche – internal os; where would you position the calipers?	40				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Method of measurements		To measure the distance niche – internal os; where would you position the calipers?	60			The necessity of measurement of the distance between niche and VV fold, and niche and external os in basic niche measurement.	
		Should we measure the distance of the niche until external os or until the most distal part of the cervix?	73				
		To measure the distance niche –external os; where would you position the calipers?	80				
		To measure the distance niche – external os; where would you position the calipers?	40				
		To measure the distance niche – external os; where would you position the calipers?	40				
Relevance	*Niche measurements in midsagittal plane*	Should a niche always be measured in the midsagittal plane?	53	Do you agree with our hypothesis that the correct sagittal plane to perform niche measurement depends on the measurement itself in case of complex niches with branches(width, depth or RMT)?	100	NA	
		Should the residual myometrium always be measured in the midsagittal plane?	67				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Relevance	*Correct plane for length and depth*	Should a niche always be measured in the sagittal plane where the niche has the largest width and depth?	53	Do you agree that the niche width (=length) and depth should be measured in the sagittal plane where the main niche has the largest width and depth?	92	NA	
		Should a niche always be measured in the sagittal plane where the main niche has the smallest residual myometrium?	67				
	Correct plane for width	NA		NA		Measurement of the width of the niche at its largest	100
	Correct plane for RMT	Should the residual myometrium always be measured where the niche has the largest width and depth?	80	Do you agree that the RMT of the main niche should be measured in the sagittal plane where the niche has the largest depth?	75	NA	
		Should the residual myometrium always be measured where the main niche has the smallest residual myometrium?	53				
	Correct plane for RMT including branch	Should the residual myometrium always be measured where the niche including a branch has the smallest residual myometrium?†	73	Do you agree that the RMT of an eventual branch should be measured in the sagittal plane where the main niche has the smallest RMT?	67	Measurement of the RMT of a branch in the sagittal plane where the main niche has the smallest RMT	100

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Relevance	*Additional value of transverse plane for niche measurement*	Is the transversal plane of additional value for niche measurement?	73	NA		NA	
		Is the transversal plane important to measure niche depth and/or length?*	72 (8/11)				
		Is the transversal plane important to identify branches?*	90 (10/11)				
	Depth and RTM in transverse plane	Is the transversal plane important to identify the thinnest RM of the niche?*	64 (7/11)	Do you agree that it is <u>not</u> necessary to repeat depth and RMT in the transversal plane now knowing these results?	67	To use the transversal plane only for the third dimension of the niche (width), not for depth and RMT	100
		Is it necessary to repeat depth and RMT measurement in transversal plane?	60				
	Additional value of AMT	Is the adjacent myometrium of additional value for niche measurement?	60	Do you agree that measurement of the adjacent myometrium is relevant?	92	NA	
	Additional value of distance VV fold-niche	Is the distance between the VV fold and the niche of additional value for niche measurement?	60	Do you agree that the distance between niche – VV fold is of additional value for surgical strategy and research and that they should be performed in niche measurement?	92	NA	
	Additional value of distance external os-niche	Is the distance between the niche and the external os of additional value for niche measurement?	53	Do you agree that the distance between niche – external os is of additional value for surgical strategy and research and that they should be performed in niche measurement?	75	NA	

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
Relevance	*Additional value of distance internal os-niche*	Is the distance between the niche and the internal os of additional value for niche measurement?	60	Do you agree that the distance between niche – internal os is <u>not</u> of additional value for niche measurement (because it is a difficult measurement)?	75	NA	
				Do you think we should measure this parameter despite difficulties in recognizing the internal os in niche patients?	75		
	Relevance branches	As earlier described branches of a niche can be detected in transversal plane. Do you think that branches are irrelevant?	67	NA		NA	
		Do you think that branches are only relevant in the transversal plane, if the branch has a minimum width?	67				
		Do you think that branches should always be registered and separately reported?	80				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
General ultrasound methods to be used	*Achieving correct sagittal plane for niche measurement*	What is the best method to achieve the correct sagittal plane for niche measurement? (by starting in midsagittal plane with good visualization of the cervical canal 1) then by moving the transvaginal probe to both lateral sides to determine the correct plane; or 2) then by rotating the transvaginal probe to determine the correct plane; or there is no best method; or otherwise)	67	Do you agree that the best method is the method described in the box above?	92	NA	
	Achieving correct transversal plane for niche measurement	What is the best method to achieve the correct transversal plane for niche measurement? (1) by using the sagittal plane - by keeping a good visualization of the niche while rotating the transvaginal probe from sagittal to transversal plane; or 2) by screening the entire LUS in transversal plane from cervix to corpus; or both are good methods; or there is no best method)	67	Do you agree that both methods as described above are good methods to achieve the correct transversal plane? The first one to visualize the niche; the second one to detect possible branches.	92	NA	

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
General ultrasound methods to be used	*Magnification for niche measurement*	In what magnification should you measure a niche; should the entire uterus be visualized?	80	NA		NA	
		In what magnification should you measure a niche; should the lower uterus segment (LUS) only be visualized?	80				
		In what magnification should you measure a niche; is this depending on the position of the uterus?	60				
		In what magnification should you measure a niche, when the uterus is in anteversed position? (entire uterus; or LUS only)@	83 (5/6)				
		In what magnification should you measure a niche, when the uterus is in retroversed position? (entire uterus; or LUS only)@	100 (6/6)				
		In what magnification should you measure a niche, when the uterus is in stretch position? (entire uterus; or LUS only)@	100 (6/6)				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
General ultrasound methods to be used	*Position of transvaginal probe*	Do you believe that the position of the transvaginal probe (in the anterior or posterior fornix) affects the correct plane for niche measurement?	53	Do you agree that the position of the transvaginal probe (in the anterior or posterior fornix) affects the correct plane for niche measurement now knowing these results?	83	NA	
Value of additional tools	*Pressure with transvaginal probe*	Do you believe that it is necessary to vary pressure with the transvaginal probe in order to achieve the best plane for niche measurement?	60	Do you agree that it is useful to vary pressure with the transvaginal probe in order to achieve the best plane for niche measurement now knowing these results?	83	NA	
	Doppler ultrasound (continue) *Doppler ultrasound*	Is Doppler ultrasound of added value niche measurement?	67	Do you agree that it is not needed to use Doppler ultrasound during standard niche measurement, but that you may use it on indication (to differentiate between hematomas, adenomyomas, adenomyosis, fibrotic tissue etc.)	92	NA	
		Is Doppler ultrasound of added value in niche measurement to differentiate between the myometrium and a hematoma in a niche?#	80 (4/5)				
		Is Doppler ultrasound of added value in niche measurement to differentiate between an adenomyoma and a niche?#	60 (3/5)				
		Is Doppler ultrasound of added value in niche measurement to estimate the existence of adenomyosis?#	60 (3/5)				

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
GIS/SCSH	*Additional value of GIS/ SCSH*	Is saline contrast sonohysterography (SCSH) or gel infusion sonography (GIS) of added value in patients with a niche?	40	Do you agree that SCSH or GIS is of added value in patients with a niche now knowing these results?	75	NA	
	Superior method; GIS or SCSH	Is there a difference in method using SCSH and GIS for niche measurement?	40	Do you agree that both methods can be used for niche measurement?	92	Preference for either GIS or SCSH	100
				What method (GIS or SCSH) is preferred for 3D measurement?	42		
	Catheter preference for GIS/SCSH	What catheter would you use for SCSH/GIS? (a smooth, flexible catheter; or a less flexible catheter, for example that is used during intra uterine insemination; or one that includes a cervical applicator to prevent leakage; or one that includes a conus to prevent leakage of the cervix?)	27	Do you agree that in general there is no preference for a catheter and that apart from 36c, all catheters can be used?	92	NA	
		Is there a catheter you would definitely NOT use? (same options as in question 35)	27	What catheter would you prefer for SCSH? (a smooth, flexible catheter; or a less flexible catheter, for example that is used during intra uterine insemination; or one that includes a conus to prevent leakage of the cervix; or no preference?)	33		

Appendix S4. (Continued)

		Round 1		Round 2		Round 3	
Category	**Item**	**Question**	**C (%)**	**Question**	**C (%)**	**Subject**	**C (%)**
GIS/SCSH				What catheter would you prefer for GIS? (a smooth, flexible catheter; or a less flexible catheter, for example that is used during intra uterine insemination; or one that includes a conus to prevent leakage of the cervix; or no preference?)	33		
	Catheter location	Where would you locate the catheter during SIS/GIS? (in the niche; or just in front of the niche; or in the uterine cavity; or this is irrelevant; or otherwise?)	47	Can you agree that the best location of the catheter is during SIS or GIS is "Just in front of the niche or starting if possible cranial of the niche then pull slowly backwards until the base of the niche?	92	NA	
	Remove/leave catheter during GIS/SCSH (continue) *Remove/leave catheter during GIS/SCSH*	Do you remove the catheter before making the ultrasound, or do you leave the catheter in situ?	47	Do you agree to leave the catheter, add the probe and make the ultrasound while performing SCSH? Do think we need to remove the catheter after applying gel in case of a GIS before ultrasound scanning?	92 42	Removal of the catheter after applying gel in case of a GIS before ultrasound scanning	100
	Intrauterine fluid accumulation	NA		NA		The additional value of GIS/SCSH in case of intrauterine fluid	100

* The illustration that was used in this question is shown as an example. Illustrations were used in multiple questions; due to lack of space these illustrations are not presented.
† This item was further explored in round 2, although consensus was reached in round 1. AMT, adjacent myometrial thickness; C (%), consensus rate in percentage; GIS, gel infusion sonography; LUS, lower uterine segment; NA, not applicable; RM(T), residual myometrial (thickness); SCSH, saline contrast sonohysterography; TVS, transvaginal sonography; VV fold, vesicovaginal fold

Table S1. Course of consensus for niche measurement, presented per item.
This table presents mean consensus rate per item in niche measurement per Delphi round. When consensus was reached (green shading), the item was excluded from the next Delphi round. In the table this is presented as 'c' (consensus achieved).

Category	Item	Final no. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)
Definitions	Niche*	2	53	67–83	c
	Main niche	1	60	100	c
	Branch	1	86	c	c
	Uterovesical fold (UV fold)	1	100	c	c
	Vesicovaginal fold (VV fold)	1	86	c	c
	Internal os	1	73	c	c
	Distance internal os–niche	2	73–73	c	c
	Length and width of niche*†	2	53	67–92	100
	Niche classification	1	53	92	c
Method of measurements	In- or exclusion of endometrium‡	6	53–100	100	c
	Length and width of niche; two measurements^	4	47–60	67	100
	Depth of niche	2	53–60	92–100	c
	Residual myometrial thickness (RMT)‡	3	60–93	83–92	c
	RMT and fibrotic tissue	2	87–93	c	c
	Depth and RMT; measurement of main niche and branch	1	73	c	c
	Measurement of branch	1	40	100	c
	Adjacent myometrial thickness (AMT)	1	67	100	c
	1. Distance VV fold–niche‡ 2. Distance internal os–niche‡ 3. Distance external os–niche‡	10	40–80	50–58	100

Table S1. (Continued)

Category	Item	Final no. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)
Relevance	Niche measurement in sagittal plane§	2	53–67	100	c
	Correct plane for length and depth§	2	53–67	92	c
	Correct plane for width¶	1	NA	NA	100
	Correct plane for RMT□	2	53–80	75	100
	Correct plane for RMT including branchΩ	1	73	67	100
	Additional value of transverse plane for niche measurement (length, width, branches)	3	72–90	c	c
	Depth and RMT in transverse plane§	2	60–64	67	100
	Additional value of AMT	1	60	92	c
	Additional value of distance VV fold–niche	1	60	92	c
	Additional value of distance external os–niche	1	53	75	c
	Additional value of distance internal os–niche*	2	60	75–75	c
	Relevance of branches	3	67–80	c	c
General ultrasound methods to be used	Achieving correct sagittal plane for niche measurement	1	67	92	c
	Achieving correct transverse plane for niche measurement	1	67	92	c
	Magnification for niche measurement	6	60–100	c	c
	Position of transvaginal probe	1	53	83	c
Value of additional tools	Pressure with transvaginal probe	1	60	83	c
	Doppler ultrasound‡	4	60–80	92	c

Table S1. (Continued)

Category	Item	Final no. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)
GIS/SCSH	Additional value of GIS/SCSH	1	40	75	c
	Superior method; GIS or SCSH*	2	40	42–92	100
	Catheter preference for GIS/SCSH*	3	27–27	33–92	c
	Catheter location	1	47	92	c
	Remove/leave catheter during GIS/SCSH*◊	2	47	42–92	100
	Intrauterine fluid accumulation¶	1	NA	NA	100

*One question about this item was added in round 2. †In round 2, consensus was reached for an added question, but not yet for the definition of this item. ‡Consensus was reached for part of the clustered questions in round 1; it was decided to repeat the item in round 2. ^The four questions about this item in round 1 were summarized in one question in round 2. §The two questions about this item in round 1 were summarized in one question in round 2. ¶This item was added in round 3. □The answers on the two questions about this item in round 1 were contradictory, as was the answer of a summarized question in the second round compared with the answers in the first round; although consensus was achieved in both rounds, it was decided to repeat the item in round 3. Ω This item was further explored in round 2, although consensus was reached in round 1. ◊In round 2 consensus was not reached for both questions; it was decided to repeat the item in round 3. AMT, adjacent myometrial thickness; GIS, gel infusion sonography; NA, not applicable; RMT, residual myometrial thickness; SCSH, saline contrast sonohysterography; VV fold, vesicovaginal fold

CHAPTER 3

INCREASED AMPLITUDE OF SUBENDOMETRIAL CONTRACTIONS IDENTIFIED BY ULTRASOUND SPECKLE TRACKING IN WOMEN WITH A CESAREAN SCAR DEFECT

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ABSTRACT

Research Question

What is the effect of a cesarean scar defect on subendometrial contractions?

Design

Prospective cohort study in a Dutch academic medical center including women with a niche in the uterine cesarean section scar. Data were compared with controls without a cesarean section scar. All women underwent a 5-min recording by transvaginal ultrasound at four phases in the menstrual cycle: during menses; late follicular; early luteal; or late luteal phase. Uterine motion analysis was evaluated by dedicated speckle tracking using two-dimensional optical flow. Main outcome: amplitude of the subendometrial contractions.

Results

Thirty-one women with a niche in the uterine scar and 11 controls, matched for menstrual cycle phase, were included. The amplitude of the subendometrial contractions was significantly higher in women with a niche compared with controls during all phases of the menstrual cycle (menses $p<0.001$; late follicular $p<0.001$; early luteal $p=0.028$; late luteal $p=0.003$). Velocity was lower in women with a niche during late follicular phase only ($p=0.012$). A positive correlation between niche sizes (depth, length) and amplitude of subendometrial contractions was found.

Conclusion

Subendometrial contractions were affected in women with a niche in the cesarean section scar compared with women who had not undergone a previous CS. Contraction amplitude was higher and independent of the menstrual phase. These findings may cause postmenstrual spotting, dysmenorrhea and lower implantation rates in women with a niche. Future studies should investigate this association and the underlying pathways.

INTRODUCTION

Cesarean section (CS) rates continue to increase globally[1] and have stimulated interest in the potential long-term morbidity of a CS scar. A niche is an indentation in the uterine wall at the site of the cesarean scar, with a depth of at least 2 mm, and is associated with postmenstrual spotting and dysmenorrhea.[2-4] Spotting can be explained by the accumulation of blood in the niche after the menstrual period due to mechanical outflow problems.[5] An alternative explanation for postmenstrual spotting could be disturbed functional outflow caused by a (large) niche, with discontinuity in the myometrium leading to dysfunctional contractility of the uterine muscle.[6] Additionally, recent data show lower implantation and pregnancy rates after a CS compared with a previous vaginal delivery.[7-9] A niche might be the underlying cause; apart from the observed coexistence of potentially embryo toxic intrauterine fluid, dysfunctional myometrial contractions may also compromise embryo implantation.[8, 10-12]

The non-pregnant uterus shows different patterns of contractile activity throughout the menstrual cycle known as uterine peristalsis (UP), originating in the subendometrial myometrium.[13] UP undergoes cyclic changes and occurs in the menstrual phase directed outward to expel endometrium and blood from the uterine cavity. The frequency of contractions increases as ovulation approaches. In the late follicular phase, the direction of subendometrial contractions switches inward, and is now directed from cervix to fundus. The contraction frequency further increases until ovulation to enhance transport of spermatozoa towards the ipsilateral tube of the dominant follicle. Subsequently, after ovulation and during the late luteal phase the combination of lower frequency and lower amplitude in the uterine activity may contribute to embryo implantation in the midsection of the uterine cavity.[14-20] The underlying physiology of uterine contractions has been studied in human uterine muscle cells, in animal models and in mathematical models to simulate the electrical, mechanical and ionic activity, but has not yet been elucidated.[21]

Transvaginal ultrasound (TVUS) has been proven to offer reliable information on UP.[22, 23] Dedicated speckle tracking has shown to be a valid and effective method for the objective assessment of uterine motion outside pregnancy.[17, 24] Myometrial disorders are reported to affect uterine peristalsis.[25-27]

Uterine contractions, however, have never been evaluated in women with a CS scar defect or niche. The aim of this study was to evaluate the amplitude of subendometrial contractions in women with a niche in the uterine CS scar compared with women without a CS scar.

METHODS

This explorative prospective cohort study (the 'WAVE study') was conducted at the Obstetrics and Gynecology department of Amsterdam UMC, Amsterdam, The Netherlands. Inclusion period was between 2018 and March 2020.

Patients

All women with a niche in the uterine CS scar participated in the Niche Cohort study (CCMO – NL37922.029.11; date of approval: 12 April 2018). The aim of the Niche cohort study is to evaluate the effect of all applied types of interventions, including expectant management on niche-related symptoms and reproductive outcomes in a prospective fashion with a long term follow-up. In this study, all women were asked to participate if they were referred to our outpatient clinic because of a niche or niche related symptoms, such as abnormal uterine bleeding or fertility problems. Exclusion criteria included the following: age younger than 18 years; a (suspected) malignancy; uterine or cervical polyps; submucosal fibroids; atypical endometrial cells; cervical dysplasia; cervical or pelvic infection; and hydrosalphinx. For the WAVE study, women from the Niche Cohort study were included on a random base, when the researcher of this project was available and after informed consent was obtained. Women were scanned only once, if the trained researcher and the specific ultrasound machine with options to record the wave ultrasound were available. The Niche Cohort study was approved by the local Research and Ethics Committee, including the performance of transvaginal ultrasound and wave evaluation for the present study**.**

Data relating to controls (women without previous CS and with no infertility problems) were collected at the Gynecology department of Catherina Hospital, Eindhoven (CCMO – NL52466.100.15; date of approval: 19 January 2018), and the results of the uterine contractions in the different phases of the menstrual cycle were reported earlier.[17] Eleven controls participated. Each woman was scanned four times during each of the four selected phases of the menstrual cycle: including menses, defined as cycle day 1-7; late follicular phase (cycle day 8-14); early luteal phase (cycle day 14-17); or late luteal phase (cycle day 18 to menses).

Ultrasound evaluation

All women underwent a standardized protocol of two and three-dimensional TVUS; general myometrium assessment was evaluated according to the MUSA guidelines[28], including examination of the uterine corpus, myometrial walls and existence of myometrial lesions. In the case of a previous CS, the niche was evaluated according to the international recommended guideline for the standard evaluation and reporting

system[3] (see Figure 1 for niche evaluation) using two-dimensional ultrasound. Additionally, a five-minute TVUS recording was carried out from the uterus in the midsagittal plane, with the operator holding the probe steady (WAVE ultrasound). Each women with a previous CS was scanned by one of the trained researchers (I.J. or J.V.). The phase of the menstrual cycle during the ultrasound was registered. Women using oral contraceptives (OC) continuously (without a stop period) were also included and registered separately as OC group. Women in the control group underwent four ultrasound evaluations by one experienced gynecologist, one in each of the four selected phases of the menstrual cycle. All ultrasound scans, in both hospitals, were performed using a Samsung WS80A ultrasound machine (Samsung Medison, Seoul, South Korea) equipped with a transvaginal V5-9 probe.

At inclusion, baseline characteristics and medical, obstetrical and fertility history were registered in both groups. Ultrasound features of the uterus (position, length, width) and niche characteristics were registered during their first ultrasound. Niche volume was calculated based on niche measurements (length x depth x width x 0.52).[29] All data were registered in a case report form and a digital database by the researchers. Reporting in accordance with the guideline for reporting a prospective study (STROBE).[30]

Finally, only the recordings in which the uterine cavity was sufficiently visible, and on which speckle tracking could be performed, were included.

Speckle tracking by using two-dimensional optical flow

For each selected TVUS recording, two grids of tracking markers with an isotropic interval in the transversal and longitudinal direction were positioned along the anterior and posterior endometrial contour of the uterine corpus and fundus in order to apply speckle tracking by two-dimensional optical flow, see Figure 2. A single operator placed the tracking markers for all the ultrasound recordings following a standard protocol. The repeatability and reproducibility of the method were also validated.[24] In women with a niche, it was not possible to measure subendometrial contractions at the site of the niche because of the (virtually) absence of the myometrium.

The principle of two-dimensional optical flow is based on the assumption that the intensity (*I*) of a certain pixel does not change between the reference and the target frames, so that the velocity in the longitudinal (x) and transversal (y) directions can be represented by the intensity gradients in spatial and temporal dimensions according to the following equation:

$$(\upsilon_x\,(\partial \mathrm{I} / \partial x)) + (\upsilon_x\,(\partial \mathrm{I} / \partial y)) + (\partial \mathrm{I} / \partial t) = 0.$$

To solve this ill-conditioned equation, Lukas *et al.*[31] proposed to include the neighboring pixels around the tracked one under the assumption of locally constant flow. The velocities in both directions are then obtained by least square estimation. This process was applied to each tracking marker in the grid frame to frame.

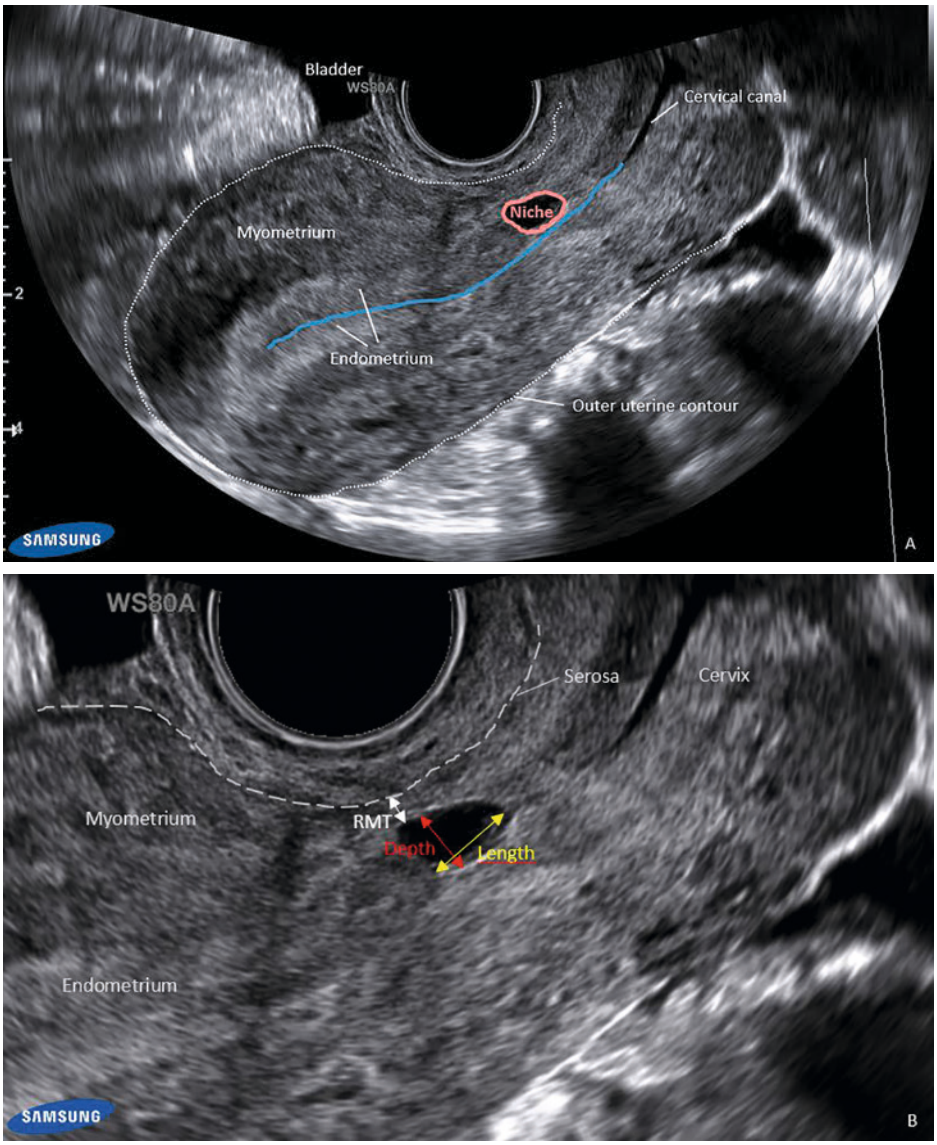


Figure 1. Example of uterine niche and its measurements in an anteverted uterus, according to Jordans et al. (2019) using transvaginal ultrasound.

(A) Niche in sagittal plane; (B) Magnification of (A). Measurements in the sagittal plane: length and depth of the niche, and residual myometrial thickness (RMT).

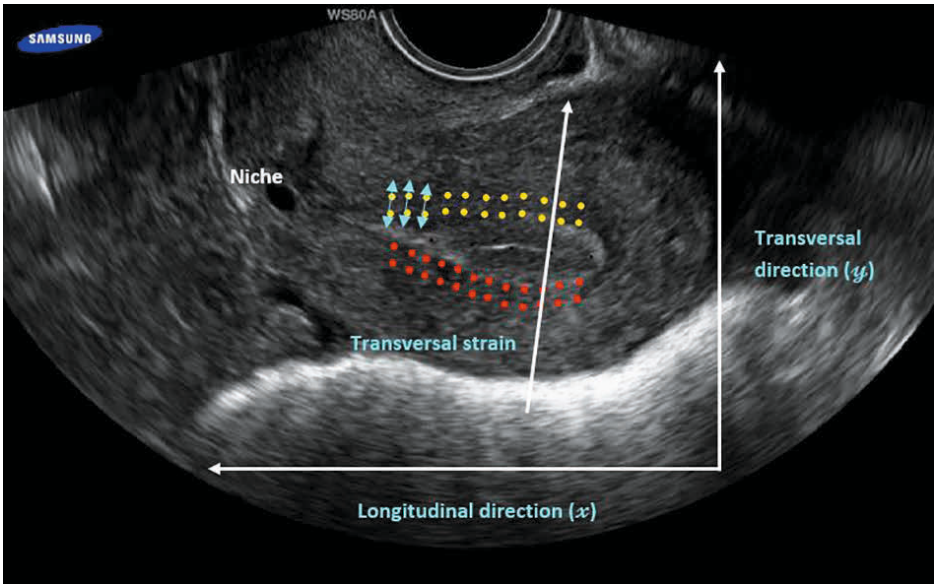


Figure 2. Example of the two grids of tracking markers defined on the lining of the subendometrium of the anterior uterine wall (yellow tracking markers) and posterior uterine wall (red tracking markers), recorded during early luteal phase in one of the patients with a niche in a retroflected uterus.

Transversal strain

Strain imaging is one of the most widely used approaches for measuring regional or global deformation of a muscle. Therefore, to characterize uterine contraction, transversal strain (TS) was derived from both the anterior and posterior sides of the endometrium. Transversal strain was calculated from the ratio between the variation in the distance between each pair of tracking markers in transversal direction (Figure 2) and their original distance as:

$$TS_t = (\sum (D_t - D_{t-1})) / D_1 \quad t = 2, 3, \ldots N,$$

where D_t represents the absolute distance between each pair of tracking markers in the transversal direction at the t_{th} frame; D_1 is the original distance; and N is the total number of frames of the recording.

Uterine contractions were not the only source of motion influencing the movement of the endometrium. Other motions, either originating from different organs, such as, bowels and bladder, or caused by heartbeat, respiration and probe movement during the acquisition, affect the ultrasound recordings. Therefore, a band pass filter was applied to the transversal strain signals to remove the interference from these undesired motion sources. The resulting transversal strain signals were then analyzed

to extract a number of relevant features characterizing the subendometrial contraction, namely, amplitude, frequency, velocity, direction and coordination features. Below is a short description of the feature extraction. More details can be found in Huang *et al.* (2022)[24] and Huang *et al.* (2020)[32].

Amplitude

Amplitude is derived from the standard deviation (SD) of the transversal strain signals between each pair of tracking markers reflecting the degree of strain (contraction strength) of the uterine muscle during the acquisition time; this is illustrated in Supplementary Figure 1. As strain is unit-less and usually represented as %, its SD is also defined as %. The average of the SD results of the entire endometrium is presented.

Frequency

The frequency is estimated as the mean of the frequency spectrum (given in Hertz) of the transversal strain signals measured over the full recording (Figure 2) in the anterior and posterior uterine wall. The mean frequency is then multiplied by 60 s to derive the corresponding number of contractions per minute.

Velocity

Based on the transversal strain signals, a time-space representation of the UP waves propagating along the endometrium was created. Two-dimensional fast Fourier transform was further applied to the time-space representation within a moving time window of 20 s to derive a two-dimensional power spectrum. The temporal and spatial frequencies of the dominant peristaltic motion were then identified at the peak of the power spectrum, and the corresponding UP velocity was calculated as the ratio between the temporal and spatial frequency averaged over the full recording.

Direction

An energy ratio (ER) metric was derived to represent the direction of UP as

$$ER = E1 \,/\, (E1 + E2)$$

where $E1$ and $E2$ are the integral of the power spectrum over the first and second quadrant, representing the strength of cervix to fundus and fundus to cervix propagation, respectively. Here $E1$ and $E2$ were derived from the two-dimensional power spectrum calculated over the full recording. Being derived as a ratio, energy ratio is clearly unitless. For energy ratio closer to 1, then the cervix-to-fundus propagation is dominant, and vice versa.

Coordination

Similar time evolution of energy ratio, measured over a running window of 20 s, from the anterior and posterior walls was expected to reflect a coordinated and symmetric propagation. Similarity measures, such as cross correlation and mean squared error, were used to assess the similarity (coordination) between the propagation patterns (in terms of energy ratio time evolution) measured from both walls. A low mean squared error indicates similar propagation patterns and, therefore, coordination of the two walls; in fact, zero error reflects identical propagation. Similarly, also a high correlation coefficient, close to one, indicates coordination propagation, whereas lower or even negative values indicate dyscoordination.

Outcomes

The primary outcome was the amplitude of subendometrial contractions in women with a (large) niche compared with women who have not had a previous CS.

Secondary outcomes included frequency and velocity of subendometrial contractions compared between the two study groups. Also, all contraction features (amplitude, frequency, velocity) were evaluated separately during the different phases of the menstrual cycle to gain insight into their cycle dependency. The direction of the subendometrial contractions was also subdivided depending on their propagation direction, cervix-to-fundus or fundus-to-cervix, and all features were also estimated for the different directions, separately. Furthermore, coordinated and symmetric propagation of the contractions were evaluated.

The influence of contraceptive use on uterine contractions is unknown. Therefore, data of women using contraceptives were analyzed separately.

Statistical analysis

IBM SPSS Statistics version 26 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Demographic data were presented as n (%) for categorical variables and mean SD or median (interquartile range (IQR)) for continuous variables. Differences in baseline characteristics were compared using the independent sample *t* test, chi-square test or Mann Whitney U test, depending on the type and distribution of the variables. The features of subendometrial contractions (amplitude, contraction frequency, velocity and direction) between the patients with a niche and controls were analyzed with linear mixed models by which the use of multiple measurements of the same patient in the control group will be corrected. Mann Whitney U test was used to analyze contraction features within the niche group because of non-normal distribution. Two-tailed $p<0.05$ was considered statistically significant. To examine any correlation between primary

outcome and niche features, the Pearson correlation coefficient (p value) and the squared correlation coefficient (R^2) were calculated, the latter ranged between 0 (no correlation) and 1 (strong correlation).

Sample size calculation

At the time of the study design, no comparable studies were available for sample size calculation. Our aim was to include (at least) 25 women with a niche in order to evaluate our primary outcome and preferably with an equal distribution per menstrual cycle phase.

RESULTS

Inclusion and baseline characteristics

In total, 114 WAVE ultrasounds were carried out, 70 in women with a niche and 44 (n= 11 women) in the controls (Figure 3). In the niche group, 39 ultrasounds were excluded because they could not be analyzed by using speckle tracking owing to poor image quality (n=25), technical problems, i.e. faltering recording (n=9), or unknown phase in the menstrual cycle (n=5). In the control group, 41 out of 44 WAVE ultrasounds were of sufficient image quality to be analyzed. Finally, 31 WAVE ultrasounds of women with a niche and 41 of the controls were analyzed; 17 women during menses, 14 during late follicular, 16 during early luteal, 19 during late luteal phase, and 6 women with continuous use of OC.

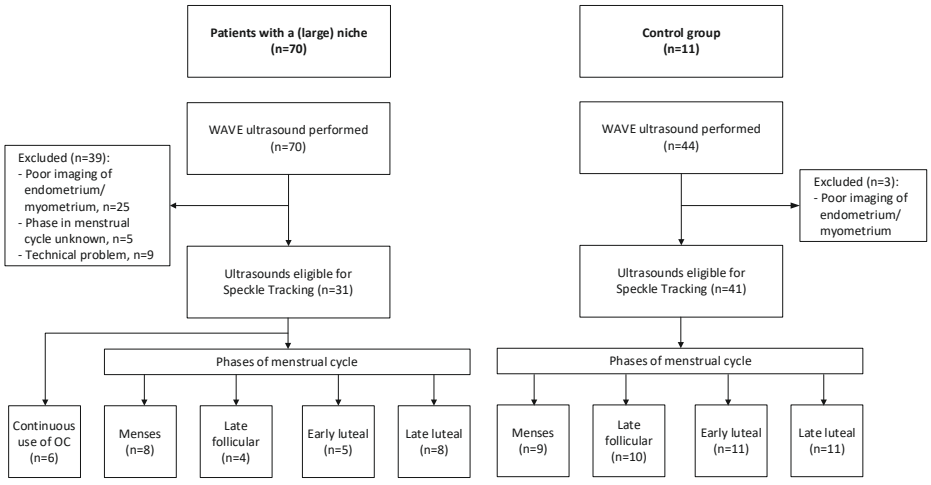


Figure 3. Study participants.
OC, oral contraceptives.

Baseline characteristics are shown in Table 1. Most women with a niche (64%) underwent one previous CS. Subfertility was seen in 58% of these patients. Amongst the controls, 91% (10/11) had never been pregnant; one had three vaginal deliveries. One women with a niche used thyroid hormones at time of the WAVE ultrasound, all other participants did not use any medication. Furthermore, one women with a niche had undergone a diagnostic laparoscopy because of pain without major abnormalities 5 years before participating in this study. The controls had no relevant medical history. All underwent hormonal profile screening to exclude the presence of infertility-related problems (anovulation). Uterine size and position were not significantly different between the study groups. A large niche, defined as a niche with a residual myometrial thickness (RMT) less than 2mm, was visible in 77% of the patients with a niche.

Table 1. Baseline characteristics WAVE study group

Characteristics	**Women with a niche (n=31)**	**Controls (n=11)**
Age, years	33.2 ±4.7	31.2 ± 5.2
BMI	24.5 ±4.9	22.6 ± 2.3
Smoking	3 (10)	2 (18)
Ethnicity		
North European	26 (83)	11 (100)
Turkish	2 (7)	0
North African	1 (3)	0
African (other)	2 (7)	0
Parity	1 (1-2)	0 (0-0)
Previous cesarean sections, n		NA
1	20 (64)	
2	8 (26)	
3	3 (10)	
Subfertility	18 (58)	0
Duration subfertility, months	36 (23-58)	NA
Previous fertility treatment (in case of subfertility)		NA
None	8/18	
Ovulation induction	1/18	
IUI	3/18	
IVF	3/18	
ICSI	3/18	
Oral contraceptive use	6 (19)	0
Position uterus		
AVF	15 (48)	9 (81)
Stretched	1 (3)	0
RVF	8 (26)	2 (19)
Extreme RVF	7 (23)	0

Table 1. (Continued)

Characteristics	Women with a niche (n=31)	Controls (n=11)
Length uterus, mm	69 (63-79)	68 (54-73)
RMT, mm	1.3 (0-1.9)	10.8 (9.2-11.6)[a]
Niche length, mm	8.6 (6.5-10.6)	NA
Niche depth, mm	6.5 (5.1-9.0)	NA
Niche size		NA
Large niche (RMT < 2 mm)	24 (77)	
Small niche (RMT ≥ 2 mm)	7 (23)	
Niche volume according to measurements (length x depth x width x 0.52[24]), cm3	0.4 (0.2-0.9)[b]	NA

Data are reported as mean ± standard deviation, median (interquartile range), n (valid %) or n/total. [a] Thickness of myometrium measured at the same location where the RMT was measured in women with a niche. [b] Available from 29 women. AVF, anteverted anteflexed uterus; BMI, body mass index (weight in kg/m2); CS, cesarean section; ICSI, intracytoplasmic sperm injection; IQR, interquartile range; IUI, intrauterine insemination; IVF, in vitro fertilization; NA, not applicable; RMT, residual myometrial thickness; RVF, retroverted retroflexed uterus.

Subendometrial contraction features in patients with a niche versus controls

Outcome measures of subendometrial contractions of the study groups are presented in Table 2. The mean amplitude of contractions in patients with a niche (without using OC) was significantly higher compared with the controls (8.5% (SD ±4.2) versus 2.9% (SD ±1.3), p<0.001), see Figure 4. No significant differences in frequency and velocity of subendometrial contractions were observed between the groups.

Table 2. Outcome measures of subendometrial contractions of patients with a niche and controls

Subendometrial measurements	Women with a niche (n=25)[a]	Controls (n=11)[b]	p value[c]
Amplitude (%)	8.5 ±4.2	2.9 ±1.3	<0.001[d]
Mean frequency (contractions/min)	1.8 ±0.2	1.9 ±0.3	0.207
Velocity (mm/sec)	1.1 ±0.5	1.2 ±0.3	0.344

Data are reported as mean ± SD. [a] Patients using continuous oral contraceptives were not included. [b] Patients in the control group underwent multiple ultrasounds in the different phases of the menstrual cycle. [c] Mann–Whitney U test. [d] Statistically significant.

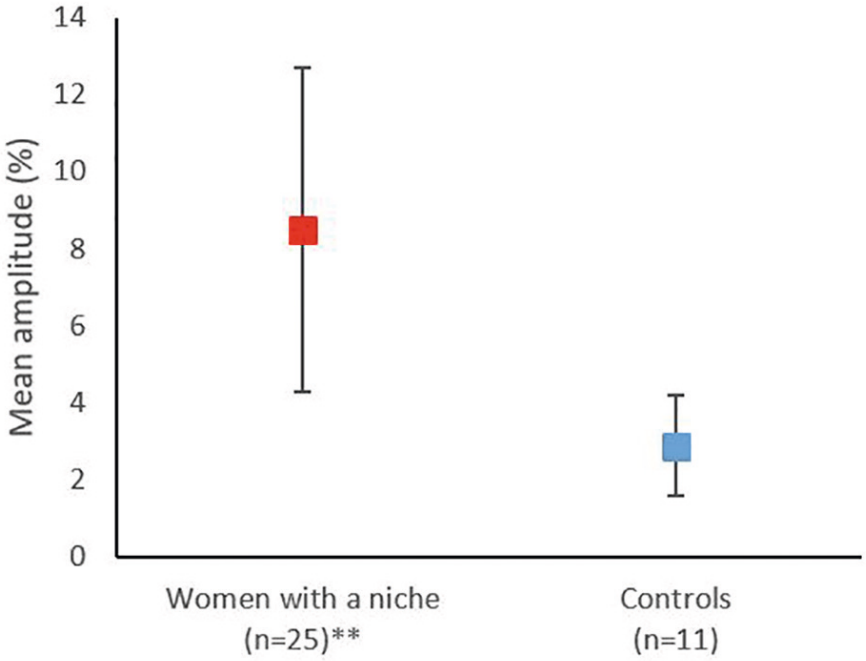


Figure 4. Mean amplitude (%) of subendometrial contractions in women with a niche (n = 25) and in controls (n = 11). **, Statistically significant difference, p<0.001.

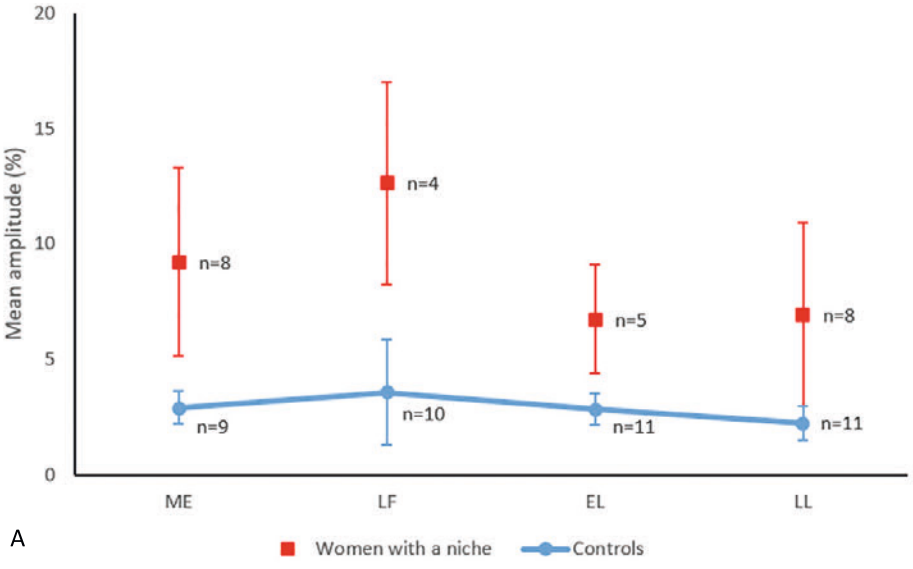
Subendometrial contraction features during different phases of the menstrual cycle in patients with a niche versus controls

The outcome of subendometrial contractions during the different phases of the menstrual cycle of both study groups is presented in Table 3. Mixed model analysis showed a significantly higher mean contraction amplitude of contractions in patients with a niche during all four phases of the menstrual cycle in patients with a niche compared with the controls (Figure 5A). No difference was found in mean frequency of subendometrial contractions between the study groups during each phase of the menstrual cycle (Figure 5B). Mean velocity of subendometrial contractions was significantly lower only during late follicular phase in patients with a niche compared with the controls (p=0.012).

Table 3. Outcome measures of subendometrial contractions during different phases of the menstrual cycle

Subendometrial measurements	Women with a niche (n=25)[a]	Controls (n=11)[b]	p value[c]	95% CI[d]
Amplitude (%)				
ME	9.2 ±4.1	2.9 ±0.7	<0.001	3.3 – 9.3
LF	12.6 ±4.4	3.6 ±2.3	<0.001	5.3 – 12.8
EL	6.7 ±2.4	2.8 ±0.7	0.028	0.5 – 7.4
LL	6.9 ±4.0	2.3 ±0.7	0.003	1.7 – 7.7
Mean frequency (contractions/min)				
ME	1.8 ±0.2	1.7 ±0.2	0.396	-0.1 – 0.3
EL	1.9 ±0.3	2.1 ±0.3	0.230	-0.4 – 0.1
LL	1.8 ±0.2	2.0 ±0.3	0.053	-0.5 – 0.0
LF	1.7 ±0.3	1.7 ±0.2	0.580	-0.3 – 0.1
Velocity (mm/sec)				
ME	1.2 ±0.4	1.0 ±0.2	0.268	-0.2 – 0.6
LF	0.9 ±0.3	1.5 ±0.5	0.012	-1.1 – -0.1
EL	1.2 ±0.6	1.3 ±0.2	0.673	-0.5 – 0.3
LL	1.2 ±0.6	1.1 ±0.3	0.505	-0.2 – 0.5

Data are reported as mean ± SD. [a] Patients using oral contraceptives continuously were not included in the table. [b] Patients in the control group underwent multiple ultrasounds in the different phases of the menstrual cycle. [c] Linear mixed model analysis. [d] Statistically significant. CI, confidence interval; EL, early lutealy; LF, late follicular; LL, late luteal; ME, menses.



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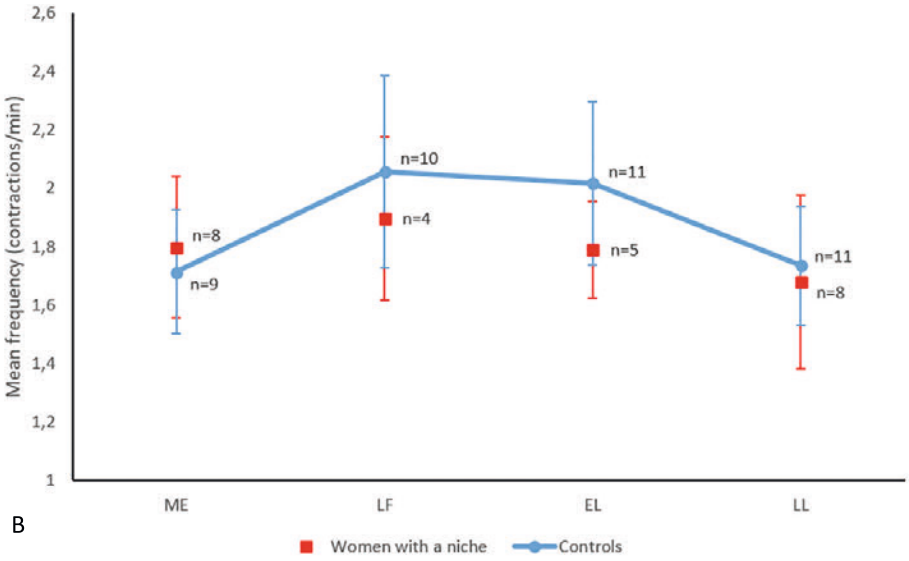

Figure 5. Features of subendometrial contractions during the four phases (menses [ME], late follicular [LF], early luteal [EL] and late luteal [LL]) of the menstrual cycle, in women with a niche (n = 25) and in controls (n = 11). (A) Mean amplitude, SD (%); (B) mean frequency, SD (contractions/min). Subendometrial contractions were evaluated in the same controls during each phase (blue line); in women with a niche, subendometrial contractions were evaluated once during one of the four phases (red dots).

Comparison of contraction features in the anterior versus posterior uterine wall and contraction direction

No significant difference was found between the number of contractions measured in cervix-to-fundus direction compared with the fundus-to-cervix direction in this group, see Supplementary Figure 2.

Coordination feature by cross correlation and mean squared error in the menses and late follicular phase, which is a parameter to evaluate the coordination between the anterior and the posterior wall, were different between women with a niche and controls (Supplementary Figure 2). During both the menses and during the late follicular phase the mean squared error of the coordination was higher in women with a niche compared with controls (p=0.200 and p=0.454, respectively). This means that contractions between the anterior and posterior wall are less coordinated (see Figure 6A and Figure 6B).

The direction of the contractions itself was not different between women with a niche and controls.

Niche features in correlation with primary outcome

Median niche depth was 6.5 mm (IQR 5.1-9.0) and median niche length was 8.6 mm (IQR 6.5-10.6). The median RMT in patients with a niche was 1.3 mm (IQR 0-1.9). The

median myometrial thickness of the controls, measured at the same location as where the RMT was measured in women with a niche, was 10.8 mm (IQR 9.2-11.6). Uterine size was comparable between the patients with a niche and controls (see Table 1). There was a strong positive correlation between depth of the uterine niche and amplitude of subendometrial contractions, see Figure 7. An amplitude with a cut-off value of 5% was observed in 16 of 20 women with a niche depth over 5 mm (80%). Furthermore, amplitude with a cut-off value of 5% was seen in 18 out of 21 women with a niche length over 5 mm (86%) and in 17 out of 21 women with an RMT less than 3 mm (81%). An amplitude of 5% or above was not observed in any of the controls.

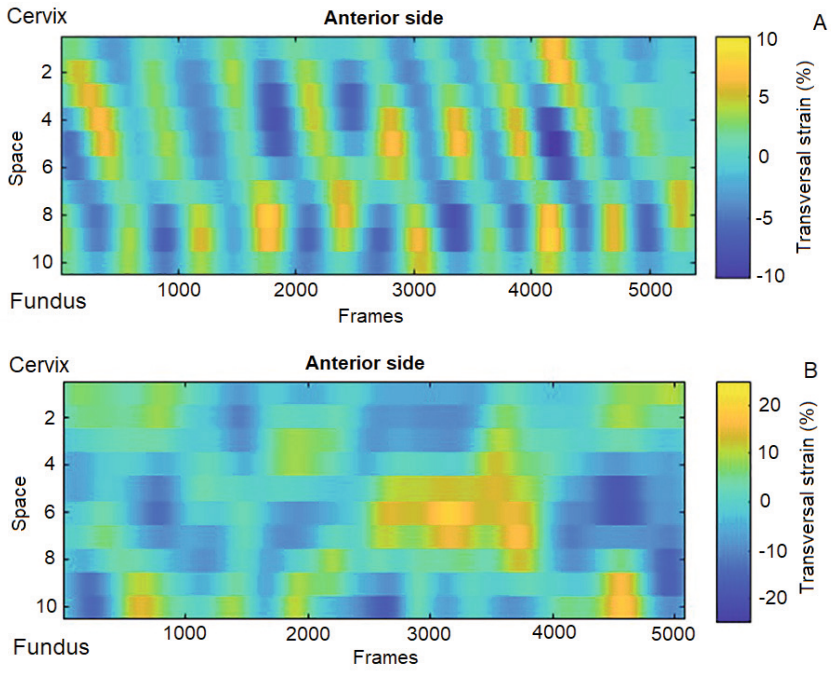

Figure 6. Coordination of endometrial contractions in a health control and in a woman with a niche.

(A) Strong coordinated contractions measured in a healthy control during the late follicular phase are shown. The uterine peristalsis, represented by the magnitude of transversal strain, from the anterior and posterior sides of the endometrium propagates in the same direction (from cervix to fundus) simultaneously; (B) weak coordinated contractions measured in a woman with niche are shown. No clear direction of the uterine peristalsis can be visualized.

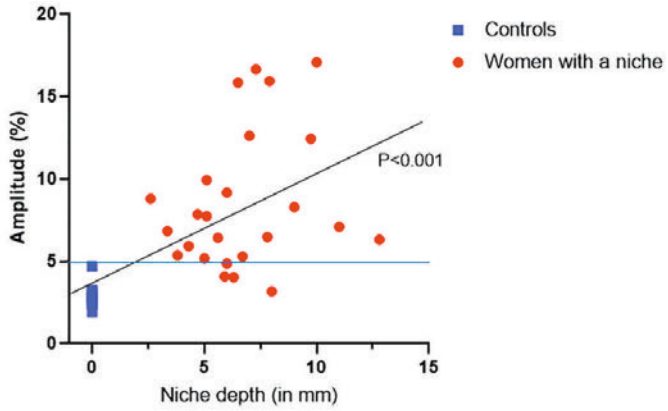

Figure 7. Scatterplots of mean amplitude by niche depth, in women with a niche (n = 25) versus controls (n = 11).

Subendometrial contraction features in patients with a niche using OC versus controls

The mean contraction amplitude in the women with a niche using continuous OC (n=6) was significantly higher compared with the controls without a niche and without using OC (p<0.001); frequency and velocity were lower (p=0.012 and p=0.010, respectively), see Supplementary Table 1.

DISCUSSION

Main findings

The present study is, to the best of our knowledge, the first to show that features of UP, measured in the subendometrial layer of the uterine corpus and fundus, differ in women with a niche in the uterine cesarean scar compared with women who have not undergone a previous CS, over all phases of the menstrual cycle. The contraction amplitude was higher in women with a niche than in controls. Contractions were less coordinated during the late luteal phase and during menses. The amplitude was correlated to niche depth and length and inversely correlated to the thickness of the residual myometrium. These findings support the hypothesis that, in women with a niche, subendometrial wave patterns are disturbed during all phases of the menstrual cycle, which could lead to spotting due to suboptimal menstrual outflow and lower implantation rates.

The underlying mechanism of uterine contractions is not yet elucidated. Uterine smooth muscle cells are specialized myocytes. Coordinated contractions in a muscular organ are typically initiated and maintained by a region of pacemaker cells that modulate

bioelectrical signals. Calcium (Ca2+) influx ultimately leads to an increase in extracellular Ca2+, which then leads to activation of myosin light-chain kinase and initiates the cross-bridging cycle leading to contractions of the uterine smooth muscle cells.[21] Increased amplitude may originate from an increased sensitivity to Ca2+ influx. The exact relation between a niche and its effect on these contractions is unknown. We have postulated three theories for the distortion of uterine contractions and higher amplitude found in women with a niche. The first theory is that the presence of intra-uterine blood in association with a niche induces stronger subendometrial contractions to expel the blood. This is supported by reports that thrombin and its receptor (protease-activated receptor, PAR1) are able to stimulate myometrial contractions, in pregnant and non-pregnant myometrial tissues.[33] A second theory is that inflammation in association with the presence of a niche induces a higher amplitude. It has also been postulated that pro-inflammatory factors (like Interleukin (IL)-1β, IL-8 and cyclo-oxygenase-2) may induce uterine contractions.[34] Studies, however, have also shown that pro-inflammatory cytokines (like IL-1β and tumor necrosis factor-α) reduce myoepithelial cells contraction, but these are of other origin.[35] Thirdly, we hypothesized that subendometrial contractions, starting in the direction from fundus-to-cervix, are interrupted by the defect in the anterior wall; the disturbance in electro-mechanical signal may in theory affect Ca2+ sensitivity or activation of uterine pacemaker cells. Although this mechanism is uncertain in the uterus, it has been described in case of myocardial infarction in which damaged tissue leads to arrhythmogenic waves.[36] Future studies are needed to elucidate the exact underlying pathways.

Clinical implication and comparison to other studies

Uterine contractions may play an important role in the success of embryo implantation. It has been previously reported that, throughout the menstrual cycle, adequate endometrial wave patterns of the uterus seem to be related to successful reproduction in natural cycles and assisted reproduction.[16, 18, 19]

A niche involves a discontinuity in the uterine scar and may play a role in the etiology of the reported lower implantation and pregnancy rates after a CS compared with women with a history of a previous vaginal delivery.[7-9, 37]

To the best of our knowledge, no other studies have reported on uterine contractions by using speckle tracking in women with a niche. Previously, an association between uterine contractions and IVF outcomes was reported by using visual inspection of uterine contractions in which no distinction was made between the different uterine layers.[38] Fanchin *et al.*[38] performed a 5-min digital recording of the uterus before IVF and embryo transfer in 209 infertile women and concluded that high contraction

frequency hinders IVF and embryo transfer outcome, using a computer-assisted image analysis system to count the number of myometrial contractions. These results may be explained by mechanical expulsion of embryos from the uterine cavity. This is in line with the study of IJland *et al.*[39] who examined 37 subfertile women and found higher endometrial wavelike activity (contraction frequency) in women who did not conceive compared with the women who did conceive.

Recently, Blank *et al.*[23] used speckle tracking to evaluate uterine contractions during IVF cycles. They reported a significantly higher contraction amplitude in women without an ongoing pregnancy compared with women with an ongoing pregnancy. In the present study, we found a higher amplitude in association with a niche; both high amplitude and niche existence were identified previously as associated with lower ongoing pregnancy rates in IVF. The fact that these amplitudes were associated with the size of the niche underlines the causality of a niche and the identified subendometrial contraction features. It also fits our hypothesis that a niche may be the intermediate factor for the reported lower implantations rates in women who have undergone a previous CS.[8, 9] Under physiological conditions, under influence of progesterone, the luteal phase is characterized by a state of relative uteroquiescence, with low amplitude contractions. These may facilitate proper positioning of embryos for implantation and pregnancy[40], see Figure 8A. High amplitude combined with frequency of the uterine contractions with a direction towards the cervix may induce displacement of the embryo towards the cervix, in particular if combined with the presence of intra-uterine fluid. This displacement may in theory hamper normal implantation of the embryo (Figure 8B).

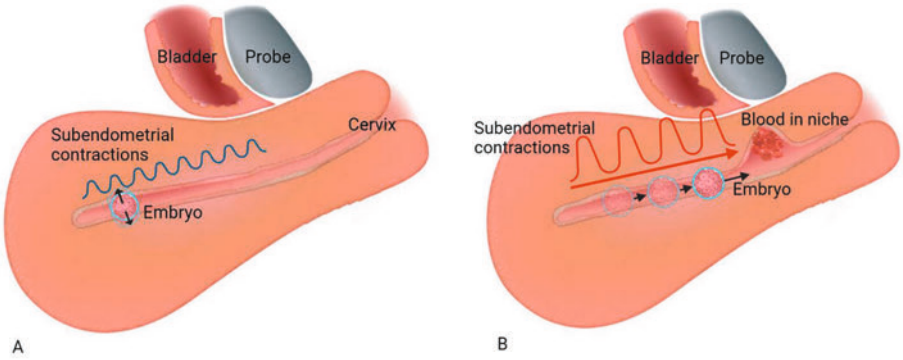

Figure 8. Hypothesized theories of the influence of subendometrial contractions on implantation of an embryo.

(A) a uterus without cesarean section scar with low amplitude contractions, which may facilitate proper positioning of the embryo for implantation; (B) a uterus with a niche illustrating distortion of contraction features (higher amplitude and lower frequency), which may increase the force on the embryo in the direction of the cervix, particularly if the niche is associated with intra-uterine fluid accumulation.

In addition, coordinated contractions with a fundus-to-cervix direction are needed to facilitate outflow of menstrual blood. Postmenstrual spotting and dysmenorrhea are most prevalent symptoms in women with a niche.[4, 11, 41] During the menstrual phase, we identified a negative correlation concerning the fundus-to-cervix contractions in the niche group, whereas a positive correlation was observed in the control group. This suggests that contractions in the direction of the cervix were less coordinated, and it may, therefore, disturb functional outflow of menstrual blood. In theory, this may be one of the causal factors for niche related postmenstrual spotting.

Strengths and limitations

Objectively assessing the uterine contractions with speckle tracking is useful in determining the effect of uterine contractions in women with a niche. In both the included groups, ultrasound recordings were carried out according to a strict protocol using one ultrasound machine with fixed settings. Another strength is that we matched for cycle phase as it is known that uterine contractions are influenced by the menstrual cycle phase.

The present study also has some limitations. The first limitation is the small data set. At the time of the study design, no relevant data of comparable studies were available to calculate a sample size. Furthermore, a high number of recordings were not suitable for speckle tracking analysis, even though the researchers were trained. The quality of the videos could only be assessed in retrospect during speckle tracking analysis. Therefore, inclusion took longer than expected. Main reasons to exclude recordings were of movement artefacts and suboptimal region of interest, but also some technical problems occurred, i.e. faltering recording. Another limitation is in that, owing to the non-randomized design of our study, there may be differences between the two groups. For example, by definition, all women had undergone a previous CS in the niche group, whereas most women had never been pregnant in the control group. Furthermore, in case of parity, there was no significant difference in uterine size between the study groups, which might have explained the significant higher amplitude in multipara (women with a niche). In the present study, we did not include women with a CS scar but without visible niche, because we had no ethical approval to include this patient group. Our goal was to assess the two extremes first: women with a niche versus women without previous uterotomy.

Future perspectives

Our study results indicate that the presence of a niche influences the amplitude and coordination of subendometrial contractions. The associated change in these

contraction features may play an important role in niche-related problems such as postmenstrual spotting and subfertility. The exact relation needs further exploration.

Furthermore, we found a strong positive correlation between niche sizes (depth, length) and RMT, and amplitude of subendometrial contractions raising the question if UP can be corrected by surgical removal of the uterine niche and restoration of the residual myometrial thickness. After the results of this study showing difference in contraction features, we plan to first evaluate the influence of a CS scar alone on subendometrial contractions in a future study to determine whether a scar itself also affects the amplitude or other characteristics of uterine subendometrial contractions. Future larger studies are needed to confirm our findings and to study the effect of current applied treatments on contraction features, gynecological symptoms and reproductive outcomes.

In conclusion, the amplitude of subendometrial contractions is higher in women with a niche compared with women who have not undergone a previous CS. The contraction amplitude is correlated to the niche size and inversely correlated to the thickness of the residual myometrium or uterine wall. Furthermore, contractions in women with a niche are less coordinated. In theory, these findings may play a role in the cause of postmenstrual spotting, dysmenorrhea and lower implantation rates in women with a niche. Future studies are needed to explore the clinical implication of our findings and to see if they can be corrected by pharmacological or surgical strategies and to elucidate the underlying mechanisms for the lower implantation rates in relation to a higher amplitude and the underlying electro-biological signaling pathways that cause these higher amplitudes in association with a niche.

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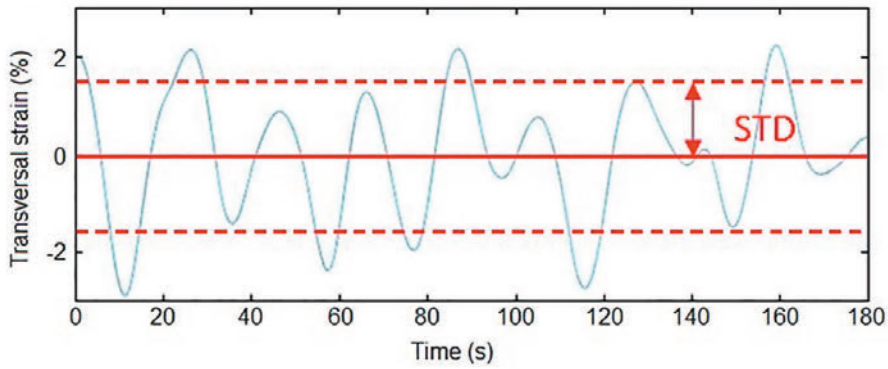
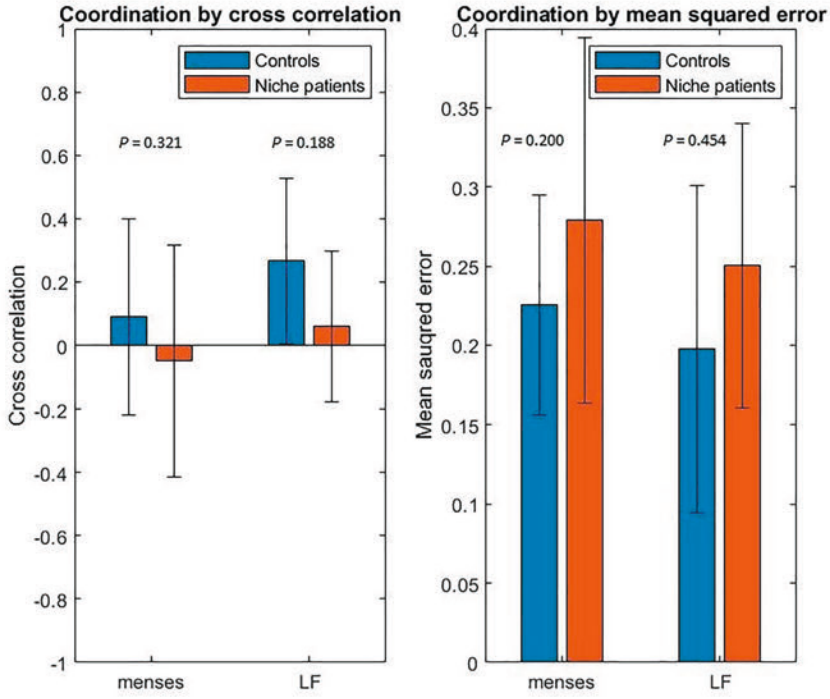
APPENDICES



Supplementary Figure 1. Example of standard deviation of the strain signal reflecting the degree of changes in deformation of the uterine muscle during the acquisition time (= contraction amplitude)



Supplementary Figure 2. Coordination feature by cross correlation and mean squared error in the menstrual and luteal phase in both study groups

LF, late follicular phase

Supplementary Table 1. Outcome measures of subendometrial contractions of women with a niche using oral contraceptives and controls

	Women with a niche using OC (n=6)	Controls (n=11)[a]	p value[b]
Amplitude (%)	10.2 ±5.7	2.9 ±1.3	<0.001
Mean frequency (contractions/min)	1.6 ±0.1	1.9 ±0.3	0.012
Velocity (mm/sec)	0.8 ±0.3	1.2 ±0.3	0.010

Data are reported as mean ± standard deviation. [a] The women in the control group underwent multiple ultrasounds in the different phases of the menstrual cycle. [b] Mann Whitney U test. CI, confidence interval; mm/s, millimeter per second; N, number; NA, not applicable; OC=oral contraceptive

CHAPTER 4

DEFINITION AND SONOGRAPHIC REPORTING SYSTEM FOR CESAREAN SCAR PREGNANCY IN EARLY GESTATION: MODIFIED DELPHI METHOD

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ABSTRACT

Objective

To develop a standardized sonographic evaluation and reporting system for Cesarean scar pregnancy (CSP) in the first trimester, for use by both general gynecology and expert clinics.

Methods

A modified Delphi procedure was carried out, in which 28 international experts in obstetric and gynecological ultrasonography were invited to participate. Extensive experience in the use of ultrasound to evaluate Cesarean section (CS) scars in early pregnancy and/or publications concerning CSP or niche evaluation was required to participate. Relevant items for the detection and evaluation of CSP were determined based on the results of a literature search. Consensus was predefined as a level of agreement of at least 70% for each item, and a minimum of three Delphi rounds were planned (two online questionnaires and one group meeting).

Results

Sixteen experts participated in the Delphi study and four Delphi rounds were performed. In total, 58 items were determined to be relevant. We differentiated between basic measurements to be performed in general practice and advanced measurements for expert centers or for research purposes. The panel also formulated advice on indications for referral to an expert clinic. Consensus was reached for all 58 items on the definition, terminology, relevant items for evaluation and reporting of CSP. It was recommended that the first CS scar evaluation to determine the location of the pregnancy should be performed at 6–7 weeks' gestation using transvaginal ultrasound. The use of magnetic resonance imaging was not considered to add value in the diagnosis of CSP. A CSP was defined as a pregnancy with implantation in, or in close contact with, the niche. The experts agreed that a CSP can occur only when a niche is present and not in relation to a healed CS scar. Relevant sonographic items to record included gestational sac (GS) size, vascularity, location in relation to the uterine vessels, thickness of the residual myometrium and location of the pregnancy in relation to the uterine cavity and serosa. According to its location, a CSP can be classified as: (1) CSP in which the largest part of the GS protrudes towards the uterine cavity; (2) CSP in which the largest part of the GS is embedded in the myometrium but does not cross the serosal contour; and (3) CSP in which the GS is partially located beyond the outer contour of the cervix or uterus. The type of CSP may change with advancing gestation. Future studies are needed to validate this reporting system and the value of the different CSP types.

Conclusion
Consensus was achieved among experts regarding the sonographic evaluation and reporting of CSP in the first trimester.

INTRODUCTION

Rising rates of Cesarean delivery worldwide have resulted in increasing numbers of pregnant women with a Cesarean section (CS) scar.[1] Pregnancies occurring after Cesarean delivery are considered to be at high risk for Cesarean scar pregnancy (CSP), low-implanted and invasive placenta (placenta accreta spectrum (PAS)[2]), failure to progress during labor, and uterine dehiscence or rupture in the second or third trimester of pregnancy.[3–6] A CSP occurs when the pregnancy implants on the uterine scar or in the niche after a previous CS.[7] Although a CSP is often considered for pregnancy termination, some cases have reportedly progressed towards an intrauterine pregnancy and resulted in viable births.[8–10]

Determination of the exact location of the gestational sac (GS) and invasion of the placenta is necessary to estimate the patient's risk and advise whether to terminate or continue the pregnancy. However, there is no uniform reporting system for CSP. Kaelin Agten *et al.*[6] distinguished between CSPs located on the 'well-healed' Cesarean scar and those implanted in the dehiscent scar (or niche). Others used the level of invasion of the GS and the remaining myometrial thickness to classify CSPs.[11–13]

Two-dimensional (2D) B-mode transvaginal ultrasound (TVS) alone or in conjunction with three-dimensional (3D) ultrasound and color Doppler has been generally considered to be the gold standard for the diagnosis of CSP.[14] Some authors have also described the use of magnetic resonance imaging (MRI).[15–17] However, there is no standardized guideline on how to locate the GS in relation to the CS scar in early pregnancy by using ultrasound. The ESHRE (European Society of Human Reproduction and Embryology) Working Group on Ectopic Pregnancy recently published recommendations on the terminology of normally sited and ectopic pregnancies, in which CSP is described briefly.[18] The aim of this study was to develop a basic and advanced standardized sonographic evaluation and reporting system for CSP in early gestation.

METHODS

Design of a modified Delphi study

A modified Delphi procedure was conducted to achieve consensus (Figure 1). We performed a systematic literature search to discover available literature on the assessment of CSP, and to identify relevant items on the subject that could be used in the development of the first questionnaire. The modified Delphi procedure contained repeat rounds of questionnaires; after each round, answers were analyzed and results were presented to the experts, including their relevant feedback. Based on the outcomes, new questions were formulated concerning topics on which consensus had not been achieved. In this way, the experts participating in the study were able to reflect on the results of each previous questionnaire round in a structured manner. The experts participating in the Delphi study answered online questionnaires anonymously. We continued to the next Delphi round until all items reached consensus. It was predetermined that the process would include at least three rounds (two online questionnaire rounds and one face-to-face meeting). The data were collected between July 2018 and August 2020.

Literature search and development of first Delphi questionnaire

The electronic databases PubMed and EMBASE were searched for articles published on the sonographic evaluation of CSP from inception to January 2018, with the assistance of a clinical librarian. The search strategy is provided in Appendix S1. Duplicate articles were excluded. All English or Dutch full-text articles were included if they reported on the definition and evaluation of CSP using ultrasound and if they addressed one or more of the research questions predefined by J.A.F.H., R.A.d.L. and I.P.M.J. to use in the first questionnaire. These questions concerned: (1) sonographic criteria to define CSP; (2) classification based on CSP type; (3) method to locate a CSP using TVS; (4) optimal timing to check for the presence of CSP; (5) relevance of color Doppler ultrasound in the diagnosis of CSP; (6) relevance of pulsed Doppler ultrasound; (7) relevance of 3D (Doppler) ultrasound; (8) value of MRI in assessment and diagnosis of CSP. Relevant items were extracted from all the reviewed and included papers and were used in the first questionnaire. In addition, the relevant items were presented in a separate background-information file that was provided for the experts in case it was needed to fill out the questionnaire.

Expert panel recruitment

Obstetrics and gynecology clinicians with expertise in advanced ultrasound evaluation of CS scars in early pregnancy and diagnosing CSP were invited to participate in this Delphi study.

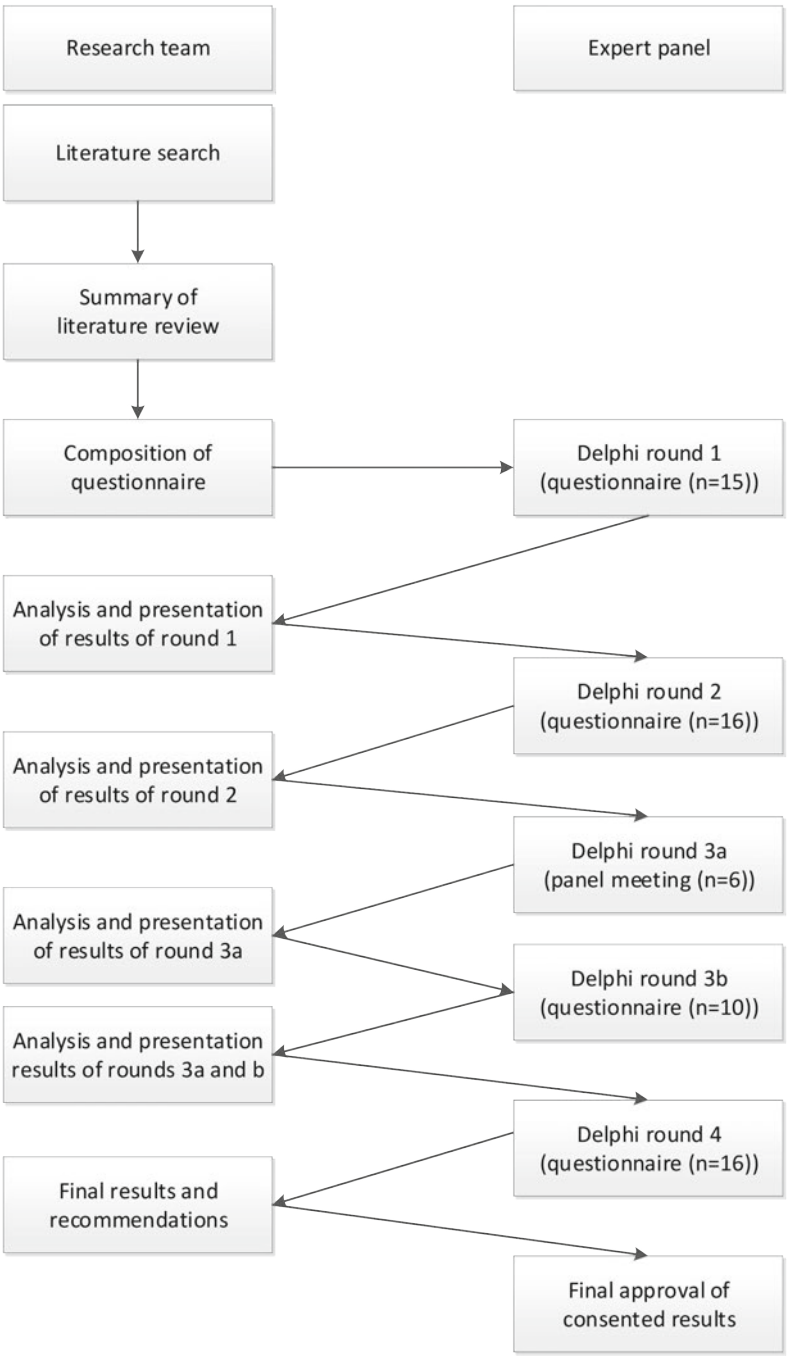

Figure 1. Study design: stepwise modified Delphi method used to reach consensus on the definition of Cesarean scar pregnancy and sonographic evaluation of the uterine scar in the first trimester of pregnancy.

The experts were selected based on their membership of the International Niche Society, including the European Niche Taskforce, and the interest group of the International Society of Ultrasound in Obstetrics & Gynecology (ISUOG) or their authorship of publications concerning the use of ultrasound in the evaluation of CSP or CS scar/niche. All the invited experts were asked to recommend other experts who were also known to have extensive experience in the field. For the purpose of this Delphi procedure, 'experts' were defined as clinicians with substantial experience in advanced ultrasound evaluation of CS scars or CSP, or who had published at least one article on CSP or CS niche evaluation. Initially, 22 experts were invited; six further experts were invited subsequently after recommendation by their colleagues. Experts had to confirm their expertise to be included.

Delphi rounds and structural consensus method

All experts received an e-mail containing a unique link to the online questionnaire after confirmation of their participation. After each round, the answers from all the experts were analyzed for each question. Consensus was predefined as a rate of agreement (RoA) of >70%, where RoA = (agreement − disagreement)/(agreement + disagreement + indifferent) × 100.[19–21] Questions were transferred to the second round if no consensus was reached, and the results of the first round were fed back anonymously, including the reasoning of the respondents. Additional questions requiring clarification were added as appropriate. Furthermore, the experts were given the opportunity to add important relevant items, which were used in the next questionnaire. All the experts who agreed to participate in the Delphi procedure were invited to participate in each round, whether they had replied to the previous questionnaire or not. A draft set of recommendations was designed based on the results of the second round. These results were presented in a face-to-face meeting in October 2019, and the items without consensus were discussed. All comments and recommendations made in that meeting were recorded. The experts could reflect on their reasoning and, if necessary, reconsider their opinion. Experts who were unable to participate in the meeting could express their opinion in a third online questionnaire reflecting the results of the face-to-face meeting. All results of the agreed items during the three rounds were presented to the experts, then a need for more detailed clarification of a few items led to a fourth digital questionnaire. The results of the agreed items were sent for final approval to all the experts who participated in the Delphi procedure.

Some adjustments were made to the manuscript during the peer-review process; these were submitted to and approved by all the experts.

RESULTS

Literature search

A systematic search for literature about CSP evaluation and niche evaluation in pregnancy resulted in 1735 articles after removal of duplicates (Figure S1). Of the 471 papers that were considered eligible after screening the title and abstract, 28 articles that reported on our predetermined research questions were finally included after full-text review. The results of the search are presented in Table S1. Some of the papers[6,14,22–27] were used for multiple questions. In total, 15 articles[6,14,22,26–37] described various criteria for the diagnosis of a CSP. Six[6,11,12,26,27,38] articles introduced a classification according to multiple CSP types or grades. Only Timor-Tritsch *et al.*[22] described in detail how to locate a pregnancy using ultrasound in order to differentiate between an intrauterine pregnancy and a CSP. The use of Doppler ultrasound, pulsed Doppler, 3D (Doppler) ultrasound and MRI for the assessment and diagnosis of CSP were described in, respectively, three[14,23,24], two[14,24], four[14,25,39,40] and eight[14,23,25,41–45] papers. None of the papers defined the optimal gestational age for assessing the presence of a CSP.

The results of the literature search were used in the development of the first questionnaire and included in the background-information document provided to the experts. The results of a previous Delphi procedure on uterine niche measurement in non-pregnant women[46], and the ISUOG recommendations on the performance of ultrasound in the first trimester of pregnancy[47], were also provided as background information.

Delphi procedure

The first questionnaire consisted of 43 relevant items comprising 93 questions. These items were categorized as: CSP definition and location; CS scar evaluation in the first trimester of pregnancy; differentiation between CSP and cervical pregnancy or miscarriage; evaluation in the transverse plane; gestational age and CSP; Doppler ultrasound and CSP; pulsed Doppler and CSP; 3D (Doppler) ultrasound and CSP; MRI and CSP; niche measurement in CSP; differentiation between basic measurements to be performed in general practice and advanced measurements to be performed in expert centers or research settings. In the second Delphi round, 10 further items were added based on the input given, and one additional category was included: referral to an expert clinic. Moreover, in the fourth Delphi round, one category (heterotopic pregnancy) and five items were added (Figure 2). An overview of the questions in all questionnaires and subjects discussed during the face-to-face meeting and their level of agreement are presented in Table S2.

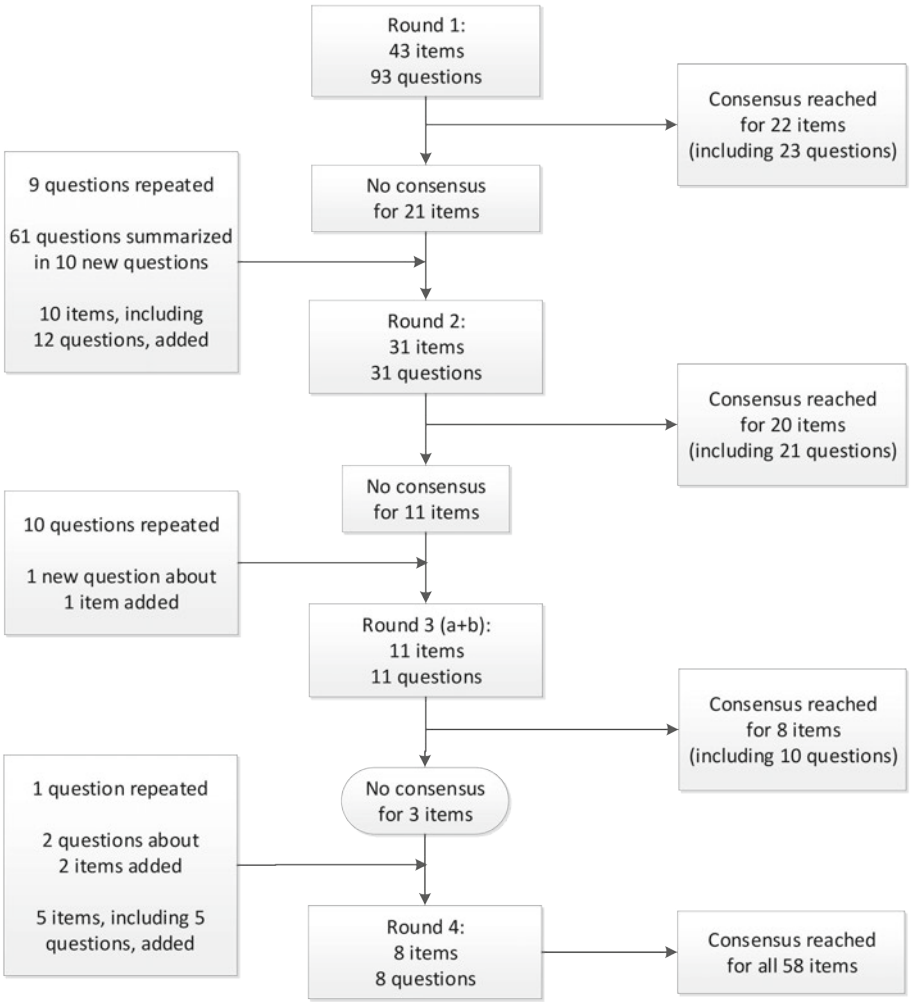

Figure 2. Flow diagram summarizing agreement with or rejection of items during Delphi procedure. Items were accepted if consensus agreement of at least 70% was reached.

Of the 28 experts contacted, one reported to have insufficient expertise. Of the remaining 27 experts, 16 agreed to participate in the Delphi study. Two junior researchers, who are also coauthors (I.P.M.J. and C.V.), facilitated the study; they did not complete the questionnaires and are not included in the table. All 16 participating experts completed the second, third and fourth Delphi rounds; 15 (94%) completed the first online questionnaire. Consensus was reached for all 58 items (Figure 2). The mean consensus achieved per item in each round of the Delphi procedure is presented in Table S3.

Agreed recommendations and statements

A complete overview of the agreed statements is presented in Table S4, and an overview of our primary research questions and recommendations is provided in Table S5.

Method of CS scar evaluation in first trimester of pregnancy

Localization of the GS and placenta depends on gestational age. For evaluation of a CSP, it was agreed that the optimal gestational age to carry out these examinations is 6–7 weeks (88–94% agreement). However, the recommendations apply for use during the entire first trimester of pregnancy (until 12 weeks). The gestational age should be based on the first day of the last menstrual period, if applicable; otherwise, it should be based on measurement of the GS or crown–rump length (81% agreement). CSP evaluation is recommended in women with a previous CS if ultrasound is performed because of symptoms, viability evaluation or other reasons such as a previous CSP.

Eighty percent of the experts agreed that the proposed standardized approach for imaging by TVS and reporting of the lower uterine segment in the first trimester of pregnancy as described by Kuleva *et al.*[48] can be used to evaluate the CS scar (see Figure S2).

CSP definition and location in first trimester of pregnancy

The first-round questionnaire contained 34 questions about defining a CSP. We observed different use of the terms 'CSP' and 'niche pregnancy', resulting in inconsistent answers. Based on this observation, we proposed a uniform definition of CSP, which should be differentiated from a low-implanted pregnancy and from an ongoing miscarriage or pregnancy remnant.

Most (94%) experts agreed that CSP can be used as a collective term that includes all pregnancies (GS and/or placenta) with implantation in, or in close contact with, the niche. The experts agreed that a CSP can occur only when a niche is present and not in relation to a healed CS scar. It should be noted that a diagnosis of CSP does not automatically mean that the pregnancy needs to be treated as discussed later. A pregnancy that is located near the CS scar should be called 'low-implanted pregnancy' and not a CSP (94% agreement). A low-implanted pregnancy is defined as any pregnancy implanted near the niche/CS scar without being in direct contact with it (Figure 3).

There was consensus (94%) on describing a CSP depending on the GS crossing two imaginary lines: the 'uterine cavity line' (UCL) and/or the 'serosal line' (SL) (Figure 4). Specifically, it was agreed that a CSP can be described as follows: (1) CSP in which the largest part of the GS crosses the uterine cavity/cervical canal (the UCL) (Figure 5a,b);

(2) CSP in which the largest part of the GS is embedded in the myometrium and does not cross the UCL, and the GS does not cross the SL (Figure 5c,d); and (3) CSP in which the GS crosses the SL; the pregnancy is covered by a thin layer of myometrium or visceral peritoneum and is herniating towards the vesicouterine pouch or into the broad ligament (Figure 5e,f). The definitions of a niche and related features were taken from a previous Delphi study concerning niche measurement in non-pregnant women.[46]

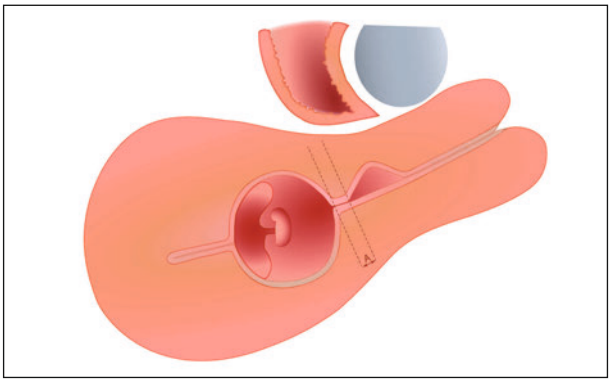

Figure 3. A pregnancy located near the Cesarean scar/niche without being in direct contact with it should be called 'low-implanted pregnancy'. 'Distance A' is the distance between the proximal border of the niche and the most distal border of the gestational sac.

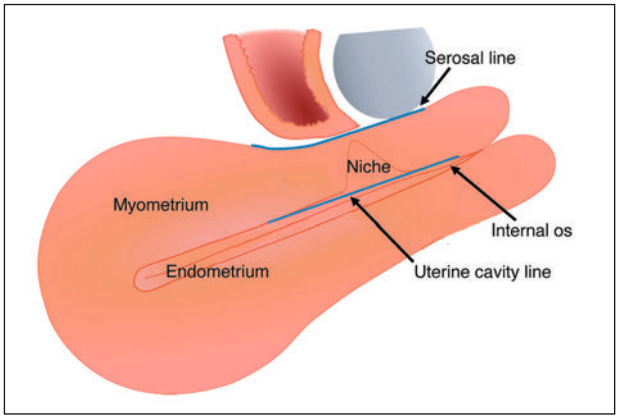

Figure 4. Differentiation of Cesarean scar pregnancy according to position of the gestational sac in relation to two imaginary lines: the 'uterine cavity line', i.e. the imaginary line at the transition of the endometrium and myometrium, and the 'serosal line', i.e. the imaginary line at the outer border of the myometrium.

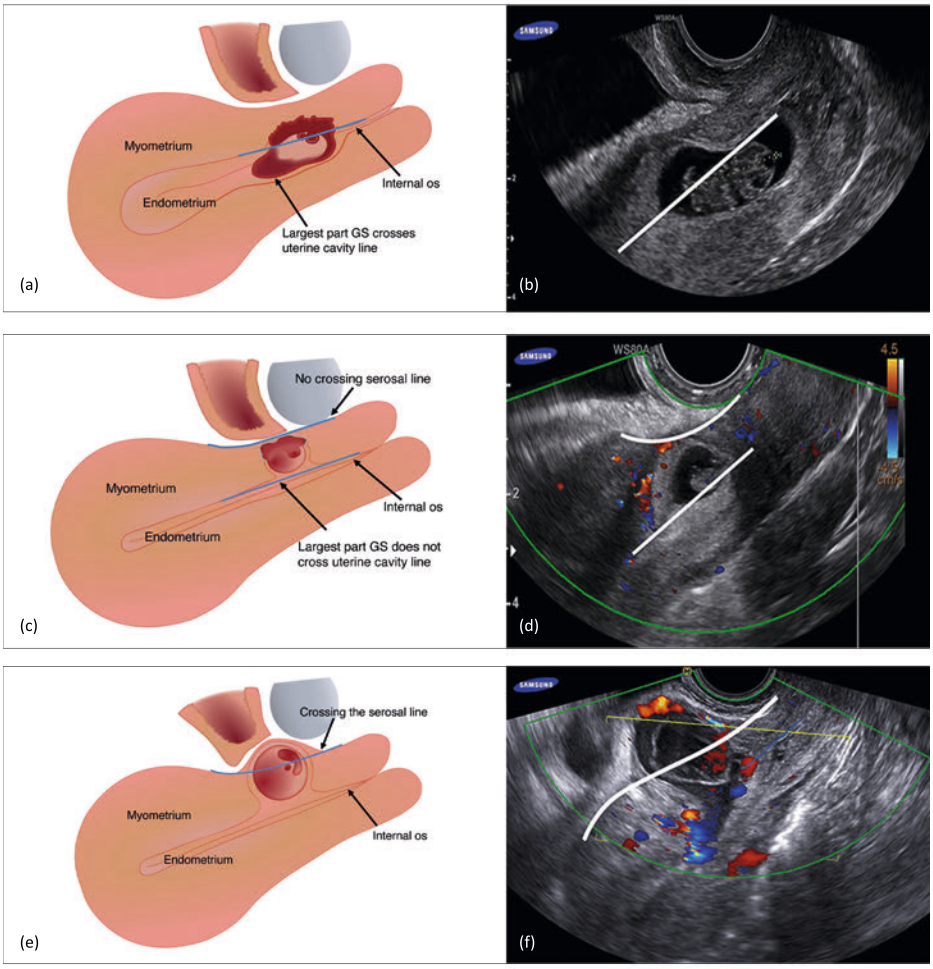

Figure 5. Schematic (a,c,e) and ultrasound (b,d,f) images, showing differentiation of Cesarean scar pregnancy (CSP) according to position of the gestational sac (GS) in relation to the uterine cavity line and the serosal line. (a,b) CSP with the largest part of the GS crossing the uterine cavity line. (c,d) CSP with the largest part of the GS embedded in the myometrium and not crossing the uterine cavity line, and the GS not crossing the serosal line. (e,f) CSP crossing the serosal line.

Method of CSP evaluation in first trimester of pregnancy

2D ultrasound. It was agreed that the residual myometrial thickness (RMT) and adjacent myometrial thickness (AMT) in the sagittal plane should be measured and reported in cases of CSP, as illustrated in Figure 6. Measurements of the niche (length, depth and width) in cases of CSP were found irrelevant because of its change as the pregnancy progresses (100% agreement). Measurement of the position of the GS in relation to the external os (88% agreement) and in relation to the vesicovaginal fold (94% agreement) may be performed in the research setting and is not mandatory for basic evaluation.

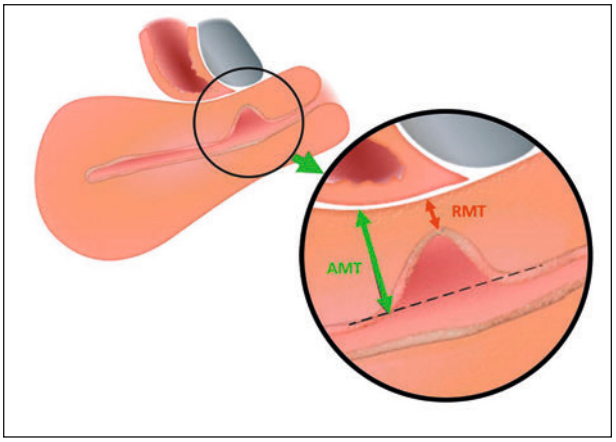

Figure 6. Measurement of residual myometrial thickness (RMT) and adjacent myometrial thickness (AMT) in the sagittal plane in cases of a niche in the non-pregnant state. Adapted with permission from Jordans et al.[46].

Color (flow) Doppler. According to the expert panel, color (flow)Doppler helps in the evaluation of trophoblast invasion, recognition of a CSP and differentiating a CSP from a low-implanted pregnancy or miscarriage. It is therefore advisable to use color-flow Doppler in case of a suspected CSP, but it is not mandatory in all pregnancies in women with a previous CS (88% agreement). For a suspected CSP, evaluation of the vascular pattern and its relation to the niche, cervix and adjacent uterine vascular anatomy using color (flow) Doppler is recommended (80% agreement). A proposal for evaluation of the CSP in the transverse plane, including its location in relation to the uterine arteries, reached consensus (80%) and was added to the reporting system for CSP (Figure 7).

Remnants of placental tissue within the uterine scar following partial spontaneous expulsion of a CSP can cause persistent bleeding with the risk of intermittent major hemorrhages.[49] These remnants can also often be seen following medical treatment of CSP and after incomplete surgical evacuation.[50,51] Retained placental tissue can be difficult to differentiate from blood clots on ultrasound and it may resemble other uterine abnormalities such as fibroids. The experts agreed that color Doppler examination is essential for the differential diagnosis of remnants of placental tissue and to search for the signs of enhanced myometrial vascularity, which is associated with a high risk of bleeding with both conservative and surgical management of CSP (94% agreement).

Some of the experts stressed that the value of quantitative color (flow) Doppler parameters (i.e. vascular score, vessel diameter, flow velocity) should be evaluated in further research.

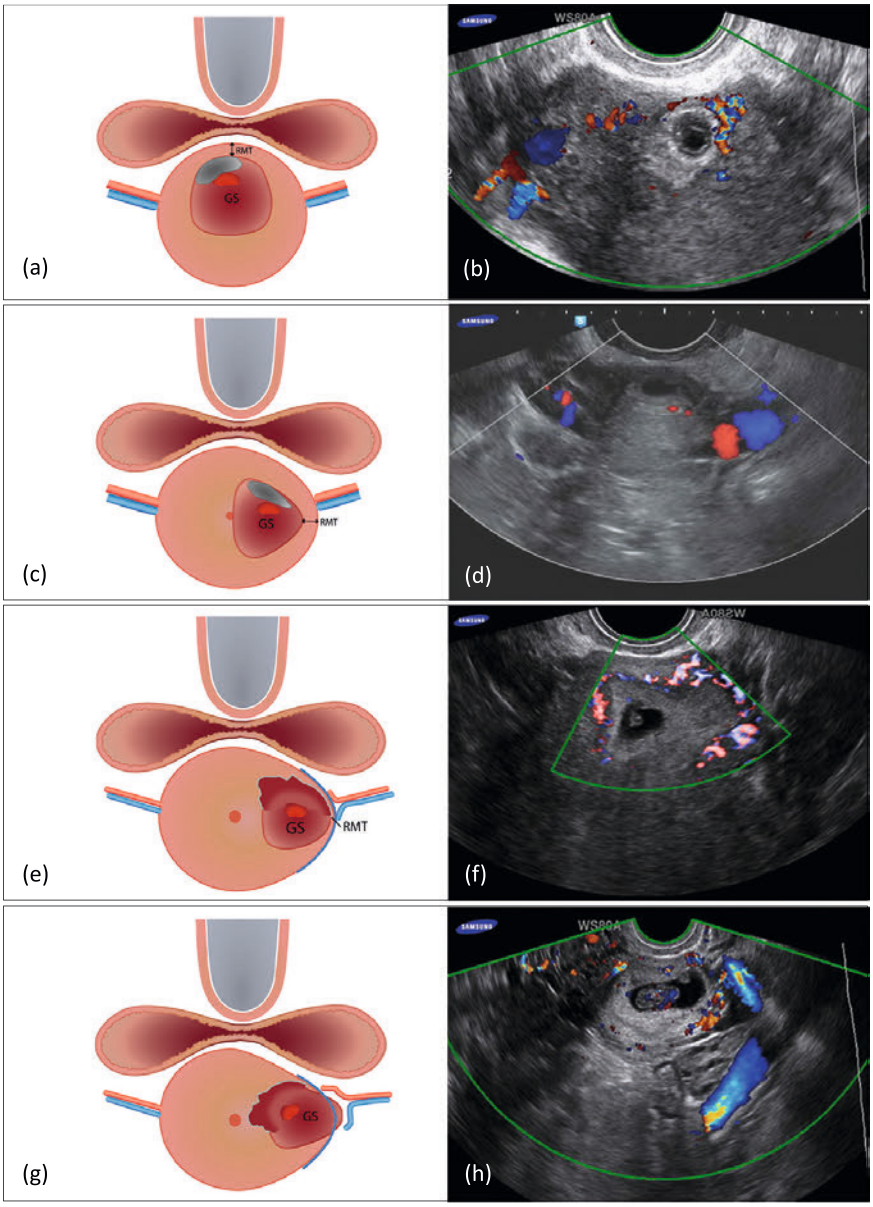

Figure 7. Schematic (a,c,e,g) and ultrasound (b,d,f,h) images showing assessment of location of Cesarean scar pregnancy (CSP) in relation to the uterine arteries in the transverse plane. (a,b) Median location of CSP. (c,d) Eccentric location of CSP; the gestational sac (GS) is connected with the cervical canal and is within the outer cervical contour. (e,f) Lateral location of CSP; the GS protrudes towards the broad ligament within the virtual outer cervical contour and the residual myometrium is visible (CSP with largest part of GS embedded in the myometrium and not crossing the serosal line). (g,h) Lateral location of CSP; the GS is bulging beyond the outer cervical contour and residual myometrium is absent (CSP crossing the serosal line). RMT, residual myometrial thickness.

Most respondents did not consider that these quantitative color features should be part of the basic or advanced evaluation. It is important to stress that proper Doppler settings are essential for flow detection, description of the vessel pattern and flow-velocity measurement in order to obtain reproducible results. The optimal settings for the use of color Doppler in CSP should be ascertained in future research.

Pulsed Doppler, 3D (Doppler) ultrasound and MRI. Most experts agreed that pulsed Doppler (81% agreement) and 3D (Doppler) ultrasound (88% agreement) are not mandatory for routine evaluation of CSP, but may be relevant in a research setting. MRI does not add value to the diagnosis of a CSP according to 73% of the experts.

Differentiation between CSP and cervical pregnancy or miscarriage

A flowchart was introduced that presents different situations that can be encountered during sonographic evaluation of an early pregnancy in women with a previous CS (Figure 8). A pregnancy can be located high in the uterine cavity or low in the uterine cavity or in the cervical canal, the latter two being difficult to distinguish from a CSP. If located low in the uterus or in the cervix, it can be a low-implanted pregnancy, a CSP or a miscarriage. The site of trophoblast invasion and vascularity are relevant for their discrimination. Note that the type of CSP may change over time as described earlier. Agreement (94%) was reached for the content of the flowchart and for the different steps to be used in clinical practice (Figure 8).

Various sonographic features were agreed upon by the experts to differentiate between the three distinct clinical situations of CSP, cervical pregnancy and ongoing miscarriage. It needs, however, to be emphasized that the signs of a CSP may change over time with advancing gestation, and that the signs described in this paper are applicable in early pregnancy (up to 12 weeks' gestation). First, bulging of the GS towards the bladder is relevant for differentiating between a CSP and a cervical pregnancy (87% agreement). Second, if sliding tissue is visible at the level of the CS scar, it is more likely to be an ongoing or incomplete miscarriage than a CSP (100% agreement). Additionally, vascularization, the location of implantation and trophoblast invasion are useful features for discriminating between a CSP, a low-implanted pregnancy and an ongoing miscarriage (all 88% agreement), for which the use of color (flow) Doppler is endorsed. According to 73% of the experts, the shape of the GS is not relevant for discriminating between a CSP and a cervical pregnancy.

Evaluation of the presence of a GS, fetal pole or yolk sac with or without heart activity can be used to differentiate a CSP from another structure (artifact, nabothian cyst,

miscarriage, inclusion cyst and a remnant after miscarriage of a CSP) according to 84% of the experts.

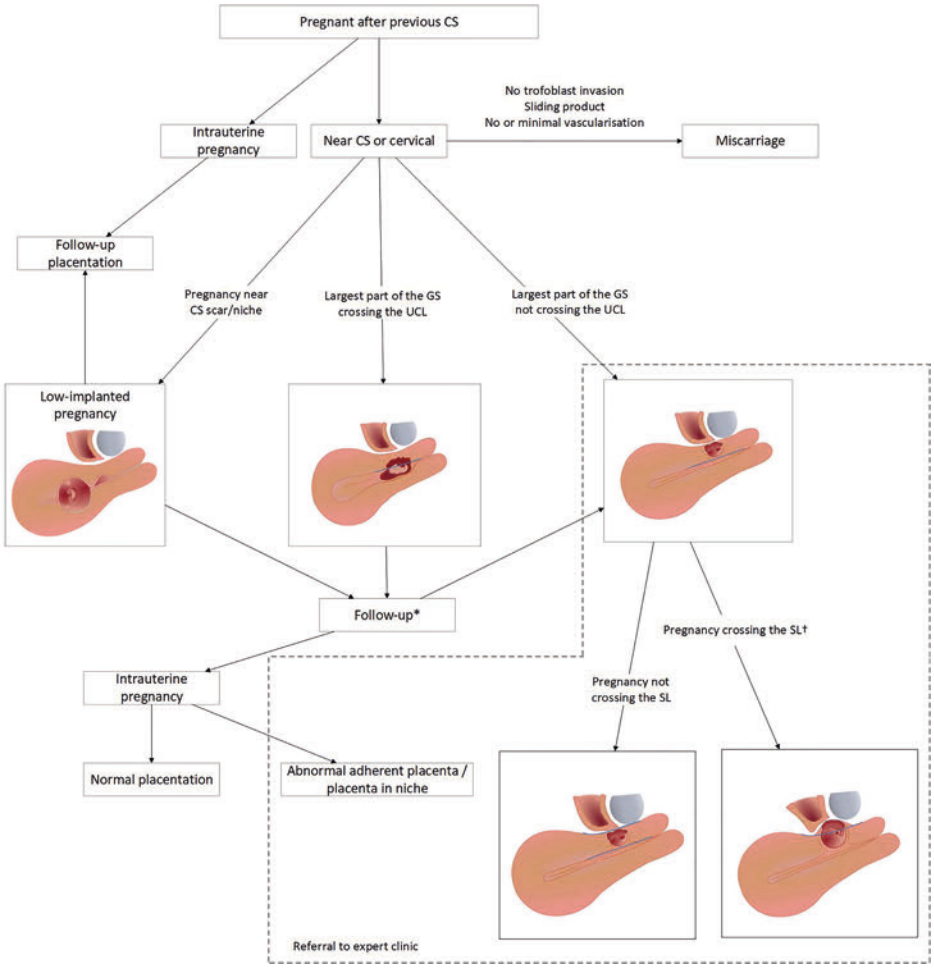

Figure 8. Flowchart showing evaluation of the Cesarean section (CS) scar in first trimester of pregnancy. Step 1: determination of location of the pregnancy: intrauterine pregnancy, low-implanted pregnancy, Cesarean scar pregnancy (CSP) or miscarriage. Step 2: determination of type of CSP depending on whether the largest part of the gestational sac (GS) is crossing the uterine cavity line (UCL): (a) if the largest part of the GS is crossing the UCL, it should be determined whether the location of the largest part of the GS is in the uterine cavity or in the cervical canal; (b) if the largest part of the GS is not crossing the UCL, the existence of bulging should be determined: (i) if there is no bulging, i.e. the pregnancy is located completely within the level of the serosa/serosal line (SL), it is a CSP with the largest part of the GS in the myometrium and not crossing the SL; (ii) if there is bulging, i.e. the pregnancy is located partly beyond the contour of the outer cervix/SL, it is a CSP crossing the SL. Step 3: determination of location of the placenta: in the niche, near the niche or placenta previa. Step 4: evaluation of presence of signs of abnormally adherent placenta: yes or no? *Management regarding follow-up or treatment will depend on patient characteristics and wishes. †To be evaluated in future cases and validated by peer-reviewed articles.

Approximately half of CSPs that are diagnosed contain a living embryo, while the remaining pregnancies are classified as failing.[49,52] All the experts agreed that the criteria used for the differential diagnosis between normally developing pregnancies within the uterine cavity and miscarriages[53,54] can also be applied in cases of CSP to differentiate between failing CSP and those with potential to grow beyond the first trimester (Table S6).

Required sonographic items of CS scar evaluation in cases of CSP in first trimester of pregnancy

Basic assessment. An overview of agreed items that should be evaluated during routine ultrasound in cases of low-implanted pregnancy or CSP is shown in Table 1. In cases of low-implanted pregnancy, the location of the pregnancy/placenta in relation to the uterine scar was agreed to be more important than the precise location of the pregnancy (88% agreement). Evaluation of placental location, placental or trophoblast invasion into the myometrium and presence of a niche and CSP is recommended in early pregnancy (up to 12 weeks) in all women with a previous CS, if an ultrasound scan is carried out because of symptoms or to assess viability. Also, when there is an intracavitary pregnancy, an additional CSP should be excluded (73–75% agreement). The latter is also relevant to exclude the existence of a heterotopic pregnancy (one intracavitary and one CSP, as discussed later). RMT and AMT are required measurements in the sagittal plane (93–100% agreement). Furthermore, the exact amount of protrusion of the GS beyond the UCL, and the SL if applicable, should be estimated. The location of the GS in relation to the external os and in relation to the vesicovaginal fold is not mandatory for basic evaluation, as described earlier.

Advanced assessment. In expert centers, color Doppler ultrasound should be used to evaluate circular flow around the GS (100% agreement). This helps to determine the site of implantation and the degree of placental myometrial invasion. It also helps to determine the depth of placental invasion in relation to the arcuate and main uterine arteries. The location of the GS in relation to the uterine arteries was considered relevant when choosing different treatment options, in addition to the RMT in the sagittal plane (73% agreement). Also, the experts agreed that the level of CSP sac herniation should be assessed in both the sagittal and transverse planes if therapy is considered (100% agreement).

Heterotopic pregnancy

Although considered rare, CSP may coincide with a normally sited pregnancy within the uterine cavity or with ectopic pregnancies in other locations within or outside the uterus.[55] It was agreed that the possibility of a heterotopic pregnancy in the CS scar should be considered in all women with a previous CS (94% agreement).

Table 1. Overview of items that should be evaluated in the first trimester after previous Cesarean section in cases of low-implanted pregnancy or Cesarean scar pregnancy, according to Delphi consensus

Item	Consensus (%)
Basic evaluation	
Sagittal plane	
Localization of the GS	100
Presence of embryonic cardiac activity	100
Localization of the placenta in relation to the uterine scar	93
Presence of placenta previa	94
Placenta /trophoblast invasion into the myometrium (experts' advise: Color Doppler)	75
Niche presence	87
RMT or LUS thickness	93
AMT	100
Bulging of the gestational sac outside the level of the serosa towards bladder or bowels	87
Bulging of the vessels outside the level of the serosa towards bladder or bowels	73
The exact amount of protrusion of the GS beyond the UCL and SL	100
*Advanced evaluation / research setting**	
Sagittal plane	
Circular flow around the GS (Color Doppler)	100
Lining of the endometrium covering the niche may be relevant to detect an abnormal adherent placenta	81
Placenta / trophoblast location (Color Doppler)	88
Placental ingrowth and its relation to the myometrium/serosa/bladder (Color Doppler)	80
Distance of the vessels of the placenta and serosa (to give some indication concerning chance of presence of PAS)	75
Pulsed Doppler (research setting)	81
3-D ultrasound (research setting)	88
Transversal plane	
The distance between the GS and the uterine arteries (Color Doppler)	100
The level of protrusion in relation to the outer serosa contour	100

*Additional items besides those of basic evaluation. 3D, three-dimensional; AMT, adjacent myometrial thickness; GS, gestational sac; LUS, lower uterine segment; PAS, placenta accrete spectrum; RMT, residual myometrial thickness.

In cases of assisted reproductive techniques (ART), heterotopic pregnancies occur more frequently.[56] Therefore, it is advised that a CSP is excluded in all women with a previous CS and an apparent singleton pregnancy conceived following ART and in those with evidence of multiple ovulation on ultrasonography (94% agreement).

Referral to expert clinic

Expert clinics are considered to have extensive experience in CSP evaluation and management. In cases of CSP with the largest part of the GS located in the myometrium, whether or not it crosses the SL, it is recommended that the patient be referred to an expert clinic for ultrasound evaluation and further management (88% agreement). Doubt about the diagnosis and type of CSP and suspicion of an abnormally adherent placenta are also reasons to refer the patient to a specialized clinic (81% and 94% agreement, respectively). According to all the experts, a solitary finding of a thin residual myometrium in a patient with an intrauterine pregnancy, or a suspicion of placenta previa without abnormal invasion, is not necessarily an indication for referral. However, in cases in which the gynecologist/sonographer is not sure about the diagnosis or further management, referral is advised. Referral to an expert clinic is preferred over MRI in cases of a suspected CSP with the largest part of the GS located in the myometrium whether or not it crosses the SL (100% agreement) or in cases of diagnostic uncertainty. For a CSP with the largest part of the GS crossing the UCL, referral can also be considered in case of doubt about further management or lack of experience as to how to treat patients with PAS.

Advanced gestational age and follow-up

As pregnancy progresses, evaluation of a CSP becomes more difficult because the GS and placenta are growing and vascularization increases. Furthermore, in case of a CSP, there is a high risk of PAS due to extensive trophoblast invasion.[49,57] The type of CSP may also change with advancing gestation. For example, a CSP in which the largest part of the GS is located in the myometrium may progress into a CSP that crosses the imaginary SL but it can also progress into a CSP in which the largest part of the GS crosses the UCL or an intrauterine pregnancy with a placenta (partly) located in the niche or PAS (as illustrated in Figure S3).[57] Also, in cases of a low-implanted pregnancy, PAS may occur. The progress of a CSP or low-implanted pregnancy depends on the size of the niche (RMT), degree of trophoblast invasion and gestational age.

It is important to be aware of these changes with advancing gestational age, and the increased risk of PAS during follow-up of a CSP or low-implanted pregnancy. Furthermore, the importance of early detection of CSP was confirmed in a recent review in which CSP diagnosed at or before 9 weeks was associated with a significantly lower risk of composite adverse outcome (including massive hemorrhage and uterine rupture) than if diagnosed after 9 weeks (odds ratio, 0.14 (95% CI, 0.1–0.4); $p<0.001$; $I2 = 1.6\%$).[58]

DISCUSSION

Main findings

Our modified Delphi procedure resulted in consensus for all items concerning the ultrasound diagnosis, evaluation and reporting of CSP in early pregnancy (up to 12 weeks' gestation). Ultrasound evaluation of the CS scar/niche, to eliminate or confirm CSP, was recommended at 6–7 weeks using TVS in all women with a previous CS if an ultrasound scan is carried out because of symptoms or to assess viability. This is in line with previous literature.[59]

A CSP was defined as a pregnancy with implantation in, or in close contact with, the niche. The experts agreed that a CSP can occur only when a niche is present and not in relation to a healed CS scar. Relevant ultrasound features to record in cases of CSP included GS size, vascularity, location in relation to the uterine vessels, thickness of the residual myometrium and location of the pregnancy in relation to the uterine cavity and serosa. A CSP can be classified depending on the location of the largest part of the GS relative to the UCL, and on the existence of protrusion of the GS beyond the contour of the outer cervix/uterus. With advancing gestation, a CSP with the largest part of the GS in the myometrium and not crossing the SL may progress towards either of the other two CSP types or an intrauterine pregnancy (with or without PAS). In cases of a low-implanted pregnancy, detailed follow-up is required owing to the possibility of PAS. It should be stressed that identification of a CSP is not equivalent to an indication for treatment. CSP management depends on the gestational age at the time of the evaluation, the RMT, vascularity around the GS, the level of trophoblast invasion into the myometrium, location of the GS in relation to the UCL and SL, signs of PAS and upon the desire of the patient after evidence-based counseling. However, evidence-based counseling is possible only after the collection of evidence. Our reporting system for CSP should facilitate the collection of such information, but this should be confirmed by future studies.

Comparison with other studies

In the last decade, an increasing number of CSP cases and studies on CSP evaluation have been published. However, a standardized guideline on uterine-scar evaluation in (early) pregnancy, including CSP, was lacking and different definitions of CSP are in use. Du *et al.*[60] classified CSPs according to the size of the CS diverticula. Kaelin Agten *et al.*[6] classified a CSP as 'on the scar' (partially or fully on top of a well-healed scar) or 'in the niche' (within a deficient or dehiscent scar) depending on the level of invasion of the placenta into the CS scar. Others have proposed a more detailed classification system including different grades of CSP based on the level of protrusion into the uterine wall

towards the bladder, some including vascularity at the site of the CS scar.[11,12] However, some of these classifications may prove more difficult for clinicians who are not experts in early pregnancy ultrasound. Cali *et al*.[61] suggested a classification that is partly in line with our reporting system, including location of the GS with respect to the 'endometrial line', corresponding to our UCL. However, this classification is less detailed and the GS crossing the SL was not part of it. Balci and Ercan[38] described Type 1 and Type 2 CSPs as a GS that implants on the CS scar with progression in the cervico-isthmus and uterine cavity (Type 1) or with progression towards the myometrium (Type 2), without defining the depth. The experts in our study elected to use the latter proposal as a base and approved the use of some additional items from other classification systems to refine the type and reporting of CSPs. To improve the reproducibility of the reporting system, the experts defined a CSP based on the location of the GS in relation to its protrusion into the cervix or uterine cavity and the extent of myometrial involvement. It should be stated that the classification of a CSP is not fixed and that it may change with advancing gestation. Interpretation of the type of CSP becomes very difficult with advancing gestational age, which may have different consequences for treatment.

The ESHRE Working Group categorized CSPs as 'partial CSP', which corresponds to our suggested classification of CSP with the largest part of the GS crossing the UCL, and 'complete CSP', which corresponds to our classification of a CSP in which the largest part of the GS is located in the myometrium (crossing or not crossing the SL).[18] We present a more detailed definition and description of CSP and provide an item list for reporting a CSP.

Strengths and limitations

A strength of our study lies in the use of a modified Delphi method, in which the participants' anonymity was ensured during the questionnaire rounds, preventing domination by any individual, and allowing participants to revise their opinion during successive rounds. Furthermore, all relevant literature available at that time was put at their disposal, by including it in the background information and questionnaires. Another strength is that we did not aim to provide a complete overview of CSP therapies. A third strength is the high response rate during all the rounds, emphasizing the agreement of the experts with the study content.

A limitation of the study is that not all the experts (10/16) participated in the face-to-face round. Therefore, we added two more questionnaires after which consensus was achieved for all items. Although we invited a number of international experts with extensive experience in the sonographic evaluation of the uterine CS scar in early pregnancy, we recognize that not all experts in the field were included in this study.

Furthermore, our recommendations focus on early pregnancy, so the reporting system may be less suitable at advanced gestation. Validity of the construction and accuracy of the item list of sonographic CS scar features in pregnancy and the value of its use when developing treatment policies should be determined in future studies.

Future perspectives

These recommendations on the evaluation and reporting of a CSP are intended to guide gynecologists and ultrasound examiners when performing ultrasonography in early pregnancy, and provide a framework for experts to use during advanced evaluation. Several cases have been described in which a CSP was misdiagnosed as a cervical ectopic pregnancy, a miscarriage in progress or even as a malignant tumor, resulting in massive blood loss and/or emergency hysterectomy.[62–64] On the other hand, it is critical that we prevent the termination of potentially viable pregnancies that appear to be CSPs but that may progress towards intracavitary pregnancies with low-located placentae; this is expected to occur in 75% of CSPs in which the largest part of the GS crosses the UCL (also called Type 1 in the literature).[49] We hope that our recommendations will increase awareness and recognition of CSPs, and we aim to develop a free e-learning program to ease implementation.

Although evaluation of CSP is advised at 6–7weeks' gestation, our recommendations can be used during the whole first trimester (until 12 weeks). After 12 weeks, it becomes more difficult to evaluate the level of protrusion. In the case of a CSP that protrudes toward the uterine cavity in the late first trimester or early second trimester, the most relevant items to evaluate are its vascularity and its relation with the myometrial/uterine vascular architecture and bladder. These items determine future treatment policy.

The relevance of the different CSP types described in this paper needs to be evaluated in future research. This will be achievable only if future studies record the same features and use the same terminology as those recommended in this paper. In addition to the terminology, it is important to record the precise extent of protrusion beyond the UCL and SL to allow future (meta-)analyses. To further research in this important area, we propose that all expert clinics submit their cases to the international Cesarean Scar Pregnancy registry, which can be found online (www.csp-registry.com).

Surgical and medical management of CSPs and niche measurement (during pregnancy) of intracavitary pregnancies were beyond the scope of this Delphi study. International use of this reporting system should enable consistent data collection regarding treatment outcomes of CSP, allowing the development of evidence-based guidelines in the future.

Conclusions

We have described recommendations for the evaluation and reporting of a CSP in early gestation that can be used by all sonographers in order to facilitate future studies and the development of guidelines. Consensus was achieved for all 58 items concerning the sonographic evaluation of CSP, using a modified Delphi procedure among experts in advanced ultrasound evaluation of CS scars or CSP. Treatment of different CSP types and cut-off values of niche measurements in pregnancy have yet to be determined.

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APPENDICES

Appendix S1. Search strategy

Search strategy for Pubmed (January 15th, 2018)

Search	Query	Items found
#6	#4 AND #5	711
#5	"Ultrasonography"[Mesh] OR ultraso* [tiab] OR sonohysterograph*[tiab] OR sonograph*[tiab] OR hysterosonograph*[tiab] OR hysteroscop*[tiab] OR echograph*[tiab]	564,814
#4	#1 AND #2 AND #3	2,051
#3	"Cesarean Section"[Mesh] OR cesarea*[tiab] OR caesarea*[tiab] OR "c section"[tiab] OR "c sections"[tiab] OR (abdominal[tiab] AND deliver*[tiab]) OR postcesarea*[tiab] OR postcaesaria*[tiab]	564,814
#2	"Uterus"[Mesh] OR "Uterine Diseases"[Mesh] OR uterus[tiab] OR uterine[tiab] OR myometri*[tiab] OR endometri*[tiab] OR endomyometri*[tiab] OR myoendometri*[tiab]	322,249
#1	"Cicatrix"[Mesh] OR cicatr*[tiab] OR scar[tiab] OR scars[tiab] OR scarring[tiab] OR isthmocele*[tiab] OR niche[tiab] OR niches[tiab] OR anechoic[tiab] OR pouch*[tiab] OR diverticul*[tiab]	163,376

[Mesh], Medical subject headings (MeSH); [Mesh:NoExp], Medical subject headings (MeSH) without explosion; [tiab], words in title or abstract

Search strategy for Embase.com (January 15th, 2018)

Search	Query	Items found
#6	#4 AND #5	1,315
#5	'echography'/exp OR 'color ultrasound flowmetry'/exp OR ultraso*:ab,ti OR sonograph*:ab,ti OR echograph*:ab,ti OR echotomograph*:ab,ti OR sonohysterograph*:ab,ti OR hysterosonograph*:ab,ti OR hysteroscop*:ab,ti	931,665
#4	#1 AND #2 AND #3	3,124
#3	'cesarean section'/exp OR cesarea*:ab,ti OR caesarea*:ab,ti OR 'c section':ab,ti OR 'c sections':ab,ti OR (abdominal:ab,ti AND deliver*:ab,ti) OR postcesarea*:ab,ti OR postcaesarea*:ab,ti	109,164
#2	'uterus'/exp OR 'uterus disease'/exp OR uterus:ab,ti OR uterine:ab,ti OR myometri*:ab,ti OR endometri*:ab,ti OR endomyometri*:ab,ti OR myoendometri*:ab,ti	426,708
#1	'wound dehiscence'/exp OR 'scar formation'/exp OR 'scar'/exp OR cicatr*:ab,ti OR scar:ab,ti OR scars:ab,ti OR scarring:ab,ti OR isthmocele*:ab,ti OR niche:ab,ti OR niches:ab,ti OR anechoic:ab,ti OR pouch*:ab,ti OR diverticul*:ab,ti	221,342

:ab,ti, words in title or abstract; /exp, EMtree keyword with explosion

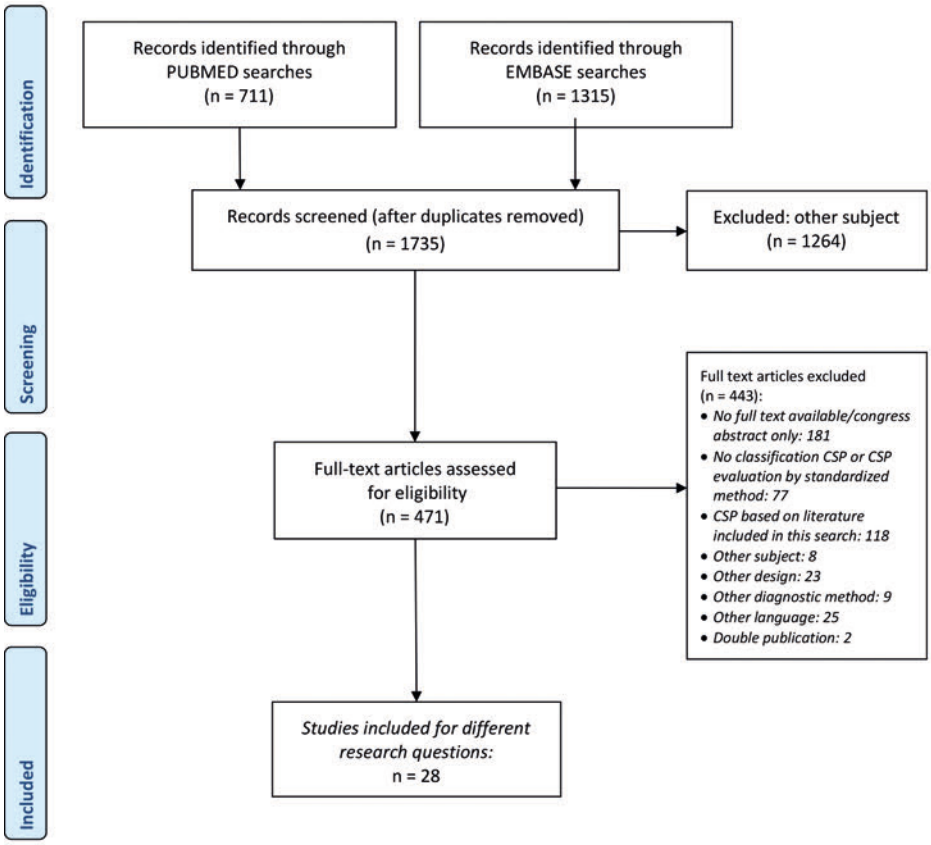

Figure S1. Flowchart showing studies identified through literature search.

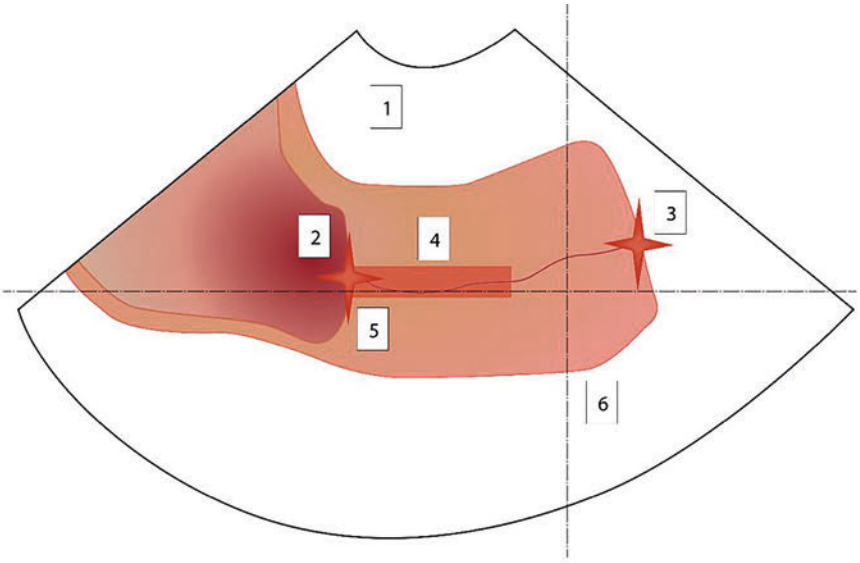

Figure S2. Principal setting of transvaginal ultrasound during evaluation of uterine scar in first trimester of pregnancy. Modified from Kuleva et al.[48]

1. The bladder is not visible (empty)
2. The internal os is clearly visible
3. The external os is visible
4. The cervico-isthmic canal is visible
5. The internal os is situated in the median third of the image
6. The posterior aspect of the posterior labia of the cervix is in the deepest half of the image

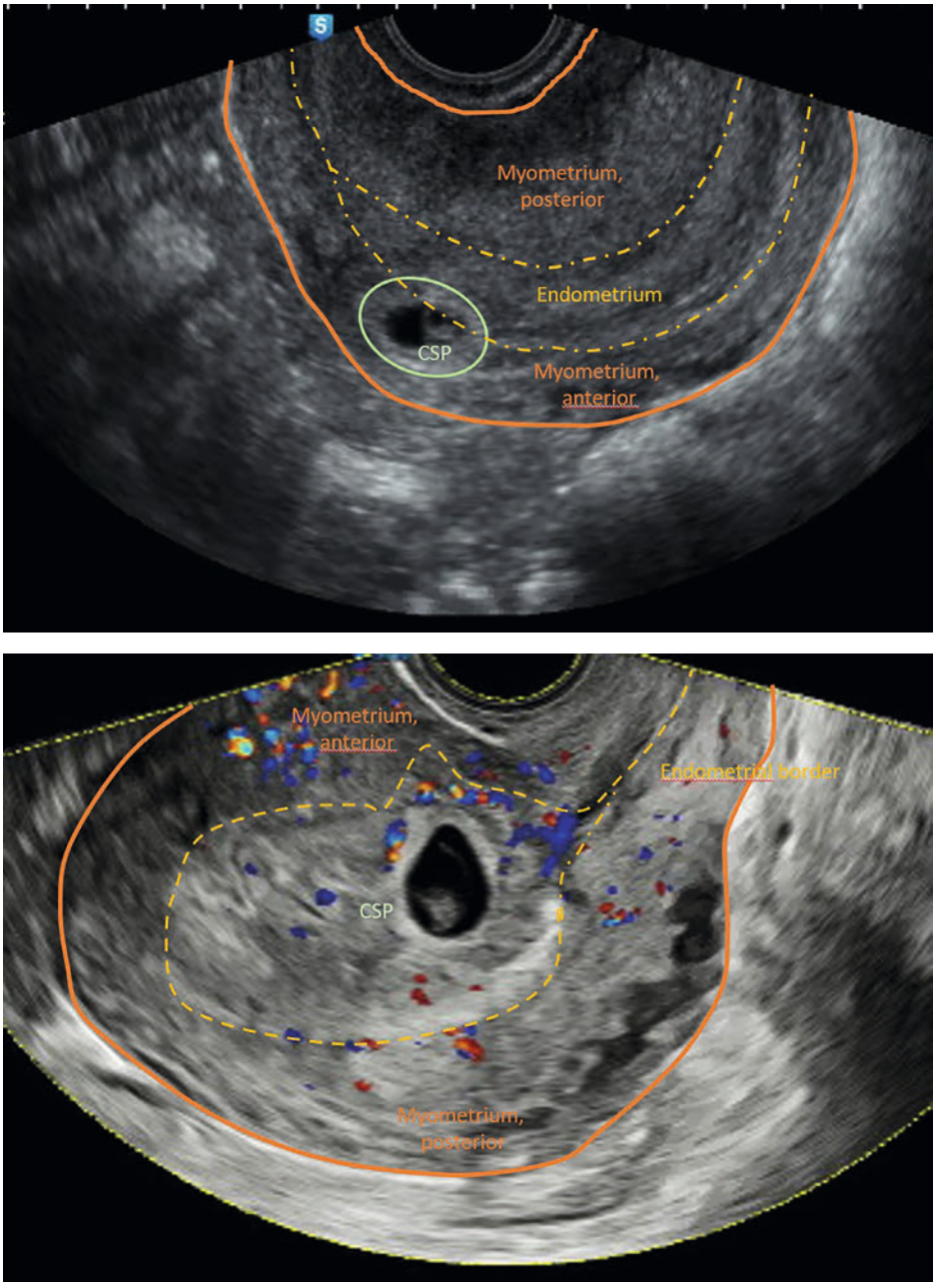

Figure S3. Example of a Cesarean scar pregnancy with the largest part of the gestational sac located in the myometrium, which progressed to intrauterine pregnancy with advancing gestation (1 week difference between ultrasound images).

Table S1. Results of literature search that identified 28 papers reporting on predefined items regarding Cesarean scar pregnancy definition, diagnosis and evaluation

Subject	Publication	Study type	Results
Sonographic criteria to define CSP	Ash (2007)[14]	Overview of literature	1) An empty uterine cavity, without contact with the GS; 2) A clearly visible empty cervical canal, without contact with the GS; 3) Presence of the GS with or without a fetal pole with or without fetal cardiac activity (depending on the gestation age) in the anterior part of the uterine isthmus; 4) Absence of or a defect in the myometrial tissue between the bladder and the sac.
	Cheng (2014)[29]	Retrospective cohort study	1) An empty uterine cavity; 2) A GS located anteriorly at the level of the internal os, equivalent to the prior LUS of the CS scar; 3) Evidence of functional trophoblastic/placental circulation on Doppler scans.
	Godin (1997)[30]	Case report	1) Empty uterus; 2) Empty cervical canal; 3) Development of the sac in the anterior part of the isthmic portion; 4) Absence of healthy myometrium between the bladder and the sac.
	Jungkman (2015)[31]	Case reports	1) An empty uterine cavity and an empty cervical canal with the GS or hypoechoic mass located in the anterior wall of the uterus at the area of cesarean scar from the previous delivery; 2) Visualization of a very thin (less than 5 mm) or nonexistent layer of overlying myometrium anterior to the GS; 3) Discontinuity of the anterior uterine wall in the sagittal plane with a bulging GS; 4) Color and/or spectral Doppler evidence of perfusion around the GS/mass.
	Jurkovic (2003)[32]	Case series	1) Empty uterine cavity; 2) GS located anteriorly at the level of the internal os covering the visible or presumed site of the previous LUS Cesarean section scar; 3) Evidence of functional trophoblastic/placental circulation on Doppler examination, which was defined by the presence of an area of increased peritrophoblastic or periplacental vascularity on color Doppler examination, and high-velocity (peak velocity > 20 cm/s), low-impedance (pulsatility index < 1) flow velocity waveforms on pulsed Doppler examination; 4) Negative 'sliding organs sign', which was defined as the inability to displace the GS from its position at the level of the internal os using gentle pressure applied by the transvaginal probe.
	Kaelin Agten (2017)[6]	Retrospective study	1) A GS embedded eccentrically (in relation to the uterine cavity) in the LUS; 2) The GS is implanted in the location of the previous uterine cesarean scar; 3) An empty uterine cavity and cervical canal; 4) A thin or absent myometrial layer between GS and the bladder; 5) The presence of a rich vascular pattern in the area of the uterine cesarean scar and the placenta on Doppler ultrasound evaluation.

Table S1. (Continued)

Subject	Publication	Study type	Results
	Li (2016)[27]	Retrospective study	1) Empty uterus and cervical canal; 2) Development of the GS or identification of a mixed-echo mass in the anterior part of the cesarean scar; 3) Very thin myometrium or an absence of healthy myometrium between the bladder wall and the sac/mass or when running through the amniotic sac; 4) The GS or mixed-echo mass being located toward either the cervical isthmic space or the uterine cavity in CSP-I†, or the infiltration of the GS or mixed-echo mass into the myometrium and/or forming a bulge from the uterine serosal layer in CSP-II†.
	Seow (2001)[34]	Case report	1) An empty uterus; 2) An empty cervical canal; 3) The GS being in the anterior part of the isthmic portion of the uterus; 4) Prominent peritrophoblastic flow.
	Seow (2004)[33]	Case series	1) The uterus was empty, with clearly demonstrated endometrium; 2) The cervical canal was empty, without a gestational sac or ballooning at the early diagnosis; 3) The GS showed the 'double ring' sign in the anterior part of the isthmic portion of the uterus; 4) The GS, with or without cardiac activity, was embedded and surrounded by the myometrium, the fibrous tissue of the scar, and it was separated from the endometrial cavity or Fallopian tube.
	Takahashi (2015)[35]	Letter to editor	Presence of an intrauterine hypoechoic mass suggestive of hematoma cephalad to the CSP site.
	Timor-Tritsch (2012)[16]	Retrospective case series	1) Visualization of an empty uterine cavity as well as an empty endocervical canal; 2) Detection of the placenta and/or a GS embedded in the hysterotomy scar; 3) In early gestations (<8 weeks), a triangular GS that fills the niche of the scar; at >8 postmenstrual weeks this shape may become rounded or even oval; 4) A thin (1-3 mm) or absent myometrial layer between the GS and the bladder; 5) A closed and empty cervical canal; 6) The presence of embryonic/fetal pole and/or yolk sac with or without heart activity; 7) The presence of a prominent and at times rich vascular pattern at or in the area of a cesarean scar in the presence of a positive pregnancy test.
	Timor-Tritsch (2016)[23]	Retrospective study	1) A positive pregnancy test in a patient with a history of cesarean delivery; 2) Several sonographic characteristics such as a low anterior uterine implantation of a GS with very thin or no recognizable myometrial tissue between the chorionic sac and the bladder or the anterior surface of the uterus; 3) The presence of an intensive and an obviously rich blood vessel pattern at the insertion of the tiny placenta into or onto the scar of the previous surgical site.
	Vial (2000)[28]	Case report	1) The trophoblast must be mainly located between the bladder and the anterior uterine wall; 2) No fetal parts must be visible in the uterine cavity; 3) On a sagittal view of the uterus running through the amniotic sac, a discontinuity in the anterior wall of the uterus should be demonstrated.

Table S1. (Continued)

Subject	Publication	Study type	Results
	Weilin (2014)[36]	Case series	1) An empty uterine cavity and cervical canal; 2) A gestational sac located at the anterior wall of the isthmic portion, separate from the endometrial cavity or fallopian tubes; 3) A GS embedded within the myometrium and the fibrous tissue of the CS scar at the LUS, with an absence of the defect in the myometrium between the bladder and the sac.
	Yin (2014)[37]	Retrospective study	1) The empty uterine cavity without contacting with GS; 2) The cervical canal was empty; 3) The GS was located at the anterior wall of the uterine isthmus with or without cardiac activity; 4) The fluff implantation site myometrial blood stream are rich, presenting a low-speed low resistance flow rate curve; 5) Absence of or a defect in the myometrial layer between the bladder and the sac.
CSP classification based on type	Balci (2017)[38]	Retrospective study	* CSP I refers to the implantation of the gestational sac on a previous cesarean scar with progression in the cervico-isthmus and the uterine cavity. * CSP II refers to a deep implantation of the amniotic sac in a cesarean scar defect with progression towards the myometrium and the uterine serosal layer. In CSP II cases, the thickness of the uterine myometrium between the gestational sac and the bladder wall is usually less than 4 mm.
	Kaelin Agten (2017)[6]	Retrospective study	* CSP on the scar: the placenta implanted partially or fully on top of a well-healed scar. * CSP in the niche: the placenta implanted into a deficient or dehiscent scar.
	Li (2016)[27]	Retrospective study	* CSP type I was defined as endogenous, caused by the implantation of the amniotic sac at the cesarean-scar site followed by progression towards either the cervical isthmic space or the uterine cavity. * CSP type II was defined as exogenous, resulted from the deep implantation of the amniotic sac into a previous cesarean scar defect with growth that infiltrates the uterine myometrium, creating a bulge from the uterine serosal layer.
	Lin (2018)[11]	Retrospective study	* Grade I CSP represented the depth of CSP embedded in less than one-half thickness of the lower anterior corpus. * Grade II CSP implied CSP occupied more than one-half thickness of the lower anterior corpus. * In grade III CSP, the GS bulged out the overlying myometrium and uterine serosa. * In grade IV CSP, the GS became an amorphous tumor with rich vascularity at the cesarean scar.
	Vial (2000)[28]	Case report	* CSP type 1 is due to the implantation of the amniotic sac on a scar with progression of the pregnancy in the cervico-isthmic space and in the uterine cavity. Such a situation may allow a viable birth but at an increased risk of massive bleeding from the site of implantation. * CSP type 2 is a deep implantation in a Cesarean scar defect with progression towards rupture and bleeding during the first trimester of pregnancy.

Table S1. (Continued)

Subject	Publication	Study type	Results
	Zhang (2017)[12]	Prospective study	* Stable CSP: CSP patients without obvious vaginal bleeding or significantly elevated serum β-hCG at admission can be treated with selective operation. * Risky CSP: CSP has a high risk of severe hemorrhage and should be treated immediately. Three subtypes: * Risky CSP type I is defined as cases in which the thickness of the myometrial wall between the sac and the bladder is <3 mm. Type Ia refers to those with lower cesarean scars. Type Ib refers to those with a cesarean scar on the higher uterine segment. Type Ic refers to those with a giant protruding mass either on the lower or higher uterine segment. * Risky CSP type II is a thick-walled type, in which the thickness of the myometrial wall between the sac and the bladder is ≥3 mm. * Risky CSP type III refers to the situation when the gestational sac is located partly on the cesarean scar, which has a risk of severe bleeding or the tendency of dangerous placenta previa.
CSP location and measurement	Timor-Tritsch (2016)[23]	Retrospective study	CSP location based on marking the midpoint section of the uterus and determination of the GS between midpoint and uterine fundus or between midpoint and cervix.
Best moment for CSP evaluation			None.
Doppler US and CSP diagnosis	Ash (2007)[14]	Overview of literature	Color flow Doppler distincts circular peritrophoblastic perfusion surrounding the GS that can help delineate the CSP sac with location of the placenta in relation to the scar and proximity to the bladder.
	Gonzalez (2017)[24]	Systematic review	On Doppler imaging, the GS embedded in a scar defect is surrounded by vascular flows characterized by high velocity and low impedance blood flow. On the other hand, an aborted intrauterine pregnancy has no vascular flow bordering.
	Honemeyer (2013)[25]	Overview of literature	The sensitivity of transvaginal color/power and pulsed Doppler in diagnosis of ectopic pregnancy has been analyzed in several studies, and ranges from 73 to 96%, with a specificity of 87 to 100%.
Pulsed Doppler and CSP diagnosis	Ash (2007)[14]	Overview of literature	With pulsed Doppler functions, more information on the flow pattern of the peritrophoblastic vasculature can be obtained. Typically, a prominent high-velocity (peak velocity > 20 cm/second), low impedance (pulsatility index < 1) flow velocity waveforms can be demonstrated, consistent with normal early pregnancy.
	Honemeyer (2013)[25]	Overview of literature	The sensitivity of transvaginal color/power and pulsed Doppler in diagnosis of ectopic pregnancy has been analyzed in several studies, and ranges from 73 to 96%, with a specificity of 87 to 100%.

Table S1. (Continued)

Subject	Publication	Study type	Results
3-D (power) Doppler and CSP diagnosis	Ash (2007)[14]	Overview of literature	Combination of the multiplanar views and surface-rendered images helps identify subtle anatomical details of a well-developed trophoblastic shell around the GS. The thin myometrium between the GS and the bladder wall can be recognized with confidence. Furthermore, peritrophoblastic flow surrounding the CSP may be illustrated by 3-D power Doppler.
	Köroğlu (2013)[26]	Overview of literature	3-D ultrasound may aid in the diagnosis of CSP, confirming the location of the sac.
	Pascual (2007)[39]	Case report	3-D ultrasonography and its applications such as multiplanar views or 3-D–rendered images allow obtaining better images, improving the ability to identify anatomic details that permit a more accurate diagnosis.
	Wang (2004)[40]	Case report	The combination of 3-D and power Doppler sonography allows physicians to study the total blood flow in a confined area in more detail.
MRI and CSP diagnosis	Ash (2007)[14]	Overview of literature	MRI may be reserved for cases where TVS and color flow Doppler are inconclusive.
	Dibble (2016)[41]	Overview of literature	MRI may be useful for problem solving when ultrasound is inconclusive in determining pregnancy location. MRI can show thinning of myometrium between the GS and the bladder.
	Gonzalez (2017)[24]	Systematic review	MRI could be helpful when TVS combined with power Doppler sonography is inconclusive. Yet, MRI was found to be equally accurate in the diagnosis of CSP compared with TVS but better for the evaluation of scar implantation.
	Huang (2014)[42]	Prospective cohort study	The specificity of MRI in diagnosing CSP was 97.6% (41/42) versus 81% (34/42) of the initial ultrasound ($P < 0.05$). However, the specificity of repeated ultrasound was improved significantly with 96.6% (28/29), comparable to that of MRI ($P > 0.05$).
	Kao (2012)[43]	Overview of literature	A very thin layer of myometrium should be seen separating the maternal urinary bladder wall and the GS. This latter finding may be best appreciated using MRI.
	Köroğlu (2013)[26]	Overview of literature	MRI may aid in the diagnosis of CSP, confirming the location of the sac.
	Peng (2014)[44]	Retrospective study	MRI findings: Type I CSP: A thin-walled diverticulum is visible at the CSS defect. The GS is fully or mostly embedded in the diverticulum; type II CSP: A thin-walled diverticulum is visible at the CS scar defect. The GS is partially embedded in the diverticulum and partially growing into the uterine cavity; type III CSP: A niche is visible in the CS scar defect. The GS is mainly embedded in the isthmus.
	Rosen (2008)[45]	Overview of literature	MRI has been proposed as adjuncts to ultrasound, but at least in early pregnancy, TVS is an accurate diagnostic tool, and additional modalities are rarely necessary.

† Definition of CSP type I and II of Lin *et al.* can be found in the Table under subject "CSP types". 3-D, three-dimensional; CSP, cesarean scar pregnancy; GS, gestational sac; LUS, lower uterine segment; MRI, magnetic resonance imaging; TVS, transvaginal sonography; US, ultrasound

Table S2. Overview of questions of all Delphi rounds, including answers and consensus rate

Round 1

Category	Question	Answer	C (%)
CSP definition and location	*Do you consider the following items relevant for the definition of a niche pregnancy? (question 1a-1h)*		
	A gestational sac embedded eccentrically (in relation to the uterine cavity) in the lower uterine segment.	relevant	67
	The gestational sac is implanted at the site of the previous uterine cesarean scar	relevant	87
	Thin or absent myometrial layer between gestational sac and the bladder	relevant	80
	Is the residual myometrium thickness (RMT) of importance for definition CSP?	yes	53
	How should "thin" be defined in the criterion 1c?	Residual myometrium is <3 mm	50
	Could you live with the definition of "thin" RM being <3mm?	yes	80
	Bulging of gestational sac towards bladder	relevant	80
	An empty uterine cavity	relevant	73
	Presence of embryonic/fetal pole and/or yolk sac with or without heart activity	relevant	67
	The presence of a rich vascular pattern in the area of the uterine cesarean scar and the placenta on Doppler ultrasound evaluation to differentiate from an (ongoing) miscarriage	relevant	87
	Negative 'sliding organs sign', which was defined as the inability to displace the gestational sac from its position at the level of the internal os using gentle pressure applied by the transvaginal probe to differentiate from an (ongoing) miscarriage.	relevant	60
	In your opinion, what is the usefulness of the "subjective-simple" measurement method?	useful	93
	In your opinion, what is the usefulness of the "relative" measurement method?	useful	67
	In your opinion, what is the usefulness of the "absolute quantitative" method?	useful	53
	Which of these methods has your preference if you are allowed to choose only one?	subjective-simple method	60
	Which of these methods has your preference if you are allowed to choose two?	subjective-simple method and relative method	53
	In general do you think that such a classification could be helpful?	yes	93
	Do you have any adjustments for the individual items in this table? (question 7a-7f)		

Round 1 (Continued)

Category	Question	Answer	C (%)
	Adjustment for "Scar visible but no niche (no indentation in the myometrium)"	no	87
	Adjustment for "Niche and location pregnancy and placenta"	yes	40
	Adjustment for "Niche and thin RM"	yes	40
	Adjustment for "Placenta praevia"	yes	40
	Adjustment for "Abnormal placenta location (placenta accrete/increta)"	yes	47
	Adjustment for "Placenta percreta"	yes	33
	Do you have any other adjustments?	no	87
	Which ultrasonography features allow differentiation between a cervical pregnancy that is not located in the niche (figure 1c), and a CSP (figure 2c)? (question 8a, 8b, 8h)		
	RM thickness	yes	47
	AMT/RMT ratio	no	67
	Excentric location of the gestational sac	yes	67
	Do you call the situations in the following situations a niche pregnancy? (question 9a-9b)		
	Pregnancy low in uterine cavity, but not in niche, placenta reaches niche, thick RM (≥3mm)	no niche pregnancy	93
	Intra uterine located gestational sac, placenta increta/percreta towards niche, infiltration placenta in RM	niche pregnancy	60
	Do you agree that a placenta located in the niche is not enough to define it as a niche pregnancy, but that also the gestational sac needs to be located in the niche?	yes	53
	In your opinion what term should be used for a pregnancy that is (partly) located in the niche?	niche pregnancy (7/15); cesarean scar pregnancy (7/15)	47
	If your preference is otherwise, can you live with the term niche pregnancy?	yes	63 (5/8)
	Do you agree that it is more important to use RMT and placenta ingrowth to classify a niche pregnancy as addressed before instead of using the term "well healed scar"?	yes	73
	Do you think we could or should add this "well healed scar" item to the classification? If yes please motivate how.	no	73
	Is there a minimal distance of the gestational sac to the niche to call it a CSP?	yes	87
	Do you call the situations in the following situations a niche pregnancy? (question 9c-9d)		
	Intra uterine located gestational sac, placenta increta/percreta towards niche, infiltration placenta in RM	niche pregnancy	47
	Pregnancy low in uterine cavity, placenta increta/percreta	niche pregnancy	67
	Do you agree that 5a, b and c are three different entities?	yes	53

Round 1 (Continued)

Category	Question	Answer	C (%)
Measurements in 1st trimester	*Which items should in your opinion routinely be included during the first trimester ultrasound (besides fetal heartbeat and CRL (crown rump length) or mean gestational sac diameter) in women with a previous CS? (question 2a-2j)*		
	Localisation of the gestational sac	relevant	100
	Localisation of the placenta in relation to the uterine scar	relevant	93
	Presence of placenta praevia	relevant	67
	Invasion of the placenta into the myometrium	relevant	73
	Niche presence	relevant	87
	Thickness of the residual myometrium/thickness lower uterine segment	relevant	93
	Bulging of the gestational sac outside the level of the serosa towards bladder or bowels	relevant	87
	Distance between the pregnancy and serosa	relevant	60
	Distance vessels of the placenta and serosa	not relevant	53
	Bulging of the vessels outside the level of the serosa towards bladder or bowels	relevant	73
Differentiation between CSP and cervical pregnancy/ miscarriage	*Which ultrasonography features allow differentiation between a cervical pregnancy that is not located in the niche (figure 1c), and a CSP (figure 2c)? (question 8c, 8d, 8f-h)*		
	Bulging of gestational sac towards bladder	yes	87
	Shape of the gestational sac	no	73
	Lining of the endometrium covering the niche	no	67
	The sliding product	no	60
	Vascularisation? For example: absent in case of a cervical pregnancy, and circulated local in the niche in case of CSP?	yes	73
	In conclusion, do you think it is possible to differentiate between those 2 situations?	yes	93
Transversal plane	We consider it relevant to use color Doppler in this transversal plane, to assess the relation of the pregnancy with the uterine arteries (and illustrated some examples below). Do you agree?	yes	93
	Do you agree that the level of protrusion in relation to the outer serosa contour could be useful if a therapy concerning the CSP is considered (and therefore should be assessed)?	yes	100
	Do you agree that the distance between gestational sac and the uterine arteries could be of additional value?	yes	73
	Do you agree that the location influences the decision for treatment of niche pregnancy: whether or not to perform for example a curettage (in addition to the thickness of the RM in the sagittal plane)?	yes	73
	Do you agree to add the transversal pictures and its relation to the uterine arteries into the proposed classification?	yes	80
	Can you rate the relevance of this item (transversal imaging to evaluate of the location of a pregnancy):	relevant	53
	Can you live with it if we add this point to the classification?	yes	93

Round 1 (Continued)

Category	Question	Answer	C (%)
Gestational age and CSP	Assuming that the gestational age influences the niche appearance, should (items that determine) the gestational age be added to the scar pregnancy classification?	yes	80
	What is in your opinion the preferred timeframe to evaluate the presence of a niche pregnancy and to discriminate from IUG?	6-7 weeks	73
	What is in your opinion the best timeframe to assess a niche pregnancy in terms of optimal therapeutic options?	6-7 weeks	53
	What is in your opinion the best timeframe to differentiate between niche pregnancy and IU pregnancy with placentation close to the niche or CS scar? (In terms of optimal discriminating features)	6-7 weeks (5/15); 8-9 weeks (5/15)	30
	What time frame is in your opinion the most optimal moment in early pregnancy to evaluate the presence of a niche or a niche pregnancy?	6-7 weeks	60
	Is there a minimal gestational age to evaluate the location of the placenta with respect to the niche?	yes	93
	If yes, a gestational age based on …	LMP or day of conception	50 (7/14)
	Do you think that it could be of additional value to assess the placenta localization and the presence of a niche and niche pregnancy in early pregnancy in all women with a previous CS?	yes	73
Doppler US and CSP	Do you agree that color flow Doppler should be mandatory in uterine scar evaluation?	yes, definitely	80
	*What features should be at least be evaluated with color Doppler in **basic evaluation**? (question 19a-19d)*		
	Evaluation of circular flow around the gestational sac	yes	100
	Evaluation of the placenta location	yes	87
	Evaluation of the placental ingrowth and its relation to the myometrium/serosa/bladder	yes	80
	Evaluation of relation between gestational sac and uterine arteries	yes	53
	Are there any other items that should be evaluated with color flow Doppler?	no	87
Pulsed Doppler and CSP	Do you agree to perform pulsed Doppler in research setting only?	agreement	67
3D ultrasound and CSP	Is in your opinion the use of 3-D ultrasound of additional value in the evaluation of possible CSP?	yes	60
	Should in your opinion 3-D evaluation be advised to use in patients in which a CSP is suspected?	yes	47
	Should in your opinion the 3-D power Doppler evaluation be advised to use in patients in which a CSP is suspected?	yes	47
MRI and CSP	Do you think an MRI is of additional value to differentiate in the diagnosis of niche pregnancy and in which situations do you think this is of additional value?	no	73

Round 1 (Continued)

Category	Question	Answer	C (%)
	Do you think an MRI is of additional value to experts who are used to evaluate CSP with ultrasound including the use of color doppler?	no	87
	Do you think an MRI is of additional value to experts able to make 3-D ultrasound?	no	87
	Do you think an MRI should be advised to less experienced sonographers in case of a suspected CSP?	no	67
	If "not sure", "no, probably not" or "no, definitely not": Should we advise a referral to an expert center in this case?	yes	100 (14/14)
Niche measurement in case of CSP	Do you agree on this proposal as being the most optimal setting to evaluate the CS scar in the first trimester?	yes	80
	Do you agree that we can use the same method for measuring the niche as was consented for non-pregnant patients in the first Delphi procedure, in case of a niche pregnancy?	yes	93
	In non-pregnant women with a niche the transversal plane is only used for the third dimension of the niche (width), not for depth and RMT. Do you agree to use this plane for width only in niche pregnancy as well?	yes	87
Setting of specific niche measurements	Do you think measurement of the distance between niche and the VV fold is relevant in case of a niche pregnancy?	yes	47
	Do you think measurement of the distance between niche and the VV fold is relevant in BASIC niche evaluation in the 1st trimester in case of INTRA UTERINE PREGNANCY?	only during advanced evaluation or in research	67
	Do you think measurement of the distance between niche and the VV fold is relevant in case of NICHE PREGNANCY?	only during advanced evaluation or in research	60
	Do you think measurement of the distance between niche and the external os is relevant in case of a niche pregnancy?	yes	87
	Do you think that the distance between niche and the external os is relevant in BASIC niche evaluation in the 1st trimester in case of intra uterine pregnancy?	only during advanced evaluation or in research	73
	Do you think that the distance between niche and the external os is relevant in BASIC niche evaluation in the 1st trimester in case of NICHE PREGNANCY?	only during advanced evaluation or in research	47
	Do you think there are additional measurements needed unique to the 1ste trimester, that were not needed in the non-pregnant uterus?	no	87

Round 2

Category	Question	Answer	C (%)
CSP definition and location	Do you agree with the flow chart above including the definitions of CSP type 1 and CSP type 2 (niche pregnancy)?	yes	94
	Can you agree with the term CSP (including both type 1 AND 2) to be used for all pregnancies that are located near/on/in the cesarean scar?	no	(1/1)*
	Can you agree with the subclassification type 1 CSP; defined as a gestational sac that is located for >50% outside the level of the myometrium/niche, thus >50% of the sac is located in the cervical channel/uterine cavity?	no	(1/1)*
	Can you agree with the subclassification type 2 CSP; defined as a gestational sac that is located for ≤50% outside the level of the myometrium/niche, thus ≤ 50% of the sac is located in the cervical channel/uterine?	no	(1/1)*
	Can you agree that a type 2 CSP can also be called a niche pregnancy?	no	(1/1)*
	Do you agree with the flow chart as presented above?	no	(1/1)*
	Can you agree with the 50% cut-off to classify a type 1 and type 2 CSP (in line with the differentiation between a type 1 or type 2 submucous fibroid)?	yes	94
	We propose the following subclassification: TYPE 2A: the pregnancy/gestational sac is entirely located within the outer contour (blue line) of the cervix/uterus. TYPE 2B: the pregnancy/ gestational sac is partly located outside the outer contour (blue line) of the cervix/uterus		
	Do you agree with this subclassification?	yes	94
	In case of a pregnancy NEAR the CS; do you agree that distance A (see figure 1) should be 0 mm to call the pregnancy CSP? (Distance A = distance between the proximal border of the niche and the most distal border of the GS)	yes	100
	Do you agree that situation 1 (figure 2 & 3) is a type 1 CSP with malplacentation problems?	yes	94
	Do you agree that situation 2 (figure 4 & 5) is not CSP but should be registered as an intra-uterine pregnancy with abnormal adherent placenta (increta or percreta at the side of the niche)?	yes	75
Measurements in 1st trimester	Do you agree that it is more important to evaluate the relation of the pregnancy/placenta with a previous CS scar than the precise location of the pregnancy in case of a low lying pregnancy?	yes	88
	Do you agree to add the item "Presence of placenta praevia" to the items evaluated in the first trimester, mentioning that it may change over time?	yes	69
	In case of an intra-uterine pregnancy with a visible niche, do you agree that evaluation of the placentation is required? (for possible follow-up)	yes	75

Round 2 (Continued)

Category	Question	Answer	C (%)
	Do you agree to add the item "Distance vessels of the placenta and serosa" to the items evaluated in the first trimester to give some indications concerning a chance of the presence of malplacentation?	only during advanced evaluation or in research	75
Differentiation between CSP and cervical pregnancy/ miscarriage	Do you agree that the item "lining of the endometrium covering the niche" may be relevant to detect an abnormal adherent placenta?	only during advanced evaluation or in research	81
	Do you agree that, when a sliding product is visible, it is more likely that it is an ongoing/incomplete miscarriage?	yes	100
	Do you agree that the implantation location and vascularisation are very useful items to differentiate between a CSP and a miscarriage?	yes	88
	Do you agree that "the trophoblast localisation" is relevant to differentiate between a CSP and miscarriage?	yes	63
	Can you agree with it if the item "Presence of gestational sac, fetal pole or yolk sac with or without heart activity" can be used to differentiate between a CSP and something else (artefact, nabothian cyst, miscarriage, inclusion cyste)?	yes	94
Transversal plane	Do you agree that the transversal plane is important to be used in our niche evaluation?	yes in basic and advanced evaluation	50
Gestational age and CSP	Can you agree that the most optimal moment to start with the evaluation of a CSP is 6-7 weeks? (although ultrasound can be repeated later in case of no clear diagnosis)	yes	88
	Can you agree that assessment of a type 2 CSP (niche pregnancy) is advised from 6-7 weeks? (although expected management and ultrasound can be repeated later in case of no clear diagnosis)	yes	94
Doppler US and CSP	Do you agree to evaluate of relation between gestational sac and uterine arteries with colour flow Doppler in case of type 2 CSP and treatment is considered?	yes	94
	Do you think that it is possible to evaluate the amount of vascularity with colour flow Doppler?	yes	75
	In your opinion, should the "amount of vascularity" be evaluated with colour flow Doppler?	yes in basic and advanced evaluation	69
	Could you agree with the item "evaluation of relation between gestational sac and uterine arteries" to be performed with colour flow Doppler in case of type 2 CSP in ADVANCED evaluation?	yes	94
Pulsed Doppler and CSP	Could you agree with it to perform pulsed Doppler in case of a type 2 CSP (niche pregnancy) in research setting only, at this moment based on the current (lack of) evidence?	yes	81
3D ultrasound and CSP	Can you agree, to recommend 3-D ultrasound (including 3-D power Doppler) in research setting only, and that it is not mandatory for routine evaluation of a type 2 CSP (niche pregnancy)?	yes	88

Round 2 (Continued)

Category	Question	Answer	C (%)
MRI and CSP	Do you agree that referral is preferred over MRI in less experienced sonographers in case of a suspected type 2 CSP (niche pregnancy)?	yes	100
Referral to specialized clinic in case of CSP	*Which of the following situations concerning a CSP would you advise to refer to a specialized clinic? (multiple answers possible)*		
	In case of thin RM	yes	56
	In case of a type 2 CSP (type 2a and 2b)	yes	88
	In case of a suspicion of abnormal adherent placentation	yes	81
	In case of a suspicion of placenta praevia	yes	31
	In case of doubt about the diagnosis	yes	94
Setting of specific niche measurements	*Other suggestion of experts that possibly should be determined or measured during the first trimester ultrasound, after previous CS: distance between external os and the pregnancy (lower part of the sac).* *Please give us your opinion concerning this item:*	not relevant	56
	In which situations do you find the item relevant? (multiple choice)	CSP	(3/3)*
	When should it be measured?	in basic and in advanced evaluation	(2/3)*

Round 3

Category	Question	Answer	C (%)
Measurements in 1st trimester	*About: measurement of the presence of placenta praevia* 69% agreement in round 2 that it should be measured during basic evaluation. During face to face meeting all agreed to measure this during basic evaluation. Can you agree?	yes	94
Differentiation between CSP and cervical pregnancy/ miscarriage	It was agreed by all attendees of the meetings that trophoblast localisation is useful and should be examined in advanced evaluation. Do you agree?	yes	88
Transversal plane	*The transversal plane was found relevant in basic evaluation in first trimester for the use of Doppler ultrasound, for the level of protrusion in relation to the outer serosa contour and for examining the distance between the GS and the uterine arteries.* All attendees of the meetings agreed that the items as described above, seen in the transversal plane, should be evaluated during advanced evaluation. Can you agree?	yes	100
Gestational age and CSP	All attendees of the meetings agreed that GA should be based on LMP if applicable and otherwise gestational sac or CRL should be used. Can you agree?	yes	81

Round 3 (Continued)

Category	Question	Answer	C (%)
Doppler US and CSP	*Although it was agreed on during the first rounds that the use of color doppler is beneficial in the evaluation of CS pregnancies there was one member of the niche taskforce (who did not participate in the previous delphi rounds) who mentioned that the use of Doppler ultrasound may be harmful during the first trimester. During the meeting it was consented by the delphi members that in case of a CS pregnancy the potential benefits of a proper diagnosis seems to be more relevant than theoretical possible side effects of the use of doppler ultrasound during a pregnancy.* Do you agree that color or power doppler may be used in case of a type 2 CS pregnancy?	yes	100
	Do you agree that color or power doppler may also be used in case of a type 1 CS pregnancy if we want to differentiate between a miscarriage and CS pregnancy?	yes	94
	It was agreed by all attendees of the meetings in case of a type 2 CSP: that the use of color flow Doppler, 3D power doppler and pulsed doppler are optional (i.e its relevance needs to be confirmed during research). Do you agree?	yes	94
Referral to specialized clinic in case of CSP	It was agreed by all attendees of the meetings that a thin RM only in a patient with an intra-uterine pregnancy is not a reason to refer to a specialized clinic. Do you agree?	yes	100
	It was agreed by the attending participants of the meeting that a suspicion of a placenta preavia only is not a reason to refer to a specialized clinic Do you agree?	yes	100
Setting of specific niche measurements	*About localization of a pregnancy in relation to the external os and localization of a niche during pregnancy and external os and vesico-vaginal fold.* It was agreed by all attendees of the meetings that measurement in relation to external os should be performed in basic evaluation and measurement in relation to vesico-vaginal fold should be performed in research setting. Do you agree?	yes	88

Round 4

Category	Question	Answer	C (%)
CSP definition and location	In our Delphi there was consensus about the definition of CSP "all pregnancies near/on/in the uterine cesarean scar". Based on the comments, there are concerns about using the term CSP for a pregnancy NEAR the CS scar, which may be result in (unnecessary) termination of pregnancy in such situation. Therefore, we propose to define CSP as all pregnancies on or in the uterine cesarean scar and to call a pregnancy near the CS a "low implanted pregnancy". We hope you can agree on this, do you agree?	Yes	94
Differentiation between CSP and cervical pregnancy/ miscarriage	Approximately half of the diagnosed CSPs contain live embryo, whilst the remaining pregnancies are classified as failing. In pregnancies with visible gestational sac it is important to differentiate between failing CSPs and those which have potential to grow and progress beyond the first trimester. We propose that the criteria which have been used for the differential diagnosis between normally developing pregnancies within the uterine cavity and miscarriages, proposed by Doubilet et al., should also be applied in cases of CSP, see below. Do you agree with this?	Yes	100
Doppler US and CSP	It was agreed that Color (flow) Doppler should be performed in case of a type 2 CSP and if treatment is considered. However, it can be helpful to evaluate the placental implantation during basic evaluation as well in case of suspect CSP. And therefore some experts really stressed that we should advise it to distinguish a CSP from an ongoing miscarriage or a low implanted pregnancy. Therefore, we propose to advise to use of Color (flow) Doppler during US evaluation in case of a suspected CSP. Do you agree with this?	Yes	88
	Remnants of placental tissue within the uterine scar following partial spontaneous expulsion of CSP can cause persistent bleeding with the risk of intermittent major hemorrhages. Retained placental tissue is also often seen following medical treatment of CSP and in 10% of cases after surgical evacuation. Retained placental tissue can be difficult to differentiate from blood clots on B-mode scan and it may resemble other uterine abnormalities such as fibroids. Color Doppler examination is essential for the differential diagnosis and to search for the signs of enhanced myometrial vascularity which is associated with a high risk of bleeding with both conservative and surgical management of CSP. Do you agree with this?	Yes	94
Niche measurement in case of CSP	There was consensus about the measurements of a niche (concerning length, depth etc). The niche should be measured the same way during pregnancy as in non-pregnant woman. But since we are now only looking at CS pregnancies, the measurements of depth, length, etc. might not be relevant anymore and will change with advancing pregnancy. Experts even suggested that those measurements are not possible because it is very difficult and irrelevant to differentiate between the placenta and the borders of the niche. Therefore we propose to skip the measurements that are related to the size of the niche (thus length, depth, width). Do you agree to skip the measurements to measure the niche in case of a CSP because of the reasons mentioned above?	Yes	100

Round 4 (Continued)

Category	Question	Answer	C (%)
Setting of specific niche measurements	4. Consensus was achieved on measuring the distance between niche and external os during basic evaluation. However, in the previous Delphi about niche measurement in non-pregnant women this was recommended to perform in research setting only, because the relevance of this measurement in uncertain. To make advices of both papers consistent we propose to advice this measurement in research setting only, instead of during basic evaluation. Do you agree on that?	Yes	94
Heterotopic pregnancies	CSP may coincide with normally-sited pregnancies within the uterine cavity or with ectopic pregnancies in other locations within or outside the uterus. Although considered rare, in some series 4% of CPS were heterotopic. In all women with a history of previous Cesarean section who are diagnosed with multiple pregnancy on ultrasound scan, the possibility of heterotopic pregnancy in the Cesarean section scar should be considered. Do you agree with this?	Yes	94
	In case of IVF heterotopic pregnancies occur more frequently (Ouyang, 2015). Therefore a CSP should be excluded in all women with a previous CS despite the visualization of an apparent singleton pregnancies who conceived following ART and in those with evidence of multiple ovulation on ultrasound scan. Do you agree with this?	Yes	94

* Question was answered by few of the experts. 3-D, three-dimensional; C (%), consensus rate in percentage; CRL, crown-rump length; LMP, last day of menstrual period; LUS, lower uterine segment; NA, not applicable; RMT, residual myometrium thickness; US, ultrasound; VV-fold, vesico-vaginal fold

Table S3. Summary of consensus for definition, diagnosis and evaluation of Cesarean scar pregnancy (CSP) in the first trimester, presented per item

This table presents the mean consensus per item in niche measurement per Delphi round. When consensus was reached (green marking), the item was excluded from the next Delphi round. In the table this is presented as 'c' (consensus achieved).

Category	Item	No. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)	Round 4 consensus (%)
CSP definition and location	Definition CSP and flowchart*†	34	33-93	94	c	c
	Low uterine pregnancyφ	1				94
	50% cut-off‡	1		94	c	c
	Type 2A and 2B CSP‡	1		94	c	c
	Pregnancy near the niche	1	87	100	c	c
	CSP with malplacentation	1	47	94	c	c
	Intra-uterine pregnancy with abnormal adherent placenta§	2	53-67	75	c	c
CS scar evaluation in 1st trimester of pregnancy	Location of the pregnancy/placenta§¶	2	93-100	88	c	c
	Placenta praevia	1	67	69	94	c
	Placental invasion¶	1	73	75	c	c
	Presence of a niche in pregnancy	1	87	c	c	c
	RMT or LUS thickness in pregnancy	1	93	c	c	c
	Bulging of the gestational sac	1	87	c	c	c
	Distance of the vessels of the placenta and serosa§	2	53-60	75	c	c
	Bulging of the vessels outside serosa	1	73	c	c	c

Table S3. (Continued)

Category	Item	No. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)	Round 4 consensus (%)
Differentiation between CSP and cervical pregnancy/ miscarriage	Bulging of gestational sac to differentiate	1	87	c	c	c
	Shape of the gestational sac	1	73	c	c	c
	Lining of the endometrium	1	67	81	c	c
	Sliding product	1	60	100	c	c
	Vascularization¶	1	73	88	c	c
	Differentiation between CSP and cervical pregnancy	1	93	c	c	c
	Trophoblast location‡	1		63	88	c
	Presence of gestational sac, fetal pole or yolk sac with or without heart activity‡	1		94	c	c
	Differentiation between failing CSP and CSP that has potential to growthφ	1				100
Transversal plane	Color Doppler ultrasound	1	93	c	c	c
	Level of protrusion	1	100	c	c	c
	The distance between gestational sac and the uterine arteries	1	73	c	c	c
	Location of the gestational sac in relation to the uterine arteries	1	73	c	c	c
	Transversal plane in CSP classification	1	80	c	c	c
	Relevance of transversal plane†§	2	53-90	50	100	c

Table S3. (Continued)

Category	Item	No. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)	Round 4 consensus (%)
Gestational age and CSP	Adjustment to CSP classification	1	80	c	c	c
	Time of evaluation†□	4	30-73	88-94	c	c
	Gestational age determination§◊	2	50-93	-	81	c
	Assessment of the placenta location and presence of a niche	1	73	c	c	c
Doppler ultrasound and CSP	Adjustment to uterine scar evaluation	1	80	c	c	c
	Circular flow around the gestational sac	1	100	c	c	c
	Placenta location	1	87	c	c	c
	Placental ingrowth	1	80	c	c	c
	Gestational sac and uterine arteries¤	1	53	94	-	88
	Setting of evaluation with Doppler ultrasound‡	3		69-94	94-100	c
	Remnents of placental tissueφ	1				94
Pulsed Doppler and CSP	Setting of evaluation with pulsed Doppler	1	67	81	c	c
3-D ultrasound and CSP	Setting of evaluation with 3-D ultrasound§	3	47-60	88	c	c
MRI and CSP	Additional value	1	73	c	c	c
	Additional value to experts	2	87	c	c	c
	Referral to an expert clinic†§	2	67-100	100	c	c
Referral to specialized clinic	In case of thin RM‡	1		56	100	c
	In case of type 2 CSP (2A and 2B)‡	1		88	c	c
	In case of suspicion of abnormal adherent placentation‡	1		81	c	c

Table S3. (Continued)

Category	Item	No. of questions	Round 1 consensus (%)	Round 2 consensus (%)	Round 3 consensus (%)	Round 4 consensus (%)
	In case of suspicion of placenta praevia‡	1		31	100	c
	In case of doubt about diagnosis‡	1		94	c	c
Niche measurement in case of CSP	Optimal setting to evaluate the CS scar	1	80	c	c	c
	Method for measuring a niche in case of CSP (including AMT)	2	87-93	-	-	100
Setting of specific niche measurements	Vesico-vaginal fold§◊λ	3	47-67	-	88Ω	94
	External os†§	3	47-87	56	88Ω	c
	Other measurements in first trimester	1	87	c	c	c
Heterotopic pregnancy	Previous CSφ	1				94
	ART and multiple ovulation on ultrasoundφ	1				94

* All questions about this item in round 1 were summarized in one new question in round 2. This is described in detail in the results; † Consensus was reached for part of the clustered questions in round 1; it was decided to repeat the item in round 2; φ This item was added in round 4; ‡ This item was added in round 2; § The questions about this item in round 1 were summarized in one question in round 2 and round 3; ¶ Although consensus was reached in round 1, it was decided to further specify the item in round 2; □ The four questions about this item in round 1 were summarized in two questions in round 2; ◊ Consensus of the clustered questions was partly/not reached in round 1; accidentally the item was not repeated in round 2 and therefore it was repeated in round 3; λ Although consensus was reached in round 3, it was decided to further specify the item in round 4; Ω Two items were asked in one question. 3D, three-dimensional; ART, assisted reproductive technology; CS, cesarean section; CSP, cesarean scar pregnancy; LUS, lower uterine segment; RM, residual myometrium

Table S4. Overview of agreed statements after four Delphi rounds, on the definition of Cesarean scar pregnancy (CSP) and sonographic evaluation of the Cesarean section (CS) scar in the first trimester of pregnancy

Statements	Consensus (%)
Method of CS scar evaluation in first trimester of pregnancy	
Optimal gestation to carry out these examinations is at 6-7 week GA	88-94
The GA should be based on the first day of the menstrual period if applicable; otherwise it should be based on the measurements of the GS or CRL	81
Standardized approach for imaging and reporting the LUS by TVS in the first trimester of pregnancy is shown in Appendix 6	80
CSP definition and location in first trimester of pregnancy	
CSP can be used as a collective term that includes all pregnancies (GS and/or placenta) with implantation in the scar defect	94
A pregnancy that is located *near* the CS scar should be called "low implanted pregnancy"	94
CSP can be described depending on the pregnancy crossing two imaginary lines; the "uterine cavity line" (UCL) and/or crossing the "serosal line" (SL) (Fig. 4)	94
A CSP can be described as follows: (1) CSP in which the largest part of the GS crosses the uterine cavity/cervical canal (the UCL); (2) CSP in which the largest part of the GS is embedded in the myometrium and does not cross UCL, and the GS does not cross SL; and (3) CSP in which the GS crosses SL; the pregnancy is covered with a thin layer of myometrium/visceral peritoneum and is herniating towards the vesico-uterine pouch or into the broad ligament (Fig. 5A-C)	94
A CSP with the largest part of the GS crossing the UCL can also be named a "type 1" CSP and the other two CSPs a "type 2"	94
A pregnancy after a CS may be combined with malplacentation, this may occur in combination with or without a CSP	94
Method of CSP evaluation in first trimester of pregnancy	
RMT and AMT in the sagittal plane should be measured and reported (Fig. 6)	94-100
Measurements of the niche (length, depth and width) in case of CSP were found irrelevant because of its change as the pregnancy progresses	100
Measurement of the location of the GS in relation to the external os may be performed in research setting	88
Measurement of the location of the GS in relation to the vesico-vaginal fold may be performed in research setting	94
Color Doppler is advised to be used in case of a suspected CSP	88
Color (flow) Doppler should be performed in case of a suspected CSP, vascular pattern and vascular mapping in relation to the niche, cervix and to adjacent uterine vascular anatomy	80
Evaluation of the CSP in the transversal plane should include the relation to the uterine arteries (Fig. 7A-D)	80

Table S4. (Continued)

Statements	Consensus (%)
Color Doppler examination is essential for the differential diagnosis and to search for the signs of enhanced myometrial vascularity which is associated with a high risk of bleeding with both conservative and surgical management of CSP	94
Pulsed Doppler is not mandatory for routine evaluation of CSP	81
3D ultrasound is not mandatory for routine evaluation of CSP	88
Differentiation between CSP and cervical pregnancy or miscarriage	
Flow chart (Fig. 8) presents different situations that can be encountered during sonographic evaluation in first trimester of pregnancy in women with a previous CS	94
Bulging of the GS towards the bladder is relevant to differentiate between a CSP and a cervical pregnancy that is not located in the niche	87
When sliding tissue is visible at the level of the CS scar, it is more likely that it is an ongoing or incomplete miscarriage instead of CSP	100
Vascularization, locations of implantation or trophoblast invasion are useful features to discriminate, for which the use of color (flow) Doppler can be endorsed	88
Shape of the GS is not relevant to discriminate between a CSP and cervical pregnancy	73
Evaluation of the presence of the GS, fetal pole or yolk sac with or without heart activity can be used to differentiate a CSP from another structure (artefact, nabothian cyst, miscarriage, inclusion cyst and a remnant after a miscarriage of a CSP)	84
Criteria which have been used for the differential diagnosis between normally developing pregnancies within the uterine cavity and miscarriages, can also be applied in cases of CSP to differentiate between failing CSP and those with potential to grow beyond the first trimester (Appendix 8)	100
Heterotopic pregnancy	
CSP should actively be excluded in all women with a previous CS despite the visualization of an apparent singleton pregnancies who conceived following ART and in those with evidence of multiple ovulation on ultrasound scan	94
Referral to expert clinics	
In case of a CSP with the largest part of the GS in the myometrium (and crossing SL), doubt about the diagnosis and suspicion of abnormal adherent placenta it is recommended to refer the patient to an expert clinic for ultrasound evaluation and further management	81-94
Referral to an expert clinic is preferred over MRI in case of a suspected CSP with largest part of GS in the myometrium (and crossing SL) (100% agreement) or in case of diagnostic uncertainty	100

AMT= adjacent myometrium thickness; CRL=crown-rump length; CS=cesarean section; CSP=cesarean scar pregnancy; GA=gestational age; LUS=lower uterine segment; MRI=magnetic resonance imaging; RMT= residual myometrium thickness; SL=serosal line; TVS=transvaginal sonography; UCL=uterine cavity line

Table S5. Overview of recommendations on primary research questions

Question	Recommendation
1. What are sonographic criteria to define CSP?	Definition CSP: all pregnancies (GS and/or placenta) with implantation in or in close contact with the niche
2. What is the classification based on CSP type?	(1) CSP in which the largest part of the GS crosses the uterine cavity/cervical canal; (2) CSP in which the largest part of the GS is embedded in the myometrium and does not cross UCL, and the GS does not cross SL; (3) CSP in which the GS crosses the SL
3. What method should be used to locate a CSP by using transvaginal ultrasonography?	See Appendix 6 for standardized approach according to Kuleva *et al.*[48] and see Table 1 for all items in basic and advanced evaluation
4. What is the optimal timing to check for the presence of a CSP?	6-7 weeks GA, but the reporting system can be used during the entire first trimester till 12 weeks GA
5. (How) should color Doppler ultrasound be used in case of CSP?	It helps in the evaluation of trophoblast invasion, recognition of a CSP and differentiating with a low implanted pregnancy or miscarriage and is therefore strongly recommended if a CSP is suspected
6. (How) should pulsed Doppler ultrasound be used in case of CSP?	Not mandatory for routine evaluation of CSP. Its relevance needs to be studied in a research setting
7. (How) should 3D (Doppler) ultrasound be used in case of CSP?	Not mandatory for routine evaluation of CSP. It may be used in advanced and research setting
8. What is the value of MRI?	No additional value

CSP=cesarean scar pregnancy; GS=gestational sac; UCL=uterine cavity line; SL=serosal line; GA=gestational age; 3D=3-dimensional; MRI= magnetic resonance imaging

Table S6. Criteria for transvaginal ultrasonographic diagnosis of pregnancy failure, which can also be used to diagnose failing Cesarean scar pregnancy (CSP). Adapted from table 2 in Doubilet et al.[54]

Findings diagnostic of CSP failure	Findings suspicious for, but not diagnostic of, CSP failure
CRL of ≥7 mm and no heartbeat	CRL of <7 mm and no heartbeat
Mean sac diameter of ≥25 mm and no embryo	Mean GS diameter of 16-24 mm and no embryo
Absence of embryo with heartbeat ≥2 weeks after a scan that showed a GS without a yolk sac	Absence of embryo with heartbeat 7-13 days after a scan that showed a GS without a yolk sac
Absence of embryo with heartbeat ≥11 days after a scan that showed a GS with a yolk sac	Absence of embryo with heartbeat 7-10 days after a scan that showed a GS with a yolk sac
	Absence of embryo ≥6 weeks after last menstrual period
	Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)
	Enlarged yolk sac (>7 mm)
	Small GS in relation to the size of the embryo (<5 mm difference between GS diameter and CRL)

PART 2

NICHE DEVELOPMENT AND CHANGES OVER TIME AFTER CESAREAN SECTION

CHAPTER 5

CHANGES IN THE UTERINE SCAR DURING THE FIRST YEAR AFTER A CESAREAN SECTION: A PROSPECTIVE LONGITUDINAL STUDY

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ABSTRACT

Aim

To study changes in a cesarean section (CS) scar during the first year after a CS using gel installation sonography (GIS).

Methods

Proof-of-concept study, prospective cohort study. Twenty women who delivered by their first CS were evaluated by both transvaginal sonography and GIS 2 months and 1 year after CS. A niche was defined as an anechogenic space at the uterine cesarean scar with a depth >2 mm. The primary outcome was any change in the residual myometrium thickness (RMT) as evaluated by GIS.

Results

Mean RMT changed in time from 11.9 mm at 2 months to 6.5 mm at 12 months after the CS ($p<0.001$). Niche prevalence did not change. The adjacent myometrial thickness (AMT) reduced from 15 to 12.4 mm ($p=0.04$). The ratio between RMT and AMT with GIS decreased from 0.80 at 2 months to 0.54 at 12 months ($p=0.002$).

Conclusion

The RMT, the AMT and the ratio between the RMT and AMT reduces from 2 to 12 months after a CS. The prevalence did not change. This needs to be taken into account when deciding on the timing of niche measurement and the interpretation of the RMT.

INTRODUCTION

Nowadays, one third of women deliver their child by cesarean section (CS) and this has become a global trend.[1] As a result, a growing number of women are experiencing complications of the cesarean section. These include cesarean scar pregnancies, uterine rupture, malplacentation and gynecological symptoms such as postmenstrual spotting and dysmenorrhea.[2–4] The uterine cesarean scar is most frequently evaluated by transvaginal sonography (TVS) and saline infusion sonography (SIS) or Gel installation sonography (GIS).[3, 4] Often one can see contrast entering into the myometrium at the site of the scar forming a triangular echolucent space in a longitudinal view of the lower uterine segment that is colloquially known as a "niche".[3, 4] Different nomenclature is used to describe this feature; a scar defect, niche, isthmocele, pouch or diverticula.[3] The prevalence of a niche, using sonohysterography varies between 56 and 84% in random populations.[3, 4] GIS or SIS is more sensitive than TVS in detecting niches.[3–5] And sonohysterography gives the best inter and intraobserver agreement.[6] Despite an increasing number of prospective cohort studies reporting on the prevalence and appearances of the uterine cesarean scar, a clear uniformly used definition is still lacking.[7] In addition, it is unclear as to what is the best moment to measure a niche after a CS because it is unclear if a niche changes over time after a CS.

All prospective studies performed in a more or less random population are based on a single measurement of the scar with TVS or SIS or GIS.[8–11] Longitudinal studies with a long-term follow-up of the cesarean scars among non-pregnant women are lacking. The aim of this study is to evaluate changes in the residual myometrial thickness (RMT), niche prevalence and size over time during a follow-up period of one year using both TVS and GIS in non-pregnant women after their first CS.

METHODS

This study is a proof-of-concept study performed as a prospective cohort study. The study was executed in a teaching hospital, Sint Antonius Hospital Nieuwegein, The Netherlands, between November 2007 and September 2011. The trial was registered in the Nederlands trial register (www.trialregister.nl, trial number NTR-2887). The protocol was approved by the local medical Ethics Committee (VCMO NL18722.100.07 R-07.14A/SCAR). All women signed the informed consent form. Women included in this study were a subgroup of a larger prospective cohort study that aimed to evaluate the prevalence of a niche and its relation with bleeding disorders after a CS.[8] Women were asked to participate in this study during their stay in the ward immediately after CS. Women

were asked to undergo a TVS and GIS 6–12 weeks after the CS and to complete a questionnaire at 6 weeks, 6 months and 12 months after their CS. A subgroup was asked to participate additionally in the current ultrasound follow-up study. Eligible women for this ultrasound follow-up study were women who had the CS performed in their first pregnancy and without any previous uterine surgery and were willing to undergo a second GIS. They were asked after their first ultrasound 6–12 weeks after CS to undergo a second TVS and GIS 9–12 months after the CS. Women who gave their informed consent were contacted by telephone 9–12 months after CS and a TVS and GIS were scheduled for them at the outpatient clinic. Ultrasound was performed in a standard way as previously described and briefly outlined below.[8]

The uterus was scanned in both the transversal and the sagittal planes and if a niche was present, the sagittal plane with the largest depth was searched and niche characteristics were measured and registered in a CRF; the presence of a niche (defined as an anechogenic space at the presumed site of the cesarean scar with a depth equal or more than 2 mm), the depth of the niche, the RMT at the site of the uterine scar, the adjacent myometrial thickness (AMT; Figure 1), the length and width of the uterus and the double endometrial thickness were all measured.

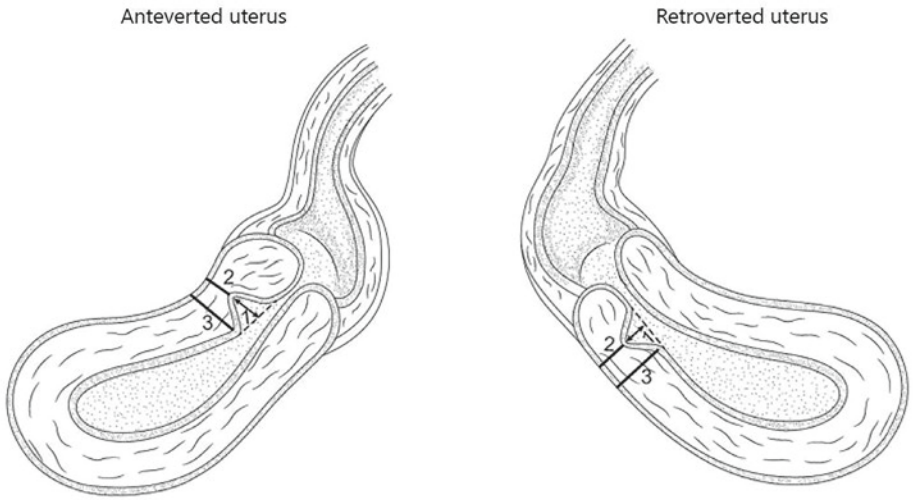

Figure 1. Measurement of the niche. 1, depth; 2, residual myometrium; 3, adjacent myometrium.

Immediately after the TVS, a GIS was performed and the same measurements were taken. All ultrasound were performed using a 7.5-MHz transducer (Philips Sonicare HD 11.XE, Philips Medical Systems, Eindhoven, The Netherlands) by 2 experienced gynecologists (L.F.V. and S.V.).

Indication and characteristics of the CS were recorded from the medical chart. A questionnaire was used to obtain details about contraceptive use, breastfeeding and bleeding pattern. All data was recorded in a CRF and a web-based database by 2 research nurses. The results of the ultrasound scans were not recorded in the case notes, and women and their doctors were not informed about the ultrasound findings. Reporting was performed based on the guidelines provided for reporting a prospective study (STROBE).[12]

Statistical Analysis

The primary outcome was the change in the RMT from 2 to 12 months after the CS evaluated by GIS. Secondary outcomes are the prevalence of a niche using TVS and GIS, depth of the niche, the AMT, ratio RMT/AMT, length and width of the uterus. IBM SPSS statistics version 22 (SPSS Inc., Chicago IL, USA) was used for the statistical analyses. To compare the RMT, the depth of the niche, width and length of the uterus, the AMT and the ratio RMT/AMT, the Wilcoxon signed Rank test was performed because of non-normal distribution. The Mc Nemar test was used to compare the prevalence of a niche. To compare baseline characteristics chi-square and Students *t* test were performed. All tests were performed as 2-sided and 2-tailed tests. A p-value of <0.05 was considered statistically significant.

Sample Size Calculation

At the time of the study design, we did not have any relevant data of comparable studies to base our sample size. Our study should be considered a proof-of-concept study; we aimed to include 20 patients.

RESULTS

Of the 115 women who had the CS performed in their first pregnancy during the first study, 46 gave informed consent immediately after their first GIS to participate additionally in the ultrasound follow-up study. Fourteen women withdrew at 9 to 12 months after CS and 12 women could not be reached 9 months after their first ultrasound. Finally 20 women showed up for their second ultrasound (Figure 2).

The mean period between the CS and the first ultrasound was 7.3 weeks (SD 1.1 range 6–10) and between the CS and the second visit was 48.9 weeks (SD 13.1 range 24–68). Baseline characteristics of the women are shown in Table 1. On the included women there were more planned CSs and gestational age was shorter compared to women who did not participate.

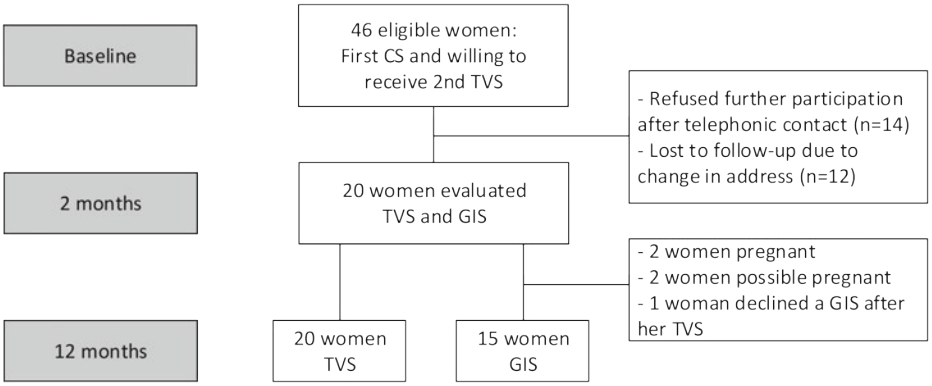

Figure 2. Flowchart of the patient-selection process.
CS, cesarean section; TVS, transvaginal sonography; GIS, gel installation sonohysterography

Among the included women, there were 11 planned CS and 9 emergency CS of which 3 were because of fetal distress. All CSs were performed with a transversal incision in the low uterine segment. In all but one patient, the uterus had been closed in one layer. Two CSs were complicated by more than 1,000 mL blood loss and one patient had had an eclamptic seizure during the CS. One women developed fever after CS, none of the women received antibiotics for more than 24 h. Contraceptive use at the time of visits 1 and 2 are shown in Table 1.

Results of both TVS and GIS are shown in Table 2. All women underwent a TVS at the second visit and 15 women received a GIS. Of the 5 women without a GIS, 2 women were pregnant, 2 women were in the luteal phase of their cycle without use of contraceptives and one woman refused to undergo an additional GIS. There was a reduction in the mean RMT in time with both GIS and TVS – it reduced from 11.9 mm at 2 months to 6.5 mm at 12 months ($p<0.001$) using GIS, with a mean difference of 5.4 mm (95% CI 3.6–7.3; Table 2; Figures 3, 4a, b). Reduction with TVS was from 10.1 mm at 2 to 7.0 mm at 12 months ($p=0.008$), with the mean difference being 2.82 mm (95% CI 0.61–5.02; Table 2; Figures 4 a, b). A non-significant increase in the niche depth was observed using GIS from 3.8 mm at 2 months to 5.3 mm at 12 months ($p=0.46$), while the mean niche depth remained 5.3 mm using TVS (Table 2). The AMT reduced from 15 to 12.4 mm ($p=0.048$), with mean differences being 2.6 mm (95% CI 0.13–5.0) using GIS. Similar results were found using TVS. The ratio between RMT and AMT decreased from 0.8 at 2 months to 0.54 at 12 months with GIS ($p=0.008$), with mean differences being 0.26 (95% CI 0.11–0.42). TVS results showed a non-significant decrease in the ratio RMT/AMT (Table 2; Figures 4 a, b). The prevalence of a niche did not change.

Table 1. Patient characteristics

	Included n=20	**Not participated n=26**	**p-value**
Age, years, mean (SD)	31 (2.8)	32 (3.4)	0.352
Gestational age, days, mean (SD)	274 (8.7)	279	0.046
Labor, *n* (%)	9 (45)	22 (85)	0.004
Cervical dilatation, cm, mean (SD)	4.1 (4.4)	5.8 (3.7)	0.171
Augmentation oxytocine, *n* (%)	7 (35)	13 (50)	0.351
Induction of labor, *n* (%)	2 (10)	6 (23)	0.246
PIH/PE, *n* (%)	4 (20)	7 (27)	0.732
Blood loss >1,000 mL, *n* (%)	2 (10)	3 (12)	0.868
Niche*	11 (55)	14 (54)	0.997
	Visit 1	**Visit 2**	
Weeks after CS, mean (SD)	7.3 (1.1)	48.9 (13.2)	
Regular cycle, *n* (%)	None	13 (65)	
Breastfeeding, *n* (%)	15 (75)	3 (15)	
Oral contraceptive, *n* (%)	5 (25)	10 (50)	
Pregnancy, *n* (%)		2 (10)	

* Niche measured with gel installation sonohysterography. CS, cesarean section; PIH/PE, pregnancy-induced hypertension/pre-eclampsia.

Table 2. Ultrasound characteristics

	TVS visit 1 (n=20)	**TVS visit 2 (n=20)**	**p-value**	**GIS visit 1 (n=20)**	**GIS visit 2 (n=15)**	**p-value**
Length uterus, cm*	7.1 (0.92)	6.8 (0.83)	0.38			
Width uterus, cm*	3.9 (0.65)	3.7 (0.52)	0.13			
Endometrial thickness, mm*	3.4 (1.2)	5.0 (3.5)	0.16			
Niche ≥2 mm, *n* (%)	12 (60)	10 (50)	0.69	11 (55)	9 (60)	0.69
Niche depth, mm	5.3 (4.6)	5.3 (3.8)	0.92	3.8 (2.8)	5.3 (3.8)	0.67
RMT, mm	10.1 (3.8)	7.0 (3.1)	0.008	11.9 (3.3)	6.5 (3.0)	0.001
AMT, mm	14.5 (3.5)	10.8 (2.6)	0.001	15 (2.9)	12.4 (3.4)	0.048
RMT/AMT ratio	0.72 (0.22)	0.65 (0.23)	0.11	0.8 (0.20)	0.54 (0.26)	0.008

Given as mean (SD) unless stated different. * Excluding pregnant women at visit 2 did not change significantly the outcome of these measurements. AMT, adjacent myometrial thickness; GIS, gel installation sonohystergraphy; RMT, residual myometrial thickness; TVS, transvaginal sonography

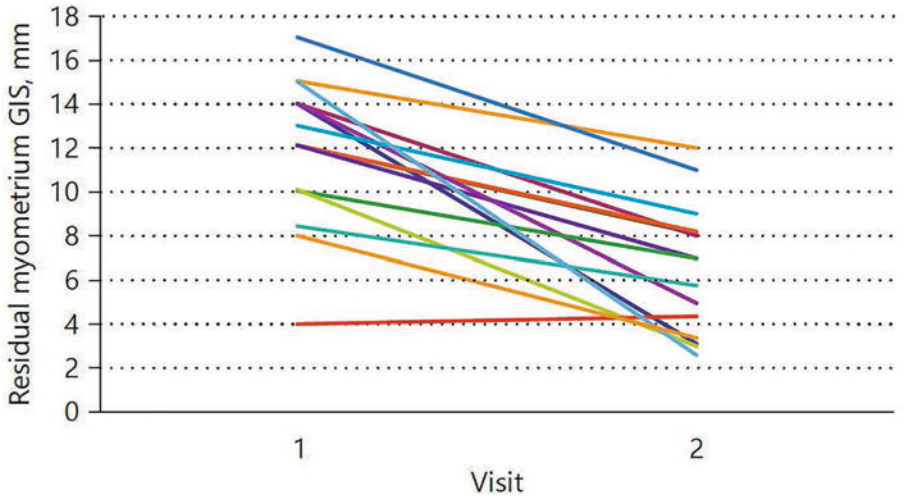

Figure 3. Changes in the thickness of the residual myometrium in women evaluated with gel installation sonohysterography (GIS), n=15. Visit 1: 2 months after cesarean section. Visit 2: 12 months after cesarean section.

In 5 women, there was a change in the position of the uterus between 2 and 12 months. Four women had a uterus in retroversion position at 6 weeks and an anteversion position at 12 months. One woman had a uterus in the straight position, which was turned to retroversion position at 12 months. Four of these 5 women had a niche.

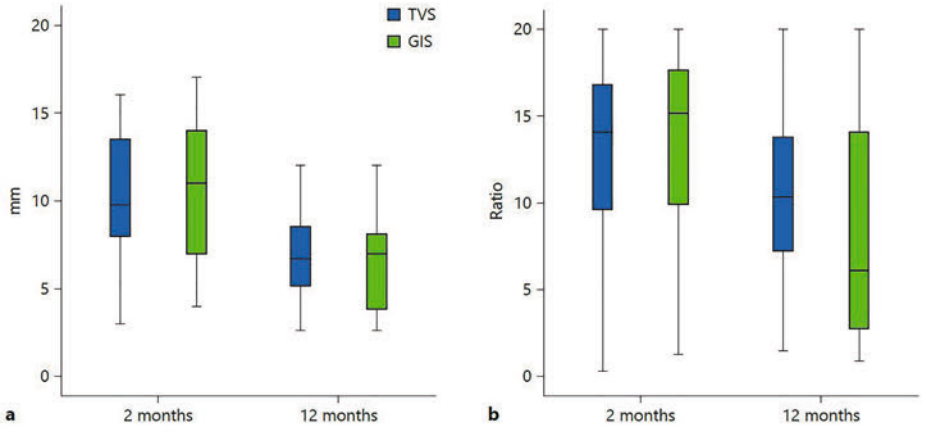

Figure 4. a) Residual myometrium. b) Ratio residual myometrium/adjacent myometrium.
GIS, gel installation sonohysterography; TVS, trans vaginal sonography

DISCUSSION

Between 2 and 12 months after CS, the RMT, the AMT at the site of the cesarean scar and the ratio RMT/AMT decreased significantly using both GIS and TVS. However, niche depth, prevalence of a niche, uterine length and width did not change in time. Our findings implicate that the myometrium at the site of the cesarean scar is not a static feature and changes over time.

A strength of our study is that we included patients immediately after their first CS, reducing the risk on bias to participate. Another strength is that we used both TVS and GIS at 2 and 12 months after CS. Sonohysterography increases the delineation of the niche and myometrium.[4, 5] A recent study shows the best inter- and intraobserver agreement of RMT measurements with contrast sonohysterography compared to other niche characteristics.[6] Also, in a 3D study, the RMT has shown to have a good inter-observer agreement.[13] In addition, we used a standardized method for niche evaluation using predefined criteria.[8]

A limitation of this study is the small sample size due to the relatively high number of patients who did not want to undergo a second GIS after their first one due to the discomfort it creates. There were no differences between the women who participated and women who did not participate in ultrasound findings at 12 weeks or gynecological symptoms at 12 months after the CS. Women who participated in the current study had more often a planned CS than the women who did not participate. However, given the fact that participating women were their own controls, eventual selection bias would not have affected the outcomes, but it may have consequences for the extrapolation of the result to other populations. Given the fact that 2 gynecologists performed the ultrasound independently, interobserver variability cannot be excluded. However, measurements were randomly performed, so it is not likely that it played a structural role. This is underlined by the fact that RMT reduces in most individual patients. Since the majority of the included women had a uterus closed in one layer, these results cannot be extrapolated to women who received double layer closure of their uterus.

So far only 2 peer-reviewed studies and four abstracts were published on longitudinal follow-up within patients with niches by 2D or 3D ultrasound.[14–19] They all evaluated niches with a follow-up between 6 weeks and 24 months. Three of these studies also found a reduction of the RMT in time.[14–16] A reduction in the RMT and the RMT/AMT ratio over time could be induced by the continuing tissue reaction or reduction of edema during the healing process. Another theory includes the retraction of adhesions between the uterus and the abdominal wall inducing an increase in niche depth and reduction of RMT.[20] Also, peristaltic contractions of the uterus could influence the

traction on the residual myometrium, and blood accumulation in the niche may induce a continuous pressure on the residual myometrium.

In women with symptomatic niches, the RMT is one of the key parameters for the selection of different surgical approaches; hysteroscopic resection should in general be considered only in the case of an RMT of at least 2.5–3 mm to prevent bladder injury.[21] The results of our study show that the RMT is a dynamic feature that changes during the first year after CS. Therefore, measurement of the RMT after a CS should be timed carefully before considering surgical interventions. Also, for research purposes, it is relevant to realize that timing of measurement of the niche may affect the RMT. Our results also indicate that TVS may be a good alternative to assess changes of the niche over time in the same patient. However, for the determination of treatment possibilities or in the assessment of possible risks for future pregnancies, it remains important to perform GIS or SIS.[5, 8] Larger studies and longer follow-up are needed to know whether the changing of the scar continues after one year follow-up and to gain more insight in factors that affect wound healing of the uterine scar and niche development in order to develop preventive strategies.

Conclusion

The uterine scar after a CS is not a static feature and changes over time. The RMT between the niche and the bladder at the site of the CS scar measured with sonohysterography decreases significantly over time between 2 and 12 months after a CS.

Acknowledgements

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Disclosure of interests

J.A.F.H. received 2 grants from ZonMw, a Dutch organization for Health Research and development for to compare (1) the effect of a hysteroscopic niche resection versus no treatment in women with postmenstrual spotting (Hysniche study, ZonMw project number 80-82305-97-12030) and (2) the (cost)effectiveness of double-layer closure of the cesarean (uterine) scar in the prevention of gynecological symptoms in relation to niche development (ZonMw project number 843002605) and received grants from Samsung Medison and Gedeon Richter outside the submitted work. H.A.M.B. received grants from Olympus and Gynesonics and non-financial support from Samsung Medison, outside this study. S.V. is consultant for Bayer and Norvartis. He is a member of the advisory board of Hologic and Johnson and Johnson. And S.V. is patentee for a new hysteroscopy.

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CHAPTER 6

NICHE PRESENCE AND ITS CHANGE OVERTIME AFTER CESAREAN SECTION AND IN SUBSEQUENT PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objectives

To review the presence of a niche during the first two years after a cesarean section (CS) and in the subsequent pregnancy. Furthermore, to examine the changes of the residual myometrium thickness (RMT) and niche size overtime, during the first two years after a CS and during pregnancy after a CS.

Data sources

PubMed, EMBASE, and Clarivate Analytics/Web of Science Core Collection databases, up to March 31th 2023.

Study eligibility criteria

Systematic review and meta-analysis. All types of clinical studies were included reporting the presence of a niche and niche measurements (niche length, depth and width, and RMT) performed at least twice in the period after CS or in subsequent pregnancy using transvaginal ultrasound.

Study appraisal and synthesis methods

Two reviewers independently screened all records and assessed eligible articles. Quality of the included studies was assessed by using the Downs and Black scoring system.

Results

Fourteen papers were selected for inclusion in the review; seven studies in non-pregnant women (n=1,098) and seven studies in pregnant women (n=1,086). Six studies in non-pregnant women (n=1,031) could be used for a meta-analysis. The niche presence after previous CS increased during the first two months and seemed to stabilize at six months after CS. Meta-analysis showed no significant change between six weeks and two years after CS (p=0.102). RMT decreased slightly overtime (p=0.017); niche depth remained similar, (p=0.158). The niche presence and RMT in subsequent pregnancy decreased as the pregnancy progressed. Niche depth and width tended to decrease during pregnancy, whereas niche length increased.

Conclusion

Because of an increase of the assessed presence of a niche and change in size during the first half year after CS, six months after CS seems to be the best moment to evaluate the CS scar. Timing of niche evaluation after a CS and during subsequent pregnancy is of influence on the thickness of the RMT and size of the niche. In general, RMT decreases overtime during the first two years and during pregnancy.

INTRODUCTION

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METHODS

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RESULTS

Study selection

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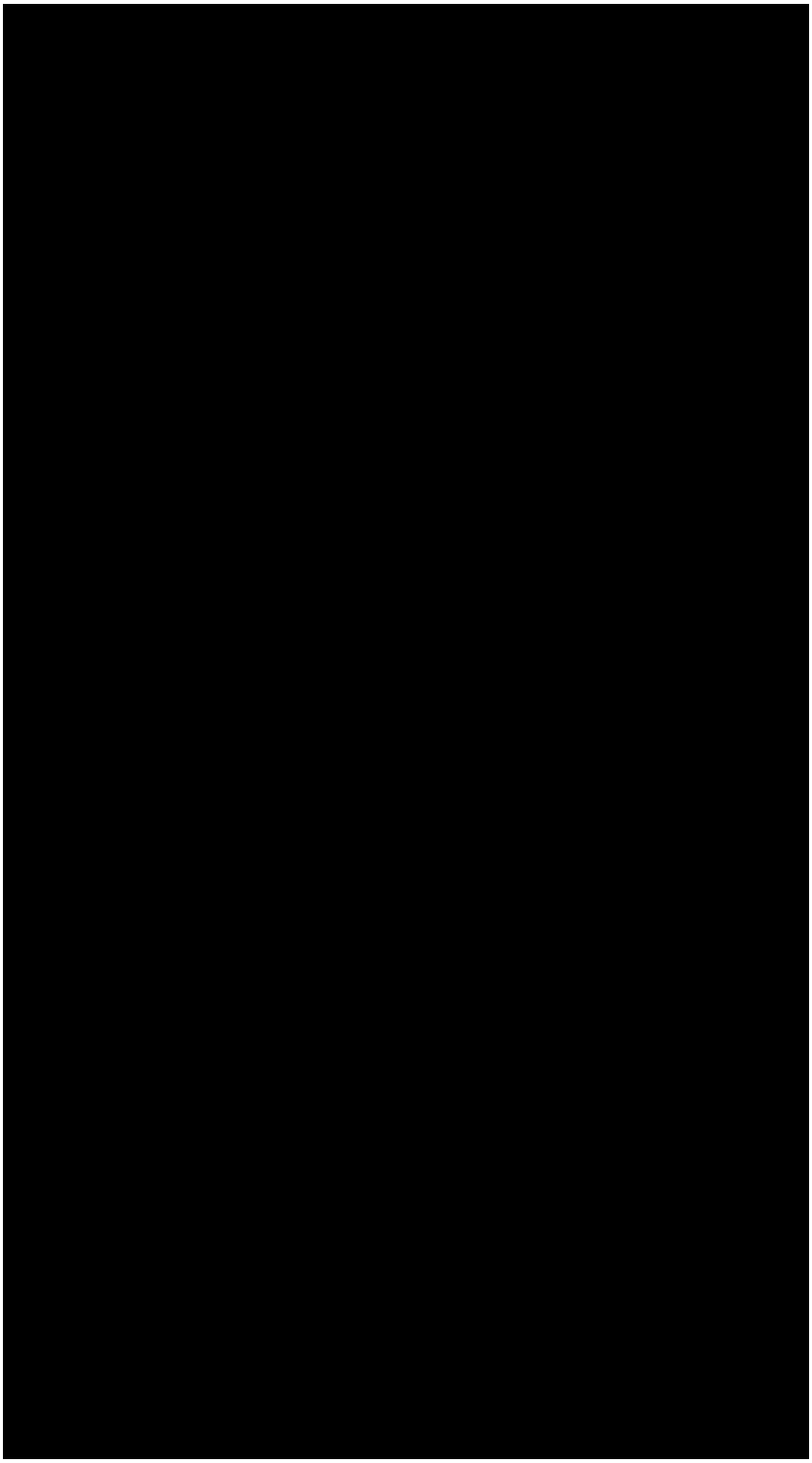

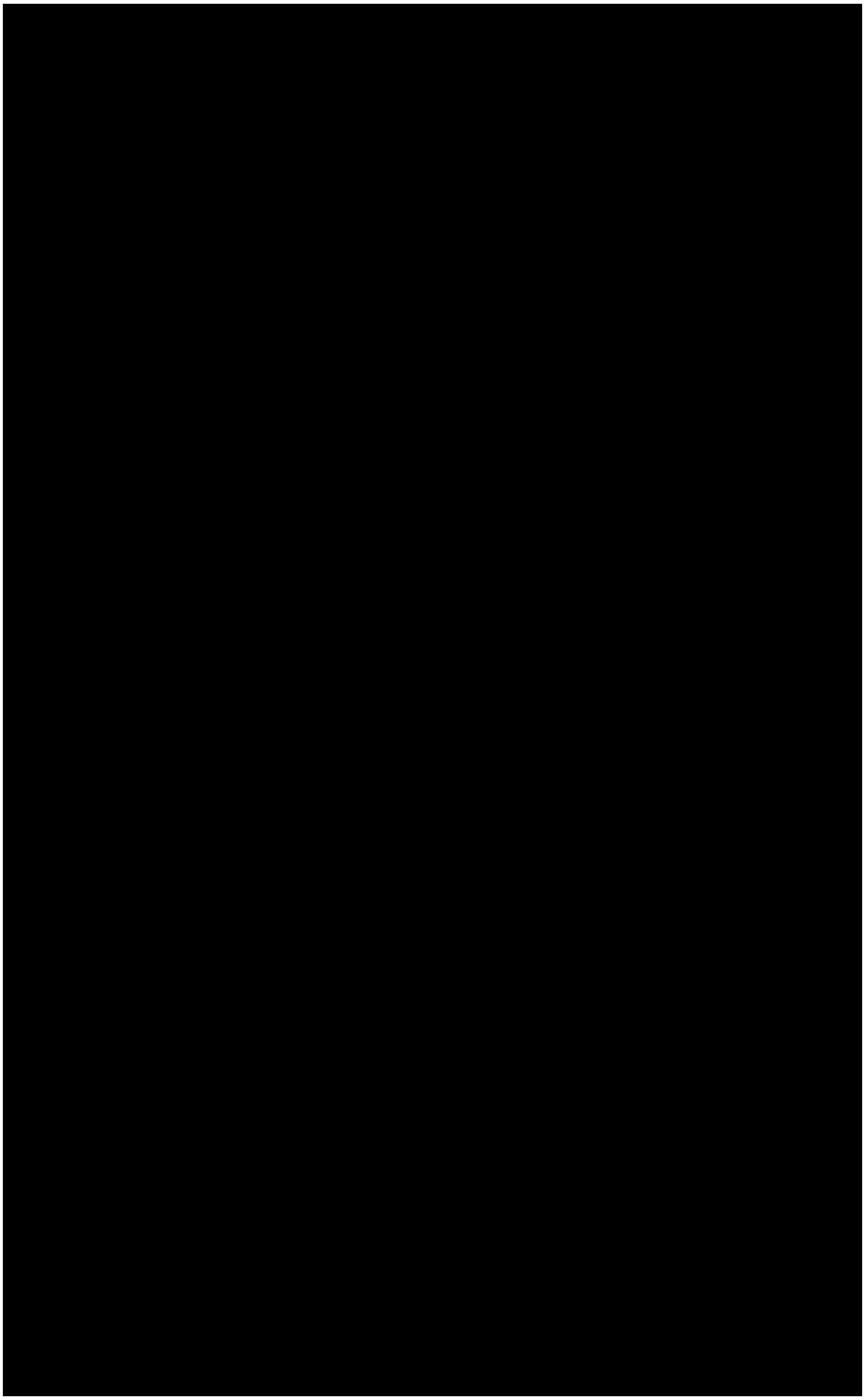

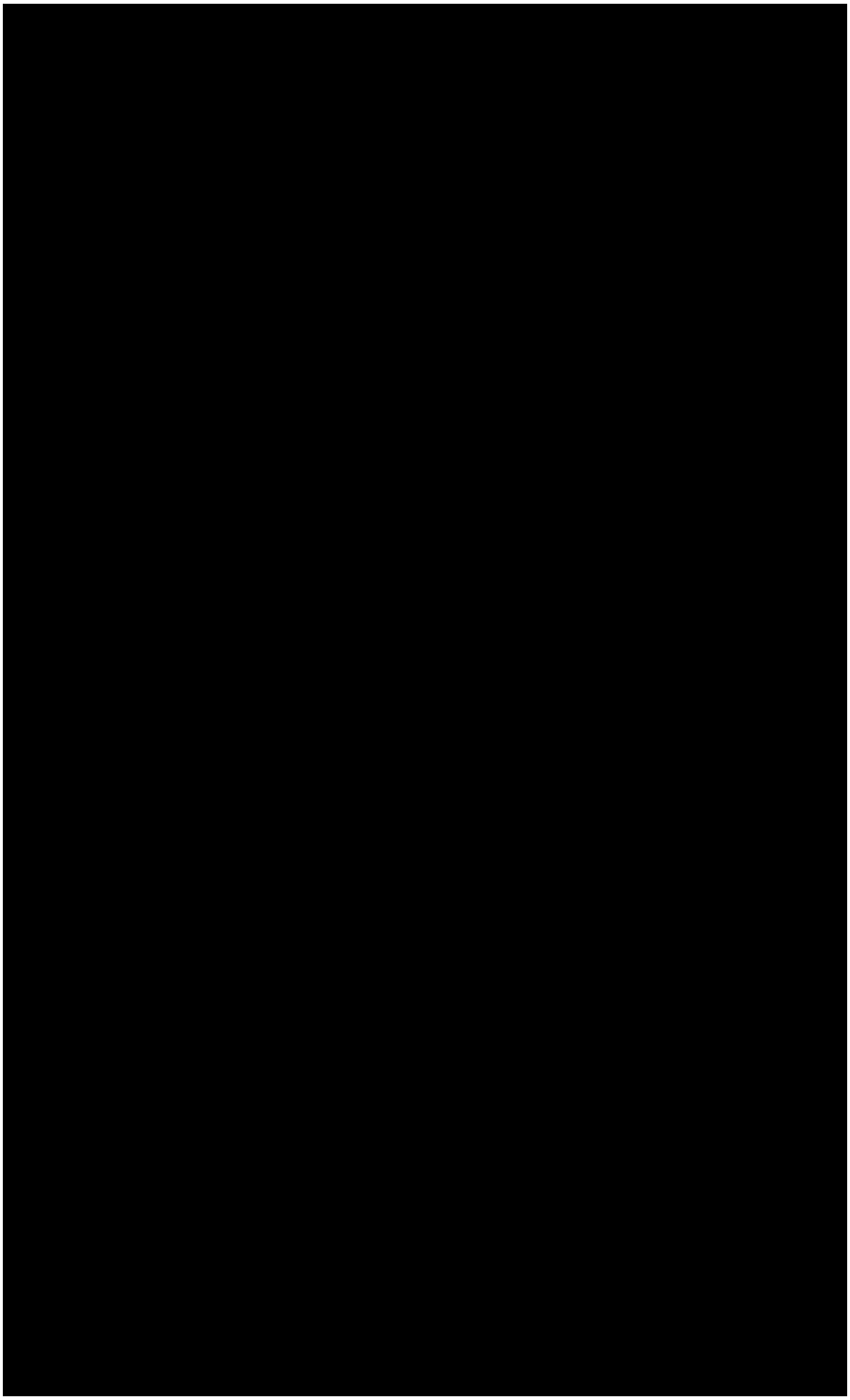

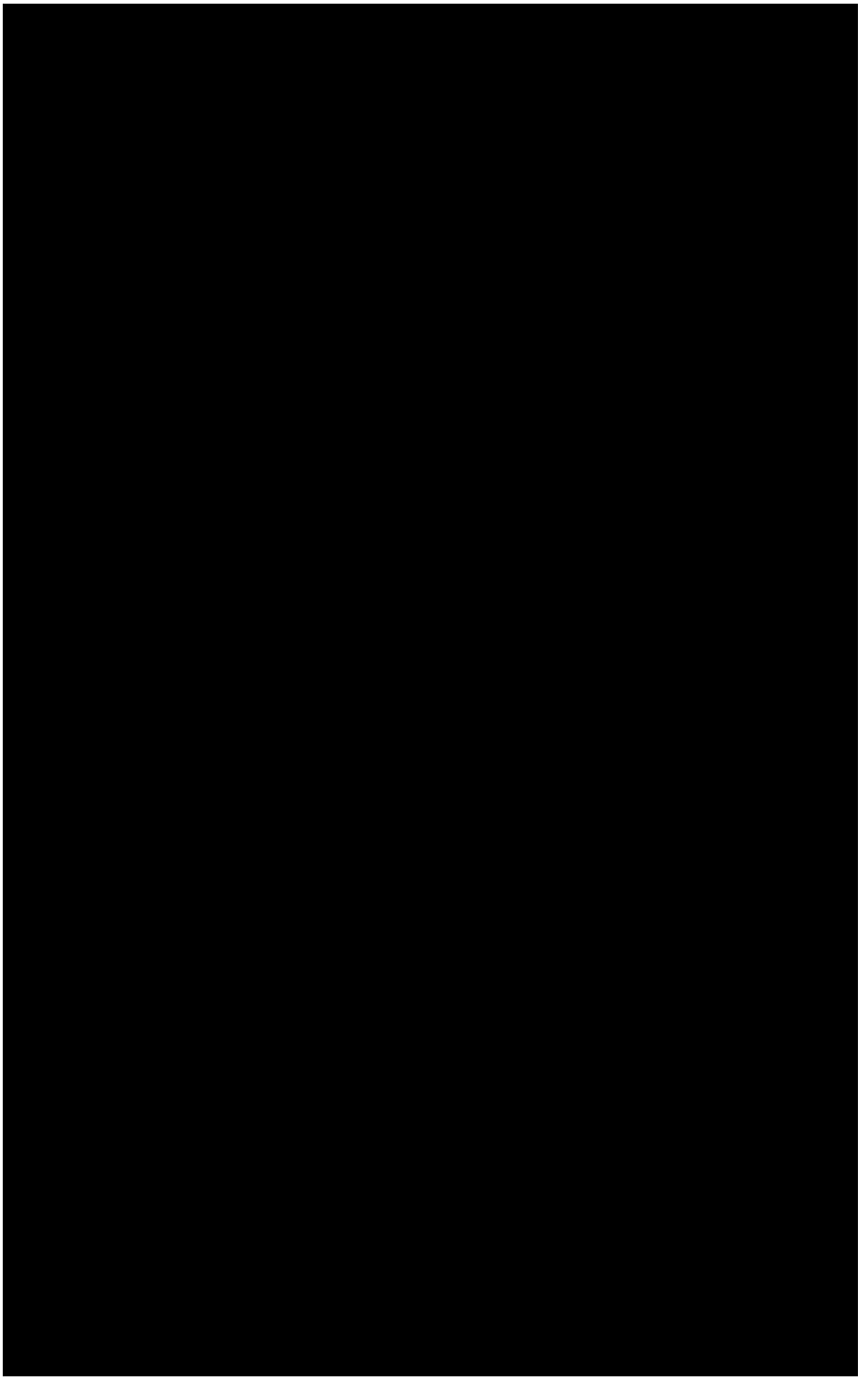

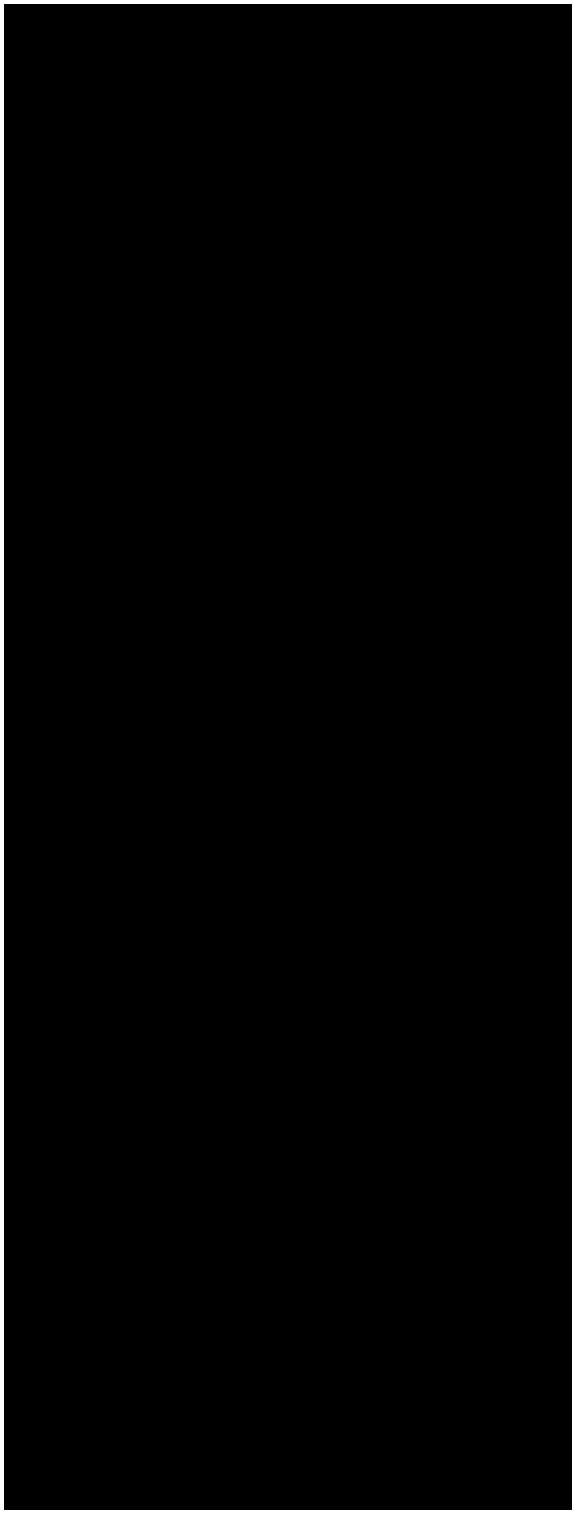

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SYNTHESIS OF RESULTS

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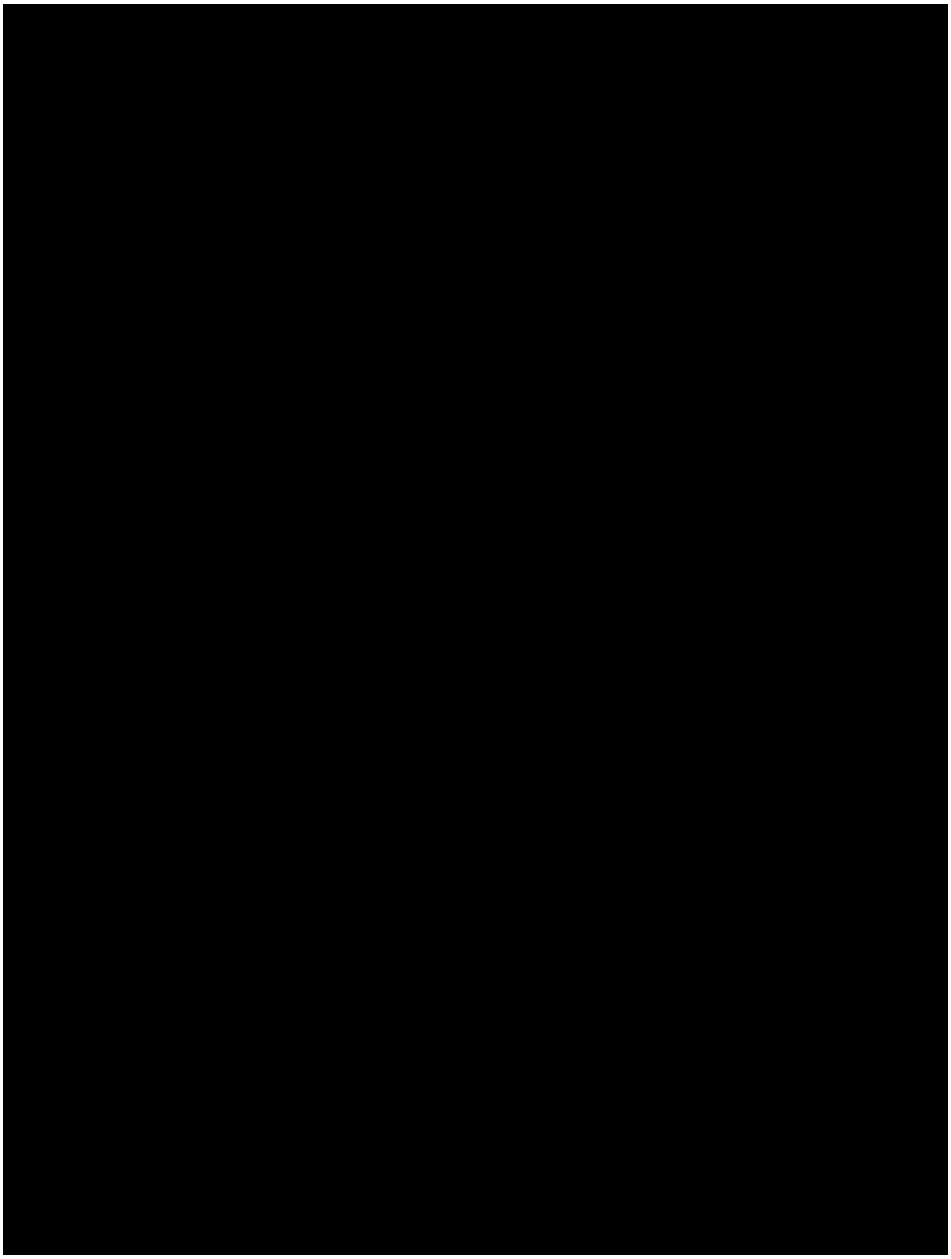

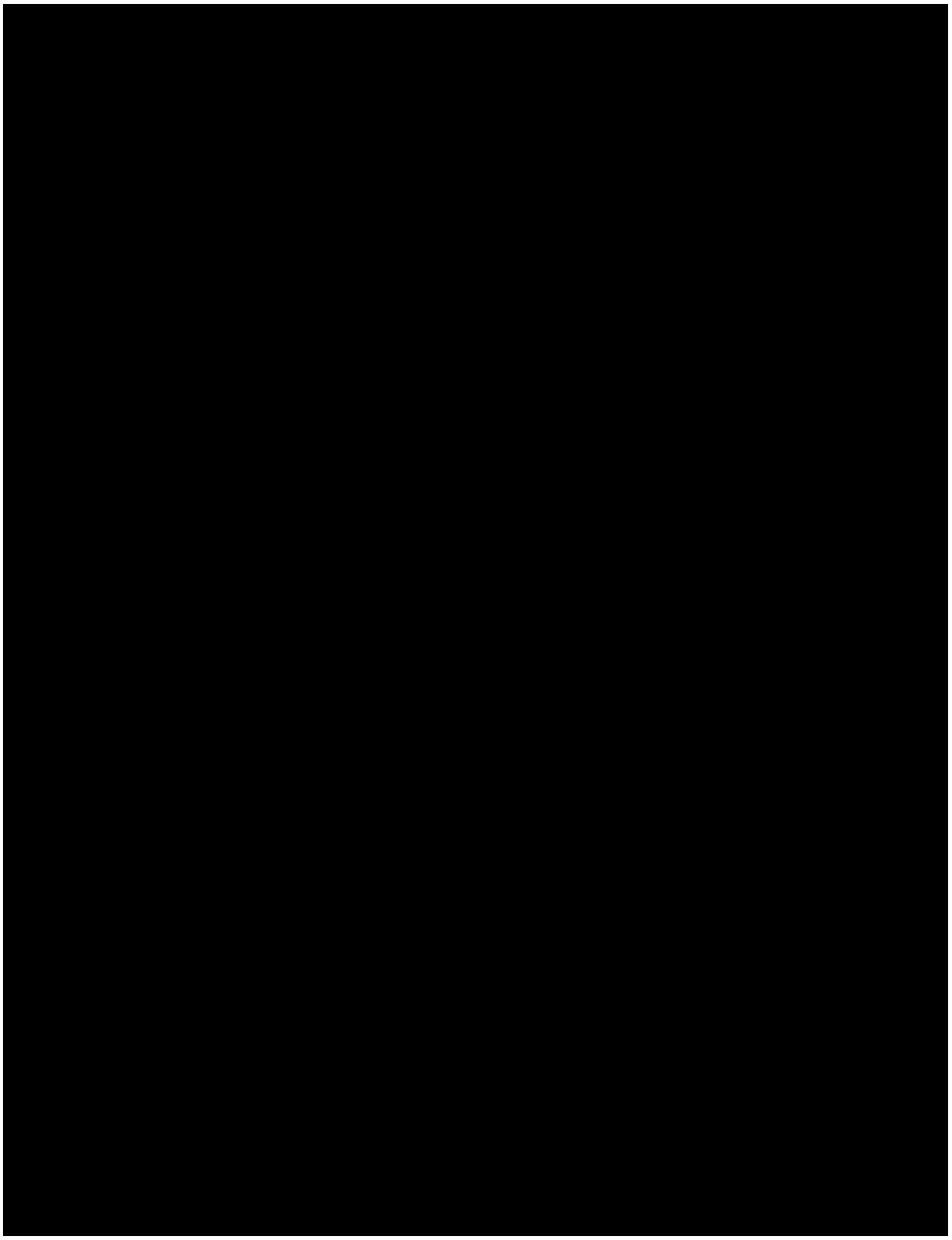

COMMENT

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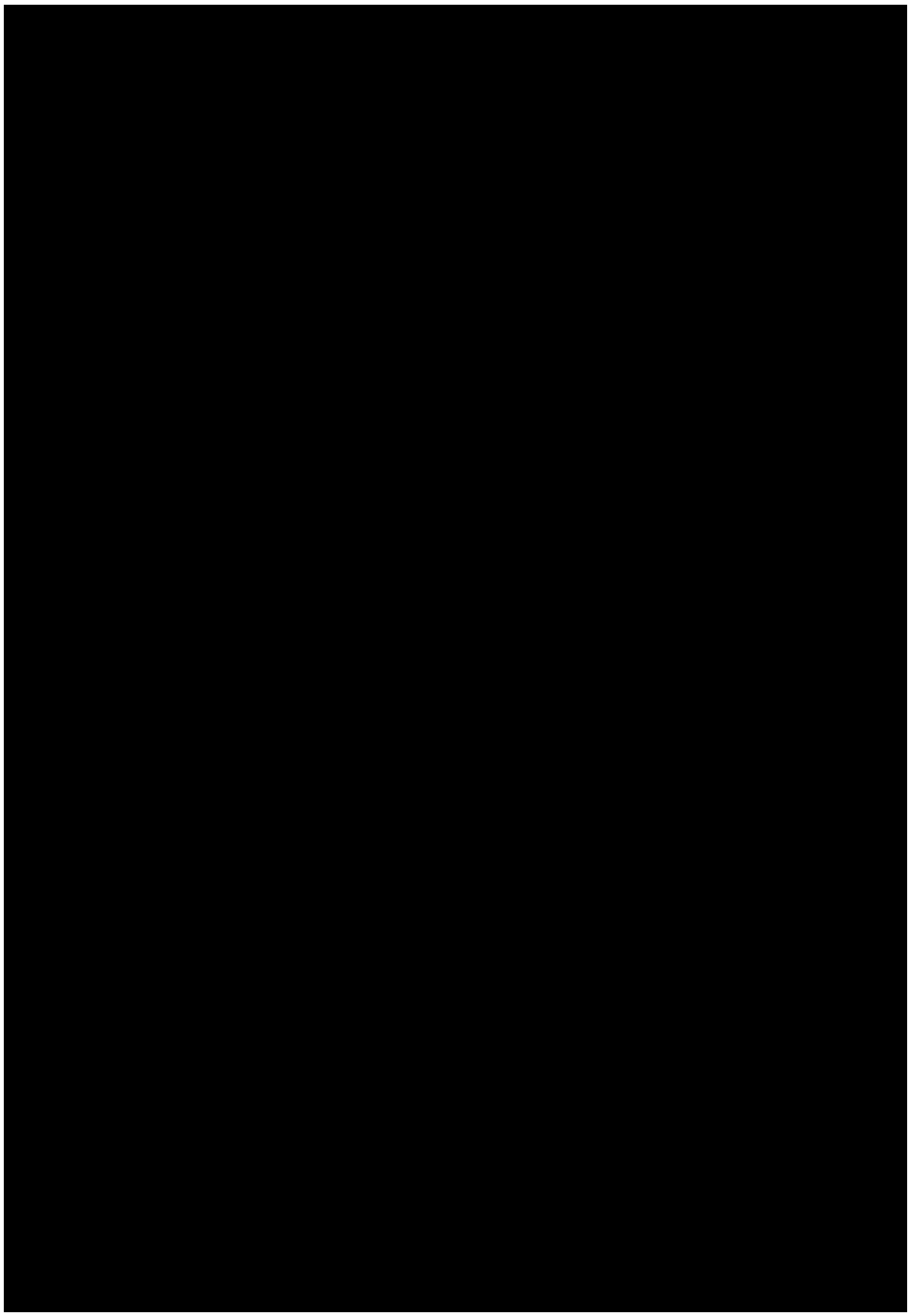
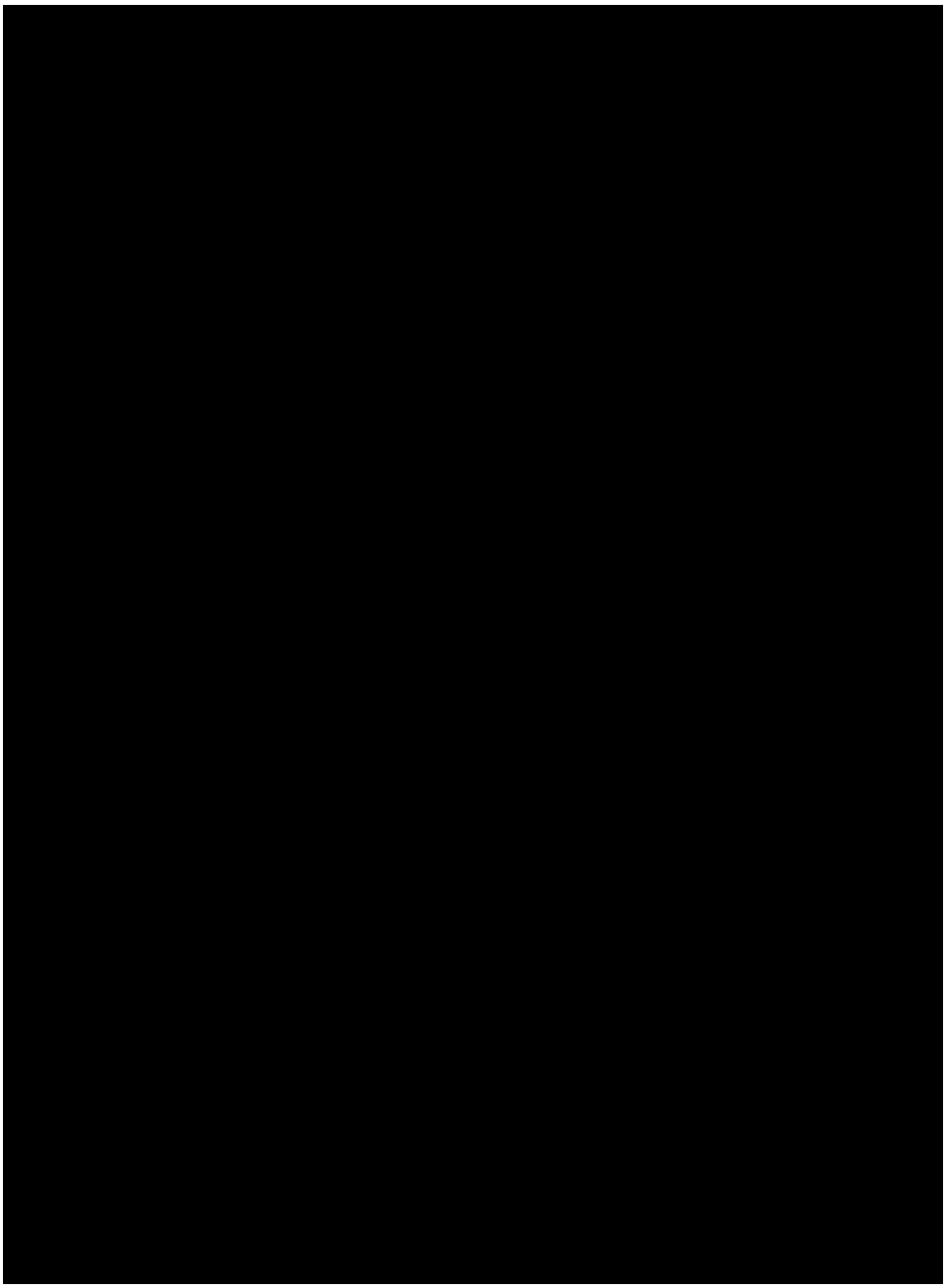
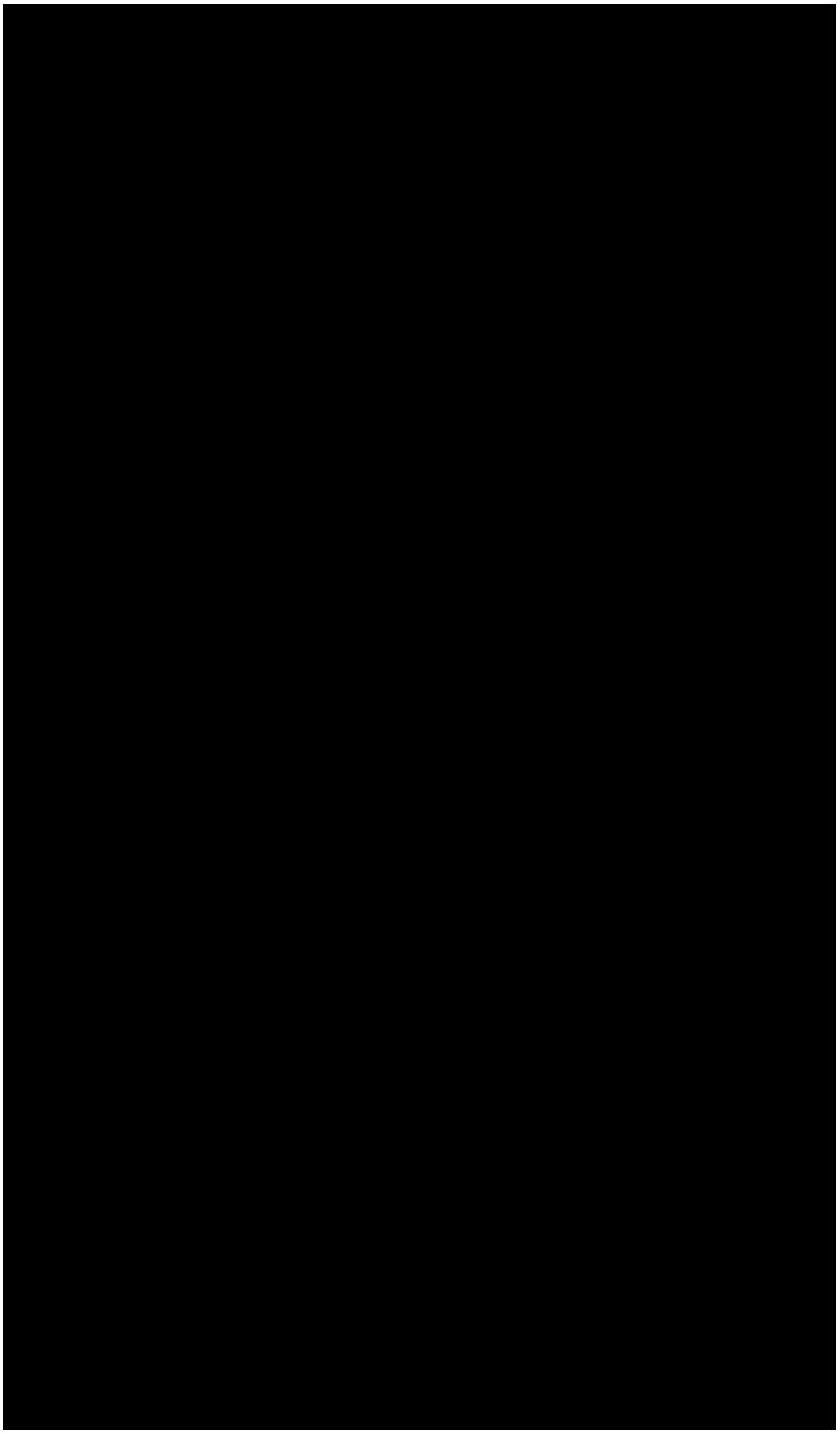
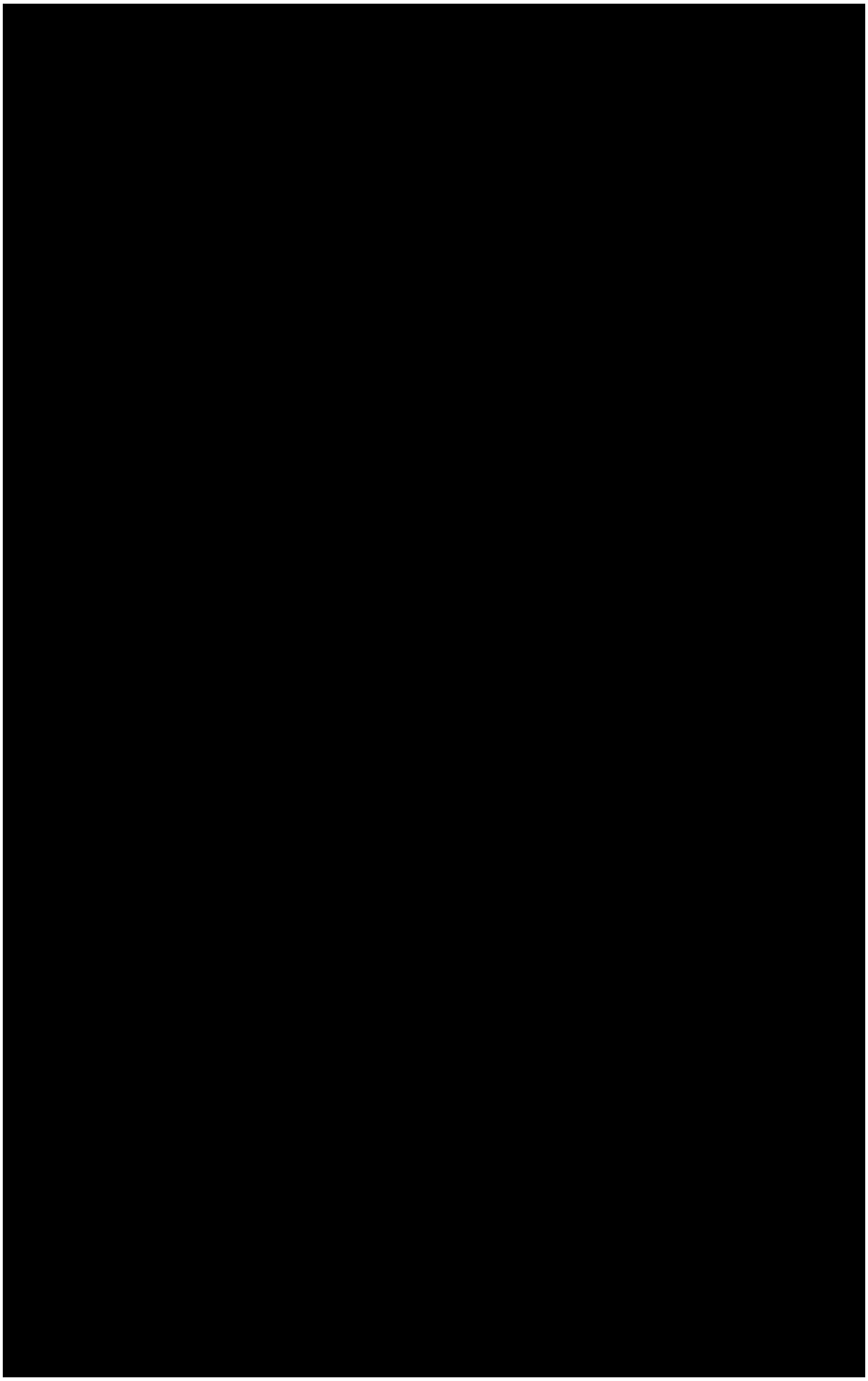
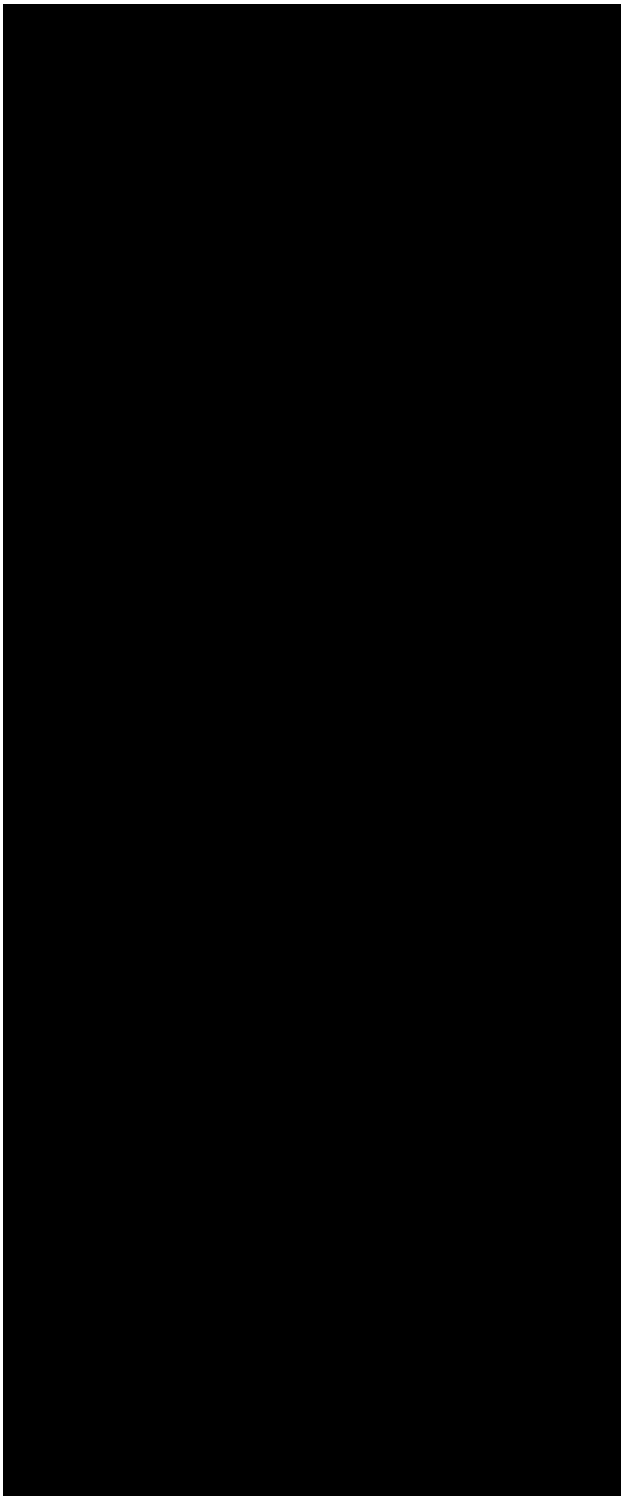
APPENDICES

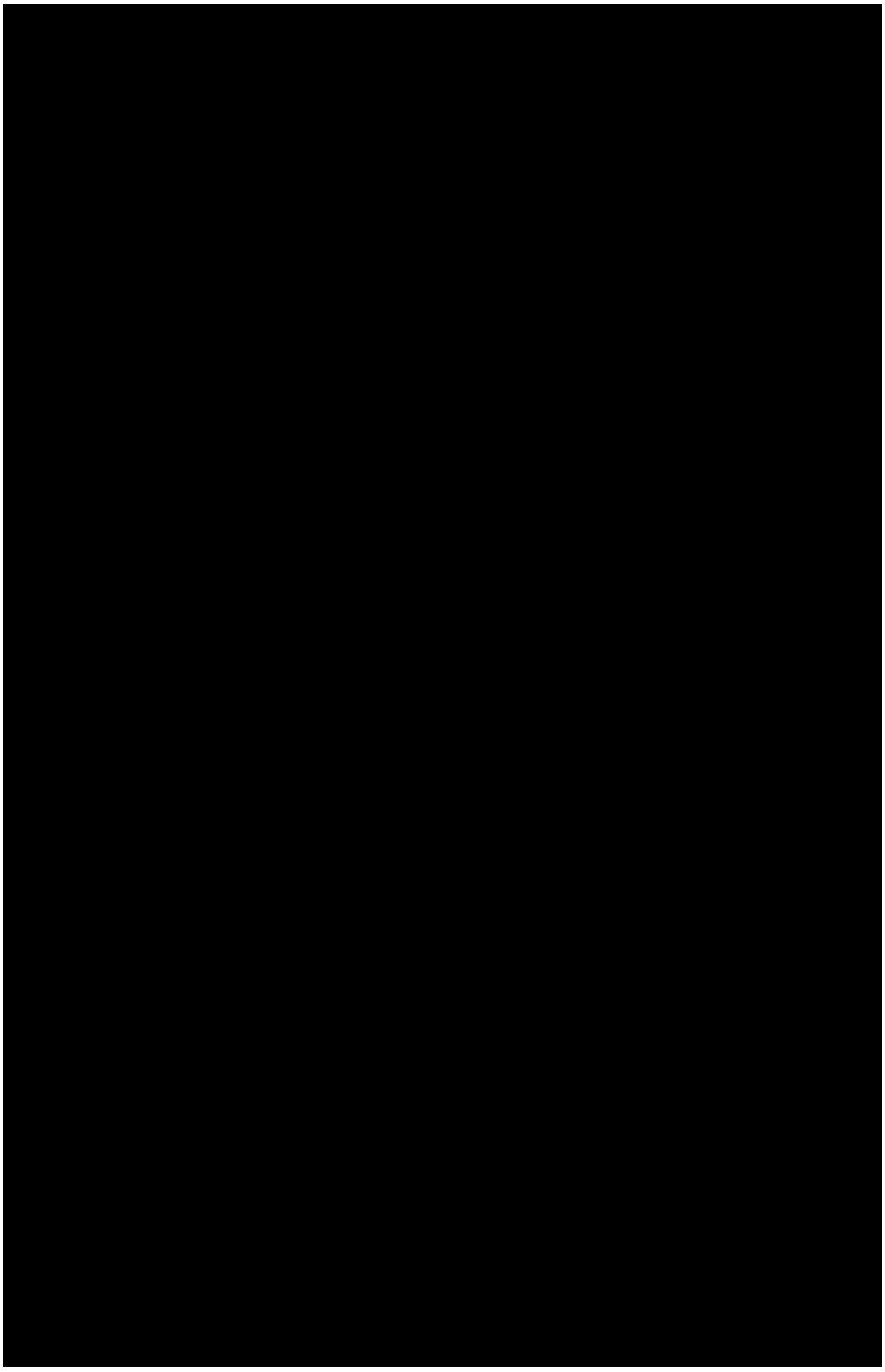


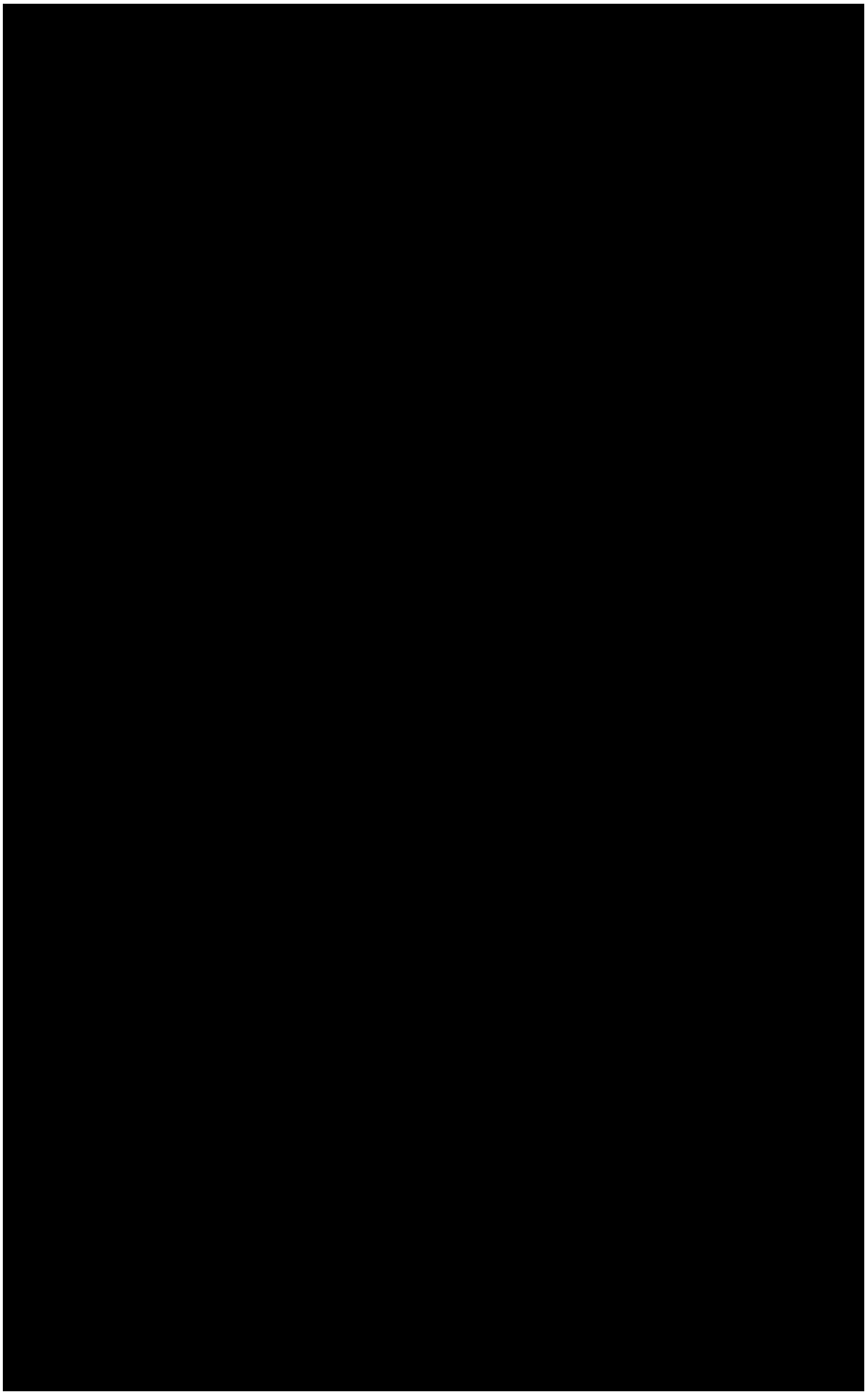


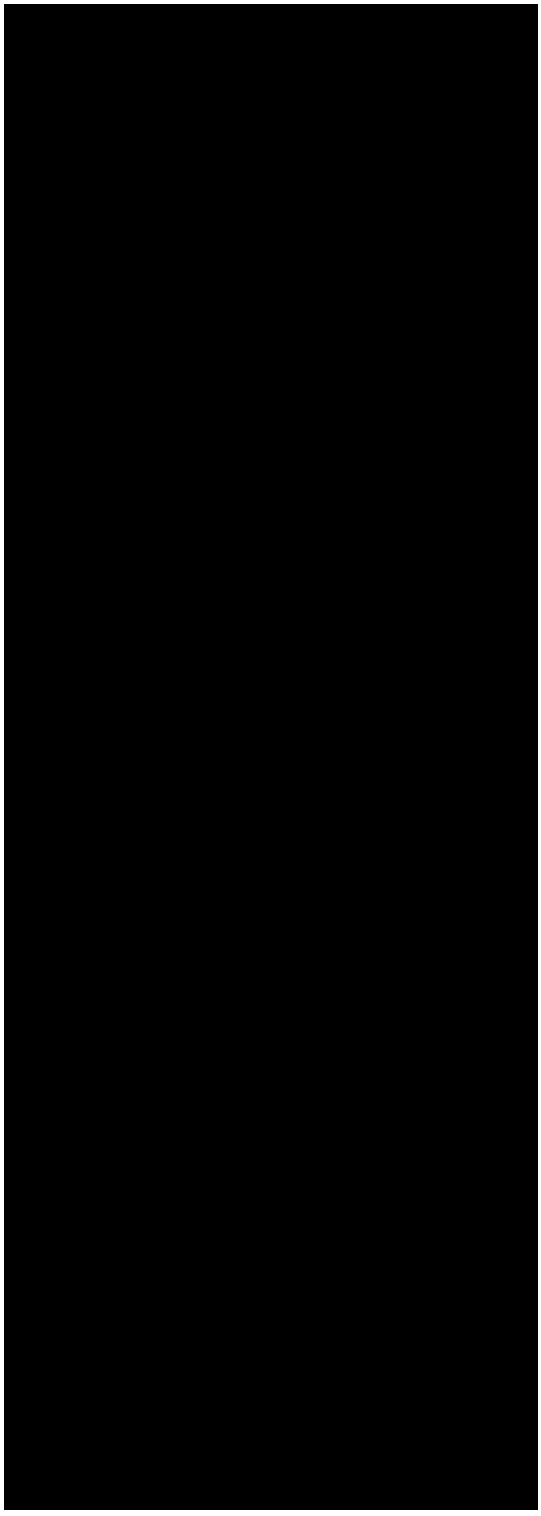


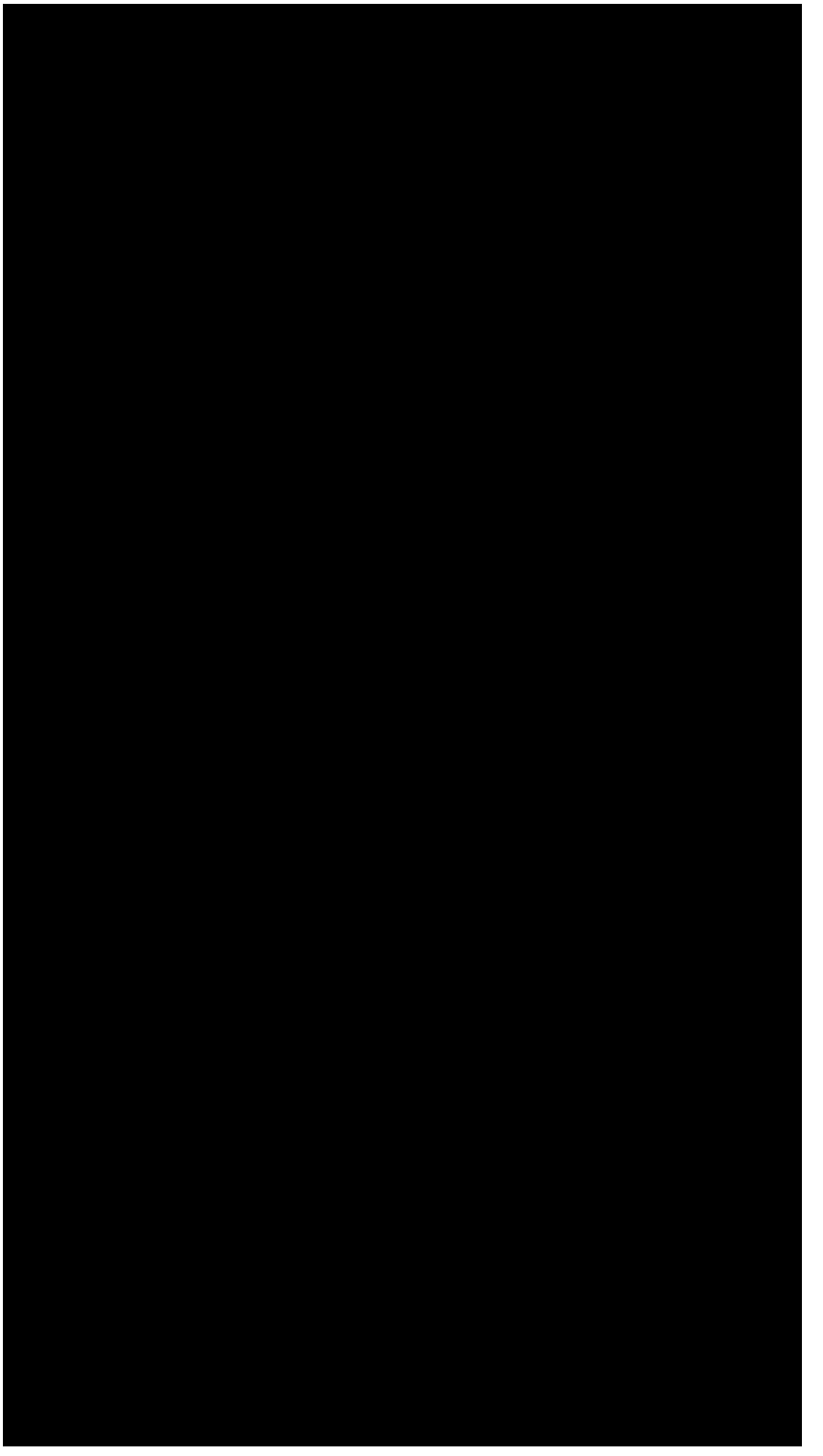


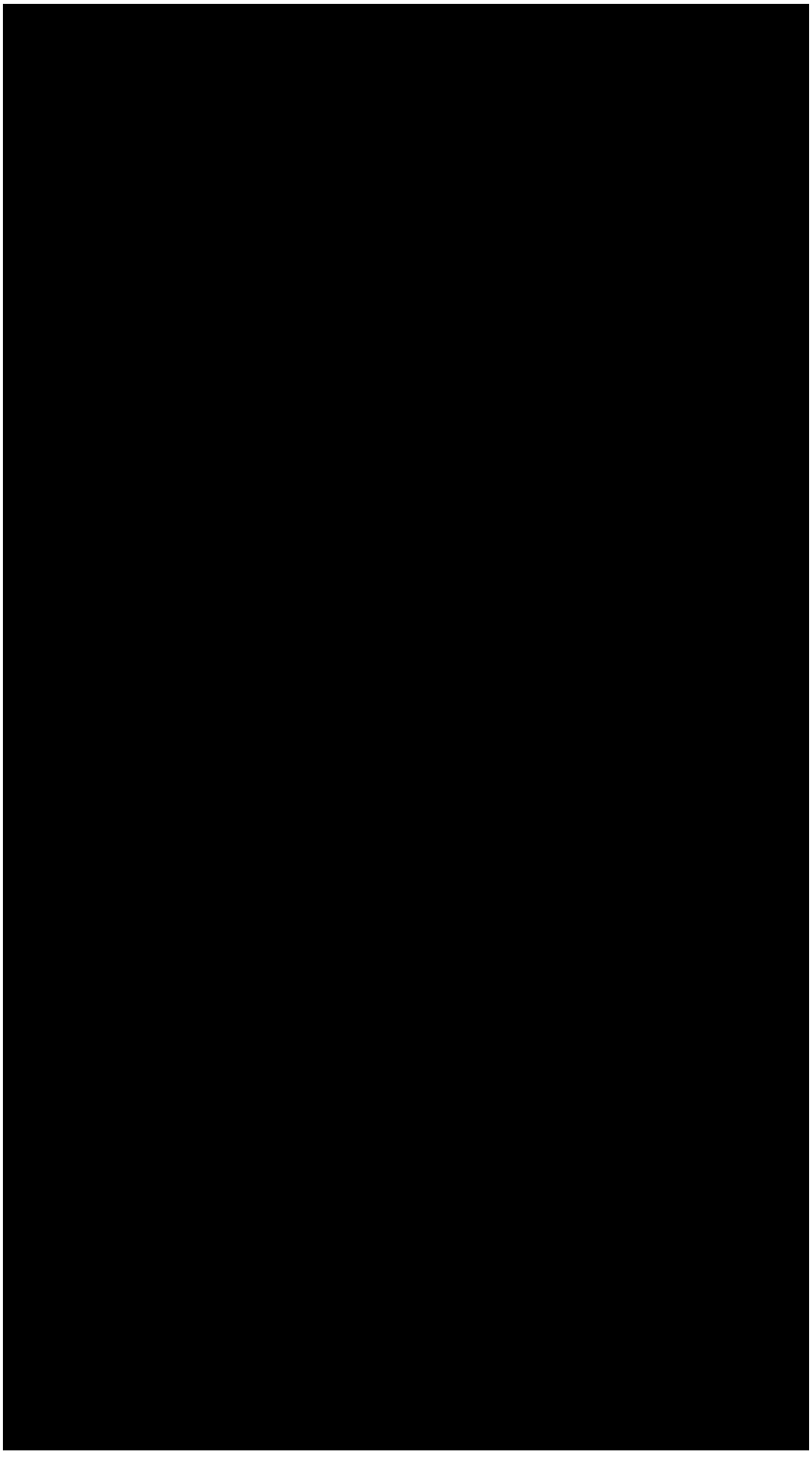


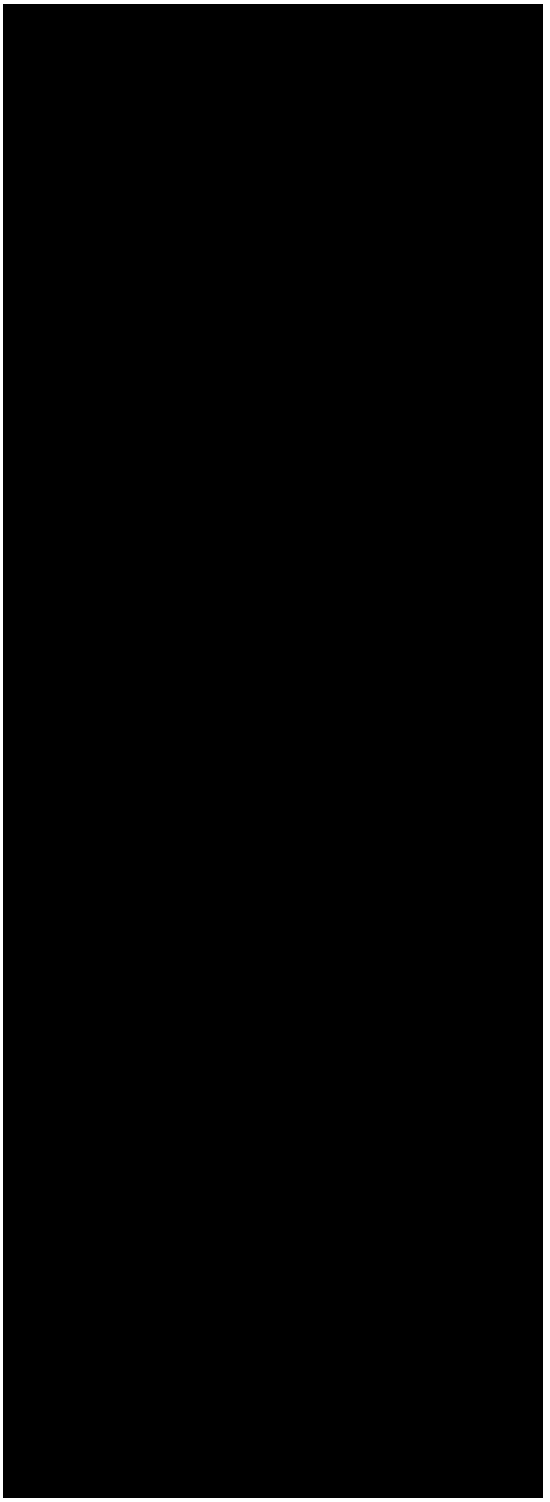


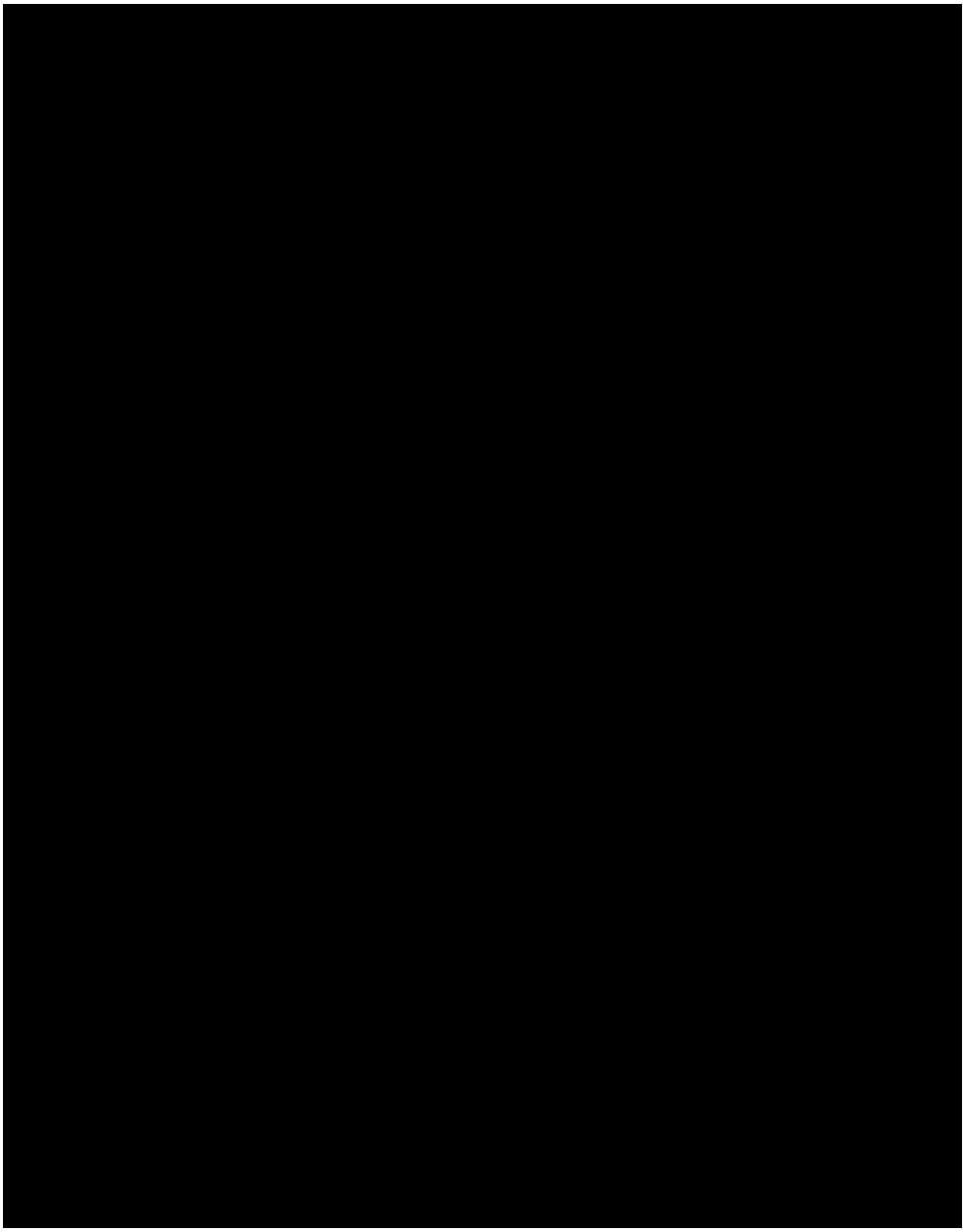


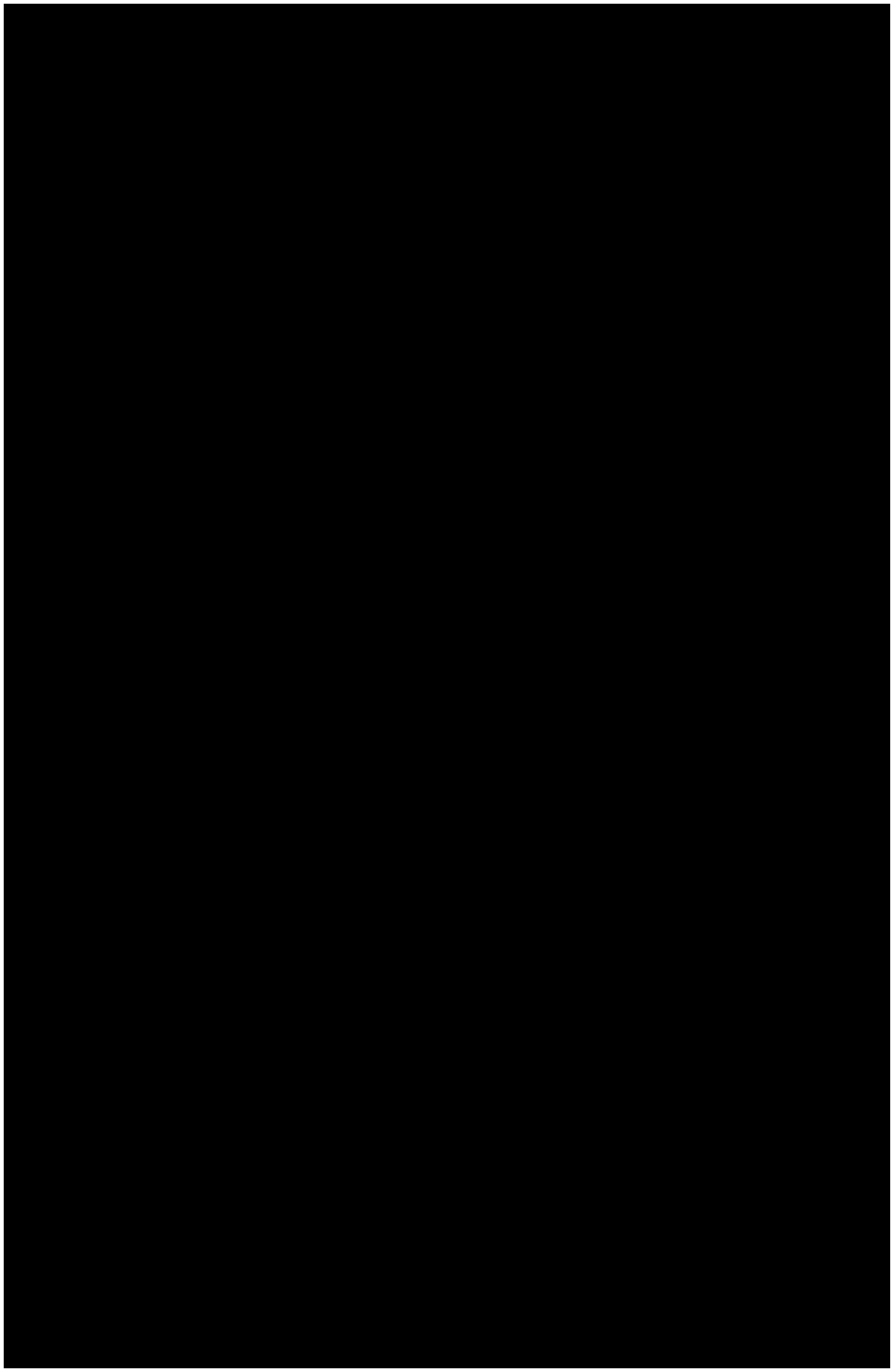












CHAPTER 7

CHANGE OF THE RESIDUAL MYOMETRIAL THICKNESS DURING PREGNANCY IN WOMEN WHO UNDERWENT LAPAROSCOPIC NICHE RESECTION COMPARED WITH CONTROLS WITHOUT NICHE SURGERY: A PROSPECTIVE COMPARATIVE COHORT STUDY

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ABSTRACT

Background

Reduced residual myometrial thickness before and during pregnancy is associated with uterine rupture or dehiscence after vaginal birth after cesarean delivery. Laparoscopic niche resection performed in case of gynecologic symptoms has shown to increase residual myometrial thickness 6 months after surgery.

Objective

This study aimed to evaluate the change in residual myometrial thickness (RMT) from baseline value before pregnancy to the third trimester of pregnancy in women with and without laparoscopic niche resection and evaluate niche presence, niche size during pregnancy versus before pregnancy, and obstetrical outcomes, including uterine rupture and dehiscence in both study groups.

Study Design

This was a prospective cohort study conducted in an academic medical center. Of note, 2 groups of pregnant women with a previously diagnosed niche were included: (1) women with a large symptomatic niche (RMT of <3 mm) followed by laparoscopic niche resection (LNR group), and (2) women with a niche without niche resection because of minimal symptoms or a RMT of ≥3 mm diagnosed before current pregnancy (expectant group). Participants underwent a transvaginal ultrasound at 12, 20, and 30 weeks of gestation. Changes in RMT and changes in niche measurements over time were analyzed with linear mixed models.

Results

A total of 100 women were included, 61 in the LNR group and 39 in the expectant group. The change in RMT from baseline value before niche resection to the third trimester of pregnancy was +2.0 mm in the LNR group versus −1.6 mm in the expectant group ($p<0.001$). RMT decreased from the first trimester of pregnancy onward in both groups. Although RMT was thinner at baseline in the LNR group, it was thicker in the LNR group than in the expectant group during all trimesters: 3.2 mm ($p<0.001$) in the first trimester of pregnancy, 2.5 mm ($p<.001$) in the second trimester of pregnancy, and 1.8 mm ($p=0.001$) in the third trimester of pregnancy. Uterine dehiscence was reported in 1 of 50 women (2%) in the LNR group and 7 of 36 women (19%) in the expectant group ($p=0.007$) and was related to the depth of niche–to–RMT ratio before pregnancy (after niche resection) and RMT in the second trimester of pregnancy. No uterine rupture was reported. Most patients received a scheduled cesarean delivery in both groups.

There was more blood loss during subsequent cesarean delivery in the LNR group than in the expectant group.

Conclusion
Here, laparoscopic niche resection resulted in an increased RMT during a subsequent pregnancy. Moreover, a lower number of dehiscence was found in the LNR group than in the expectant group without niche surgery. Per-section blood loss was higher in the LNR group than in the expectant group. In general, laparoscopic niche resection is performed to improve gynecologic symptoms. Currently, there is no evidence to support a laparoscopic niche resection to improve obstetrical outcomes, but the trend toward less uterine dehiscence encourages further research.

INTRODUCTION

A worldwide increase in the cesarean delivery (CD) rate has led to a rising number of patients with complications after a CD. A niche, defined as a defect at the site of the uterine scar with a depth of at least 2 mm, is visible with sonohysterography (with gel or saline infusion) in 60% to 70% of women after CD.[1-3] A large niche, defined as a niche with a residual myometrial thickness (RMT) of <3 mm or with a depth of >50% of the myometrial thickness, is reported in approximately 25% of all women after CD.[3,4] A niche is frequently described to be associated with long-term symptoms, including gynecologic symptoms (abnormal uterine bleeding or dysmenorrhea), fertility problems, and obstetrical complications, such as uterine dehiscence or rupture in a subsequent pregnancy.[2,5-7] The effectiveness of a uterine repair by performing a laparoscopic niche resection (LNR) has been reported for gynecologic symptoms, but little is known about the effect on obstetrical outcomes.[8-10]

RMT or thickness of the lower uterine segment (LUS) may be predictive of the risk of uterine rupture. Although no exact cutoff point is determined yet, an RMT of <3 mm before and during subsequent pregnancy was associated with uterine rupture or dehiscence after vaginal birth after CD (VBAC).[11, 12] Naji *et al.*[13] demonstrated that RMT, measured transvaginally in pregnant women with a niche, decreases as the pregnancy progresses and that niche width increases.

The influence of LNR before pregnancy on the thickness and changes of the residual myometrium in the subsequent pregnancy and its associated risk of uterine rupture or dehiscence is unknown. Therefore, we conducted a prospective cohort study, including pregnant women with a niche diagnosed before their current pregnancy. This study

aimed to compare the change in RMT from the baseline before pregnancy (before LNR in the LNR group) to the third trimester of pregnancy in women with and without previous LNR. Furthermore, we evaluated the changes in niche size in pregnancy versus baseline and related them to the obstetrical outcomes and the occurrence of uterine dehiscence.

MATERIALS AND METHODS

This prospective cohort study was conducted between February 2012 and October 2019 at the Department of Obstetrics and Gynecology, Amsterdam University Medical Centers (UMC), Amsterdam, The Netherlands. Of note, 2 groups of pregnant women with a previously diagnosed niche were included: (1) women with a large symptomatic niche (RMT of <3 mm) followed by an LNR before their current pregnancy (LNR group), and (2) women with a niche without niche surgery because of minor symptoms or relatively small niche (RMT of ≥3 mm) diagnosed before current pregnancy (expectant group). Women participated in the Niche Cohort study (www.trialregister.nl; trial number NL6844) and were included consecutively. They were referred primarily to our clinic because of symptoms, fertility problems, and presence of a niche. They received a transvaginal ultrasound (TVUS) while not being pregnant. LNR was only offered if RMT was <3 mm and if there were substantial symptoms (including abnormal uterine blood loss, dysmenorrhea, or chronic pelvic pain) or fertility problems that could be related to the niche (i.e., problems with embryo transfer because of a large niche and distorted anatomy, negatively affecting the insertion of the catheter). These women received a second TVUS after surgery. If these inclusion criteria were not met, expectant management was advised, and the participating women were asked, if pregnant, to come to our clinic for the evaluation of the niche, CD scar, and residual myometrium thickness during the pregnancy. This study was approved by the local research and ethics committee, including follow-up during pregnancy. Informed consent was obtained from all women.

Laparoscopic niche resection

Here, details of the LNR technique have been described and illustrated in a step-by-step tutorial by Huirne *et al.*[14]. The LNR was performed by 2 of 3 experienced gynecologists (J.A.F.H., W.J.K.H., and R.A.D.L.) and guided using hysteroscopy. The bladder was filled with 200 mL blue dye solution. Next, the niche was opened using a monopolar hook and excised with a cold scissor. All fibrotic tissue was excised. The wound was sutured in 2 layers, approximating the full thickness, including the endometrium. The first suture layer included 4 separate Vicryl sutures, and the second layer was a single double inverting suture. An adhesion barrier (hyaluronic acid) was used. In the case of an extreme retroflexed uterus,

the round ligaments were shortened to minimize counteracting forces on the wound. The anatomic result was assessed at the end of the procedure using hysteroscopy.

Niche evaluation

Participants received a TVUS at 12, 20, and 30 weeks of gestation using a Samsung Accuvix A30 or Samsung WS80 ultrasound machine (Medison, Hoofddorp, The Netherlands). Niche evaluation performed before pregnancy according to study protocol of the Niche Cohort study was included in this study. In the LNR group, niches had been evaluated both before and after an LNR. Here, we focused on the measurement before niche resection (mentioned as "baseline") to study the effect of the surgery. During each visit, RMT and the length and depth of the niche were measured in the sagittal plane, and the width of the niche was measured in the transversal plane following the standardized guideline concerning niche evaluation in non-pregnant women (Figure 1).[1] If a niche was not visible (because of the progress of pregnancy), only thickness of the LUS was measured at its thinnest point. Of note, 4 researchers (J.A.F.H, W.J.K.H., I.P.M.J., and R.A.D.L.), who are all experienced in niche evaluation, performed the measurements. No gel or saline contrast sonography was performed during pregnancy. Patients were informed of the ultrasound findings.

All sonographic images were stored digitally. The measurements were randomly checked whether they corresponded to the original. Previous studies showed good to excellent inter- and intraobserver agreement on niche measurement.[15]

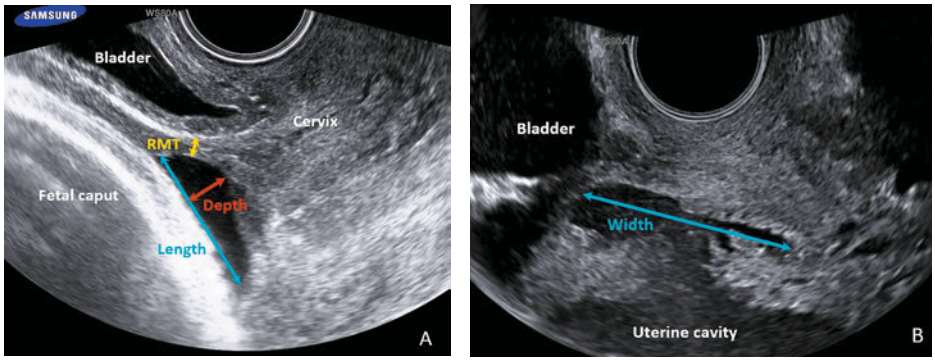

Figure 1. Niche measurements in pregnancy according to Jordans et al.[11] using transvaginal ultrasound

An example of measurement in 3rd trimester of pregnancy. A, Measurements in the sagittal plane: length and depth of the niche, and RMT. B, Measurement in the transversal plane: width of the niche. RMT, residual myometrial thickness

Peri- and postpregnancy characteristics

Patient characteristics and obstetrical and medical history, including number of previous CDs, were obtained in the first trimester of pregnancy at their first scan visit. Niche characteristics before pregnancy were collected on a routine basis in the Niche Cohort database.

According to the local protocol, a scheduled CD was advised after LNR independent of the RMT during a subsequent pregnancy. In the expectant group, the mode of delivery was individualized by the gynecologist and patient. In general, a scheduled CD was advised to be performed at 39 weeks of gestation, independent of the niche measurements. However, in case of a very thin or absent residual myometrium, we mostly advised scheduling the CD between 38 and 39 weeks of gestation or earlier in case of premature contractions. CD was performed early only if women had contractions. Obstetrical care was mostly provided by gynecologists in other Dutch hospitals. Obstetrical outcomes were collected from the medical file of Amsterdam UMC, if applicable, or were requested and collected after the patient's signed approval from the hospitals where the women gave birth. All data were recorded in a paper case report form and a web-based database by the researcher and the research nurse. Reporting was performed according to the guideline for reporting a prospective study (Strengthening the Reporting of Observational Studies in Epidemiology).[16]

Outcome measures

The primary outcome was RMT in the third trimester of pregnancy versus baseline before pregnancy in the expectant group and before LNR in the LNR group. The secondary outcome measures included RMT after LNR (before pregnancy) and in the first and second trimesters of pregnancy, niche presence and niche measurements in all trimesters of pregnancy, and obstetrical outcomes (gestational age (GA) at the time of delivery, mode of delivery, uterine dehiscence or rupture, blood loss, birthweight, Apgar score, and admission to the neonatal intensive care unit). The blood loss was the registered blood loss in the surgical report. We did not define a clear method to measure the blood loss during the CD; we could not exclude potential contamination with amniotic fluid. Furthermore, the depth of niche–to–RMT (D/RMT) ratio before pregnancy (after LNR) was calculated to determine the possible relation with uterine dehiscence. "Pre-pregnancy" was determined as after an LNR in the LNR group and before pregnancy in the expectant group. According to Pomorski *et al.*[17], this ratio is of prognostic value on uterine dehiscence; a high D/RMT ratio (>1) was previously reported to be strongly related to uterine dehiscence.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 26; SPSS Inc, Chicago, IL). Demographic data were presented as number (percentage) for categorical variables and mean±standard deviation (SD) or median (interquartile range [IQR]) for continuous variables. The differences in baseline characteristics were compared using the independent sample *t* test, chi-square test, or Fisher exact test, depending on the type and distribution of the variables. The distributions of the residuals were assessed by visual inspection as normal, allowing the performance of a linear mixed model analysis. Changes in RMT and changes in niche measurements over time were analyzed with linear mixed models. The differences in pregnancy outcomes were analyzed using chi-squared test, Fisher exact test, independent *t* test, or Mann-Whitney U test, depending on the distribution of the variables. A 2-tailed p value of <0.05 was considered statistically significant.

RESULTS

Inclusion and baseline characteristics

A total of 101 pregnant women were eligible to participate in the study (Figure 2). Of note, 1 woman was excluded because she did not attend the ultrasound appointments despite informed consent. Of the 100 women who were included in our analyses, 61 underwent a previous LNR, and 39 received expectant management before pregnancy. Moreover, 4 women in the expectant group indicated an LNR but were pregnant before their scheduled surgery; thus, their surgery was canceled. Of note, 6 baseline niche measurements were missing in the expectant group, and 1 baseline niche measurement was missing in the LNR group. Ultrasound measurements were reported in 84% to 97% at the different moments in pregnancy. Baseline characteristics are presented in Table 1. Most women had only 1 previous CD (80% in the LNR group and 69% in the expectant group). All previous CDs were performed with a transversal incision in the LUS. Of note, 6 women were diagnosed with preeclampsia or hemolysis, elevated liver enzymes, and low platelet count during the previous CD: 5 in the LNR group and 1 in the expectant group. Moreover, 1 woman (in the LNR group) had a previous uterine rupture before her LNR. The interval between pre-pregnancy uterotomy and onset of current pregnancy was significantly shorter in the LNR group than in the expectant group (p<0.001) (Table 1 and Supplemental Figure).

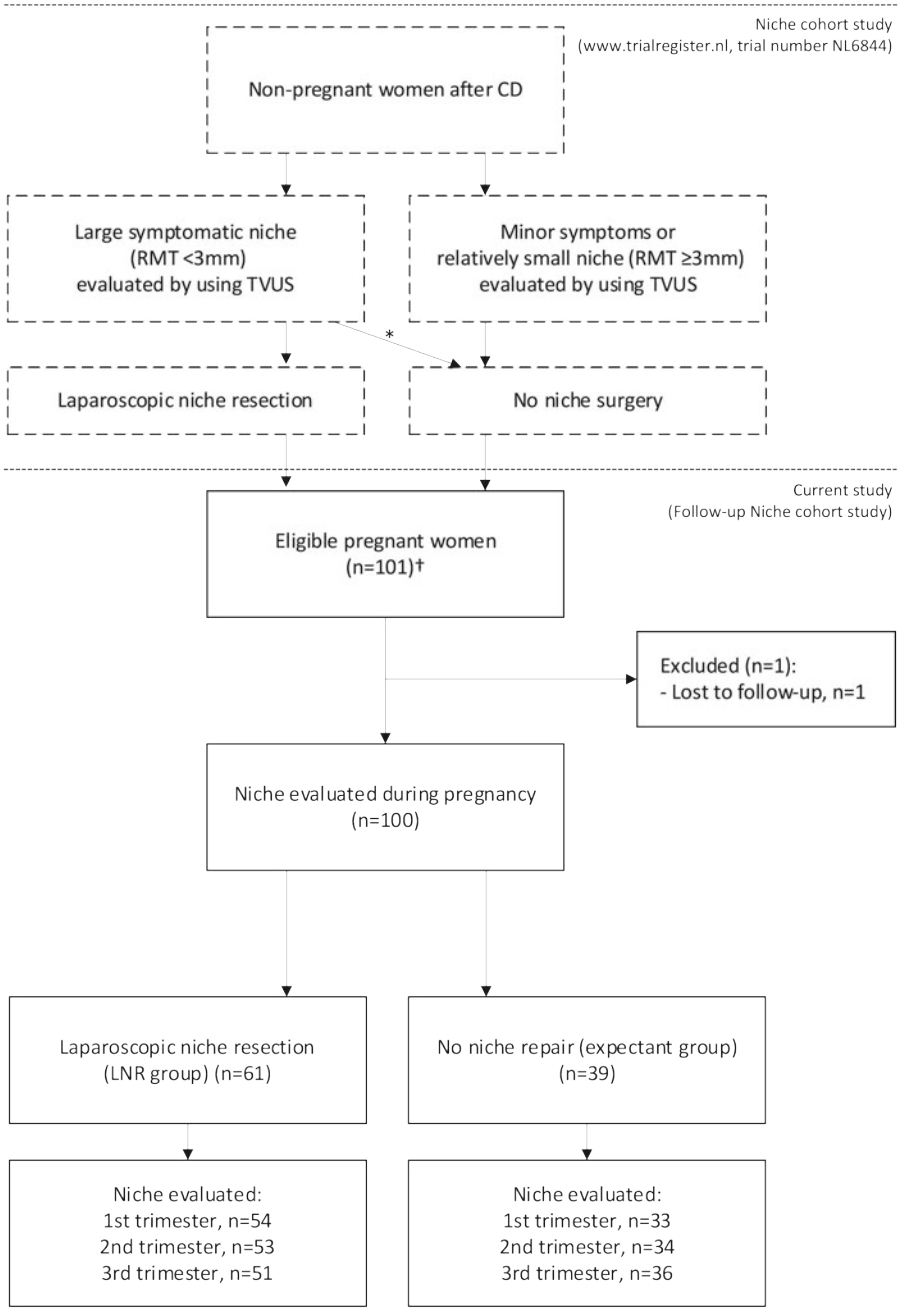

Figure 2. Flow diagram of study participants

* Pregnancy before scheduled niche surgery with no laparoscopic niche resection. † Consecutive inclusion. CD, cesarean delivery; TVUS, transvaginal ultrasound

Table 1. Baseline characteristics of study group

Characteristics	LNR group (n=61)	Expectant group (n=39)	p value
Age (y)	34.5 ± 3.5	34.1 ± 4.2	0.542
BMI (kg/m^2)	24.2 ± 3.4	24.6 ± 4.9	0.215
Smoking	3 (5%)	6 (15%)	0.148
Parity	1 (1-2)	1 (1-2)	0.351
No. previous CSs			0.438
1	49 (80%)	27 (69%)	
2	10 (17%)	9 (23%)	
3	2 (3%)	2 (5%)	
4	0	1 (3%)	
Indication first CS			0.024
Primary CS	24 (39%)	5 (13%)	
Secondary CS	33 (54%)	31 (80%)	
Failed progression 1st stage of labor	19	12	
Failed progression 2nd stage of labor	3	6	
Fetal distress	11	11	
Maternal indication	0	2	
Unknown	4 (7%)	3 (7%)	
Time between previous uterotomy[a] and subsequent pregnancy[b], in months	10 (7-15)	33 (21-45)	<0.001
Large niche (RMT <3 mm)	60 (98%)	19 (49%)	<0.001
RMT <2 mm	49 (80%)	11 (28%)	<0.001
Pregnant in waiting time for niche resection	NA	4 (10%)	NA

Data are reported as mean ± standard deviation, number (percentage), or median (interquartile range), unless otherwise indicated. a Uterotomy includes laparoscopic niche resection in the LNR group and previous CD in the expectant group; b First day of the last menstrual period. BMI, body mass index; CD, cesarean delivery; NA, not applicable; RMT, residual myometrial thickness.

At baseline, the median RMT was 1.0 mm (IQR, 0.6–1.8) in the LNR group versus 2.5 mm (IQR, 1.6–4.0) in the expectant group. After an LNR, median RMT increased to 6.2 mm (IQR, 4.6–8.9).

The median GA at the time of niche evaluation was 12 4/7 weeks of gestation (IQR, 11 4/7 to 13 6/7) in the first trimester of pregnancy, 20 3/7 weeks of gestation (IQR, 19 6/7 to 21 4/7) in the second trimester of pregnancy, and 30 2/7 weeks of gestation (IQR, 29 6/7 to 31 0/7) in the third trimester of pregnancy. The niche was visible in 79% of all

patients during the first trimester of pregnancy, in 78% of all patients during the second trimester of pregnancy, and in 62% of all patients in the third trimester of pregnancy.

Residual myometrial thickness during pregnancy

The change in RMT from baseline to the third trimester of pregnancy was +1.2 mm (1.0 mm [IQR, 0.6–1.8] at baseline and 2.2 mm [IQR, 1.6–4.8] in the third trimester of pregnancy) in the LNR group, whereas the change in RMT from baseline to the third trimester of pregnancy was −1.2 mm (2.5 mm [IQR, 1.6–4.0] at baseline and 1.3 mm [IQR, 0.7–2.2] in the third trimester of pregnancy) in the expectant group (p<0.001) (Table 2).

Table 2. Outcome measures at different time points for both groups

Measurements (mm)	Baseline	GA at 12 weeks	GA at 20 weeks	GA at 30 weeks
RMT				
Lapniche	1.0 (0.6-1.8)	5.3 (3.8-9.0)	4.8 (2.7-7.8)	2.2 (1.6-4.75)
Expectant	2.5 (1.6-4.0)	2.3 (1.6-4.0)	1.6 (1.1-3.6)	1.3 (0.7-2.2)
Niche length				
Lapniche	NA	6.3 (3.9-8.8)	7.4 (5.0-9.6)	8.8 (5.1-19.4)
Expectant	NA	6.3 (4.1-7.5)	7.0 (4.4-14.1)	17.4 (8.5-23.3)
Niche depth				
Lapniche	NA	5.9 (4.1-7.9)	4.3 (2.6-7.4)	4.0 (2.2-6.9)
Expectant	NA	5.5 (3.6-8.8)	6.7 (3.1-8.6)	7.3 (3.9-9.2)
Niche width				
Lapniche	NA	9.0 (5.2-18.1)	9.8 (5.2-18.1)	16.4 (4.5-27.0)
Expectant	NA	8.0 (3.8-14.3)	8.5 (5.7-17.9)	14.9 (10.6-22.6)

Data are presented as median (interquartile range). GA, gestational age; NA, not applicable; RMT, residual myometrial thickness.

Figure 3 shows the course of RMT over time in both study groups. During pregnancy, a gradual decline was observed in both groups from the first trimester of pregnancy onward. However, mixed model analysis (Table 3) showed that RMT was significantly thicker in the LNR group than in the expectant group during the entire pregnancy; RMT was 3.2 mm thicker (p<0.001) in the first trimester of pregnancy, 2.5 mm thicker (p<0.001) in the second trimester of pregnancy, and 1.8 mm thicker (p=0.001) in the third trimester of pregnancy. Similar results were found in the analysis of only women with 1 previous CD.

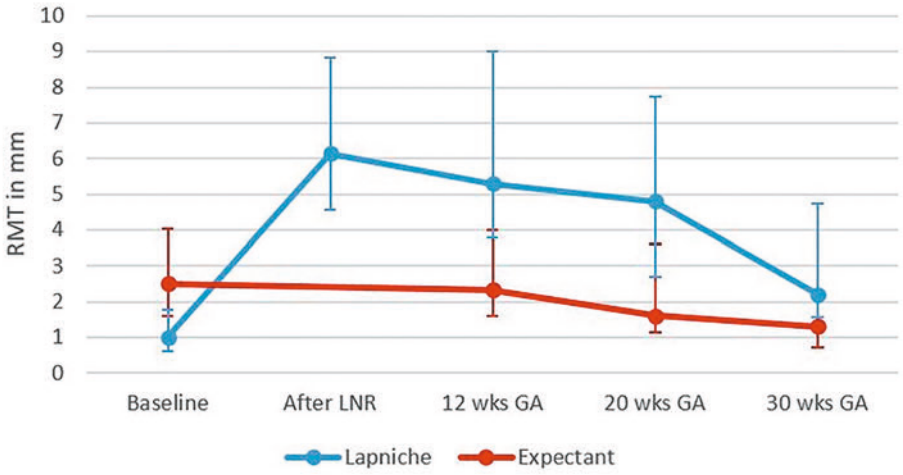

Figure 3. Median RMT over time in study group

GA, gestational age; LNR, laparoscopic niche resection; RMT, residual myometrial thickness

Change in niche size during pregnancy

Both niche length and width showed an increase during pregnancy in both groups, but no substantial difference was observed between the groups at different time points (Tables 2 and 3). Niche depth did not change substantially during pregnancy in both groups.

Obstetrical outcomes

Pregnancy outcomes were obtained in 86 of 100 women (50 in the LNR group and 36 in the expectant group) (Table 4). All pregnancies were singletons apart from 1 twin pregnancy in each group. The median GA at delivery was 38 0/7 weeks of gestation (IQR, 36 5/7 to 38 6/7) in both groups. Most women received a repeat CD; this was consistent in both groups. No uterine rupture was reported. Uterine dehiscence was reported during the CD in 8 patients: 1 of 50 (2%) in the LNR group and 7 of 36 (19%) in the expectant group (p=0.008). Blood loss of >1000 mL during CD was only reported in the LNR group (10 [20%]). Table 4 shows the reported reasons. No difference in neonatal outcomes was observed between the study groups (Table 4).

Table 3. Analysis of outcome measures at different time points

Measurements (mm)	Baseline			12 weeks GA			20 weeks GA			30 weeks GA		
	Diff[a]	95% CI	p	Diff[a]	95% CI	p	Diff[a]	95% CI	p	Diff[a]	95% CI	p
RMT	-1.8	-2.8 – -0.9	<0.001	+3.2	2.1 – 4.2	<0.001	+2.5	1.5 – 3.4	<0.001	+1.8	0.7 – 2.8	0.001
Niche length	NA	NA	NA	+1.5	-2.0 – 4.9	0.406	-1.1	-4.6 – 2.4	0.546	-3.4	-7.1 – 0.3	0.069
Niche depth	NA	NA	NA	-0.2	-1.9 – 1.4	0.773	-0.8	-2.5 – 1.0	0.394	-1.4	-3.4 – 0.5	0.141
Niche width	NA	NA	NA	+1.1	-4.4 – 6.7	0.687	-0.4	-6.0 – 5.3	0.902	-0.5	-6.9 – 5.8	0.869

Data show the presentation of the linear mixed model analysis. a Difference of means between LNR group compared with expectant group is presented. Residuals of measurements were evaluated as normally distributed. CI, confidence interval; Diff, difference; GA, gestational age; NA, not applicable; RMT, residual myometrial thickness.

Table 4. Pregnancy outcomes

Outcome	LNR group (n=50)	Expectant group (n=36)	p value
GA at delivery	37+5 (36+4-38+4)	38+2 (37+2-39+1)	0.102
Mode of delivery			0.653
CS	48 (96%)	33 (92%)	
Scheduled (no contractions)	46	32	
Not scheduled (after contractions)	2	1	
VBAC	2 (4%)[a]	3 (8%)	
Uterine dehiscence	1 (2%)	7 (19%)	0.007[b]
Uterine rupture	0	0	NA
Blood loss >1000 mL	10 (20%)[c]	0	0.004
Birth weight	3,002 ±730	3,228 ±612	0.123
Apgar score			
After 1 minute	9 (8-9)	9 (9-9)	0.431
After 5 minutes	10 (9-10)	10 (9-10)	0.385
Admission to NICU	13 (26%)	9 (25%)	0.830

Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range), unless otherwise indicated. a Of note, 2 women in the LNR group had a vaginal delivery because of fetal death. Of these, 1 woman had a spontaneous immature delivery because of chorioamnionitis at 22 weeks of gestation. The other woman had an unexplained intrauterine fetal death at 29 weeks of gestation and delivered vaginally after induction of labor. She had 1 previous CD on maternal indication (preeclampsia); b P value was calculated, including women that underwent a scheduled CD only and excluding women with VBAC; c Reported reasons were placenta accreta (n=1), placenta previa (n=1), retention placentae after vaginal delivery (n=1), intra-abdominal blood loss of unknown cause (n=1), and insufficient hemostasis (n=3). However, in 3 women, cause of blood loss was not reported. CD, cesarean delivery; GA, gestational age; NA, not applicable; NICU, neonatal intensive care unit; VBAC, vaginal birth after cesarean delivery.

Residual myometrial thickness during pregnancy in women with a uterine dehiscence

Most women with dehiscence underwent ≥2 previous CDs. The measurements of RMT before and during pregnancy of the 8 cases with uterine dehiscence are presented in Table 5. At baseline, the RMT was <3 mm in 3 cases; in 1 case, the baseline RMT was unknown. The mean RMT was thinner during all trimesters in women with dehiscence than in women without dehiscence. The RMT in the second trimester of pregnancy seemed to have the best discriminating value for dehiscence at term (Figure 4).

Table 5. Depth of niche–to–residual myometrial thickness ratio in cases with uterine dehiscence

Group	No.	Number of previous CSs	RMT before pregnancy[a] (mm)	RMT in 1st trimester (mm)	RMT in 2nd trimester (mm)	RMT in 3rd trimester (mm)	D/RMT ratio pre-pregnancy[a]	D/RMT ratio 1st trimester
LNR	1	1	4.6	–[b]	–[b]	1.5	0.4	–[b]
Expectant	2	1	4.0	–[b]	–[b]	2.2	1.8	–[b]
	3	2	4.6	–[b]	–[b]	–[b]	NA	–[b]
	4	2	2.0	2.2	0	–[b]	8	1.9
	5	2	2.5	2.1	1.4	0	3.5	5.7
	6	4	–[b]	3	0	0	NA	0.8
	7	3	1.8	0.5	0	0	3.1	19.8
	8	3	5.0	4.7	1.5	1	0.8	2.3

a After niche resection and before pregnancy in the LNR group and before pregnancy in the expectant group; b Indicates missing data. CD, cesarean delivery; D/RMT ratio, depth of niche–to–residual myometrial thickness ratio; NA, not applicable; RMT, residual myometrial thickness.

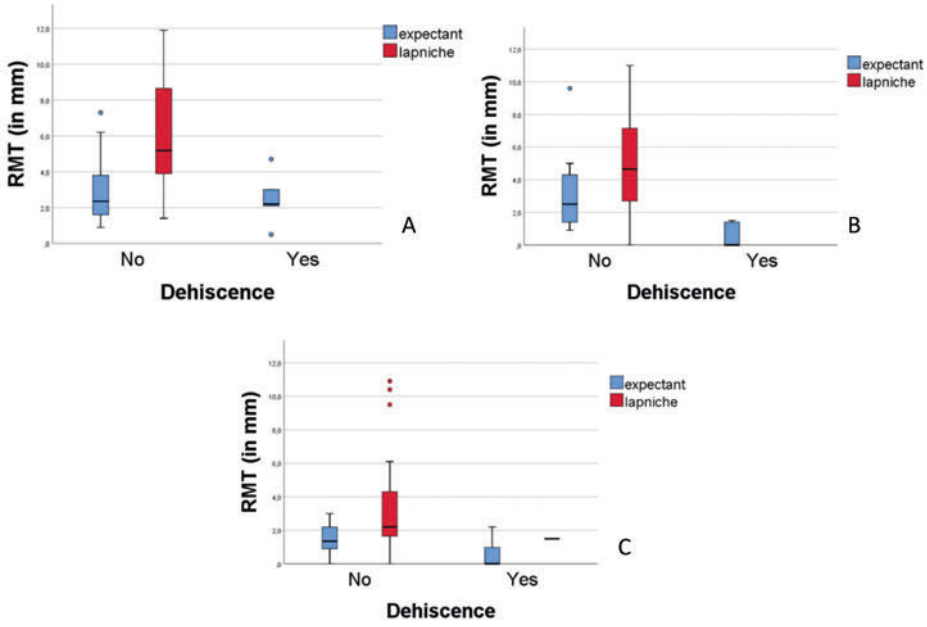

Figure 4. Boxplot of median RMT in pregnancy (in mm) in women with or without dehiscence

A. First trimester of pregnancy. B. Second trimester of pregnancy. C. Third trimester of pregnancy. The RMT in the first and second trimester of pregnancy of 1 case with uterine dehiscence in the LNR group is missing. RMT, residual myometrial thickness

Depth of niche–to–residual myometrial thickness ratio before pregnancy

D/RMT ratio before pregnancy is associated with a higher risk of uterine dehiscence or rupture. The median D/RMT ratio just before pregnancy was significantly higher in the expectant group than in the LNR group after LNR (2.5 [IQR, 1.9–3.8] and 0.6 [IQR, 0.4–1.0], respectively; p<0.001). Moreover, the number of women with a D/RMT ratio of >1, which indicates that niche depth is larger than the RMT, just before pregnancy was significantly higher in the expectant group (56%) than in the LNR group (23%) (p<0.001).

COMMENT

Principal findings

The change in RMT from baseline (before pregnancy in the expectant group and before LNR in the LNR group) to the third trimester of pregnancy was +1.2 mm in the LNR group versus −1.2 mm in the expectant group (p<0.001). Despite a smaller mean RMT at baseline in the LNR group, the mean RMT remained larger during all trimesters in the LNR group than in the expectant group. Uterine dehiscence was more prevalent

in the expectant group and was associated with a smaller RMT during pregnancy if measured during the second trimester of pregnancy and with a D/RMT ratio just before pregnancy. Per-section blood loss was higher in the LNR group than in the expectant group. Neonatal outcomes were similar in both groups.

Results in the context of what is known

To the best of our knowledge, no previous study has reported on uterine CD scar evaluation during pregnancy and related these findings to obstetrical outcomes after an LNR. Few studies[18-20] reported on obstetrical outcomes after LNR, but no sonographic measurement was performed during a subsequent pregnancy.

There are previous studies that evaluated the relation between RMT and thickness of the LUS in women with a previous CD. In line with our findings, a gradual decrease in RMT and thickness of the LUS during pregnancy in women with a previous CD was reported.[13, 21-24] Of note, 1 previous study evaluated the thickness of the LUS in the third trimester of pregnancy and found a correlation with uterine rupture or dehiscence.[25]

The prognostic value of the D/RMT ratio just before pregnancy on uterine dehiscence in women with a previous CD was previously described by Pomorski *et al.*[17] They reported a significantly higher mean D/RMT ratio before pregnancy in women with uterine dehiscence (n=7) than in women without dehiscence (n=34); the mean D/RMT ratio was 1.4 (SD, ±0.39) and 0.36 (SD, ±0.07), respectively (p=0.040). Our results were in line with these findings, but the number of women with dehiscence and registered D/RMT ratio in our study was too small to draw any strong conclusion concerning its value. The mean D/RMT ratio increased significantly after LNR (p<0.001). No other study evaluated this value after LNR compared with controls.

Higher blood loss during subsequent CD after previous LNR was not earlier reported. In 1 case in our study, blood loss of >1000 mL was caused by abnormal adhesive placentation and, in another case, owing to a placenta previa. However, the relation between LNR and placental problems is unknown. Currently, it is more likely that the presence of a uterine CD scar was related to the placental problems in these cases based on available literature.[26]

Clinical implications

Insight into the behavior of the uterine CD scar during pregnancy and its relation to pre-pregnancy measures may facilitate the development of prediction models on the risk of uterine rupture or dehiscence and may contribute to future decision-making concerning the mode of delivery. Here, we showed that RMT during pregnancy decreases during

gestation. The cut-off values of RMT or thickness of the LUS during pregnancy to predict a successful VBAC or uterine rupture or dehiscence still need to be determined in future research. However, even though most women received a scheduled CD, we found a significantly higher prevalence of uterine dehiscence during CD in women without LNR (p=0.008). The mean RMT was <3 mm during the entire pregnancy in women with dehiscence during the CD. RMT in the second trimester of pregnancy seemed to be the most discriminating value for dehiscence at term.[11, 12]

LNR has a positive effect on the RMT before and during the entire pregnancy and may decrease the prevalence of uterine dehiscence, although this study was not powered to evaluate the latter outcome. This lower prevalence of dehiscence must be weighed against higher blood loss during repeat CD.

Research implications

It is important to stress that the indication of the performed LNRs was primarily to improve gynecologic symptoms. Currently, there is no evidence underlining the need for an LNR for the improvement of obstetrical outcomes. Randomized studies are needed to study the effect of LNR in women with a large niche to improve reproductive outcomes.

Strengths and limitations

To our knowledge, this is the first study describing the effect of LNR on RMT and niche measurements during a subsequent pregnancy. Another strength of this study was the long-term follow-up after LNR; besides the measurements during subsequent pregnancy, these outcomes were also related to pregnancy outcomes. RMT measurements before and during pregnancy provide a clear insight into changes in the CD scar features over time. Here, we deliberately chose to evaluate niche changes during pregnancy concerning baseline before surgery and not after surgery, as we aimed to study the effect of surgery on the RMT and uterine CD features during pregnancy, and therefore, baseline data should be similar in both groups. Follow-up rates were high; ultrasound measurements were reported in 84% to 97% at different moments, and obstetrical outcomes were available in 86% of the included women. Another strength was that measurements were performed in a structured way by experienced sonographers.

In addition, we compared the outcomes after LNR to a control group of women with expectant management. However, because of the nonrandomized design, selection bias was obvious as women in the expectant management group had, in general, smaller niches with thicker residual myometrium. The sonographers performed niche

measurements according to protocol and were not aware whether women had received an LNR or not, which limited the chance of interpretations of differences. Another limitation was the limited sample size for the evaluation of the prevalence of uterine dehiscence and ruptures. The non-blinded design and individualization of the mode of delivery by practitioner and patient may have contributed to the high CD rates in the expectant group. The one case in the LNR group with uterine dehiscence occurred after having contractions, whereas dehiscence in the expectant group was reported in 7 women who all had a scheduled CD without contractions. Of note, 3 women (2 in the LNR group and 1 in the expectant group) had an unsuccessful trial of labor (TOL) and underwent an unscheduled CD. Moreover, 5 women (2 in the LNR group and 3 in the expectant group) experienced successful TOL. Given the fact that TOL was attempted equally in both groups, we do not think that TOL is a large confounder for the presence of dehiscence. However, the advice of a scheduled CD after an LNR can be debated; future studies are needed to evaluate its need, particularly in the case of a thick residual myometrium after an LNR. Other potential confounders may have influenced the prevalence of uterine dehiscence, including the indication of previous CD (emergency or scheduled CD), GA during previous CD (preterm or term birth), or maternal diseases (i.e., preeclampsia or diabetes mellitus). However, the study groups were too small to correct for all potential confounders. Furthermore, the presence of dehiscence was assessed only in women who underwent a CD; this was unknown in the VBAC group. Finally, we observed that large niches are associated with the presence of adenomyosis. In addition, this may induce a higher risk of trophoblast invasion and abnormal adhesive placentation, resulting in higher blood loss during the delivery. Because most patients received obstetrical care and surgery in another hospital, details on the exact placenta localization and slight signs of abnormal adhesive placentation were not always registered.

Conclusions

An LNR compared with expectant management in women with a niche resulted in a larger RMT during subsequent pregnancy and a lower number of uterine dehiscence despite a smaller RMT at baseline. Median blood loss during the subsequent pregnancy was higher in the LNR group than in the expectant group. Future studies are needed to study the indications for LNRs to prevent complications during subsequent pregnancies in women with a large niche.

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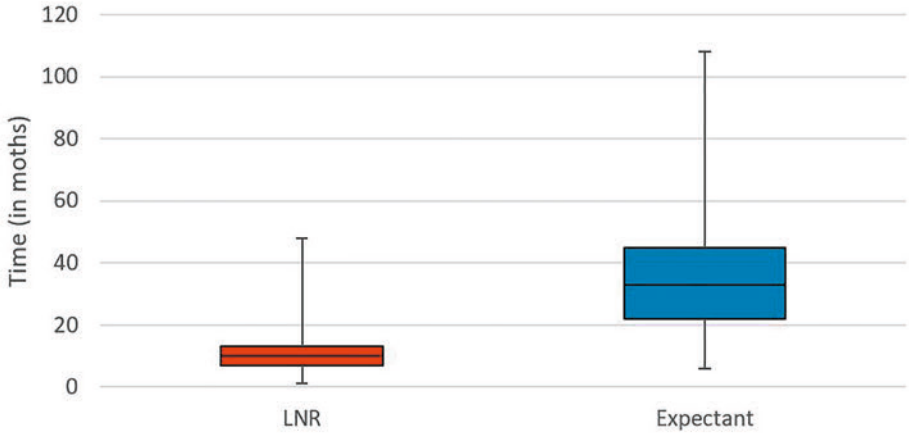
APPENDICES



Supplemental Figure. Median time between pre-pregnancy uterotomy[a] and onset of subsequent pregnancy

a Pre-pregnancy uterotomy includes laparoscopic niche resection in Lapniche group and previous cesarean section in expectant group.

PART 3

INFLUENCE OF SURGICAL CLOSURE TECHNIQUE ON NICHE DEVELOPMENT

CHAPTER 8

UTERINE CESAREAN CLOSURE TECHNIQUES AFFECT ULTRASOUND FINDINGS AND MATERNAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

Cesarean section (CS) rates are rising globally. Long-term adverse outcomes after CS might be reduced when the optimal uterine closure technique becomes evident.

Objective

To determine the effect of uterine closure techniques after CS on maternal and ultrasound outcomes.

Search strategy

Literature search in electronic databases.

Selection criteria

Randomised controlled trials (RCTs) or prospective cohort studies that evaluated uterine closure techniques and reported on ultrasound findings, perioperative or long-term outcomes.

Data collection and analysis

Twenty studies (15,053 women) were included in our meta-analyses for various outcomes. We calculated pooled risk ratios (RR) and weighted mean differences (WMD) with 95% CI through random-effect analysis.

Main results

Residual myometrial thickness (RMT), reported in eight studies (508 women), decreased by 1.26 mm after single- compared with double-layer closure (95% CI –1.93 to –0.58), particularly when locked sutures were used. Healing ratio [RMT/ adjacent myometrial thickness (AMT)] decreased after single-layer closure (WMD –7.74%, 95% CI –13.31 to –2.17), particularly in the case of locked sutures. Niche prevalence increased (RR 1.71, 95% CI 1.11–2.62) when the decidua was excluded. Dysmenorrhea occurred more often in the single-layer group (RR 1.23, 95% CI 1.01–1.48), whereas incidence of uterine rupture was similar (RR 1.91, 95% CI 0.63–5.74).

Conclusion

Double-layer unlocked sutures are preferable to single-layer locked sutures regarding RMT, healing ratio and dysmenorrhoea. Excluding the decidua seems to result in higher niche prevalence. As thin residual myometrium or niches may serve as intermediates for gynecological and reproductive outcomes, future studies should focus on these outcomes.

INTRODUCTION

Cesarean section (CS) is a frequently performed surgical intervention conducted in up to 27.2% of the deliveries in developed regions.[1] It can be life-saving for both mother and child, but CS has also been associated with several short-term and long-term adverse maternal outcomes. Short-term adverse outcomes include infection, haemorrhage and venous thromboembolism. Reported long-term gynecological symptoms after CS include abnormal uterine bleeding, pain related to menstruation or micturition, and possibly infertility.[2,3] Long-term adverse outcomes related to a subsequent pregnancy following a CS comprise uterine dehiscence or rupture, placental adherence complications and cesarean scar pregnancy. Recent studies indicate a relation between long-term outcomes and the occurrence of a niche in the uterine cesarean scar.[4,5]

The presence of a niche on post-cesarean ultrasound has only been reported recently. A niche is defined as a triangular anechoic area at the site of the previous uterine cesarean incision[6] and can best be visualised with saline or gel contrast hysterosonography.[4] At the apex of a niche, residual myometrial thickness (RMT) is often small. Presence of a niche and small RMT may function as an intermediate for long-term outcomes, as they are related to gynecological and reproductive outcomes such as postmenstrual spotting[4,5], uterine dehiscence[7] or rupture[8], a higher incidence of complications when cesarean scar pregnancy occurs[9], placental adherence problems[10] and failure of trial of labour.[11] Various hypotheses have been postulated recently to play a role in niche development after CS. One of these hypotheses is that closure technique of the uterine incision is associated with niche development and related adverse outcomes.[12]

Despite the high incidence of cesarean deliveries worldwide, there is no uniform technique for performing a CS and uterine closure techniques vary. Variations include: single- versus double-layer closure, locked versus unlocked sutures and full thickness versus split thickness (including or excluding the decidual layer, respectively). It is still unresolved what the best combination is of the three different uterine suture techniques in relation to adverse outcomes.

Previous reviews focused mainly on short-term outcomes or ultrasound findings and performed no correction for possible confounders.[13–15] Therefore, the aim of our systematic review and meta-analysis is to study the effect of three different closure techniques of the uterine incision at CS independently, first on ultrasound findings and second on intraoperative and short-term postoperative outcomes, long-term gynecological symptoms and reproductive outcomes.

METHODS

This systematic review and meta-analysis were performed according to recommendations in the Cochrane Handbook and we developed a review protocol based on the PRISMA statement[16] which was registered in the PROSPERO International prospective register of systematic reviews; registration number CRD42017052958.

We searched PubMed, Embase.com and Wiley/Cochrane Library (S.S. and J.K.) from inception up to 7 April 2017 and World Health Organization/International Clinical Trials Registry Platform (WHO/ICTRP) trial database from inception up to 10 May 2017. The full search strategies for all the databases can be found in Appendix S1. All languages were accepted.

We included all published RCTs and prospective cohort studies that compared uterine closure techniques (single- versus double-layer closure, locked versus unlocked suturing or inclusion versus exclusion of the decidua) after a cesarean delivery, independent of the indication or number of previous cesarean or vaginal deliveries. We subdivided our study characteristics table in whether women had one or more previous CS. When co-interventions took place, such as blunt versus sharp abdominal entry, exteriorization of the uterus before suturing, closure of the peritoneum and the different use of suture material, studies were only included when correction for co-interventions was performed. Outcomes were divided into four categories:

1. Ultrasound findings after CS: residual myometrial thickness (RMT, mm, primary outcome), niche prevalence, healing ratio [%, defined as RMT/adjacent myometrial thickness (AMT) or RMT/(RMT + niche depth)].
2. Intra-operative and short-term postoperative assessments: duration of operation (minutes), blood loss (milliliters), hospital stay (days), maternal infectious morbidity [fever, (wound) infection, need for antibiotic treatment].
3. Gynecological symptoms: post-menstrual spotting, dysmenorrhoea, chronic pelvic pain.
4. Reproductive outcomes: infertility, need for fertility treatment, pregnancy rate, cesarean scar pregnancy, uterine dehiscence or uterine rupture in subsequent pregnancy.

We selected studies according to the PRISMA flowchart (Figure S1). First, S.S. and I.J. independently screened titles and abstracts of the records. Secondly, the same reviewers assessed the full text of the possibly eligible articles based on this first screening. Subsequently, S.S. extracted data from the eligible studies using a data

extraction form, based on the Cochrane Consumers and communication template.[17] I.J. checked the extracted data. From each included study we extracted data on items, specified in Appendix S2. When relevant data were not applicable directly from the written text, we contacted the authors for additional information.

Two independent reviewers (S.S. and I.J.) assessed the risk of bias of all included studies independently using The Cochrane Collaboration tool for assessing risk of bias.[18] We assessed six domains related to risk of bias for all included studies. We added a question to the tool to determine the additional risk of selection bias ('other bias') and checked whether correction for confounders (for non-randomised studies, NRS) or other surgical techniques (for RCTs) had been applied. Depending on the performed methods to reduce selection bias, 'other bias' was scored as low/unclear/high risk. When RCTs performed additional surgical techniques, this item was scored low/unclear/high depending on correction. Consequently, in prospective cohort studies, we scored items 'random sequence generation' and 'allocation concealment' as 'high risk of bias'.

Any disagreement between the reviewers as to study selection, data collection or risk of bias assessment, was resolved through discussion. If required, a third person and expert in the area was consulted (J.H.). We achieved final consensus between the three reviewers.

Our primary outcome was RMT measured by ultrasound. When measurements were repeated at different follow up, we used the latest ultrasound evaluation.

Data analysis was performed with Review Manager 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Results were presented as the average treatment effect with risk ratio (RR) in the case of dichotomous variables or weighted mean difference (WMD) in the case of continuous variables, 95% confidence intervals (CI), the estimates of I^2 and p values. Additional information about the use and recalculation of data from included studies is available in Appendix S3. Random-effect meta-analysis for combining data was used. However, with a low number of studies it is not possible to obtain a reliable estimate for the between-study variance in a random-effects analysis.[19] For this reason we used a fixed-effects model if the number of studies included was six or less. For each different closure technique we performed subgroup analysis for additional surgical techniques, if applicable.

We calculated statistical heterogeneity between studies with an I^2 test, according to Higgins.[20] Heterogeneity was considered low (when $I^2 \leq 25\%$ or less), moderate (when I^2 25–75%) or high (when $I^2 > 75\%$). We determined potential publication bias statistically for our primary outcome using Egger's and Begg's test.[18] We performed predefined

sensitivity analysis regarding our primary outcome for population (with or without previous CS), ultrasound evaluation (timing, method) and study characteristics such as design and quality (Appendix S4) to assess to what extent differences in these items affected the conclusions. We also stratified the results for risk of bias. A p value <0.05 was considered statistically significant.

RESULTS

Figure S1 shows the reviewing process of potentially eligible articles. Ultimately, we included 20 studies (15,053 women) in our meta-analysis. One study (n=50)[21] evaluated our primary outcome without any of our secondary outcomes, resulting in 15,003 included women for secondary outcome evaluation. Additional information regarding the selection process is provided in Appendix S5. The overall methodological quality of included RCTs was moderate to high (Figure S2). Three studies[22–24] were considered of high risk of bias for the item 'incomplete outcome data', due to incomplete follow-up data and imbalance in missing data across intervention arms. One study[25] did not report on blinding of the ultrasound examiner or on all prespecified outcomes (ultrasound at 6 weeks follow up) so it was scored as high risk of bias for both 'blinding of outcome assessment' and 'selective reporting'. All other RCTs were not considered to have a high risk of bias for one of the items in the tool. Overall quality for the prospective cohort studies was considered low (Figure S2). As we used the same tool for randomised and non-randomised trials, with the first two items (randomisation and allocation concealment) consequently scored as high risk of bias for the four cohort studies, we looked at the remaining five items to determine overall risk of bias. Three of four cohort studies[26–28] were considered to have a high risk of bias for 'blinding of outcome assessment', as they did not report on blinding. Two studies[26,29] were scored as high risk of bias for 'other bias', as they performed no correction for confounders. Egger's and Begg's tests to assess potential publication bias regarding our primary outcome were not statistically significant for single- versus double-layer closure (p=0.98 and 1.00, respectively) or for locked versus unlocked sutures (p=0.19 and 0.73, respectively).

Table 1 shows the study characteristics and is divided into three parts; single- versus double-layer closure, locked versus unlocked closure, and inclusion or exclusion of the decidual layer. Three RCTs compared both single- versus double-layer and locked versus unlocked closure[22,23,30] and one prospective cohort study compared both single- versus double-layer closure and inclusion versus exclusion of the decidual layer.[27]

Table 1. Study characteristics of included studies

Study	Design	N	Inclusion criteria	Intervention	Control	Short-term outcomes	Long-term outcomes	Scar evaluation (Method: outcome)	Follow-up moment
Bennich, 2016	RCT	76	First elective CS > 37weeks gestation	Single-layer Continuous unlocked Incl decidua	Double-layer Lateral-lateral unlocked, incl decidua	Blood loss, operative time	Dysmenorrhea	First TAUS: RMT Second SIS: RMT, niche prevalence, healing ratio	First: 3 days Second: 5 months
CAESAR, 2010	RCT	2979	First elective LTCS	Single-layer Continuous, locked or unlocked	Double-layer Continuous, locked or unlocked	Maternal infectious morbidity, operative time, hospital stay, readmission	NA	NA	6 weeks
El-Gharib, 2013*	RCT	150	First CS	Single-layer Continuous locked	Double-layer 1st continuous locked, 2nd imbricating	Operative time, wound sepsis, hospital stay	NA	TAUS (if possible) or TVUS: RMT	First: 0 days Second: 2 days Third: 2 weeks Fourth: 6 weeks
Hamar, 2007*	RCT	30	First CS, non-emergent	Single-layer Continuous locked	Double-layer 1st layer continuous locked, 2nd imbricating	Operative time, blood loss	NA	TAUS (if possible) or TVUS: RMT	First: 0 days Second: 2 days Third: 2 weeks Fourth: 6 weeks
Roberge, 2016†	RCT	54	First CS, elective ≥ 38 weeks gestation	Single-layer Continuous locked Incl decidua	Double-layer 1st locked Incl decidua	Operative time, blood loss, maternal infectious morbidity	NA	TVUS: RMT, niche prevalence, AMT, healing ratio	6-12 months
Sevket, 2014	RCT	36	First CS, > 36 weeks gestation	Single-layer Continuous locked Incl decidua	Double-layer 1st layer continuous locked incl decidua, 2nd continuous unlocked	Blood loss, operative time	NA	TVUS SIS: RMT, healing ratio	6 months
Shrestha, 2015	RCT	50	First CS >37 weeks gestation	Single-layer Continuous locked Incl decidua	Double-layer 1st continuous locked incl decidua, 2nd imbricating	NA	NA	TAUS: Scar thickness	6 weeks
Hayakawa, 2006†	Prospective study	101	First CS between 26-41 weeks gestation	Single-layer Interrupted Excl decidua	Double-layer Interrupted Excl decidua	Blood loss, maternal infectious morbidity	NA	TVUS: Risk of a wedge defect	1 month
Kataoka, 2016‡	Prospective study	267	First CS	Single-layer Interrupted Incl decidua	Double-layer Interrupted Incl decidua	Blood loss	NA	TVUS SIS: ratio depth / depth + RMT, niche prevalence	3-4 months

Table 1. (Continued)

Study	Design	N	Inclusion criteria	Intervention	Control	Short-term outcomes	Long-term outcomes	Scar evaluation (Method: outcome)	Follow-up moment
Bamberg, 2016†	RCT	278	First or repeat elective CS	Single-layer Unlocked Incl decidua	Double-layer 1st unlocked incl decidua, 2nd unlocked imbricating	Blood loss, operative time, maternal infectious morbidity	NA	TVUS: Scar thickness	First: 6 weeks Second: 6-24 months
CORONIS, 2013	RCT	9286	First or repeat elective CS	Single-layer Any method	Double-layer Any method	Maternal infectious morbidity, operative time, hospital stay, readmission	NA	NA	6 weeks
CORONIS, 2016 *(follow-up of CORONIS 2013)*	RCT	7411	First or repeat elective CS	Single-layer Any method	Double-layer Any method	NA	Uterine rupture, (sub)fertility, dysmenorrhea	NA	3 years
Chapman, 1997 *(follow-up of Hauth, 1992)*	RCT	145	First or repeat LTCS	Single-layer Continuous locked	Double-layer 1st layer continuous locked, 2nd imbricating	Hospital stay	Uterine dehiscence, maternal infectious morbidity	NA	4 years
Hauth, 1992	RCT	906	First or repeat LTCS	Single-layer Continuous locked	Double-layer 1st layer continuous locked, 2nd imbricating	Maternal infectious morbidity, operative time, hospital stay	NA	NA	Unknown
Sood, 2005*	RCT	208	First or repeat LTCS	Single-layer Continuous unlocked	Double-layer 1st continuous unlocked, 2nd imbricating	Maternal infectious morbidity, operative time, hospital stay, blood loss	NA	NA	First: 2 weeks Second: 6 weeks
Yasmin, 2011†	RCT	60	Only repeat CS, singleton pregnancy	Single-layer Continuous locked Incl decidua	Double-layer 1st continuous locked incl decidua or 1st continuous unlocked	Operative time, blood loss	Uterine dehiscence	TAUS: RMT	6 weeks
Batioglu, 1998	Prospective study	118	First or repeat LTCS	Single-layer Continuous unlocked	Double-layer 1st continuous locked, 2nd continuous unlocked	Maternal infectious morbidity, endometritis, operative time, hospital stay	NA	NA	At least 2 days

Table 1. (Continued)

Study	Design	N	Inclusion criteria	Intervention	Control	Short-term outcomes	Long-term outcomes	Scar evaluation (Method: outcome)	Follow-up moment
Heidenreich, 1995	Prospective study	125	First or repeat LTSC	Single-layer Interrupted excl decidua	Double-layer 1st layer interrupted excl decidua, 2nd layer imbricating	Operative time, maternal infectious morbidity, blood loss/ transfusion	NA	TVUS: RMT	10-12 days
Ceci 2012	RCT	60	First LTCS at term	Single-layer Unlocked Excl decidua	Single-layer Locked Excl decidua	Operative time	NA	TVUS + hysteroscopy: Presence and size of niche	First: 6-12 months Second: 24 months
Bamberg, 2016†	RCT	306	First or repeat elective CS	Single-layer Unlocked Incl decidua	Single-layer Locked Incl decidua	Blood loss, operative time, maternal infectious morbidity	NA	TVUS: Scar thickness	First: 6 weeks Second: 6-24 months
Turan 2014‡	Prospective study	82	First or repeat elective LTCS	Single-layer Unlocked Incl decidua	Single-layer Locked Incl decidua	Operative time	NA	Only first CS: TVUS: RMT, AMT, depth, healing ratio	3 months
Roberge, 2016†	RCT	54	First CS, elective ≥ 38 weeks gestation	Double-layer 1st unlocked excl decidua, 2nd imbricating	Double-layer 1st locked incl decidua 2nd imbricating	Operative time, blood loss, maternal infectious morbidity	NA	TVUS: RMT, prevalence, AMT, healing ratio	6-12 months
Yasmin et al, 2011†	RCT	60	Only repeat CS, singleton pregnancy	Double-layer 1st unlocked incl decidua, 2nd continuous unlocked	Double-layer 1st locked incl decidua, 2nd continuous unlocked	Operative time, blood loss	Uterine dehiscence	TAUS: RMT	6 weeks
Yazicioglu 2006	RCT	78	First CS, elective or during labour	Single-layer Continuous locked Incl decidua	Single-layer Continuous locked Excl decidua	NA	NA	TVUS: Niche prevalence, healing ratio	40-42 days
Hayawaka 2006†	Prospective study	87	First CS between 26-41 weeks	Double-layer unlocked Incl decidua	Double-layer Unlocked Excl decidua	Blood loss, maternal infectious morbidity	NA	TVUS: Risk of a wedge defect	1 month

Table is ordered comparing three closure techniques (first single- versus double-layer, second locked versus unlocked closure, third inclusion versus exclusion of decidua). Subsequently, studies are displayed in order of 1) studies that included women who underwent first CS, 2) studies that included women who underwent first or repeat CS. *Authors were contacted for additional information about decidual layer but did not respond. † Studies that compared 3 study arms, with the number of specific subgroups that we included for meta-analysis displayed (N). ‡ Authors were contacted for additional information about decidual layer and responded. AMT, adjacent myometrial thickness; CS, cesarean section; excl, excluding; incl, including; LTCS, low transverse cesarean section; NA, not available; RCT, randomized controlled trial; RMT, residual myometrial thickness; SIS, saline infusion sonography; TAUS, transabdominal ultrasound; TVUS, transvaginal ultrasound

A summary of our analyses for the three studied techniques and for all outcome measures is shown in Table 2. The primary outcome (RMT) was studied in 665 unique women; in the single- versus double-layer group', 256 (50.4%) and 252 (49.6%) women were allocated, respectively. In the 'locked versus unlocked sutures group' 124 (48.8%) and 130 (51.2%) were allocated, respectively. A total of 97 women were included in both comparisons because they came from three studies[22,23,30] that initially compared three arms.

Single- versus double-layer closure

We included fourteen RCTs[21–25,30–38] and three prospective cohort studies[27–29] in the meta-analysis regarding single- versus double-layer closure.

Eight studies (n=508, all RCTs) reported on RMT, which showed a statistically significant decrease in the single- layer group when results over all studies were pooled: weighted mean difference (WMD) –1.26 mm, 95% CI –1.93 to –0.58, p=0.0003 (Figure 1). Within the additional subgroups, a decrease in RMT was most obvious when locked sutures were used (test for subgroup difference: p=0.01). Four studies (476 women, two RCTs and two prospective cohort studies) reported on niche prevalence, defined as 'anechoic area in anterior uterine wall'[27,31] or 'severe defect with RMT < 2.3 mm'[22] with no difference between the groups (Figure S4.1). Healing ratio was reported in three studies (n=139, all RCTs) and the difference was statistically significant (WMD –7.74%, 95% CI –13.31 to –2.17, p=0.006), which means that RMT as a proportion of AMT or of RMT + niche depth is on average 7.7% smaller after single-layer closure when results from these studies are pooled (Figure S4.2).

Operative time was studied in 11 studies (n=13,267; ten RCTs, one cohort study) and was shorter (WMD –1.53 minutes, 95% CI –2.13 to –0.93, p<0.00001, Figure S4.4) in the single-layer group. Other intraoperative and short-term postoperative outcomes were not different after single- or double-layer closure. (see Appendix S6 and Figure S4.3, S4.5, S4.6 and S4.7)

Two studies (n=7484, both RCTs) reported on dysmenorrhoea at a 5-month[31] and 3-year[24] follow-up, which occurred more frequently in the single-layer group (RR 1.23, 95% CI 1.01–1.48, p=0.04) (Figure 2A).

One study reported on infertility (Figure S4.8), applied fertility treatment (Figure S4.9) and subsequent viable pregnancy rate (Figure S4.10) after single- versus double-layer closure three years after CS, which were similar in both groups. We combined the prevalence of uterine dehiscence and rupture, which was studied in three studies (n=2379, all RCTs) and was equal in both groups (RR 1.91, 95% CI 0.63 to 5.74, p=0.25) (Figure 2B).

Table 2. Pooled results for single- versus double-layer, unlocked versus locked, and inclusion versus exclusion of the decidua.

Outcomes	Studies	Patients	Intervention (%)	Control (%)	RR (95% CI) or WMD*	I^2	p-value
Single- versus double-layer closure							
Ultrasound findings							
Residual myometrial thickness (mm)[21-23,25,30, 31,33,34]	8	508	10.47	11.73	- 1.26 [- 1.93, - 0.58]*	71%	<0.01
Prevalence (large) niches[22, 27,28,31]	4	476	65/162 (40.1)	95/314 (30.3)	1.19 [0.95, 1.49]	80%	.14
Healing ratio[22,31]	3	139	56.60	64.34	- 7.74 [- 13.31, - 2.17]*	65%	<0.01
Intra- and postoperative outcomes							
Blood loss (ml)[22,23,30,31,33,38]	9	1102	610.96	624.54	13.49 [- 54.17, 27.19]*	68%	.52
Operative time (minutes)[22,23,25,29-35,38]	11	13267	36.67	38.20	- 1.53 [- 2.13, - 0.93]*	26%	<0.01
Maternal infectious morbidity[22,23,32,35,37,38]	9	14107	826/6857 (12.0)	853/6881 (12.4)	0.96 [0.78, 1.18]	75%	.70
Length of hospital stay (days)[25,29,32,35,36,38]	6	12873	4.64	4.67	- 0.03 [- 0.09, 0.02]*	75%	.20
Readmission rate[32,35]	2	12265	71/6122 (1.2)	70/6143 (1.1)	1.02 [0.73, 1.41]	NE	.91
Gynecological outcomes							
Dysmenorrhea[24,31]	2	7484	219/3744 (5.8)	179/3740 (4.8)	1.23 [1.01, 1.48]	NE	.04
Reproductive outcomes							
Involuntary infertility[24]	1	7411	133/3709 (3.6)	132/3702 (3.6)	1.01 [0.79, 1.27]	NA	.96
Applied fertility treatment[24]	1	7410	20/3709 (0.5)	10/3701 (0.3)	2.00 [0.94, 4.26]	NA	.07
Subsequent viable pregnancy[24]	1	9234	1611/4613 (34.9)	1624/4621 (35.1)	0.99 [0.94, 1.05]	NA	.82
Uterine scar dehiscence or rupture[24,30,36]	3	2379	8/1175 (0.7)	4/1204 (0.3)	1.91 [0.63, 5.74]	0%	.25
Locked versus unlocked sutures							
Ultrasound findings							
Residual myometrial thickness (mm)[22,23,26,30]	4	254	10.01	11.63	- 1.62 [- 2.11, - 1.13]*	79%	<0.01
Prevalence (large) niches[22,39]	2	90	20/42 (47.6)	18/48 (37.5)	1.23 [0.93, 1.61]	NE	.14
Healing ratio (%)[22]	1	48	60.00	73.00	- 13.00 [- 25.46, - 0.54]*	NA	.04

Table 2. (Continued)

Outcomes	Studies	Patients	Intervention (%)	Control (%)	RR (95% CI) or WMD*	I^2	p-value
Intra- and postoperative outcomes							
Blood loss (ml)[22,23,30]	3	420	588	550	37.29 [15.31, 59.26]*	43%	<0.01
Operative time (min)[22,23,30,39]	5	562	26.53	27.32	- 0.79 [- 1.57, - 0.01]*	0%	.05
Maternal infectious morbidity[22,23]	2	360	2/184 (1.1)	1/176 (0.6)	1.90 [0.17, 20.71]	NE	.60
Reproductive outcomes							
Uterine dehiscence (at repeat CS)[30]	1	29	2/14 (14.3)	1/15 (6.7)	2.14 [0.22, 21.10]	NA	.51
Exclusion versus inclusion of decidual layer							
Ultrasound findings							
Prevalence (large) niches[27,40]	2	157	30/83 (36.1)	19/74 (25.7)	1.71 [1.11, 2.62]	NE	.02
Healing ratio[40]	1	70	0.77	0.86	- 0.09 [- 0.17, - 0.01]*	NA	.03
Intra- and postoperative outcomes							
Blood loss (ml)[27]	1	87	1022	895	127.00 [- 79.12, 333.12]*	NA	.23
Maternal infectious morbidity[27]	1	87	5/51 (9.8)	3/36 (8.3)	1.18 [0.30, 4.61]	NA	.82

* Weighted mean difference are displayed. I^2, Higgins test for heterogeneity; NA, not applicable (when one study was included); NE, not estimable (when two studies were included); RR, risk ratio; 95% CI, 95% confidence interval; WMD, weighted mean difference (all with double-layer, unlocked closure, or inclusion of decidual layer as control group)

We could not distinguish between additional intervention (locked versus unlocked) or first versus repeat CSs as these were not reported. Additional information can be found in Appendix S7.

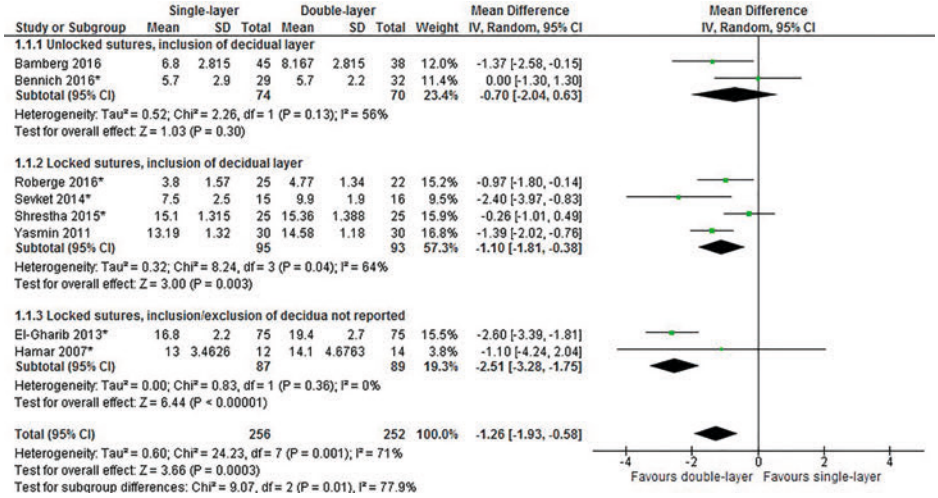

Figure 1. Residual myometrial thickness (mm) after single- versus double-layer closure

*Studies that only included women with a first CS.

Locked versus unlocked sutures

Five studies (three RCTs[22,23,30] and two prospective cohort studies[26,39]) compared locked and unlocked sutures.

RMT was reported in four studies (n=254, two RCTs and two prospective cohort studies) and showed a statistically significant decrease when locked sutures were used (WMD –1.62 mm, 95% CI –2.11 to –1.13, p<0.00001; Figure S3.1). Subgroup analysis revealed that the difference was more obvious in the case of double-layer closure (test for subgroup difference: p=0.002). Additional information regarding heterogeneity is provided in Appendix S8. Niche prevalence, defined as 'bell-shaped area under the scar'[39] or 'severe defect with RMT <2.3 mm',[22] was reported in two studies (n=90, both RCTs) and showed no statistically significant difference (RR 1.23, 95% CI 0.93 to- –1.61, p=0.14; Figure S5.1). Healing ratio was reported in one study[22] including 48 women, and was statistically significant lower for double-layer locked sutures (WMD –13.00%, 95% CI –25.46 to –0.54, p=0.04; Figure S5.2) than for double-layer unlocked sutures.

Three RCTs (n=420) reported more intraoperative blood loss after locked closure (WMD 37.29 ml, 95% CI 15.31 to 59.26, p=0.0009; Figure S5.3). Operative time, studied in four

RCTs and one cohort study (562 women), was shorter when locked sutures were used compared with unlocked sutures (WMD –0.79 minutes, 95% CI –1.57 to –0.01, p=0.05, Figure S5.4). Maternal infectious morbidity, studied in two trials including 360 women, was not different (RR 1.90, 95% CI 0.17 to 20.71, p=0.60, Figure S5.5).

No studies that compared locked with unlocked sutures reported on gynecological symptoms. One study[30] reported on uterine dehiscence, but only at repeat CS. The reported difference after locked versus unlocked sutures in the case of double-layer closure did not reach statistical significance (RR 2.14, 95% CI 0.22 to 21.10, p=0.51; Figure S5.6).

Inclusion versus exclusion of the decidual layer

Two studies (n=157) compared inclusion versus exclusion of the decidual layer. One RCT[40] evaluated this technique using single-layer locked sutures and one prospective cohort study[27] using double-layer unlocked sutures.

Neither of these studies reported on residual myometrial thickness. Both studies reported on niche prevalence, defined as 'deviation of uterine incision towards anterior abdominal wall'[40] or 'anechoic area in anterior uterine wall'[27], which was significantly higher when the decidual layer was excluded (RR 1.71, 95% CI 1.11 to 2.62, p=0.02; Figure S6.1). Healing ratio was reported by one study[40] and was more favourable after inclusion than after exclusion of the decidua (WMD –0.09%, 95% CI –0.17 to –0.01, p=0.03; Figure S6.2).

We observed no differences in intraoperative and short-term postoperative, gynecological and reproductive outcomes. Explanatory text can be found in Appendix S9.

Additional analyses

Our predefined sensitivity analyses for single- versus double- layer closure did not change our primary outcome (Figure S7.1 and S7.2 regarding previous CS yes/no, Figure S7.3 and S7.4 regarding high versus low risk of bias studies, respectively). We included only RCTs regarding single- versus double-layer closure, so sensitivity analysis was not necessary. Additional sensitivity analyses regarding locked versus unlocked closure did not change the primary outcome RMT (Figure S8.1 and S8.2 regarding previous CS, Figure S8.3 and S8.4 regarding high versus low risk of bias studies, respectively). RMT after locked versus unlocked closure was still significantly thicker after unlocked closure including only RCTs[22,23,30] (WMD –1.67 mm, 95% CI –2.19 to –1.14, p<0.00001; Figure S8.5), whereas it was not statistically significant different including one cohort study[26] (WMD –1.30 mm, 95% CI –2.66 to 0.06, p=0.06; Figure S8.6). Other preplanned sensitivity analyses regarding method of ultrasound evaluation could not be performed because of insufficient data.

Figure 2. Long-term outcomes after single- versus double-layer closure; dysmenorrhoea (A) and uterine dehiscence/rupture (B)

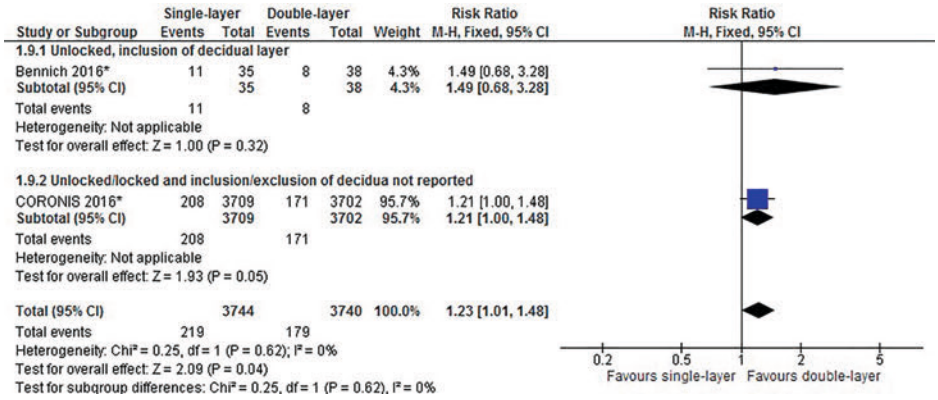

Figure 2A. Dysmenorrhea

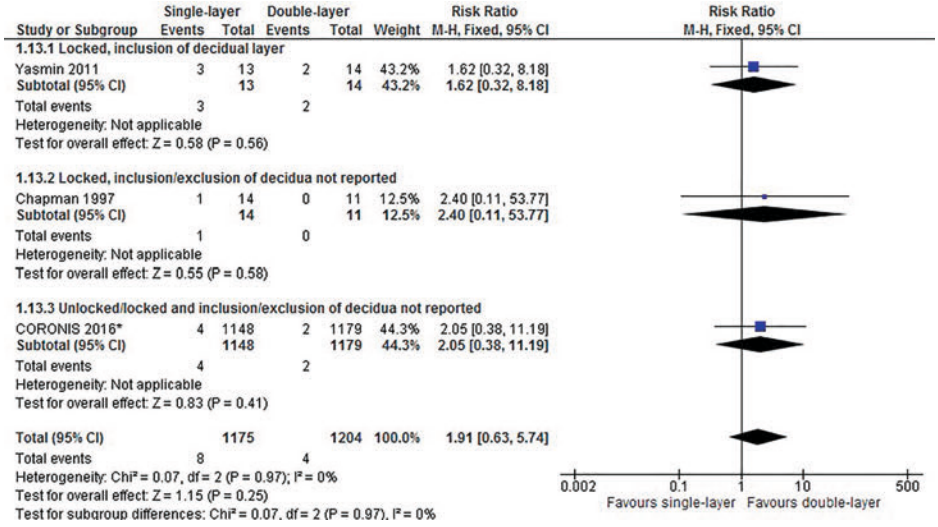

Figure 2B. Uterine dehiscence/rupture

*Studies that only included women with a first CS.

DISCUSSION

Main findings

Our systematic review and meta-analysis clearly shows that double-layer closure with unlocked sutures is more advantageous than single-layer closure with locked sutures

regarding RMT, healing ratio and dysmenorrhoea. Inclusion of the decidua decreased niche prevalence and improved the healing ratio.

Operative time decreased by 1.5 and 0.8 minutes after single-layer closure and when locked sutures were used, respectively, the latter also resulting in an increase of 37 ml blood loss. Although statistically significant, these perioperative differences are in our opinion not clinically relevant. We found a similar incidence of uterine dehiscence or rupture after single- versus double- layer closure. We were not able to draw any conclusions on other reproductive outcomes because of insufficient data.

Strengths and limitations

This is the first meta-analysis that evaluated the effect of three different uterine closure techniques after CS on ultrasonographic short- and long-term maternal outcomes. A strength of this review is that we followed the PRISMA guidelines for systematic reviews16 and included only studies that specifically evaluated single- versus double-layer closure, locked versus unlocked closure or inclusion versus exclusion of the decidua, or that corrected for surgical co-interventions. By reporting our results separately for various closure variables we demonstrated that apart from single- layer versus double-layer, locked versus unlocked and decidual inclusion or exclusion also play a role. Additionally, the robustness of our findings concerning our primary outcome was confirmed in sensitivity analyses excluding studies that included women with previous CSs, as this may be a confounder, but also after excluding cohort studies or studies with a high risk of bias.

Our study also includes some limitations. Only a limited number of studies reported on long-term outcomes. This underlines the need for future studies evaluating these outcomes that are highly relevant for patients and societal perspectives. Another limitation is that many studies did not report on other relevant surgical co-interventions but did include women with previous CS, all of which may serve as confounders. Our meta-analysis was potentially limited by the high statistical heterogeneity as well as the included populations (inclusion of women with previous CSs, elective, decision during labour or emergency CS), methods of ultrasound (with or without gel or saline contrast, transvaginal or transabdominal approach) and timing of niche measurement (varying from several days to 2 years after CS) but we could not perform sensitivity analyses because of insufficient data. It has been demonstrated recently that the number of previous CS[41], the use of transvaginal ultrasound and application of gel or saline[12], and the time between the CS and ultrasound evaluation[23,31,33,42] influence ultrasonographic measurements of the niche. We acknowledge that due to a limited number of studies assessing our primary outcome, sensitivity analyses were limited, as

well as assessing publication bias, as the power of the available tests is very low when fewer than ten studies are included in the meta-analysis. Insufficient data regarding long-term outcomes reduces the power of our study and as a consequence the ability to identify any difference. Lastly, we do realize that there is no consensus on the minimal number of studies required to perform a random-effect meta-analysis and hence the minimum of seven studies is to some extent arbitrary and can be debated.

Interpretation

We attempted to give an overview of the effect of three different uterine closure techniques separately, which makes our systematic review more extensive than previous reviews on this topic. Our results are in line with the results of these reviews concerning short-term outcomes[13,14] or RMT[13,15] when single- and double-layer uterine closure were compared. Moreover, Roberge *et al.*[13] could not identify enough studies to report ultrasound findings after unlocked versus locked sutures. We were able to include five additional studies[21–23,31,34] for single- versus double-layer closure reporting on scar healing, and five studies[22,23,26,30,39] for locked versus unlocked suturing.

Long-term maternal outcomes after CS are registered insufficiently. We did not identify studies that reported on ultrasound findings related to gynecological and reproductive outcomes. However, RMT may very well serve as an intermediate for clinical outcomes, as a smaller RMT has been associated with unsuccessful trial of labour when measured during pregnancy[11,43] as well as the development of uterine dehiscence or rupture during a vaginal delivery after CS.[7,8] RMT and in particular the so-called healing ratio (RMT/AMT) may provide information on the strength of the anterior uterine wall. In previous research, this ratio was significantly smaller in women who were suffering from post-menstrual spotting than in women who were not (P = 0.03).[5] Moreover, the ratio between the niche depth and the RMT in the non-pregnant uterus was correlated with uterine dehiscence at repeat CS (P = 0.007).[7] Additionally, the prevalence of niches is a relevant clinical outcome, as it has been associated with postmenstrual spotting as well.[4,5] This suggests that niche features, and in particular the healing of the uterine scar, as a proportion of the non-scarred anterior wall may be the intermediate of long-term complications of a CS. Finally, a niche and associated intrauterine fluid accumulation may theoretically hamper implantation or sperm penetration and therefore negatively influence pregnancy rates.[44]

Our analyses indicate that RMT and a niche may be intermediates for long-term outcomes but future studies are needed to evaluate this in larger studies measuring these outcomes. To facilitate future meta-analyses, we suggest performing ultrasonographic evaluation after CS in a standardised way. Furthermore, when

informing patients about the mode of delivery, it is relevant for women to know the possible long-term complications. Given the impact of gynecological and reproductive problems on patients' quality of life but also on societal costs, it is relevant to study closure techniques during a CS. We identified one study in the trial register comparing single- versus double-layer closure using unlocked sutures which is powered for the evaluation of postmenstrual spotting and time to pregnancy (www.trialregister.nl, NTR5480).

Conclusion

Our results indicate that double-layer unlocked closure is preferable to single-layer and locked closure regarding RMT and healing ratio, and that double-layer closure results in less dysmenorrhoea. Inclusion of the decidua seems to be optimal regarding healing ratio and niche development. The results of this meta-analysis all point to better scar healing on ultrasound after double-layer, unlocked uterine closure including the decidual layer. However, future studies that measure niche features and their relation with long-term consequences are needed before solid recommendations can be made on the preferred closure technique during a CS.

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APPENDICES

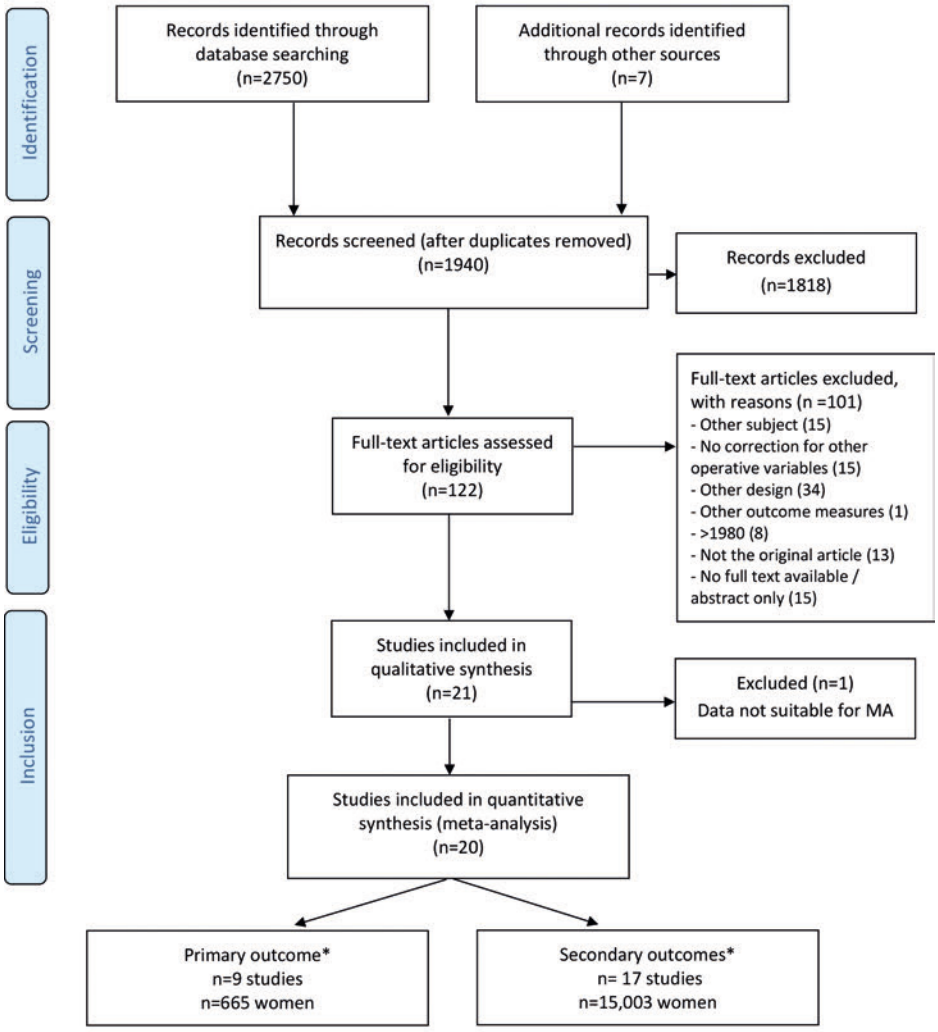

Figure S1. Method of literature search

* Multiple studies have been included for both our primary and secondary outcomes.
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figures S2. Risk of bias of individual studies

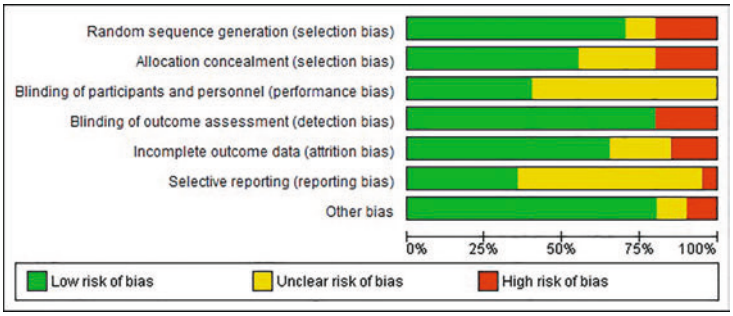

Figure S2.1 Risk of bias graph

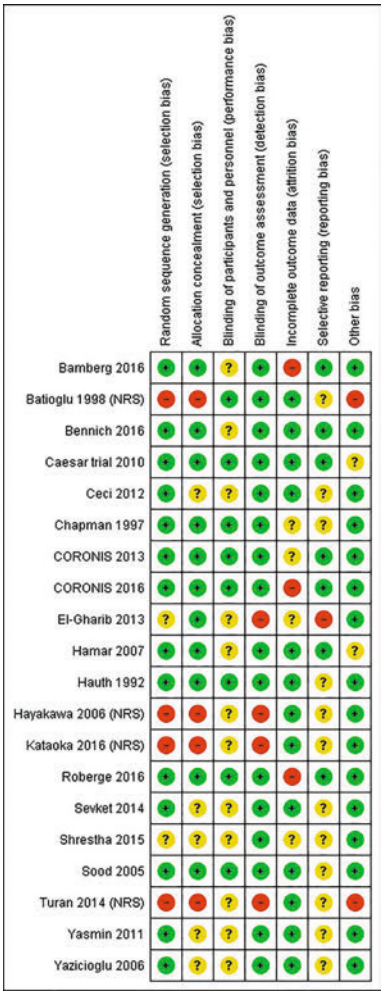

Figure S2.2 Risk of bias summary table

Figures S3. Forest plot primary outcome for locked versus unlocked sutures

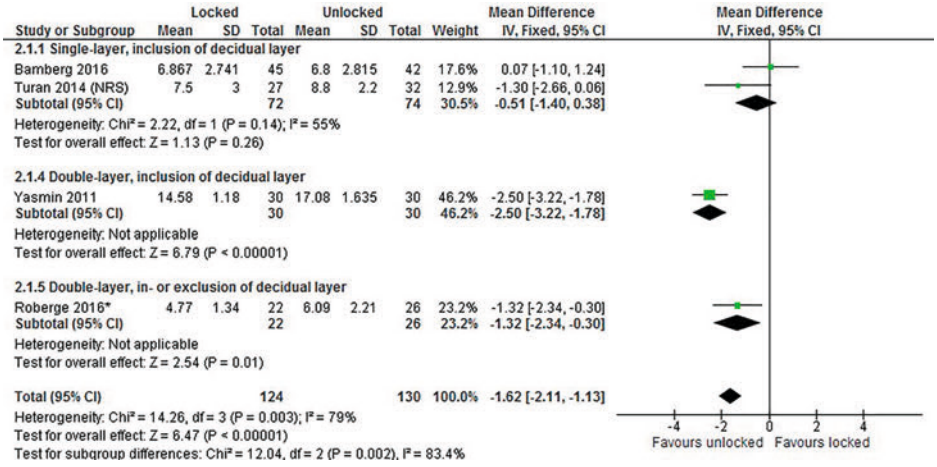

Figure S3.1 Forest plot residual myometrial thickness (mm, primary outcome) for locked versus unlocked sutures

* Studies that only included women with a first CS. NRS: non-randomized study.

Figures S4. Forest plots secondary outcomes regarding single- versus double-layer closure

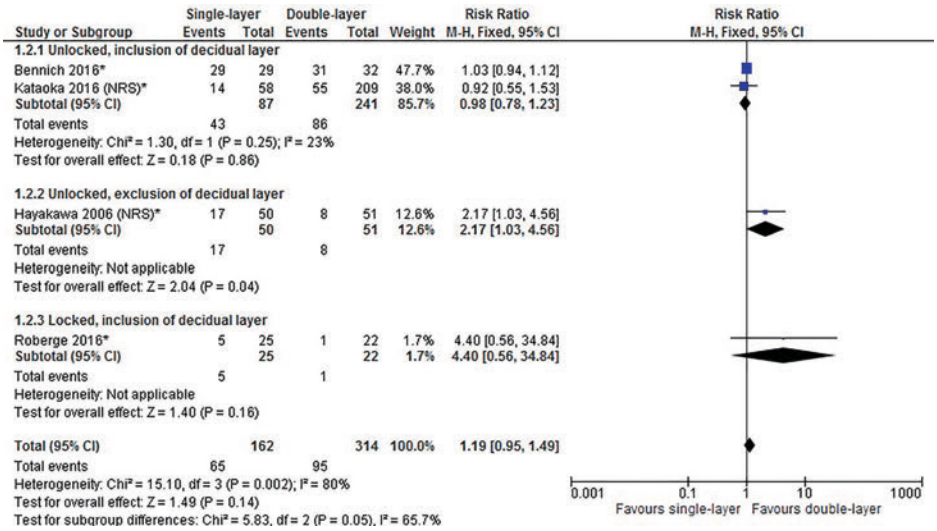

Figure S4.1 Prevalence of (large) niches after single- versus double-layer closure

Definitions of a niche: Bennich 2016: a small triangular anechoic defect in the anterior wall of the uterus (uterine niche). Kataoka 2016: no definition, Hayakawa 2006: a triangular, anechoic area at the presumed site of the incision, Roberge 2016: severe scar defect defined as the RMT <2.3 mm. *Studies that only included women with a first cesarean section. NRS, non-randomised study.

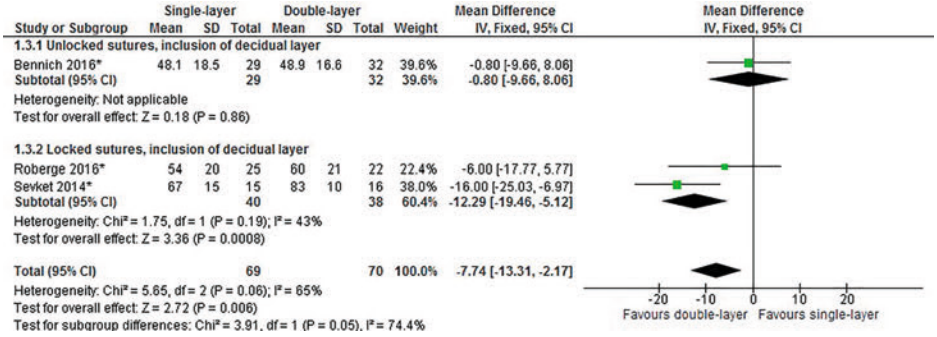

Figure S4.2 Healing ratio (%)

Definitions of healing ratio: Bennich 2016: RMT as proportion of anterior wall, Roberge 2016: RMT x (100 / total myometrial thickness) (i.e. the anterior wall), Sevket 2014: RMT / (RMT + height of the defect). *Studies only included women with a first CS.

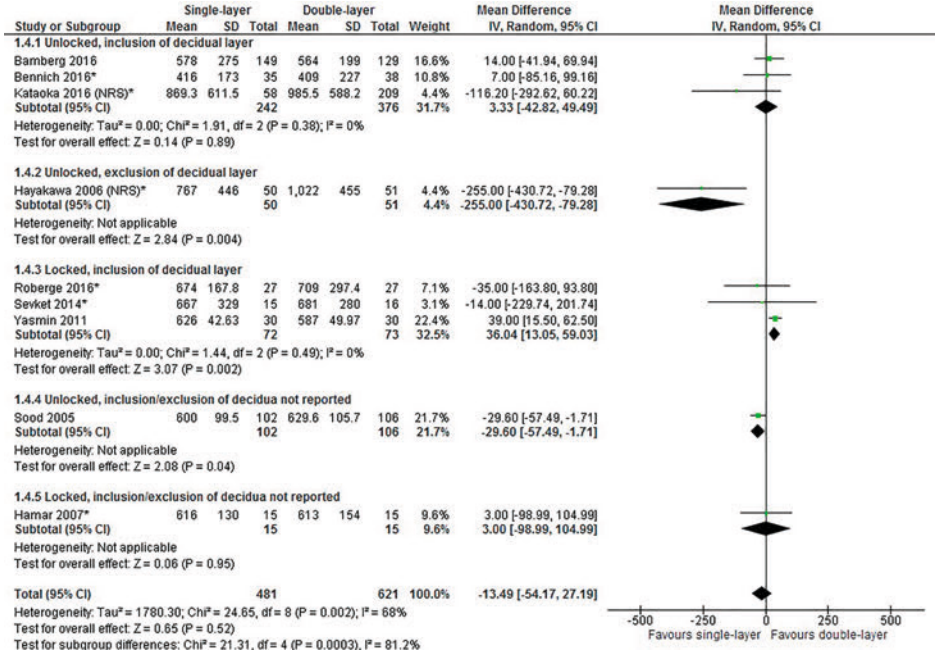

Figure S4.3 Blood loss (milliliters)

* Studies that only included women with a first CS. NRS, non-randomized study

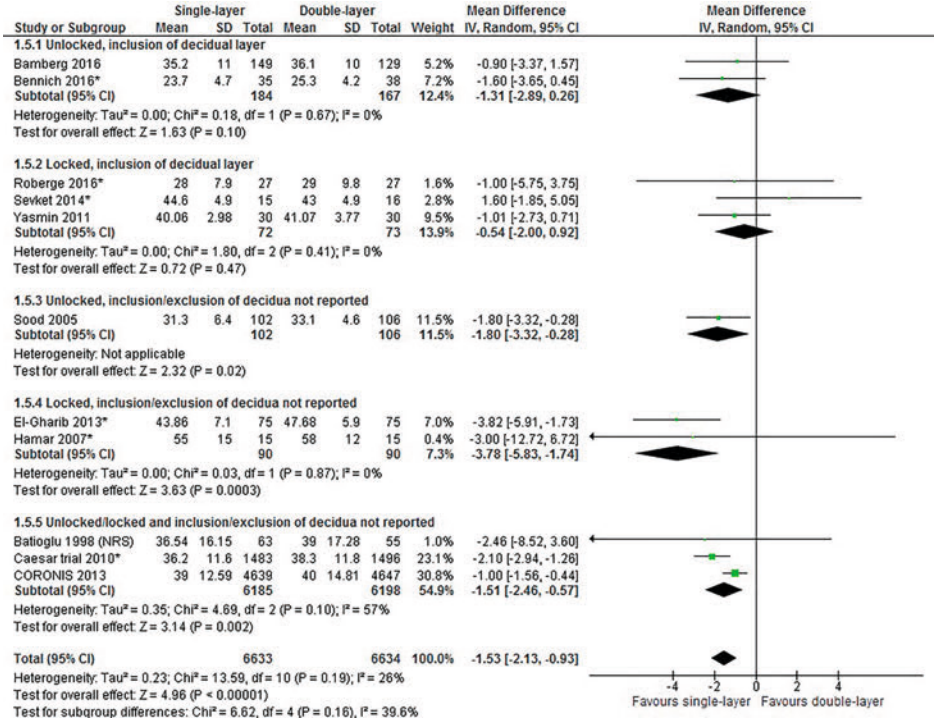

Figure S4.4 Operative time (minutes)

* Studies that only included women with a first CS. NRS, non-randomized study

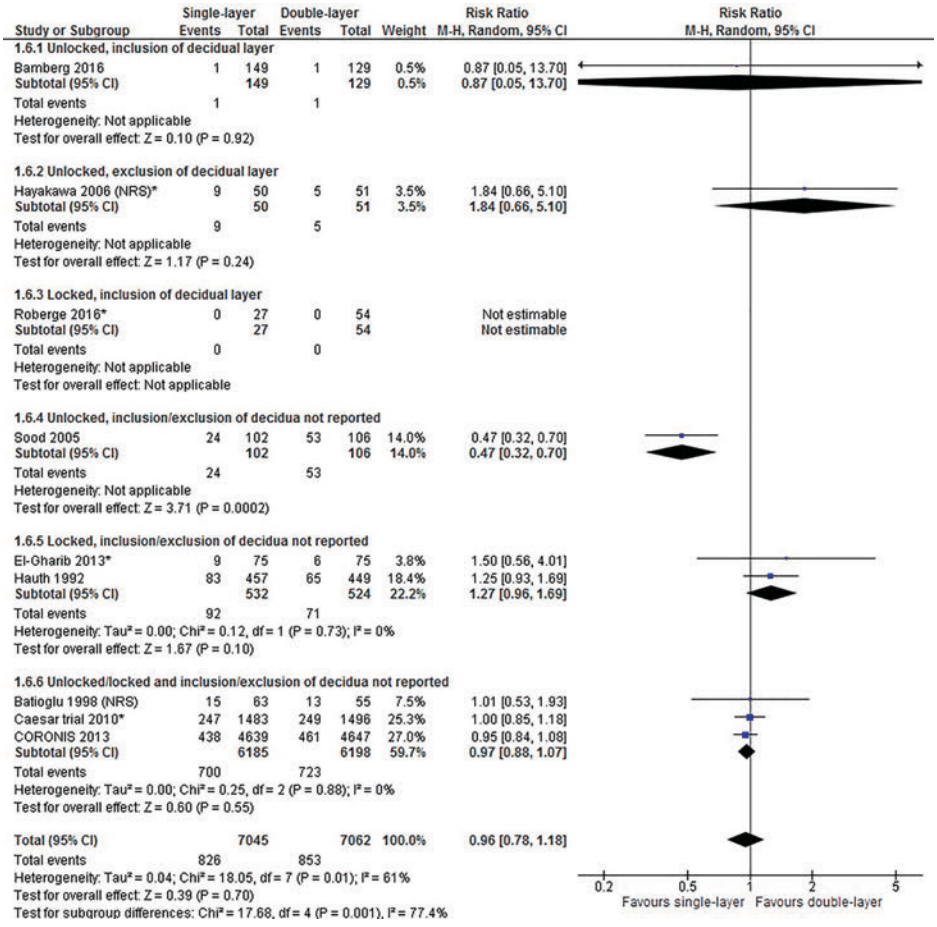

Figure S4.5 Maternal infectious morbidity

* Studies that only included women with a first CS. NRS, non-randomized study

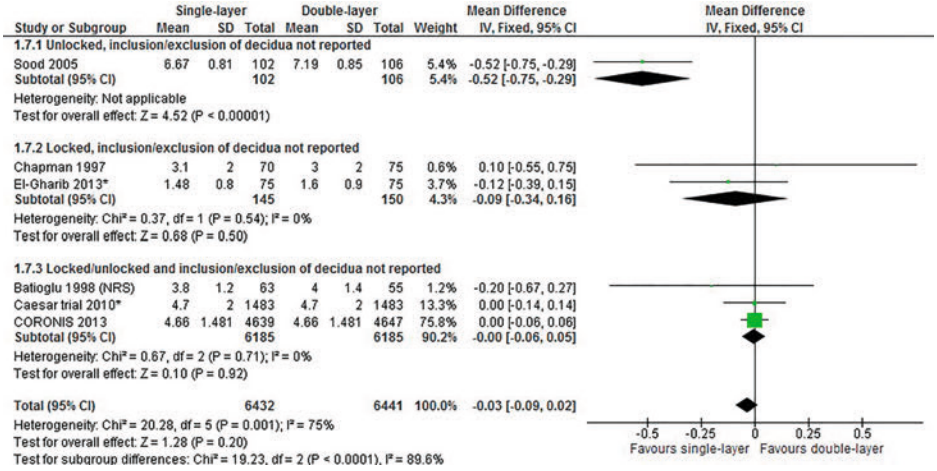

Figure S4.6 Hospital stay (days)

* Studies that only included women with a first CS. NRS, non-randomized study

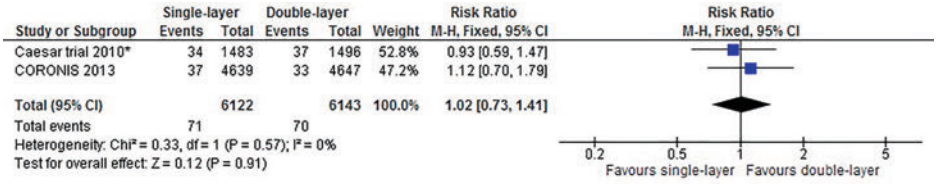

Figure S4.7 Readmission rate

* Studies that only included women with a first CS

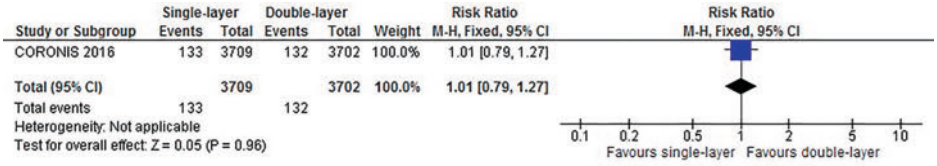

Figure S4.8 Infertility

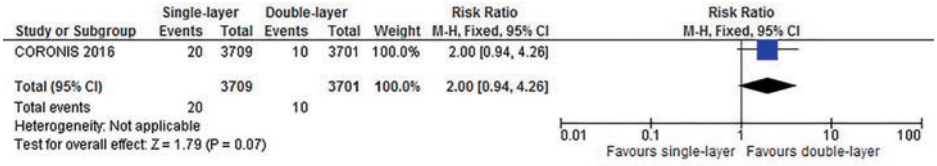

Figure S4.9 Applied fertility treatment

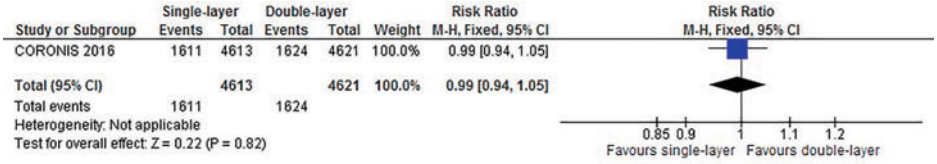

Figure S4.10 Subsequent viable pregnancy

Figures S5. Forest plots secondary outcomes regarding unlocked versus locked sutures

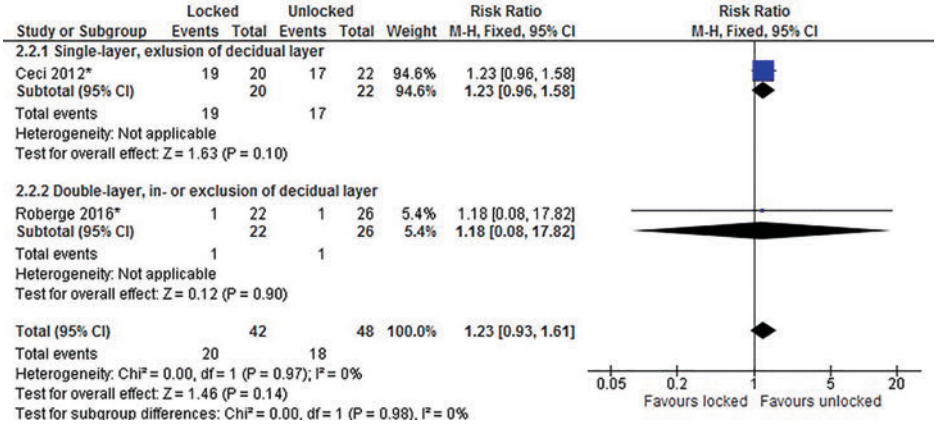

Figure S5.1 Prevalence of (large) niches

Definitions for a niche: Ceci 2012: the bell-shaped pouch area under the scar, Roberge 2016: severe scar defect defined as the RMT <2.3 mm. *Studies that only included women with a first CS.

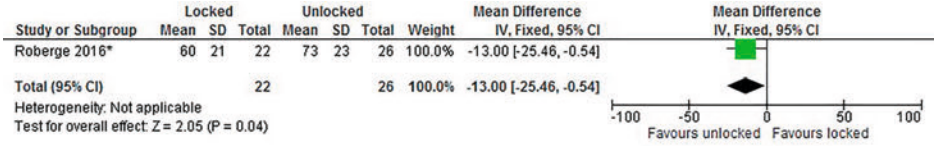

Figure S5.2 Healing ratio (%)

Definition of healing ratio; Roberge 2016: RMT x (100 / total myometrial thickness) (i.e. the anterior wall).
* Study that only included women with a first CS.

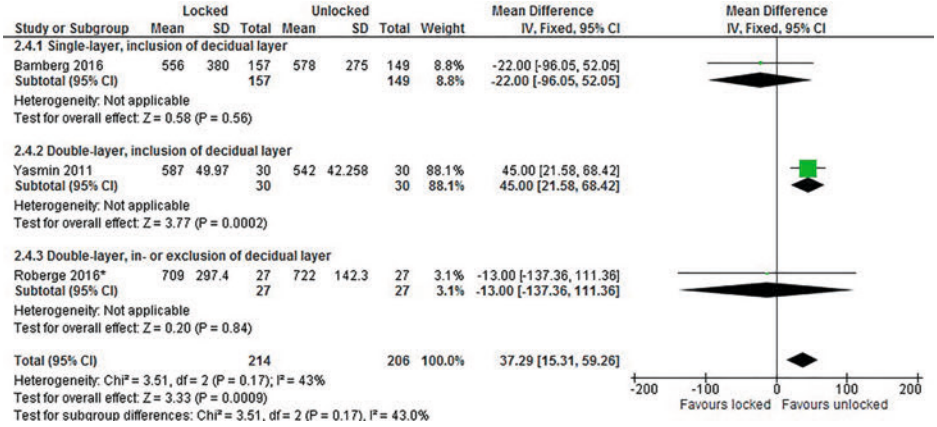

Figure S5.3 Blood loss (milliliters)

* Study that only included women with a first CS

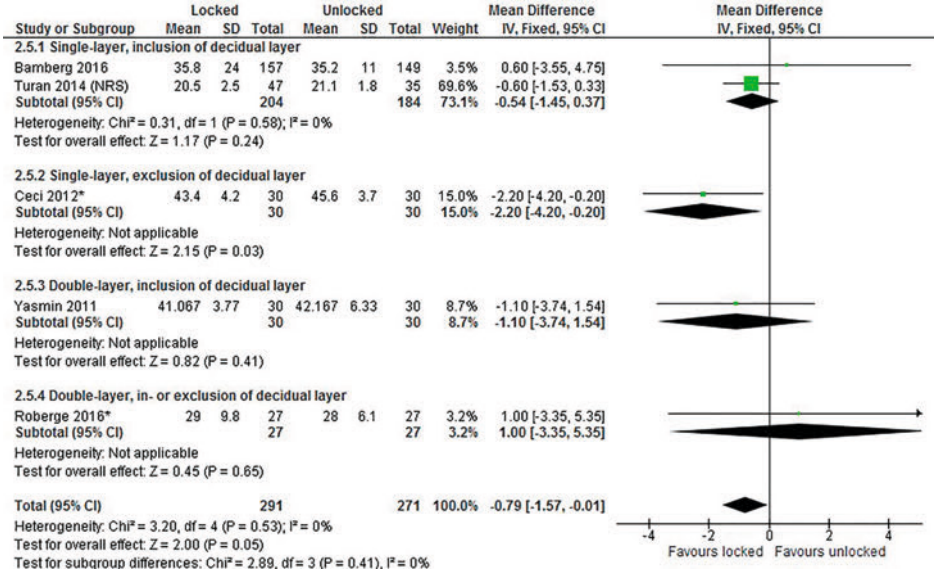

Figure S5.4 Operative time (minutes)

* Studies that only included women with a first CS. NRS, non-randomized study

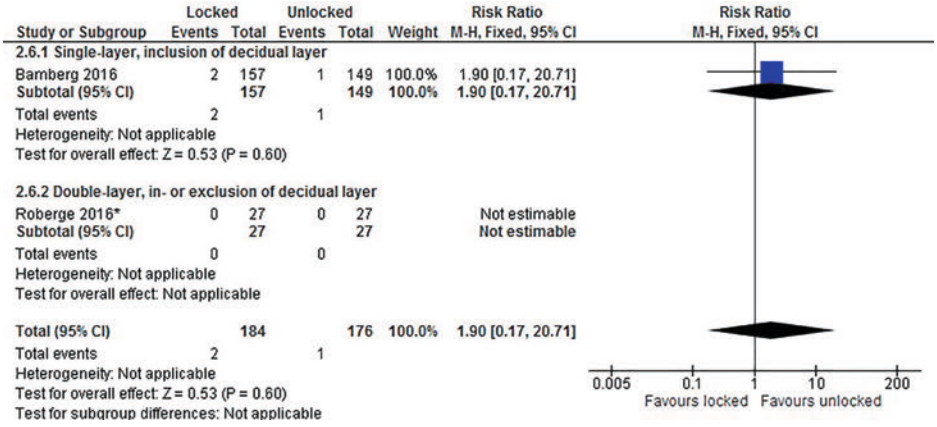

Figure S5.5 Maternal infectious morbidity

* Studies that only included women with a first CS

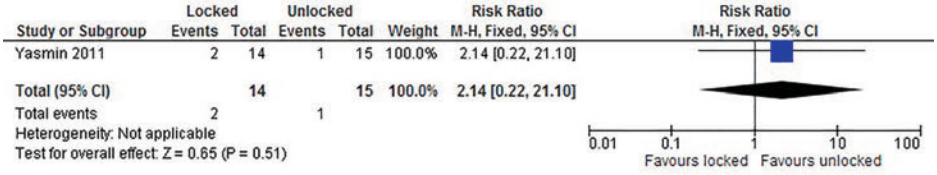

Figure S5.6 Uterine dehiscence at repeat CS

Figures S6. Forest plots secondary outcomes regarding exclusion versus inclusion of the decidua

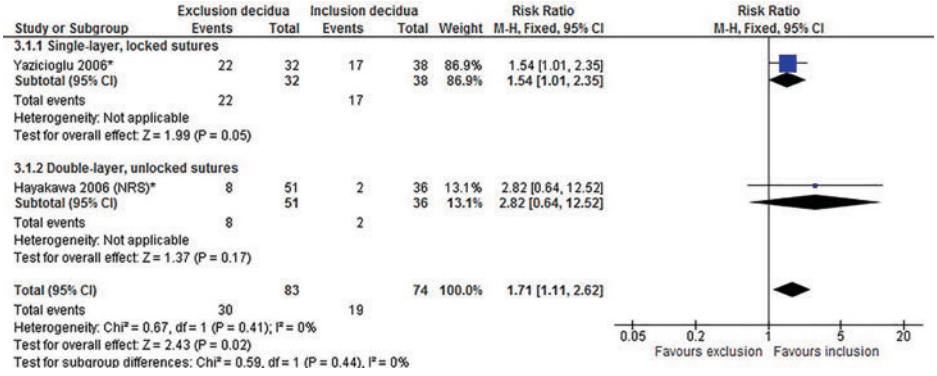

Figure S6.1 Prevalence of (large) niches

Definitions for a niche: Yazicioglu 2006: any deviation from the full apposition of the cranial and caudal edges of the uterine incision causing a tenting (ballooning out) towards the anterior abdominal wall, Hayakawa 2006: a triangular, anechoic area at the presumed site of the incision. *Studies that only included women with a first CS. NRS, non-randomized study.

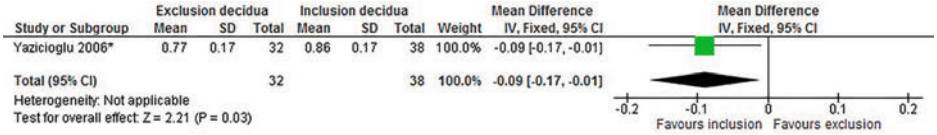

Figure S6.2 Healing ratio (%)

* Study that only included women with a first CS

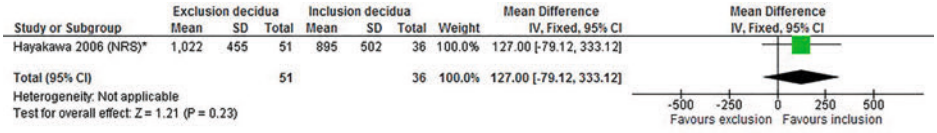

Figure S6.3 Blood loss (milliliters)

* Study that only included women with a first CS. NRS, non-randomized study

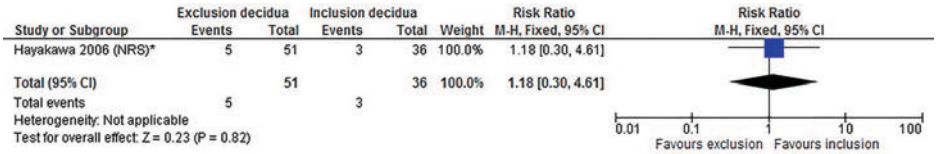

Figure S6.4 Maternal infectious morbidity

* Study that only included women with a first CS. NRS, non-randomized study

Figures S7. Sensitivity analyses regarding our primary outcome (RMT) for single- versus double-layer closure

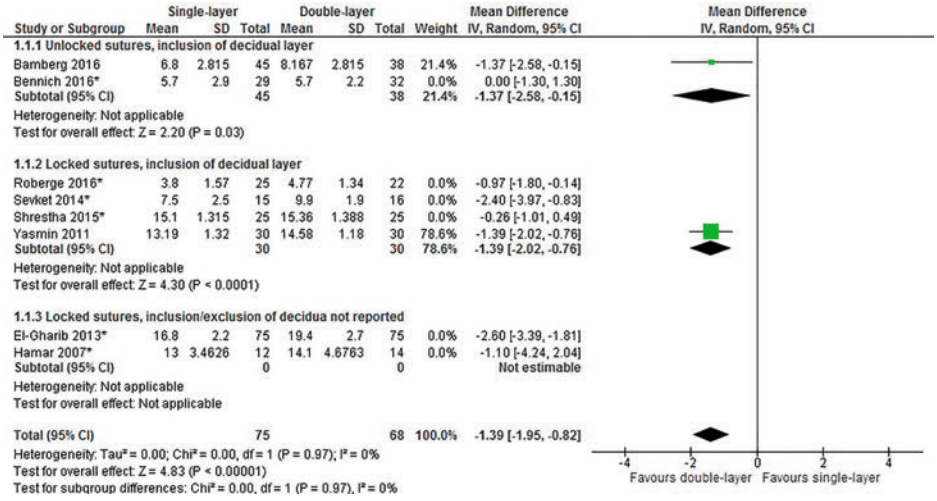

Figure S7.1 Studies that included women who underwent first or repeat cesarean section

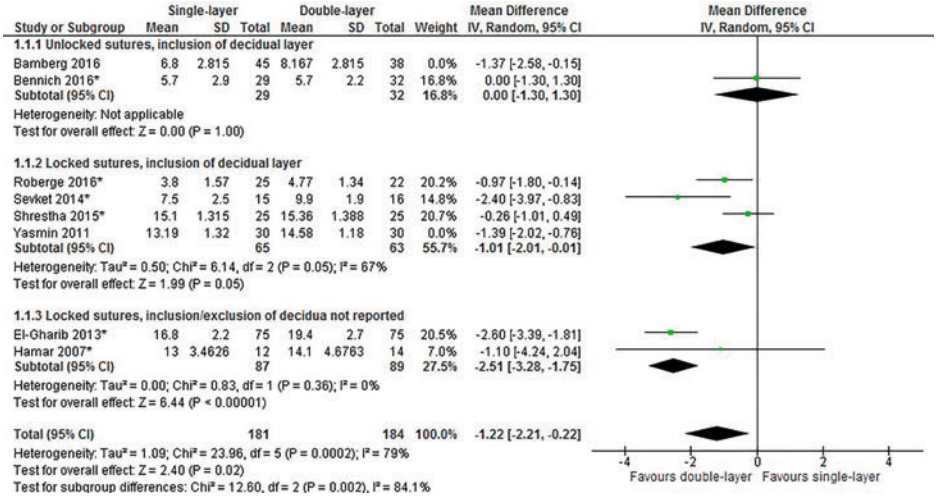

Figure S7.2 Studies that included women who underwent first cesarean section

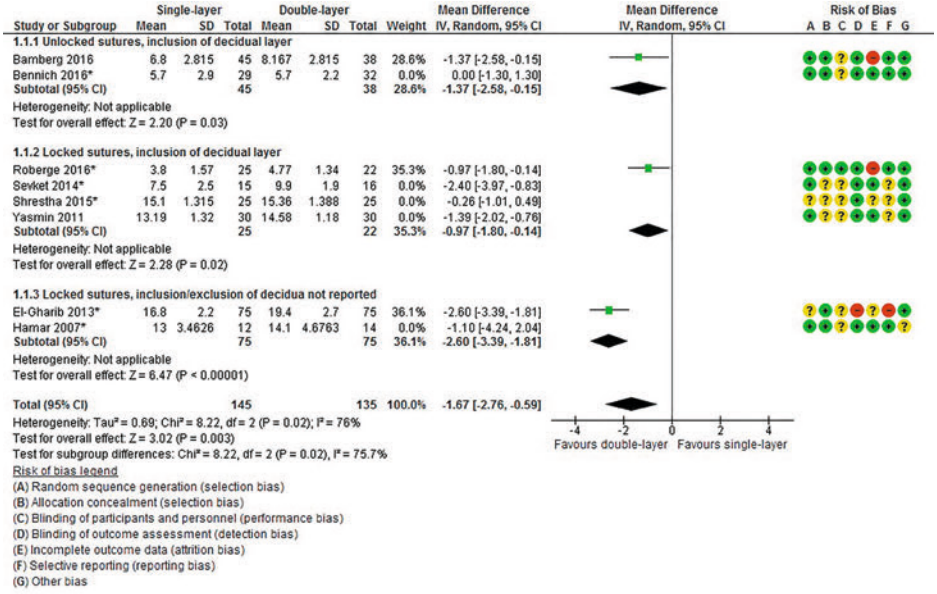

Figure S7.3 High risk of bias studies

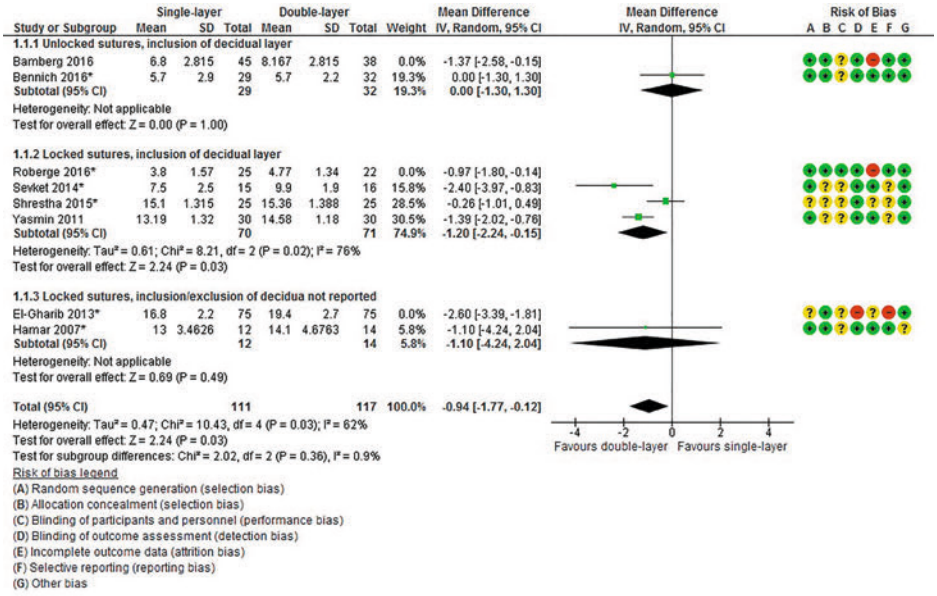

Figure S7.4 Low risk of bias studies

Figure S7.5 RCTs: no figure available, since all included studies were RCTs. This figure is Figure 1

Figure S7.6 Non-randomised studies: no figure available, since all included studies were RCTs

Figures S8. Sensitivity analyses regarding our primary outcome (RMT) for locked versus unlocked sutures

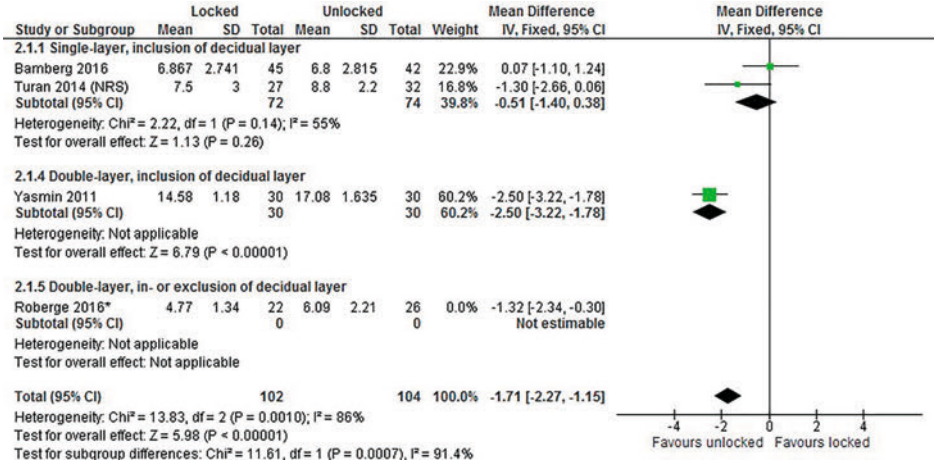

Figure S8.1 Studies that included women who underwent first or repeat cesarean section

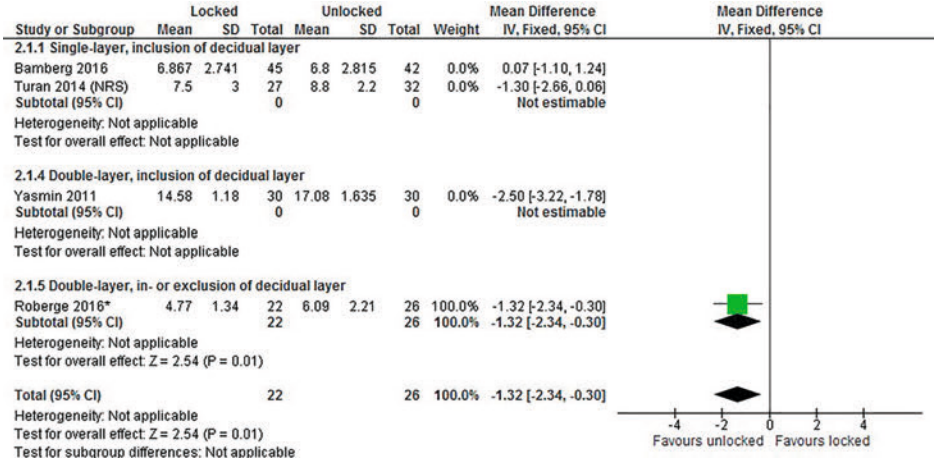

Figure S8.2 Studies that included women who underwent first cesarean section

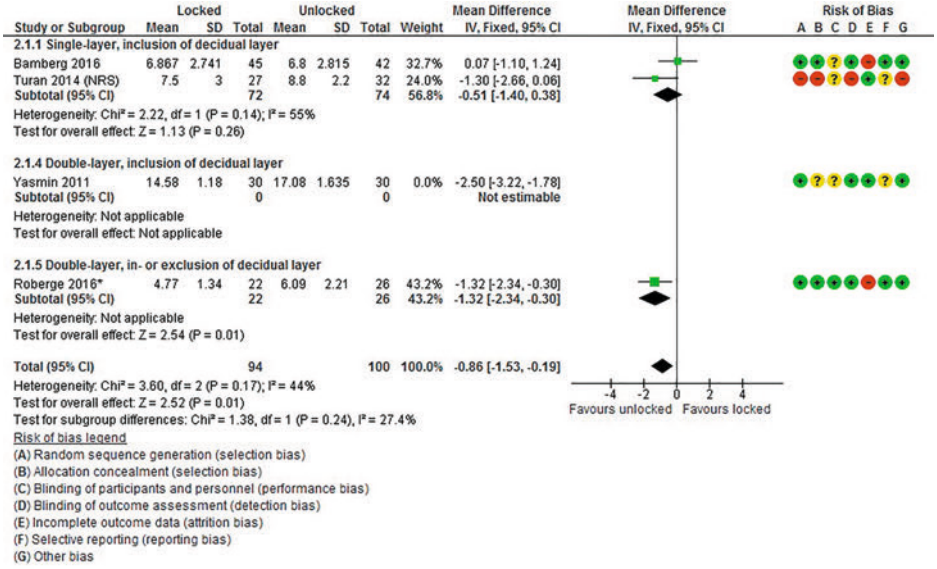

Figure S8.3 High risk of bias studies

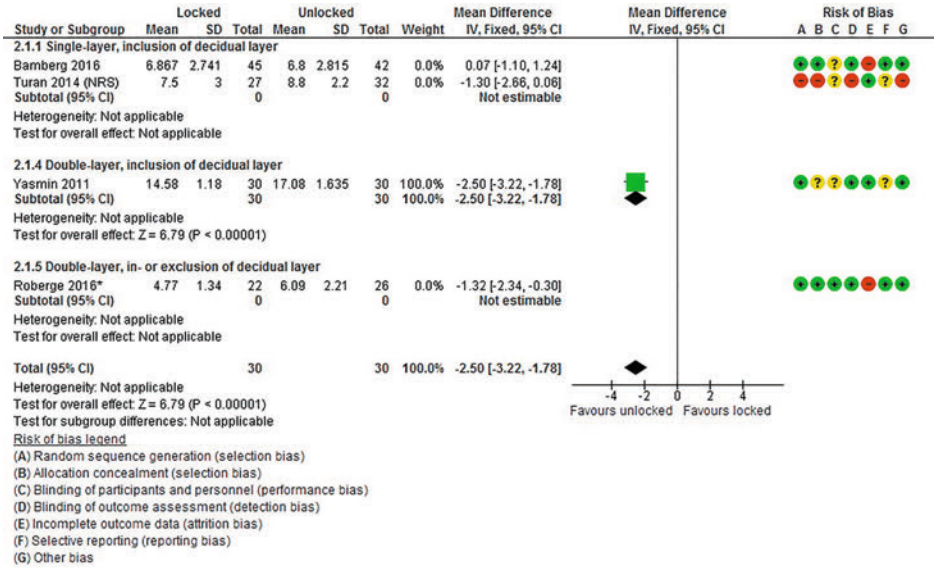

Figure S8.4 Low risk of bias studies

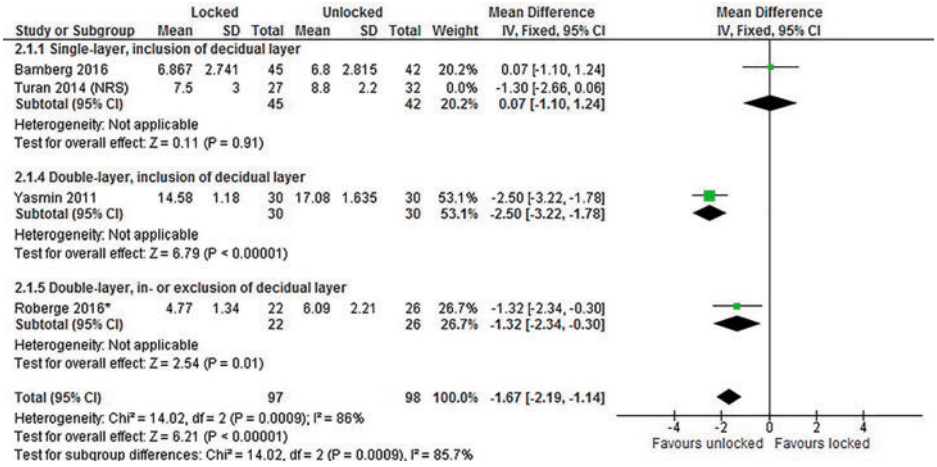

Figure S8.5 RCTs

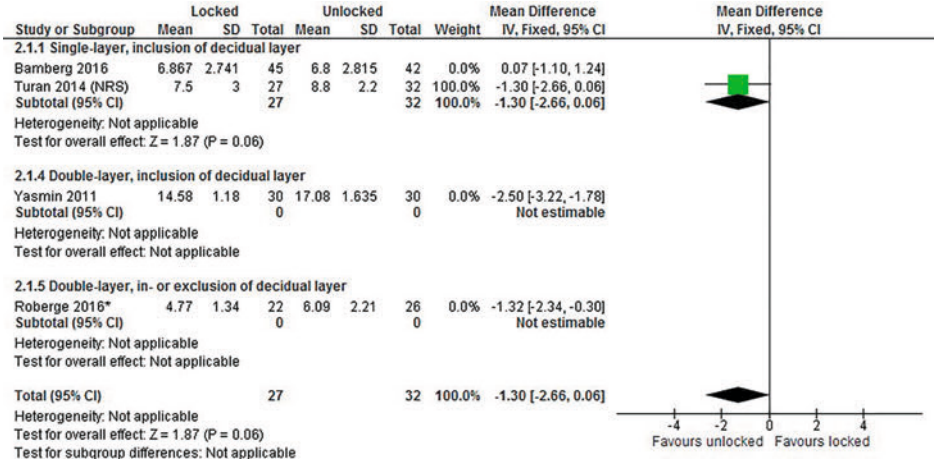

Figure S8.6 Non-randomised studies

Appendix S1. Full search strategy

Search strategy for PubMed (7 April 2017)

Search	Query	Items found
#4	#1 AND (#2 OR #3)	**1,164**
#3	((lock*[tiab] OR unlock*[tiab]) AND ("Suture Techniques"[Mesh:NoExp] OR sutur*[tiab] OR surgical technique*[tiab])) OR (("Endometrium"[Mesh] OR decidu*[tiab] OR endometria*[tiab] OR endometrium*[tiab]) AND (inclusion*[tiab] OR include*[tiab] OR exclusion*[tiab] OR exclud*[tiab]))	**10,351**
#2	"Suture Techniques"[Mesh:NoExp] OR suture technique*[tiab] OR surgical technique*[tiab] OR ((two[tiab] OR double[tiab] OR one[tiab] OR single[tiab]) AND (layer*[tiab] OR closur*[tiab]))	**260,127**
#1	"Cesarean Section"[Mesh] OR cesarea*[tiab] OR caesarea*[tiab] OR c section*[tiab] OR abdominal deliver*[tiab] OR postcesarea*[tiab] OR postcaesarea*[tiab]	**62,937**

[Mesh], Medical subject headings (MeSH); [Mesh:NoExp], Medical subject headings (MeSH) without explosion; [tiab], words in title or abstract

Search strategy for Embase.com (7 April 2017)

Search	Query	Items found
#4	#1 AND (#2 OR #3)	**1,364**
#3	lock*:ab,ti OR unlock*:ab,ti AND ('suturing method'/exp OR sutur*:ab,ti OR (surgical* NEAR/3 technique*):ab,ti) OR ('decidua'/exp OR 'endometrium'/exp OR decidu*:ab,ti OR endometria*:ab,ti OR endometrium*:ab,ti AND (inclusion*:ab,ti OR include*:ab,ti OR exclusion*:ab,ti OR exclud*:ab,ti))	**16,392**
#2	'suturing method'/exp OR ((two OR double* OR one OR single*) NEAR/3 (layer* OR closur*)):ab,ti OR (sutur* NEAR/3 technique*):ab,ti OR (surgical* NEAR/3 technique*):ab,ti	**135,519**
#1	'cesarean section'/exp OR cesarea*:ab,ti OR caesarea*:ab,ti OR 'c section':ab,ti OR 'c sections':ab,ti OR (abdominal NEAR/3 deliver*):ab,ti OR postcesarea*:ab,ti OR postcaesarea*:ab,ti	**94,713**

:ab,ti, words in title or abstract; /exp, EMtree keyword with explosion; NEAR/x, words near to each other, x places apart

Search strategy for Wiley/Cochrane Library (7 April 2017)

Search	Query	Items found
#1	cesarea* or caesarea* or 'c section' or 'c sections' or (abdominal near/3 deliver*) or postcesarea* or postcaesarea*:ti,ab,kw	**8,052**
#2	((two or double* or one or single*) near/3 (layer* or closur*)) or (sutur* near/3 technique*) or (surgical* near/3 technique*):ti,ab,kw	**8,294**
#3	(lock* or unlock*) near/3 (sutur* or surgical*) or ((decidu* or endometria* or endometrium*) and (inclusion* or include* or exclusion* or exclud*)):ti,ab,kw	**913**
#4	#1 and (#2 or #3)	**222**

Number of references per database: CDSR: 15; DARE: 4; Central: 200; Methods: 1; HTA: 1; EED: 1. ti,ab,kw, words in title, abstract or author keyword

WHO/ICTRP (10 May 2017)
((cesarea* OR caesarea* OR c section OR c sections OR abdominal deliver* OR postcesarea* OR postcaesarea*) AND (sutur technique* OR surgical technique* OR two layer* OR double layer* OR one layer* OR single layer* OR two closur* OR double closur* OR one closur* OR single closur* OR lock sutur* OR unlock sutur* OR lock surgical* OR unlock surgical* OR decidu inclusion* OR endometri inclusion* OR decidu include* OR endometri include* OR decidu exclusion* OR endometri exclusion* OR decidu exclud* OR endometri exclud*)) – **in TITLE 0 Results**

Duplicate articles were excluded. All languages were accepted. Ongoing trials or results published as abstract only were excluded. We checked related citations in PubMed as well as cross-references for all selected studies. When full text papers were not available, we contacted the authors.

Appendix S2. Items for data extraction

1) Study characteristics and design (authors, year of publication and period when the study was performed, number of participants), 2) participants (in- and exclusion criteria, whether patients with previous CS were included or not, mean age and gestational age), 3) intervention (single- or double-layer closure, and if applicable: whether locked or unlocked sutures were used, whether inclusion or exclusion of the decidual layer was performed, and if correction for other co-interventions took place), 4) control groups (same as 3), 5) primary and secondary outcome measures (type of outcome measures, methods of assessing them, timing of data collection and duration of follow-up).

Appendix S3. Additional information regarding use and recalculation of data collected from included studies

When mean and standard deviation (SD) were not directly available from initial studies, we recalculated them from median and interquartile range (mean = (median + IQR_1 + IQR_3) / 3, and SD = IQR_3 - IQR_1 / 1.35), according to Wan et al.[1] If initial studies used a 99% CI, we recalculated it into a 95% CI. When three arms were compared in the initial study we included the participants in the best applicable groups for meta-analysis. We always used data from the intention-to-treat group when different analyses (e.g. as treated analysis) were reported. When studies reported on women undergoing first CS and repeat CSs separately, we only included women who underwent first CSs to avoid confounding of previous CSs on outcomes.

Appendix S4. Predefined items for sensitivity analyses

- Previous cesarean section (yes or no)
- Ultrasound characteristics (transabdominally or transvaginally, with or without use of gel or saline, and moment of sonographic follow-up < 3 months or > 3 months after CS)
- Study design (RCT or prospective cohort study) and trial quality (low versus high risk of bias, the latter defined as at least one item scored as high risk).

Appendix S5. Additional information regarding systematic literature search

We identified 2750 articles with our literature search. After removing duplicates and including records identified through other sources (related citations, cross-references), we screened title and abstract of the 1940 remaining records. 122 records were assessed for eligibility, of which 101 were excluded because they did not meet our criteria. Figure S1 shows the flow diagram of our review process. Authors of two papers were contacted because full text article was not available, but we did not receive a reply.[2, 3]

Appendix S6. Single- vs double-layer closure – intraoperative and short-term postoperative outcomes

Six studies (n=1102, 7 RCTs and 2 cohort studies) reported on intra-operative blood loss, which was not different between groups (WMD 13.49 ml, 95% CI [-54.17, 27.19], p-value 0.52, Figure S4.2). Maternal infectious morbidity (RR 0.96, 95% CI [0.78, 1.18], p-value 0.70, Figure S4.4), hospital stay (WMD -0.03 days, 95% CI [-0.09, 0.02], p-value 0.20, Figure S4.5) and readmission rate (RR 1.02, 95% CI [0.73, 1.41], p-value 0.91, Figure S4.6) were similar between groups, and were studied in 9 (14,107 patients), 6 (12,873 patients) and 2 (12,265 patients) trials, respectively.

Appendix S7. Single- vs double-layer closure – reproductive outcomes

We were not able to distinguish between locked versus unlocked sutures or first or repeat CS, since this was not reported. Subsequent viable pregnancy rate was not corrected for applied fertility treatments. No studies reported on cesarean scar pregnancies.

Appendix S8. Locked vs unlocked closure - heterogeneity

Overall heterogeneity was high (79%), and I^2 for single-layer closure was 53% and for double-layer closure 71%. This was mainly contributed to the study of Yasmin et al.[4], in which only repeat CSs were performed and RMT reported at six weeks follow-up was relatively high compared to other studies (unlocked RMT 17.08mm, SD 1.64 and locked RMT 14.58mm, SD 1.18). Excluding this study from the meta-analysis, lowers overall heterogeneity from 79% to 44%, which still shows a statistically significant difference (WMD -0.86 mm, 95% CI [-1.53, 0.19), p-value 0.01).

Appendix S9. Inclusion vs exclusion of the decidual layer – secondary outcomes

One study[5] reported on intra-operative blood loss (WMD 127 ml, 95% CI [-79.12, 333.12], p-value 0.23, Figure S6.3) and maternal infectious morbidity (RR 1.18, 95% CI [0.30, 4.61], p-value 0.82, Figure S6.4), which were not different in the two groups.

REFERENCES WITHIN APPENDIX

1. Wan, X., W. Wang, J. Liu, and T. Tong, *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.* BMC Med Res Methodol, 2014. **14**: p. 135.
2. Banad, H.P., *Single versus double layer uterine closure in lower segment cesarean section: a comparative study.* Bijapur (India): Obstetrics Gynecology, Rajv Gandhi University of Health Science, 2006.
3. Guyot-Cottrel, A., *Essai CHORUS: Comparaison de l'aspect échographique de la cicatrice de césarienne selon une fermeture utérine en un plan ou en deux plans.* Paris: Faculté de Médecine, Université Paris Descarte, 2011.
4. Yasmin, S., J. Sadaf, and N. Fatima, *Impact of methods for uterine incision closure on repeat caesarean section scar of lower uterine segment.* J Coll Physicians Surg Pak, 2011. **21**(9): p. 522-6.
5. Hayakawa, H., A. Itakura, T. Mitsui, M. Okada, M. Suzuki, K. Tamakoshi, and F. Kikkawa, *Methods for myometrium closure and other factors impacting effects on cesarean section scars of the uterine segment detected by the ultrasonography.* Acta Obstet Gynecol Scand, 2006. **85**(4): p. 429-34.

CHAPTER 9

SINGLE- VERSUS DOUBLE-LAYER CLOSURE OF THE CESAREAN (UTERINE) SCAR IN THE PREVENTION OF GYNECOLOGICAL SYMPTOMS IN RELATION TO NICHE DEVELOPMENT – THE 2CLOSE STUDY: A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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C.B. Lambalk
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P.M. van de Ven
J.E. Bosmans
E. Pajkrt
E.A. Bakkum
C.M. Radder
M. Hemelaar
W.M. van Baal
H. Visser
J.O.E.H. van Laar
H.A.A.M. van Vliet
R.J.P. Rijnders
M. Sueters
C.A.H. Janssen
W. Hermes
A.H. Feitsma
K. Kapiteijn
H.C.J. Scheepers
J. Langenveld
K. de Boer
S.F.P.J. Coppus
D.H. Schippers
A.L.M. Oei
M. Kaplan
D.N.M. Papatsonis
L.H.M. de Vleeschouwer
E. van Beek
M.N. Bekker
A.J.M. Huisjes
W.J. Meijer
K.L. Deurloo
E.M.A. Boormans
H.W.F. van Eijndhoven
J.A.F. Huirne

BMC Pregnancy Childbirth. 2019 Mar 4;19(1):85.
DOI: 10.1186/s12884-019-2221-y.

† Contributed equally

ABSTRACT

Background

Double-layer compared to single-layer closure of the uterus after a cesarean section (CS) leads to a thicker myometrial layer at the site of the CS scar, also called residual myometrial thickness (RMT). It possibly decreases the development of a niche, which is an interruption of the myometrium at the site of the uterine scar. Thin RMT and a niche are associated with gynecological symptoms, obstetric complications in a subsequent pregnancy and delivery and possibly with subfertility.

Methods

Women undergoing a first CS regardless of the gestational age will be asked to participate in this multicentre, double blinded randomised controlled trial (RCT). They will be randomised to single-layer closure or double-layer closure of the uterine incision. Single-layer closure (control group) is performed with a continuous running, unlocked suture, with or without endometrial saving technique. Double-layer closure (intervention group) is performed with the first layer in a continuous unlocked suture including the endometrial layer and the second layer is also continuous unlocked and imbricates the first. The primary outcome is the reported number of days with postmenstrual spotting during one menstrual cycle nine months after CS. Secondary outcomes include surgical data, ultrasound evaluation at three months, menstrual pattern, dysmenorrhea, quality of life, and sexual function at nine months. Structured transvaginal ultrasound (TVUS) evaluation is performed to assess the uterine scar and if necessary saline infusion sonohysterography (SIS) or gel instillation sonohysterography (GIS) will be added to the examination. Women and ultrasound examiners will be blinded for allocation. Reproductive outcomes at three years follow-up including fertility, mode of delivery and complications in subsequent deliveries will be studied as well. Analyses will be performed by intention to treat. 2290 women have to be randomised to show a reduction of 15% in the mean number of spotting days. Additionally, a cost-effectiveness analysis will be performed from a societal perspective.

Discussion

This RCT will provide insight in the outcomes of single- compared to double-layer closure technique after CS, including postmenstrual spotting and subfertility in relation to niche development measured by ultrasound.

Trial registration

Dutch Trial Register (NTR5480)

BACKGROUND

Cesarean section (CS) rates have increased from 14.5 to 27.2% in the last two decades in the Western world.[1] In 2016, 26,664 CSs were performed in the Netherlands, being 16.0% of the total number of deliveries.[2] The increasing CS rate has stimulated an interest in the potential long-term morbidity of a CS scar, such as uterine rupture or malplacentation.[3–7] Other less severe, but more prevalent long-term symptoms are gynecological symptoms and subfertility.

Only recently, gynecological symptoms such as painful menstruations and postmenstrual spotting have been associated with CSs.[8–10] These symptoms are considered to be related to a niche, defined as "*an indentation at the site of the cesarean scar with a depth of at least 2 mm*", visible on transvaginal ultrasound (TVUS).[11] Two cohort studies reported a strong association between postmenstrual spotting and a niche: odds ratio (OR) 3.1; 95% confidence interval (CI) 1.5–6.3 [8] and OR 5.5; 95% CI 1.1–26.5.[10] In these studies, a niche was observed in 50 to 60% of the women after a CS, using transvaginal ultrasound.[8,10] Spotting was correlated to niche volume and inversely correlated to the residual myometrial thickness (RMT).[8,10]

In addition to the gynecological symptoms, a niche may influence fertility. A recent meta-analysis reported that a CS on average reduced the probability of subsequent pregnancy with 9% (relative risk (RR) 0.91; 95% CI 0.87–0.95) in comparison to a vaginal delivery.[12] None of the included studies in this meta-analysis evaluated the relation between subsequent fertility and the presence of a niche. One of the hypotheses is that intra-uterine fluid or cervical mucus or blood accumulation in the niche are expected to hamper the penetration of sperm cells or impair embryo implantation.[13] Long-term follow-up will facilitate the evaluation of the association between uterine closure, niche development, accumulation of intra-uterine fluid and subfertility.

In the last years, various therapies have been developed and implemented to treat niche related symptoms such as menstrual disorders.[14–18] Effectiveness of both hysteroscopic[19] and laparoscopic niche resection[15] have recently been published. Because both niche related symptoms and applied therapies lead to increases in medical consultations and costs, it seems to be more efficient to prevent niche development in the first place. Uterine closure technique of the CS scar has been proposed as an independent factor for niche development.[9] However, large randomised trials evaluating the effect of uterine closuring techniques on postmenstrual spotting or other gynecological or reproductive outcomes in relation to niche development and thin residual myometrium are lacking, as well as cost-effectiveness evaluations.

In order to shorten surgery time and in the absence of significant differences in short-term outcomes[20,21], most Dutch gynecologists (92%) have replaced double-layer by single-layer closure after a CS, using multifilament continuous unlocked sutures. Given the higher risk on myometrium loss and thus development of a thinner residual myometrium after single-layer closure[5,22], we hypothesise that this method introduces a higher risk on postmenstrual spotting and possibly subfertility after a CS and that it can be prevented by applying double-layer unlocked closure.

Double-layer unlocked closure is considered safe, without a clinically relevant higher risk on short-term outcomes.[5,23,24] Moreover, it results in a thicker residual myometrium, especially when unlocked sutures are applied.[5,22,24] Dysmenorrhea was reported more frequently after single-layer closure, but this was only studied in two RCTs and not always related to ultrasound findings such as myometrial thickness or niche presence.[24] Prevalence of uterine rupture seems to be similar after single- versus double-layer closure[5,22,24], but has neither been related to ultrasound findings and since it has a very low incidence, statistically significant differences are difficult to find. Since long-term outcomes such as gynecological symptoms, fertility outcomes and results of subsequent pregnancies are studied infrequently, additional evidence is needed before a preference for either technique can be indicated.

Objective

Our primary objective is to determine the effectiveness of unlocked double-layer uterine closure compared to unlocked single-layer uterine closure in the prevention of niche related gynecological symptoms nine months after a first CS. Secondary objectives are to assess niche prevalence measured by ultrasound at three months follow-up and to study both reproductive outcomes related to a subsequent pregnancy and gynecological symptoms at three years follow-up. Additionally we aim to study the cost-effectiveness alongside the trial.

METHODS/DESIGN

Design

This multicentre randomised controlled superiority trial will be performed in the Netherlands, in hospitals that collaborate within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0, www.zorgevaluatienederland.nl). Centres that participate are district, teaching or university hospitals in the Netherlands. A list of study sites is available in Appendix 1.

Participants and eligibility criteria

All women who undergo a first CS, planned or unplanned, will be asked to participate in the study. Other inclusion criteria are: sufficient command of the Dutch or English language, age ≥ 18 years and written informed consent. To prevent confounding effects on niche development during the study, we will exclude women with a previous CS. Other exclusion criteria are: inadequate possibility for counselling (e.g. indication for emergency CS without being informed about the study previously, women in severe pain without adequate therapy), previous major uterine surgery (e.g. laparoscopic or laparotomic fibroid resection, septum resection), women with known causes of menstrual disorders (e.g. cervical dysplasia, communicating hydrosalpinx, uterine anomaly or endocrine disorders disturbing ovulation), placenta in- or percreta during the current pregnancy or ≥ three foetuses during the current pregnancy.

Recruitment and randomisation

Eligible women will be asked by a gynecologist, resident, clinical midwife or research nurse to participate in the trial when they undergo a planned CS. Eligible women who are planned to undergo a vaginal delivery will also be informed about this study during pregnancy in case they need an unplanned CS. Furthermore, women during induced labour and women receiving adequate therapy for pain during labour, will be asked to participate in case a CS is needed during labour for any indication.

When the decision of a CS is made and all selection criteria are met, women will be randomly allocated to single-layer (control group) or double-layer (intervention group) closure (1:1) (see Figure 1). Randomisation will be performed using a web-based application ALEA 2.2 which displays a computer-generated random number, managed by the Clinical Research Unit of the Amsterdam UMC - location AMC. We will use a permuted block-design, stratified for recruiting centres and for planned or unplanned CS. All women that decline to participate will be registered anonymously in order to record the number and reason for refusal. Subjects who withdraw from this study will not be replaced.

Gynecologists, residents, clinical midwives or research nurses enrol participants and assign them to the intervention. The CS will be performed by either a gynecologist, a resident supervised by a gynecologist or by a resident that is authorised to perform CSs without supervision. Participants and sonographers will be blinded for the closure technique. If operative reintervention after CS is needed and the gynecologist that performs the reintervention needs to know the closure technique that the participant was assigned to, unblinding is possible through the logistic trial coordinator. We expect this situation to occur very infrequently.

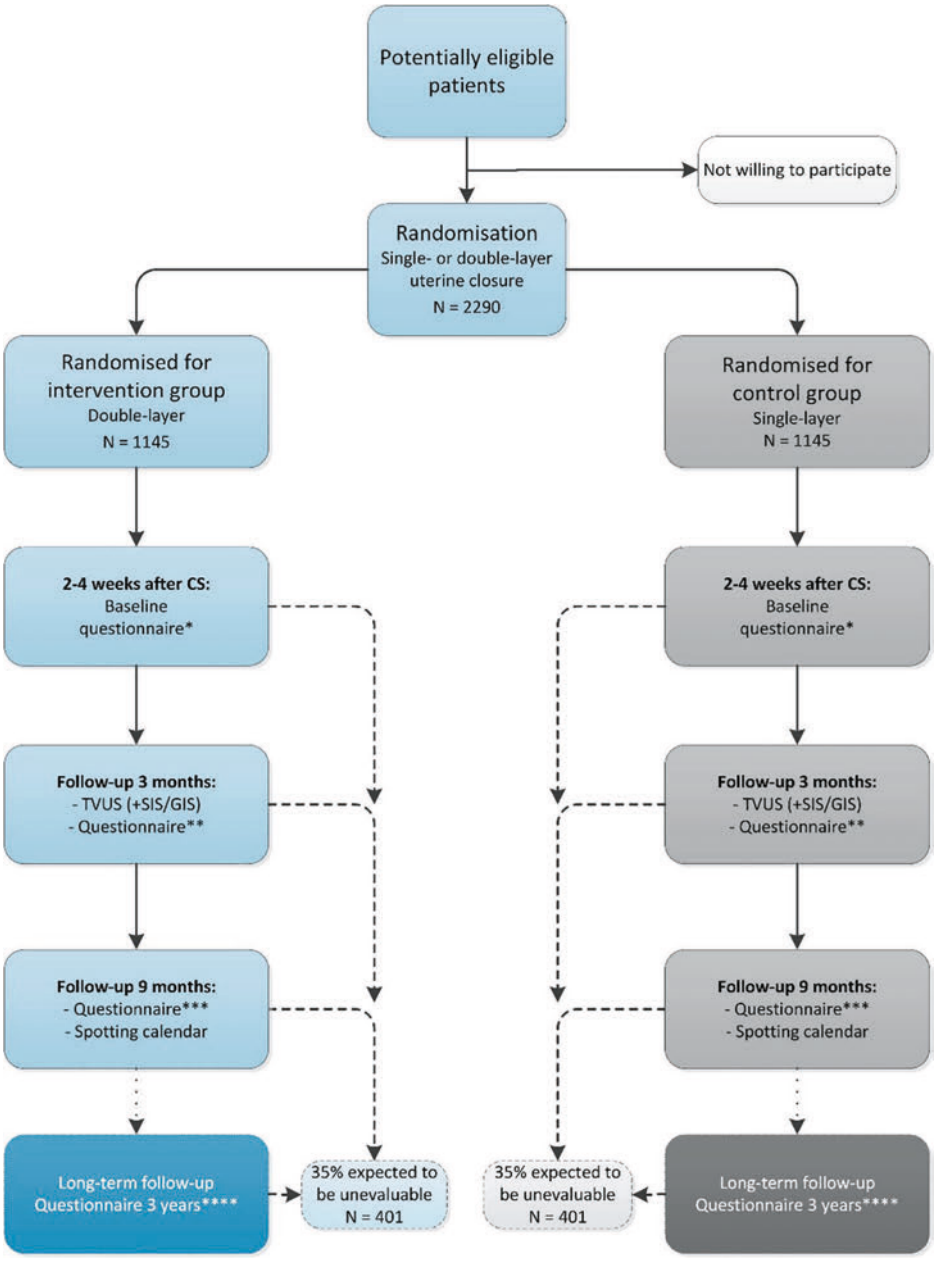

Figure 1. Flowchart of the 2Close study

* = baseline questions, EQ-5D-5L. ** = symptom questionnaire, EQ-5D-5L, SF36, PROMIS SF8a, iMCQ, iPCQ. *** = symptom questionnaire, FSFI, EQ-5D-5L, SF36, iMCQ, iPCQ. **** = symptom questionnaire, fertility questionnaire, FSFI, EQ-5D-5L, SF36, PROMIS SF8a

Intervention (double-layer closure)

In both study arms, women will undergo a CS following a standard way with respect to mode of uterotomy, correct approximations of the cutting edges and non-closure of the peritoneum. In the intervention arm, double-layer closure of the uterus will be performed using unlocked multifilament continuous running sutures for both layers and the endometrial layer will be included in the first layer (see Figure 2). The second layer is a continuous running suture that imbricates the first layer. Since this is not the standard method for uterine closure in the Netherlands, a short online instruction film will be shown to all participating centres and surgeons prior to participation (see Appendix 2). Surgical outcomes will be registered after the procedure in the electronic case report form (eCRF).

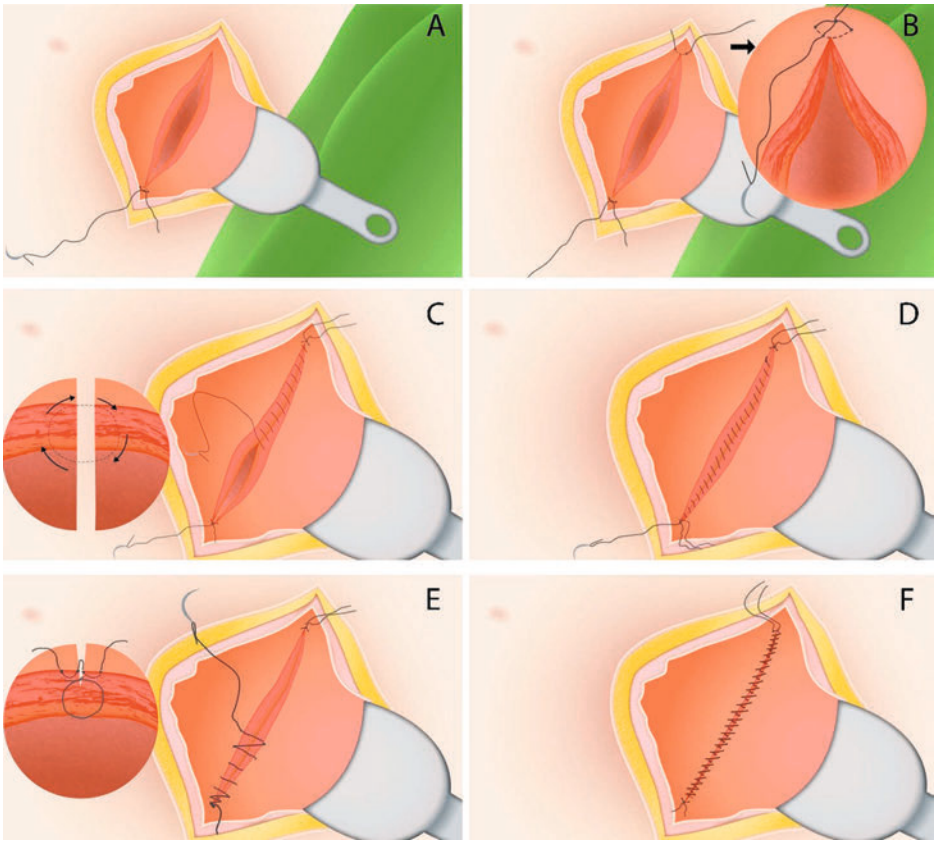

Figure 2. Double-layer uterine closure technique

A. Step 1: lateral suture; B. Step 2: lateral suture on the other side; C. Step 3: First layer: full thickness, continuous, including large part of myometrium, including the endometrial layer; D. Step 4: End of this first layer; E. Step 5: Second layer: superficial continuous layer of serosal tissue, imbricating the first layer; F. Step 6: First and second layer should be closely connected

Control group (single-layer closure)

The control group will receive usual closure technique of the uterus: a single-layer closure using unlocked continuous running multifilament sutures. The currently available evidence is inconclusive with respect to endometrial saving technique or not. Therefore, we decided that in our study surgeons are free to choose to close either full thickness (including the endometrium) or split thickness (excluding the endometrium) in the control group. The applied method, including endometrial saving technique or not, will be registered.

Niche evaluation

The care after CS will be according to the normal local protocol with the regular outpatient visit that is normally executed six weeks after the CS. This routine visit may be postponed to three months after the CS to enable an ultrasound evaluation to identify the existence of a niche, but participating centres may decide whether they want visits at six weeks (routine follow-up) and at three months (ultrasound follow-up) or only one visit after three months combining the regular control and the ultrasound follow-up. The ultrasound evaluation is standardised as proposed by Jordans *et al*.[11] (see Figure 3). Based on this standardisation, we created an obligatory e-learning for all ultrasound performers to let all ultrasounds be performed in a uniform manner. To increase consistency and to improve the learning curve, we will evaluate a sample of ultrasounds in each centre based on recorded pictures and provide feedback to the examiners. Since it is known that a niche can be missed during TVUS only[8,10,25] we will additionally perform a saline infusion sonohysterography (SIS) or gel installation sonography (GIS) in case no niche is observed during the normal TVUS or if the ultrasound is inconclusive. It would be optimal to have a contrast enhanced ultrasound in all women when the uterine cavity or niche are not naturally filled with fluid, but we have chosen for this approach to prevent unnecessary burden for the participants and to reduce costs.

Outcome measures

Primary outcome measure

The primary outcome is the number of days of postmenstrual spotting during one cycle at nine months after CS. We defined postmenstrual spotting as brownish discharge for more than two days at the end of the menstruation, with a total duration (menstruation and spotting) of more than seven days, or intermenstrual blood loss that starts after the end of the menstruation.[8] The number of days of postmenstrual spotting will be counted as follows: days with brownish discharge (> two days) when the total duration of menstruation and spotting exceeds seven days + number of days with intermenstrual

blood loss. Amenorrhoeic women, due to lactation, medication or other diseases, will not be evaluable for the primary outcome and will be left out of this analysis.

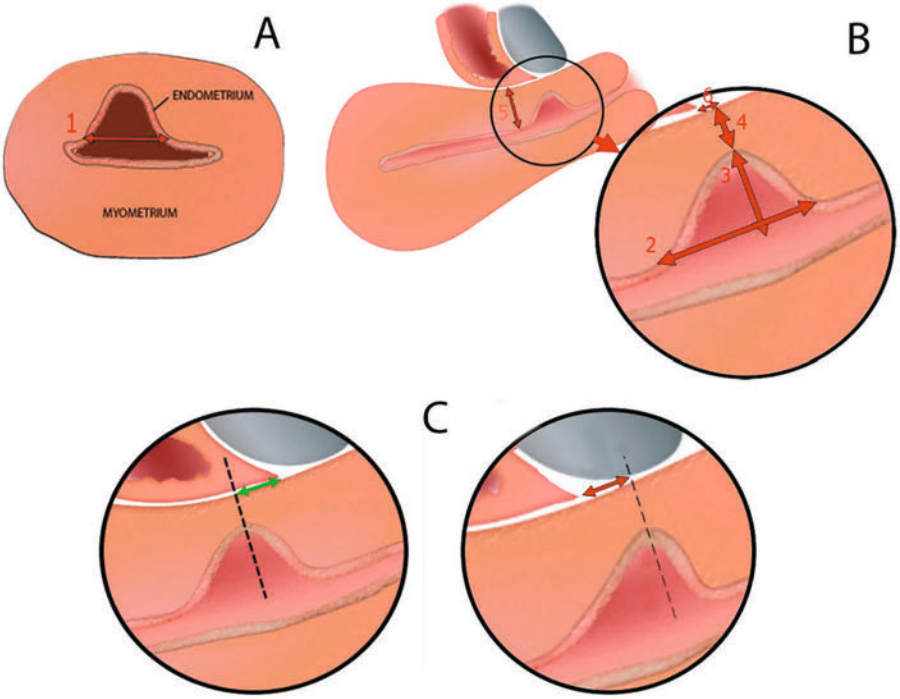

Figure 3. Standardised transvaginal ultrasound evaluation of a niche in the non-pregnant uterus

A. Measured in the transversal plane: niche width (1); B. Measured in the sagittal plane: niche length (2), niche depth (from cervical canal until apex of the niche) (3), residual myometrial thickness (from deepest part of the niche until the serosa) (4), adjacent myometrial thickness (myometrium thickness close to base of the niche) (5), distance from apex of the niche to vesico-vaginal fold (see c) (6); C. Measuring the niche relatively to the vesico-vaginal fold in the sagittal plane: positive value (green arrow, in mm) or negative value (red arrow, in mm)

Secondary outcome measures at short-term

- Perioperative outcomes including blood loss, operative time, additional haemostatic sutures and complications.
- Menstruation characteristics, dysmenorrhea (visual analogue scale (VAS)), Quality of Life (QOL) using Short-Form-36[26] and EQ-5D-5L[27,28], societal reintegration (PROMIS Short-Form-8a[29]), sexual function using the Female Sexual Function Index (FSFI[30]), applied medical and/or surgical therapy because of gynecological symptoms, all obtained through digital questionnaires, will be assessed at three and nine months follow-up.

- Ultrasound evaluation will be performed at three months follow-up using TVUS, in which RMT, adjacent myometrial thickness (AMT), presence of a niche (depth of ≥2mm), length, depth and width of the niche, presence of large niches (RMT < 50% of AMT, RMT <3mm) and niche volume will be measured.

Cost-effectiveness outcomes

Costs will be measured using adapted versions of the iMTA Productivity Cost Questionnaire (iPCQ[31]) and iMTA Medical Consumption Questionnaire (iMCQ[32]) from a health care and societal perspective at nine months of follow-up.

Secondary outcome measures at long-term

- Menstruation characteristics, pain, sexual functioning, QOL and social reintegration will be evaluated at three years follow-up.
- Reproductive outcomes at three years follow-up: % of women desiring to conceive, % of women that conceived including time to conceive, % of women with an ongoing pregnancy, the need for fertility treatment and pregnancy outcomes such as mode of delivery or complications will be determined.

Long-term outcomes will be presented in a separate article.

Data collection and data management

Intraoperative data

Immediately after the CS we will register relevant items regarding the delivery and CS in an eCRF, in which confidentiality and anonymity are ensured and audit trails are accessible. These items include: reason for planned or unplanned CS, emergency CS or not, whether women experienced contractions, dilatation, performed method for uterine closure, endometrial saving technique applied, used suturing material, extra haemostatic sutures, operative time, blood loss and complications.

Collection of baseline characteristics and patient reported outcomes

Baseline characteristics will be collected through a digital questionnaire at 2–4 weeks after cesarean section, sent to the e-mail address of participants. Since we will also include unplanned CSs, we decided that it is not possible for all participants to answer questions regarding baseline characteristics before the operation. Baseline parameters include maternal age, body mass index, social economic status, smoking habit, medical and obstetric history, gestational age and previous vaginal deliveries, all reported by the participant. We expect that the impact of niche related symptoms such as postmenstrual spotting on daily activities and sexual behaviour may be influenced by ethnic background and religion, therefore we will also register these characteristics. At three months, nine

months and three years follow-up, again digital questionnaires will be sent to participants to assess the primary and secondary outcomes (see Figure 1). At nine months, we ask participants record their exact menstrual and spotting pattern, if any, in an adjusted menstruation score chart.[33] Reminders for all questionnaires will be sent every two weeks, with a maximum of three times. When no response is given after the reminders, research nurses from participating centres will be asked to call the participant.

Data niche evaluation

Results of the TVUS and GIS or SIS, performed three months after CS, will be registered. Women will not receive information regarding the presence of a niche, since it has no clinical consequences so shortly after CS and this may influence the answers given in the questionnaires. Other important abnormalities visualised by ultrasound will be reported as usual.

Statistical issues

Sample size calculation

We use a superiority design since we expect double-layer closure to be favourable. Literature for making reliable estimations on postmenstrual spotting in relation to niches is scarce. We have used baseline data from the HysNiche[19] and LapNiche[15] study. We estimate the mean number of spotting days to be 3.5 days/month in the total group. We consider a 15% reduction in the mean number of spotting days clinically relevant, which is 0.5 day/month reduction. Assuming a standard deviation (SD) of 3.4 and a two-sided significance level of 5%, a total of 1488 women need to be included to achieve a power of 80%. Increasing the sample size to take into account 35% of women unevaluable (due to drop-out, non-response or amenorrhoea) for the primary outcome, 2290 women need to be included.

Data-analysis

Data-analysis will be performed according to the intention to treat principle and additional per protocol analyses will be performed. A test will be considered statistically significant when the two-sided test shows a p-value < 0.05. Baseline characteristics will be presented using percentages, means with SD and 95% CI or medians with interquartile ranges (IQR), where appropriate.

The primary outcome, number of days of postmenstrual spotting, will be presented for both groups as mean with SD or median with IQR, and presented in a Box-Whisker graph to show the distribution. Differences in primary outcome between the groups will be tested using the independent t-test in case of normal distribution (possible after transformation of the outcome) or Mann-Whitney U test. An adjusted analysis will be

performed using linear regression analysis in which we adjust for factors on which randomisation was stratified and for baseline factors on which relevant differences are observed despite randomisation.

Dichotomous secondary outcomes will be presented as percentages and RR with corresponding 95% CI. P-values will be calculated using the chi-square test or, if the expected count for at least one cell is below 5, using the Fisher exact test. Normally distributed continuous variables will be presented as means with SD, and differences between the groups will be calculated with an independent t-test. Non-normally distributed continuous variables will be presented as medians with IQR and differences between the groups will be calculated with Mann-Whitney U test. The questionnaires will be analyzed using the appropriate algorithms and usual presentation methods (FSFI, EQ-5D-5L, SF36, PROMIS SF8a, iMCQ, iPCQ).

Comparison of primary outcome between women receiving single- and double-layer closure will be done as secondary analyses within each of the following subgroups separately: planned (without labour) or unplanned (in labour) CS

1. Emergency CS or not
2. Preterm (< 37 weeks gestational age) or term (≥ 37 week gestational age) CS
3. Presence (> 3cm) or absence (≤ 3cm) of dilatation
4. Placenta praevia or not
5. Presence or absence of specific maternal morbidity (e.g. diabetes, pre-eclampsia, haemolysis/elevated liver enzymes/low platelet count (HELLP) syndrome, immunodeficient women)
6. Singleton versus twin pregnancy
7. Natural cycle or hormonally induced withdrawal bleeding

Within the single-layer group (control group) we will compare the primary outcome between women in whom endometrial saving technique (split thickness) was applied and women in whom an endometrial saving technique was not applied (full thickness).

Economic evaluation

The economic evaluation will be performed alongside the RCT from a societal perspective. Both a cost-effectiveness and cost-utility analysis will be performed with a time horizon of nine months to relate the difference in societal and healthcare costs between double-layer and single-layer unlocked uterine closure during a CS to the difference in clinical effects. Healthcare costs include costs of primary and secondary care, complementary care and home care. Costs in other sectors include presence and

absence from paid and unpaid work. The friction cost approach will be used to estimate indirect costs. For the valuation of health care utilization standard prices published in the Dutch Costing guidelines will be used.[34] Medication use will be valued using prices of the Royal Dutch Society for Pharmacy.

Societal costs will be related to the following effect measures in the economic evaluation: days with postmenstrual spotting and quality-adjusted life-years (QALYs) based on the Dutch tariff for the EuroQol (EQ-5D-5L).[27,28,35]

We hypothesise that double-layer uterine closure will reduce postmenstrual spotting and related consultations for gynecological or fertility related problems and applied therapies, and as a consequence that it will be cost-effective in comparison with single-layer uterine closure.

The analysis will be done according to the intention to treat principle. Missing costs and effect data will be imputed using multiple imputation. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects. Bootstrapping with 5000 replications will be used to estimate 95% CI around cost differences and the uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves showing the probability that double-layer uterine closure is cost-effective in comparison with single-layer uterine closure for a range of different ceiling ratios will also be estimated. Adjustment for confounders and effect modifiers will be done if necessary.[36]

Interim analysis and safety monitoring

Because of the type of intervention, the Medical Ethics Committee (MEC) determined that the risk for participation is negligible. Therefore, we do not have a Data Safety Monitoring Committee. No interim analysis is planned. All serious adverse events (SAEs) will be reported to the MEC by line listing yearly. Life threatening SAEs or an event that leads to death will be reported to the MEC immediately.

All SAEs will be followed until they have abated, until a stable situation has been reached or the patient was discharged. We do not expect to terminate the study prematurely given the low risk of adverse events.

Confidentiality and data security

All participating centres receive a login name and password to gain access to ALEA 2.2, the web-secured randomisation database. Randomisation is performed pseudo-

anonymously with only the initials and year of birth of the participants. Linking personal data to the study number can only be performed in the local participating centres or by the trial coordinator (SS). Written informed consent forms are stored in every centre in a lockable room. All forms and data will be archived for 15 years in the participating centres.

DISCUSSION

In the last years, studies examining complications of CSs are increasing, including the development of niches or thin residual myometrium at the site of the previous CS and related symptoms. Both RMT and the presence of a niche have been associated with postmenstrual spotting.[8,10] Double-layer unlocked closure has been shown to result in a thicker residual myometrium and as a consequence can possibly lead to a decrease of niche development after a CS compared to single-layer closure.[5,22,24,37] However, the long-term clinical outcomes in terms of postmenstrual spotting or subfertility have not been studied previously or have not been related to ultrasound findings. We hypothesise that niche related postmenstrual spotting and fertility problems will reduce together with decrease in niche prevalence, in which identification of the best uterine closure technique regarding RMT and niche development will be of great significance.

Strengths and limitations

The design of this study is one of the strengths; this is the first large RCT that will evaluate the effectiveness of double-layer uterine closure compared to single-layer uterine closure after CS regarding niche related gynecological symptoms and reproductive outcomes with a long-term follow-up. The study is adequately powered. Randomisation is performed by using a web based randomisation program. Furthermore, all participants and examiners are blinded which reduces the chance for bias regarding reported symptoms and ultrasound findings. An additional strength is the uniform manner in which we try to perform double-layer closure and ultrasound evaluation, instructed by mandatory online instruction film and e-learning, respectively. Moreover, the 2Close study will compare the cost-effectiveness of both techniques which has never been done before. As we expect that double-layer closure will reduce the incidence of niche development and as a consequence that it could possibly reduce the gynecological symptoms including postmenstrual spotting after CS, we assume double-layer closure to be more cost-effective. Also, we expect that double-layer closure will improve the chances of conceiving after CS and lower costs in fertility treatment.

We also expect some limitations. Baseline characteristics will be collected through questionnaires that are filled in by women in the first month after CS, which might lead

to recall bias regarding medical history, complications during pregnancy and labour, and other baseline measurements. We decided to lower the administrative load for participating hospitals by obtaining these characteristics through the participants. Furthermore, there is no validated questionnaire available yet for postmenstrual spotting; therefore, the questionnaires that are used in the 2Close study are not adjusted or validated for these symptoms. Moreover, the surgical techniques performed during the CS in this study are standardised in both study arms except for saving the endometrium in the control group. There is no conclusive evidence whether or not to save the endometrium in the suture according to its influence on niche development. Therefore, we chose to leave this decision with the surgeons. There may possibly be a difference in the incidence of niche development between the participants receiving single-layer split thickness or full thickness closure, also when compared to the incidence of niche development in the double-layer group. This will be further examined in a subgroup analysis.

To prevent bias regarding niche evaluation three months after CS, all ultrasonographic examiners are trained by an online learning program and a sample of ultrasounds will be evaluated. The learning module is based on the results of a Delphi procedure among international niche experts.[11] Although the niche examiners in the 2Close are trained by a standardised method, experience in measuring niches and as a consequence differences in niche measurement may occur among examiners.

Potential impact and implications

This study will gain insight in the most optimal uterine closure technique after CS which is relevant for women and gynecologists, since we will focus on long-term gynecological symptoms and reproductive outcomes in relation to changes of the lower uterine segment after CS and in particular niche development. Since many studies have already shown that RMT and niches are related to several symptoms and therapies for niche resection are being developed, we think it is necessary to provide evidence for the development of preventive strategies regarding niche related symptoms. It is important to realise that the best way to prevent a niche and its related symptoms, is to not perform a CS. But since it is often inevitable to perform a CS, care takers should perform it in the most optimal way.

After the results of this study become available, the most optimal and cost-effective technique can be implemented in order to reduce symptoms and problems in a subsequent pregnancy. This will not be difficult, since the technique is easy to learn and many gynecologists and residents are familiar with it after the trial. Especially for a scheduled CS, women should be informed about the risk to develop a niche and the risk that it might cause symptoms or complications later in life.

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APPENDICES

Appendix 1. Affiliations of participating hospitals – all departments of Obstetrics and Gynecology

1. VU University Medical Centre, De Boelelaan 1118, 1081 HV Amsterdam
2. Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE Deventer
3. Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam
4. OLVG-Oost, Oosterpark 9, 1091 AC Amsterdam
5. OLVG-West, Jan Tooropstraat 164, 1061 AE Amsterdam
6. Westfriesgasthuis, Maelsonstraat 3, 1624 NP Hoorn
7. Flevo Hospital, Hospitaalweg 1, 1315 RA Almere
8. Tergooi Hospital, Rijksstraatweg 1, 1261 AN Blaricum
9. Máxima Medical Centre, De Run 4600, 5504 DB Veldhoven
10. Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven
11. Jeroen Bosch Hospital, Henri Dunantstraat 1, 5223 GZ 's-Hertogenbosch
12. Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden
13. Groene Hart Hospital, Bleulandweg 10, 2803 HH Gouda
14. Haaglanden Medical Centre, Lijnbaan 32, 2512 VA Den Haag
15. Haga Hospital, Els-Borst-Eilersplein 275, 2545 AA Den Haag
16. Reinier de Graaf Hospital, Reinier de Graafweg 5, 2625 AD Delft
17. Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht
18. Zuyderland Medical Centre, Henri Dunantstraat 5, 6419 PC Heerlen
19. Rijnstate Hospital, Wagnerlaan 55, 6815 AD Arnhem
20. Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 10, 6525 GA Nijmegen
21. Canisius-Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen
22. Bernhoven Hospital, Nistelrodeseweg 10, 5406 PT Uden
23. Röpcke-Zweers Hospital, Jan Weitkamplaan 4 a, 7772 Hardenberg
24. Amphia Hospital, Langendijk 75, 4819 EV Breda
25. Sint Franciscus Hospital, Kleiweg 500, 3045 PM Rotterdam
26. Sint Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein
27. Birth Centre Wilhelmina Children Hospital, Lundlaan 6, 3584 EA Utrecht
28. Gelre Hospital – location Apeldoorn, Albert Schweitzerlaan 31, 7334 DZ Apeldoorn
29. Gelre Hospital – location Zutphen, Den Elterweg 77, 7207 AE Zutphen
30. Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht
31. Meander Medical Centre, Maatweg 3, 3813 TZ Amersfoort
32. Isala Clinics, Dokter van Heesweg 2, 8025 AB Zwolle

Appendix 2. Text of the online standardised instruction film for double-layer closure of the uterotomy

This instruction film is available at www.2close-trial.nl. Translation from Dutch to English:

Welcome to the instruction video regarding 'double-layer closure' after a cesarean section, designed for the 2Close study.

Step 1. Lateral suture at the surgeons side.
The animations were created to explain the real-life video. The lateral suture at the corner of the uterotomy should be placed, as usual, through all layers (serosal, myometrial and endometrial layer) of the uterus, slightly lateral of the incision. Note that one should keep the part of the suture on which the needle is attached long: this part is needed for the second layer.

Step 2. Lateral suture at the residents side.
Again, slightly lateral of the incision, another lateral suture is placed at the corner of the uterotomy at the other side. This suture should be placed, as usual, through all layers of the uterus.

Step 3. Continuous unlocked first-layer of myometrium and endometrium.
This is a continuous suture. Insert the needle right under the serosal layer and let it come out deeply, through the endometrium. Insert the needle on the opposite side of the uterotomy (at the same distance) through the endometrium and let it come out right under the serosal layer at the same level at which the needle was inserted at the other side. When you for example inserted the needle half way through the myometrial layer, the needle should come out at the opposite side half way through the myometrial layer.

Step 4. To tie the suture of the first layer with the first lateral suture at the surgeons side. Attach the suture of the first layer with the short side of the previously tied lateral suture.

Step 5. Second layer (serosal layer), in the direction of the resident.
The second layer is also continuous unlocked, which imbricates the first layer. Insert the needle approximately 5mm caudally or cranially of the incision through the serosal layer, and let the needle come out at the same side of the incision, slightly under the serosal layer. You can prevent too much serosal tissue to be included in the suture, when this 5mm distance is followed. The first layer and second layer should be right on top of each other and should be connected closely. Was the first layer a little too deep (not too much myometrial tissue), then the second layer should be placed a little deeper (including a little more myometrial tissue).

Step 6. To tie the suture of the second layer with the second lateral suture at the residents side.
Additional hemostatic sutures can, of course, be placed when needed. Closure of the peritoneum is not necessary. The fascia should be closed as usual in your hospital. Now, you can see the six steps for double-layer closure in an overview.

Thank you very much for watching our instruction video. After watching the video, you should be able to apply a double-layer suture in participants of the 2Close study. We did not create an instruction regarding single-layer closure, since this is done already in 92% of the Dutch gynecologists. We ask you to do this in a continuous unlocked suture in which you may decide yourself to include or exclude the endometrium in the suture.

CHAPTER 10

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

The ultimate goal of this thesis was to make a significant advancement in the science of preventing long- and short-term complications after cesarean section (CS) and to reduce the variation in clinical practice by developing of guidelines based on data acquired by uniform reporting systems. The main aim of the thesis was to explore how to evaluate the uterine scar after a previous CS and during subsequent pregnancy by using ultrasound and to develop uniform reporting systems to facilitate future studies on this topic (part 1). Additionally, we studied the influence of uterine peristalsis in women with a niche (part 1), the timing of niche evaluation and the influence of laparoscopic niche resection in a subsequent pregnancy (part 2), and the influence of uterine closure technique on niche development (part 3). In the current chapter, the main findings will be summarized and the answers to the research questions described in chapter 1 will be discussed concerning current literature. Subsequently, methodological considerations of the studies in this thesis will be discussed. Finally, the clinical implications of the results and future perspectives will be outlined.

NICHE DEFINITION AND EVALUATION IN NON-PREGNANT WOMEN

To answer our primary research question of how to evaluate a niche after CS using ultrasound, it was important to form a uniform definition of the uterine niche first, which was lacking at the time. At that time, different definitions were used in various studies, making comparison of the outcomes between the studies very difficult. Consequently, solid conclusions on the effect of niche therapy or niche prevention could not be drawn. In part 1 we conducted a Delphi study (chapter 2) in which fifteen international niche experts participated, and they agreed to define a niche as 'an indentation at the site of the CS scar with a depth of at least 2 mm', see Figure 1. A niche can be classified as; 1. a simple niche, 2. a simple niche with one branch, or 3. a complex niche (with more than one branch). Previously suggested classifications were based on subjective scores (mild, moderate or severe scar defect)[1] or on a scoring system including residual myometrial thickness (RMT), number of scars, number of previous CSs and menstrual pattern[2], which is much more complicated to use in daily clinical practice and less likely to be reproducible for research.

Furthermore, we developed a practical guideline for basic niche measurements and reporting which is intended to be used by gynecologists, ultrasound examiners and researchers in daily practice. Therefore, we kept the recommended method of niche

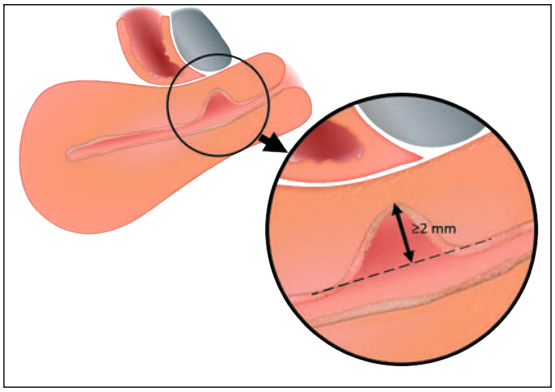

Figure 1. Niche depth of at least 2 mm, according to the niche defintion.

measurement simple and consistent to facilitate its use in daily clinical practice and thereby reducing practice variation for better outcomes. Measurement of niche length and depth, RMT and adjacent myometrial thickness (AMT) in the sagittal plane and niche width in the transverse plane was essential in basic evaluation, illustrated in Figure 2A and B. These niche features were used in previous studies[1-3], but had never been defined, or specified in case of the existence of branches. The participating experts agreed that niche evaluation with either gel or saline infusion is preferred over standard transvaginal ultrasound (TVUS), but is not mandatory if intrauterine fluid is present.

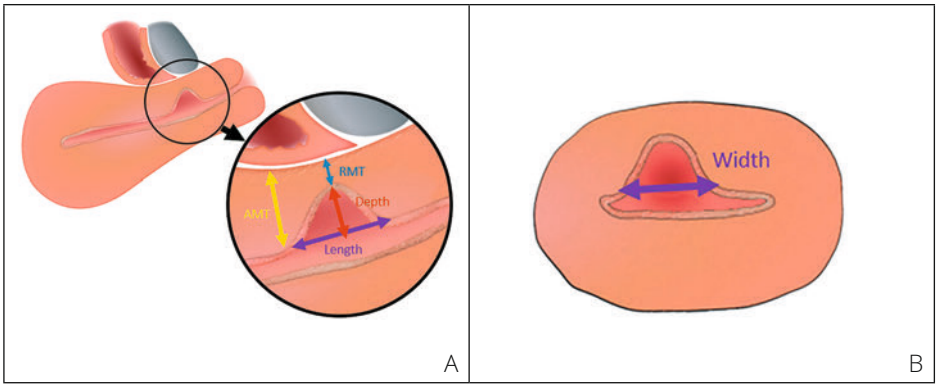

Figure 2. A) Niche measurements in sagittal plane; niche length and depth, residual myometrial thickness (RMT) and adjacent myometrial thickness (AMT). B) Niche width measured in transverse plane.

This practical guideline is the first step creating uniformity in future studies, and therefore the possibility of comparing future results. It is important to note that previously proposed terminology differs from ours; Naji *et al.* [1] named our niche 'length' measured in the sagittal plane the 'width', and our niche 'width' measured in the transversal plane the 'length'. Therefore, one should be cautious comparing the results of niche studies

performed before our publication, assuming that everyone will use our measurement terminology from now on. To facilitate the use of this practical paper, an additional step-by-step tutorial[4] was recently published. Also, an e-learning module has been developed after our Delphi study and is freely available for all interested, encouraging its use, see www.gynaecologyonline.com. Since the release of this e-learning in 2020, it has been used over 500 times.

INFLUENCE OF THE NICHE ON UTERINE PERISTALSIS

A prospective cohort study was conducted to evaluate the effect of a niche on subendometrial peristalsis (chapter 3). This study evaluated uterine motion analysis in women with a niche after previous CS (n=31) and controls without a CS scar (n=11) by dedicated speckle tracking after a five-minute recording by TVUS. We found a significantly higher amplitude of the subendometrial peristalsis in women with a niche, independent of the menstrual phase, compared to the controls ($p<0.001$), and the amplitude was correlated to niche size and inversely correlated to the RMT. Also, the subendometrial peristalsis was less coordinated in women with a niche. Although the sample size was small, we concluded that the uterine motion pattern differs in women with a niche compared to controls. Our findings may play a role in the etiology of postmenstrual spotting, dysmenorrhea and lower implantation rates in women with a niche.

This is the first study reporting uterine peristalsis in women with a niche, so we could not compare our results with other studies. However, both high amplitude and niche presence are associated with lower ongoing pregnancy rates in IVF.[5-8] Also, a poorer pregnancy and implantation rate was found in women with a high frequency compared to women with a low frequency.[9] Normally, during luteal phase, the uterus is in a resting state to facilitate embryo implantation.[10] Although we found no significant difference in frequency between the study groups in each menstrual phase, we hypothesized that the combination of high amplitude and low frequency of the uterine peristalsis, directing towards the cervix, may induce displacement of the embryo towards the cervix. As a result this displacement may hamper normal implantation of the embryo. The fact that the amplitude was associated with the size of the niche underlines the causality of a niche and the identified subendometrial peristaltic features.

Furthermore, coordinated peristalsis from the fundus to the cervix is needed to facilitate the outflow of menstrual blood. We found a negative correlation concerning peristalsis from the fundus to the cervix in the women with a niche during the menstrual phase and a positive correlation in the controls. Possibly, the uterine peristalsis in the direction

of the cervix is less coordinated and disturbs functional outflow of menstrual blood. In theory, this may be one of the causal factors for niche-related postmenstrual spotting.

Little is known about the underlying physiology of peristalsis in the human uterus. This smooth muscle organ undergoes intermittent periods of activation and relative quiescence, of which pregnancy is the most extreme example; most of the gestation, there is a lack of contractions until labor occurs. [11, 12] But also during the menstrual phase, the pattern of uterine peristalsis change. [13] In general, it is known that coordinated peristalsis in a muscular organ is typically initiated and maintained by a region of pacemaker cells that modulate bioelectrical signals, as in the sinoatrial node within the atria of the heart. [11, 12] In the uterus, the smooth muscle cells with electrical pacemaker function are specialized myocytes (interstitial Cajal-like cells). It is known that during labor, hormonal oxytocin triggers multiple actions, including the release of Ca2+ to the extracellular space and the sensitization of the contraction machinery to Ca2+ influence. Calcium (Ca2+) influx ultimately leads to an increase in extracellular Ca2+, which then leads to the activation of myosin light-chain kinase and initiates the cross-bridging cycle leading to peristalsis of the uterine smooth muscle cells. [12] Increased amplitude may originate from an increased sensitivity to Ca2+ influx. Although the exact relationship between a niche and its effect on uterine peristalsis is unknown, we have postulated three theories about the underlying pathophysiology for the increased amplitude of subendometrial peristalsis in women with a niche, as we found in our study. Firstly, we hypothesized that the presence of blood possibly induces stronger subendometrial peristalsis to expel the blood. This is based on the fact that intrauterine blood is often visualized in association with a niche and is supported by the fact that thrombin and its receptor (protease-activated receptor, PAR1) are able to stimulate myometrial peristalsis, which has been reported in a histology study including both pregnant and non-pregnant myometrial tissues. [14] In rats, pretreatment with a thrombin inhibitor prevented the uterotonic effects of thrombin[15], but this had never been assessed in humans. Our second theory is based on the idea that the higher amplitude is induced by inflammation in association with the presence of a niche. In the literature, it has been postulated that pro-inflammatory factors (like Interleukin(IL)-1β, IL-8 and cyclo-oxygenase(COX)-2) may induce uterine peristalsis. [16] However, there are also studies showing that pro-inflammatory cytokines (like IL-1β and tumor necrosis factor(TNF)-α) reduce the contractile ability of myoepithelial cells, but these are of another origin. [17] Thirdly, we hypothesized that subendometrial peristalsis, directed from the fundus towards the cervix, is interrupted by the physical defect of the subendometrial layer in the anterior wall; the disturbance in electro-mechanical signal may affect Ca2+ sensitivity or activation of specialized uterine myocytes. Although this mechanism is

uncertain in the uterus, it has been described in the case of myocardial infarction, in which damaged tissue leads to arrhythmogenic waves. [18]

EVALUATION OF THE CS SCAR AND CESAREAN SCAR PREGNANCY IN EARLY TRIMESTER OF PREGNANCY

In addition to our research question of evaluating a niche in non-pregnant women, our second aim was to develop guidance for CS scar evaluation in the first trimester of pregnancy, including relevant items for basic and advanced standardized sonographic evaluation and a reporting system for cesarean scar pregnancy (CSP), see chapter 4. A second Delphi study was performed amongst sixteen international experts in early pregnancy ultrasound. The recommendations for CSP evaluation were subdivided to be used in daily clinical care (basic evaluation) and expert clinics and research (advanced evaluation). We made this distinction to keep the method of evaluation again as simple as possible in the basics. The expert panel agreed that the first step in evaluating the CS scar in early pregnancy is to locate the gestational sac (GS) and differentiate between a pregnancy high in the uterine cavity, a low-implanted pregnancy, a CSP, or a miscarriage. Secondly, the presence of a niche should be determined, as a CSP can only occur when a niche is present and not in relation to a healed scar. This is an important recommendation in CSP evaluation because many different definitions and classifications circulate, including CSP subclassified as a pregnancy 'on a (well-) healed scar'[19]; according to our guideline, this entity would be issued as a cervical or low-located pregnancy with different follow-up and/or treatment compared to CSP.

A CSP was defined as 'a pregnancy with implantation in, or in close contact with, the niche'. It can be classified into three types depending on the location of the GS; whether or not its largest part protrudes towards the uterine cavity and/or whether or not it crosses the outer contour of the cervix or uterus, see Figure 3A-C. It is important to note that the type of CSP may change with advancing gestation.

The European Society of Human Reproduction and Embryology (ESHRE) Working Group recommended in 2020 to classify a CSP as 'partial CSP' or 'complete CSP'[20], which corresponds to our proposed classification as illustrated in Figure 3A and 3B/C, respectively. The distinction between whether or not the GS crosses the serosal line, as we introduced, is missing in the ESHRE guideline. We think making this distinction for further management is important, but this needs to be explored in future research. One retrospective cohort study[21] has already shown higher success rates if the type of CSP is used for the selection of different surgical interventions; curettage in case the GS

does not cross the serosal line and a laparoscopic niche resection in case the GS does cross the serosal line. A more detailed classification, based on a retrospective cohort study, was proposed by Lin *et al.* [22] which included four grades of CSP, of which the first three were similar to our suggested types, but the fourth also included vascularity. They concluded that this fourth grade of CSP, presenting as an amorphous tumor with rich vascularity at the CS scar, has a high risk of bleeding and can be considered a special variety of CSP. They did not propose how to evaluate the grades of CSP. Our expert panel concluded that evaluation of vascularity is important, also in other types of CSP, and should not only be identified as a fourth type, but that the presence of vascularity should be reported in all cases independent of the type of CSP.

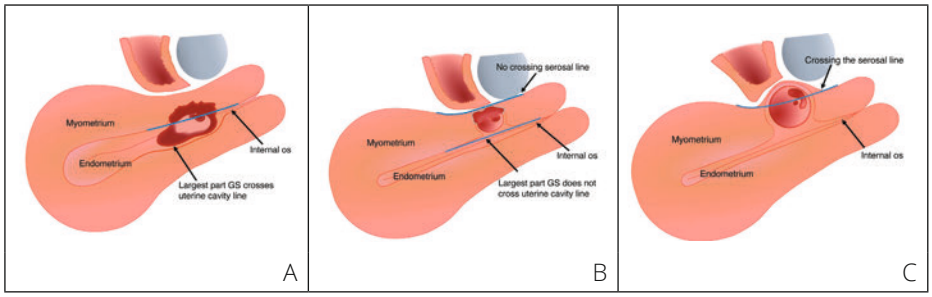

Figure 3. Uniform reporting system of cesarean scar pregnancy (CSP) in early pregnancy

A) CSP with the largest part of the gestational sac (GS) crossing the uterine cavity line; B) CSP with the largest part of the GS embedded in the myometrium and not crossing the uterine cavity line, and the GS not crossing the serosal line; C) CSP crossing the serosal line. Note: the type of CSP may change with advancing gestation.

Furthermore, a 'low-implanted pregnancy' was considered as a different entity, but follow-up is required due to the possibility of an invasive placenta (placenta accreta spectrum (PAS)). In daily practice, it is important to refer women to an expert clinic in case of CSP with the largest part of the GS located in the myometrium and in case of suspicion of PAS for ultrasound evaluation and further management.

This guideline focused on early pregnancy; at advanced gestation, the reporting system may be less suitable as an interpretation of the type of CSP becomes more difficult. The clinical implications of our reporting system have yet to be assessed. Treatment of CSP was beyond the scope of the study, but should be included in the evaluation of the clinical relevance of our reporting system. The ESHRE Working Group is currently developing a guideline on treatment of CSP. Recently, a supplementary e-learning module has been developed containing a variety of CSP cases, including examples of

preferential treatment and follow-up, which could accelerate the implementation of the guideline (see www.gynaecologyonline.com).

TIMING OF CS EVALUATION IN NON-PREGNANT WOMEN AND DURING PREGNANCY

In the second part of this thesis, two studies were performed concerning niche development to determine the optimal moment after CS and during pregnancy to visualize and evaluate a niche using ultrasound. To evaluate the change of niche prevalence and RMT in the first year after a CS, we conducted a proof-of-concept prospective cohort study (chapter 5) including twenty non-pregnant women after CS. They received a TVUS and gel infusion sonography (GIS) at two months and one year after CS. No change in niche presence was found. However, a significant decrease in RMT was seen between two months and one year evaluated with both TVUS (p=0.008) and GIS (p=0.001).

In chapter 6, we evaluated the presence of a niche and its change over the first two years after a CS and in the subsequent pregnancy through a systematic review and meta-analysis, to identify the best moment to evaluate a niche after CS. Seven studies in non-pregnant women (n=1,098) were included, of which six (n=1,031) could be used for meta-analysis, and seven studies in pregnant women (n=1,086) were included. Although meta-analysis showed no significant change in niche presence during the first two years after CS, it increased during the first two months and stabilized six months after CS. Furthermore, a significant decrease in RMT was found during the first year after CS. It is clear that the uterine niche after CS is not a static feature and that its size changes over time. We concluded that the best moment to evaluate the CS scar is six months after CS.

Also, during pregnancy niche presence, size and RMT change towards the third trimester. In our review (chapter 6), both niche presence and RMT were decreased in the third trimester compared to the first trimester, which can be explained by stretching of the uterine wall including the niche and development of the lower uterine segment as the pregnancy progresses, making visualization and measurement of the niche difficult. It was impossible to perform a meta-analysis due to the low number of studies defining the niche to determine niche presence and reporting on RMT. The presence of uterine rupture or dehiscence was reported in all studies; 4 out of 370 women (1.1%) and 7 out of 672 women (1.0%), respectively. In the literature, the reported prevalence of uterine rupture is lower (0.2%).[23] This difference probably depends on the study population; the participating women in our systematic review were all diagnosed with a niche and had probably a thinner residual myometrium to a greater or lesser extent, presumably

putting them at higher risk of uterine rupture, compared to the general population. By all means, our findings concerning the prevalence of uterine rupture should be interpreted cautiously. RMT was <3 mm in most patients with uterine dehiscence or rupture at the second-trimester scan. This is in line with previous studies reporting on the association between uterine rupture or dehiscence and an RMT <3 mm using TVUS[24] or a lower uterine segment <3.65 mm using transabdominal sonography[25], measured in the third trimester alone. Naji *et al.* [26] found no decrease in RMT between the second and third trimester. The best moment of niche evaluation during (or before) pregnancy to predict obstetric outcomes (successful trial of labor (TOL) after CS, uterine rupture) was not within the scope of this study, but it probably has no added value to measure the RMT in the third trimester if it has already been measured in the second trimester, for the detection of uterine dehiscence. A measurement of the RMT during the standard 20-week ultrasound could be sufficient.

LAPAROSCOPIC NICHE RESECTION AND OBSTETRIC OUTCOMES OF SUBSEQUENT PREGNANCY

A niche has been associated with gynecological symptoms (abnormal bleeding, dysmenorrhea), for which first-choice treatment is the contraceptive pill or a levonorgestrel intrauterine device (IUD) [27]. In case of failure of initial therapy, and for niche-related subfertility, other treatment options are limited and have not been extensively studied. One of these options is a laparoscopic niche resection (LNR) in which the defect in the uterine wall is resected and sutured again laparoscopically. LNR has been shown to increase RMT and improve gynecological symptoms. [28-30] The influence of LNR before pregnancy on the thickness and changes of the residual myometrium in the subsequent pregnancy and its associated risk of uterine rupture or dehiscence is unknown. Still, we previously showed that the RMT decreases towards the third trimester of pregnancy. Therefore, it is important to determine whether an LNR is beneficial in subsequent pregnancy according to RMT and obstetric outcomes. A prospective cohort study (chapter 7) was conducted primarily to evaluate the change in RMT from baseline value before pregnancy to the third trimester of pregnancy in women with (LNR group, n=61) and without LNR (expectant group, n=39). All pregnant women had a previously diagnosed niche and underwent a TVUS in the first, second, and third trimester of pregnancy. Other outcome measures included niche presence and niche size in all trimesters, depth of niche-to-RMT (D/RMT ratio) before pregnancy (after LNR) and obstetrical outcomes (including uterine rupture or dehiscence). Although the residual myometrium was thinner at baseline in the LNR group before surgery, after surgery it remained significantly thicker during all trimesters in the LNR group than in the expectant

group. Also, uterine dehiscence was less prevalent in the LNR group and associated with a thicker RM during pregnancy if measured during the second of pregnancy and with D/RMT ratio before pregnancy. The number of cases with per-section blood loss >1000 mL was higher in the LNR group than in the expectant group (n=10 and n=0, respectively). Insufficient hemostasis was the most reported reason for the higher blood loss; one case of PAS (placenta accreta) was reported. In line with our findings recent studies have shown no uterine dehiscence or rupture during at-term CS in women after previous LNR (n=25); RMT during pregnancy was not reported. [31, 32] In our study, the indications for LNR were gynecological symptoms and/or subfertility in the presence of a large niche. There is no supporting evidence that a laparoscopic niche resection improves obstetrical outcomes; no studies include women for this purpose alone. [33] However, we have shown that obstetric outcomes after previous LNR are, in any case, no worse than without niche surgery. The trend towards less uterine dehiscence in favor of LNR encourages further research. The number needed to treat for obstetric outcomes has not been calculated, but the number of LNRs to be performed to prevent one case of uterine rupture is probably quite high. Furthermore, we need to be aware that the groups in our study were not equal at baseline, with larger niches in the LNR group, which may also increase the risk on PAS, for example due to co-existing adenomyosis.

Recently, two case reports[34, 35] were published in which LNR was performed in the first trimester of pregnancy because of uterine dehiscence, diagnosed by ultrasound, in an asymptomatic patient; both authors reported a restored RMT, but follow-up of the RMT during pregnancy was not described. Evidence for this indication is lacking. In our study a RMT of <1 mm in the second trimester was found in five women; in none of whom uterine rupture occurred. We have the opinion that LNR during pregnancy will lead to overtreatment and a related risk on unnecessary iatrogenic damage.

UTERINE CLOSURE TECHNIQUE AND NICHE PRESENCE

The third part of this thesis discussed the question of whether the uterine closure technique influences niche development. A systematic review and meta-analysis were conducted (chapter 8) to determine the effect of uterine closure techniques after CS on maternal and ultrasound outcomes, including niche presence and RMT. Twenty studies were included (n=15,053 non-pregnant women) and closure techniques were divided into single- versus double-layer closure, locked versus unlocked closure, and in- or exclusion of the decidual layer. A large heterogeneity was found in the diversity of the population, the specific intervention or control, and the definitions, method and moment of outcome measurement. Double-layer closure of the uterine wall during CS with

unlocked sutures resulted in a thicker residual myometrium than single-layer closure with locked sutures. No significant difference in niche presence was found between these closure techniques. The inclusion of the decidua decreased niche presence. We concluded that the type of uterine closure technique influences sonographic outcomes, including RMT and niche presence, which are related to clinical symptoms. In our review, only a few studies reported on long-term maternal outcomes after CS and due to the overlap between the three variations in techniques, methodological limitations due to reduced power, and confounders in the included studies (i.e. inclusion of women with a previous CS) we could not draw solid recommendations on the preferred uterine closure technique taking clinical symptoms into account.

The findings in our review justified the conduction of a randomized controlled trial (RCT) to study long-term outcomes after CS in relation to niche features measured according to a standardized method (chapter 2). Chapter 9 describes the study protocol of a multicenter, randomized controlled superiority trial (the 2Close study) in which the (cost-)effectiveness of double-layer uterine closure was compared to single-layer closure in the prevention of niche-related gynecological symptoms nine months after a first CS. The primary outcome was the number of postmenstrual spotting, which was defined as a brownish discharge for more than two days at the end of the menstruation or intermenstrual blood loss. Niche prevalence was assessed by ultrasound at three months as a secondary outcome. Sample size calculation showed that there had to be 2,290 women included to find a difference in the number of days with postmenstrual spotting of 15% at nine months of follow-up, which was considered clinically relevant. We hypothesized that double-layer closure reduces the incidence of niche presence, and as a result, this would reduce gynecological symptoms including postmenstrual spotting.

The trial's results were outside the scope of this thesis, but are recently published; no superiority of double-layer closure compared to single-layer closure was shown in terms of postmenstrual spotting (1.26 days ±2.77 and 1.33 days ±3.00, respectively). [36] However, niche presence was slightly higher in the double-layer closure group three months after CS compared to the single-layer closure group (74% and 69%, respectively, p=0.033). The single-layer closure technique also seemed slightly favorable concerning shorter operative time and less need for treatment of (gynecological) symptoms. Also, double-layer closure was not considered cost-effective compared with single-layer closure from a societal and healthcare perspective. [37]

Recent studies reporting on niche presence dependent on uterine closure technique, the results vary in preference for single-layer closure[38], double-layer closure[39] and no preference[40]. An updated systematic review, including four new studies, including the

results of the 2Close study, reached the same conclusion.[41] The NICE (National Institute for Health and Care Excellence) guideline concerning 'Cesarean birth' prescribes performing either single- or double-layer uterine closure depending on the preference of the surgeon and the clinical circumstances, as there is no difference in outcomes; they underline that single-layer closure does not increase the risk of postoperative bleeding or uterine rupture in a subsequent pregnancy.[42] This guideline is endorsed by several professional associations (i.e. RCOG and American College of Obstetricians and Gynecologists (ACOG)).

At this moment, there is no evidence to change this policy in terms of niche presence. The long-term fertility and obstetric outcomes will be analyzed shortly; if differences are demonstrated between the single- and double-layer groups, this advice could be adjusted. Furthermore, secondary analysis of data from the 2Close study showed that less surgical experience is one of the risk factors for niche development, possibly due to inadequate approximation and tissue handling.[43] Perhaps we should pay more attention to the training of the less experienced (residents).

METHODOLOGICAL CONSIDERATIONS

Part 1: Sonographic niche evaluation

All recommendations concerning evaluating the CS scar in non-pregnant women and early pregnancy were based on the outcome of two Delphi studies. This consensus method owes its name to the Delphic oracle's skills of interpretation and foresight, and has been used since the 1960s in health and medicine to obtain expert opinion systematically.[44, 45] In our opinion, this was the most suitable study design considering the lack of evidence on these topics and the difficulty of studying this with a different methodology. The international aspect in forming the expert panel has positively contributed to the recommendations due to their different education and experience. An important limitation of this study design is that the evidence of opinion-based medicine is relatively low; however, the developed recommendations were partly based on the available literature, which was also made available for the participating experts. Also, sonographic features' clinical relevance used in both studies was not determined yet and should be in future studies.

The study conducted to evaluate uterine peristalsis in women with a niche was a small cohort but performed according to a strict sonographic protocol and analyzed by using speckle tracking as an objective technique. Due to the non-randomized design of the study, there may be differences between the two groups; most controls had

never been pregnant, unlike the women with a niche, who, by definition, had been pregnant. Furthermore, the presence of a CS scar without a niche and the possible presence of adenomyosis (see below) may be possible confounders. Sample size could not be calculated because of the need for comparable studies; in future research on this subject, including women with a niche power calculation should be performed. Most importantly, a clear difference was found in the uterine peristaltic pattern in women with a niche compared to women without a previous CS, and a larger cohort was therefore not necessarily indicated to answer that question. However, it would be interesting to determine whether the niche is disturbing the uterine peristalsis or the mere presence of a CS scar. Future studies should include this patient group.

Part 2: Niche development and changes over time after CS

In this part two prospective cohort studies and a systematic review were performed. As one of the first studies, the proof-of-concept cohort study (chapter 5) was designed to evaluate changes in niche presence and RMT in the first year after CS and was performed based on the guidelines for reporting a prospective study (STROBE)[46]. This is the only study reported in literature that evaluated the CS scar with TVUS and GIS. The latter method was preferred according to niche experts[47], and a standardized method for niche evaluation was used. Logically, the small sample size is a limitation of the study. It is known that inter- and intraobserver agreement of RMT measurement with GIS is good.[48] Still, in this study, two gynecologists performed the ultrasound independently, and thus interobserver variability cannot be excluded. However, the measurements were randomly performed, so it is not likely that it played a structural role.

The systematic review was conducted and performed according to the PRISMA guidelines[49] and was registered in PROSPERO International prospective register of systematic reviews. This study design has the highest level of evidence for prognostic studies.[50] Although an extensive search was performed in three databases with wide-ranging search terms, a limited number of studies were eligible for analysis. The meta-analysis was potentially limited by clinical heterogeneity due to the included populations (women with one or multiple previous CSs), the uterine closure technique, and ultrasound methods (with or without gel contrast). Furthermore, the determination of niche presence stands or falls with the uniformity of defining a niche. Most included studies were published before the consensus paper in 2019[47] (chapter 2) and may have used different definitions and methods. Despite these limitations, we have been able to give advice about the timing of niche evaluation based on the demonstrated course of niche presence and the change of niche size within the first two years after CS and during a subsequent pregnancy.

The second prospective cohort study (chapter 7) was registered at ISRCNT and was the first study that described the effect of LNR on RMT and niche measurements during a subsequent pregnancy. Both the LNR procedure and the niche evaluation using ultrasound were performed according to a standardized protocol. We deliberately chose to evaluate niche changes during pregnancy concerning baseline before and not after surgery, to keep baseline data similar in both study groups. It was inevitable that selection bias occurred as women in the expectant group had smaller niches and thicker residual myometrium. An RCT would probably create equal study groups at baseline concerning RMT. However, given the unknown obstetric outcomes of LNR, this technique was first assessed in a prospective study to determine its efficiency, and reveal the effects of surgeons' learning curve, before setting up an RCT, according to the IDEAL framework[51]. Furthermore, a blinded design for practitioner and patient would be preferred in future research so the mode of delivery would not be influenced, and the risk of uterine dehiscence (or rupture) can be related to a certain cut-off point of RMT.

Part 3: Influence of surgical closure technique on niche development

The systematic review in this part was also registered in PROSPERO and developed based on the PRISMA statement[49]. Sensitivity analysis was performed, excluding studies that included women with previous CSs, as potential confounder, cohort studies, and studies with a high risk of bias, strengthening the results concerning the primary outcome. However, due to the limited number of studies reporting on long-term outcomes, the power of the study was reduced.

The RCT (2Close study) to evaluate the long-term outcomes after CS in relation to niche features, of which the protocol was described in chapter 9, was designed to be the first large RCT comparing double-layer versus single-layer uterine closure during CS. It was adequately powered and blinded for both participants and examiners. All sonographers of the participating hospitals (n=32) were instructed by mandatory e-learning to limit the variation in the method of niche measurement. However, we were aware that most sonographers could not perform adequate niche measurements at the start of the study, which may improve as they gained experience. Ideally, niche measurement was only performed by a few experienced sonographers to reduce potential interobserver variability, but this was practically impossible.

CLINICAL IMPLICATIONS

Awareness of niche-related problems

By developing a guideline and freely available e-learning on niche evaluation, we aim to increase awareness of niche presence among practitioners in diagnosing and treating women with gynecologic symptoms or subfertility after SC. Awareness is important as there are probably still many women with previous CS and symptoms who have yet to be examined to diagnose a niche. This assumption is based on the many delayed referrals to expert clinics. Awareness needs to start in primary health care (general practitioners (GPs), sonographers) where most patients are seen first. The e-learning could be added to the education of sonographers by the Dutch professional association 'Beroepsvereniging Echoscopisten Nederland (BEN)'. The niche is included in the Dutch guideline for GPs (Nederlands Huisartsen Genootschap (NHG)) concerning vaginal blood loss, but should also be included in their guidelines concerning dysmenorrhea and subfertility; in case of the latter, it is most important to report whether there is secondary subfertility after CS, but further analysis should be done in the fertility clinics. Therefore, awareness of niche-related problems should also be pursued in these clinics and among gynecologists in general. The e-learning could easily be adjusted to the training program for residents in Obstetrics and Gynecology.

Furthermore, a CSP is often not recognized. Many misdiagnosis cases have been reported in which a CSP was recognized as a cervical ectopic pregnancy, a miscarriage in progress or a malignant tumor, resulting in massive bleeding and/or emergency hysterectomy.[52-56] All healthcare professionals evaluating a pregnancy after previous CS in the first trimester should be trained in CSP recognition, including gynecologists, midwifes, sonographers, abortion doctors and fertility doctors. Still, therefore an additional training and implementation project is needed. Recently, an e-learning is being developed to support CSP recognition, see www.gynaecologyonline.com. As our Delphi study progressed, it became clear that all experts agreed that in the case of diagnosis of a CSP, the patient should be referred to an expert clinic. They had a clear vision about ultrasound features that should be added in advanced evaluation. Also, in a research setting, it is important to record the same features and use the same terminology to study CSPs' relevance and therapeutic management.

As many doctors are not aware of niche-related symptoms, so are their patients. Therefore, alerting women to potential complaints they may experience after a CS is beneficial. Through good counseling, they can connect the CS scar and their complaints and feel understood by their doctor. This requires recognition and training of GPs, as stated before. Unawareness of the connection between a niche and symptoms

can negatively influence patients' quality of life due to the complaints and not-feeling understood, and cause an unnecessary delay in therapeutic management. The impact of niche-related symptoms on the quality of life was also described in chapter 1. [57] In addition, surgical repair of the niche by LNR has been shown to improve the quality of life, both in the short and long term, concerning physical (postmenstrual spotting, physical functioning, bodily pain, general health) and mental complains (vitally, social functioning). [28, 58]

Content of CS counseling

Not all CSs can and should be prevented as it can be the only possible life-saving intervention, for example, in case of fetal distress. But if women have a choice between vaginal delivery or CS (i.e. in case of breech position of the fetus) or ask for an elective CS, they must be well informed about this abdominal surgery. Good counseling is also the key to creating awareness amongst women for niche-related symptoms. Any practitioner's task is to discuss all pros and cons concerning a CS; guidelines detail what needs to be discussed[42, 59]. The risks on high blood loss per-operatively and wound infection post-section are probably named by default during counseling in Dutch hospitals. Still, it is doubtful whether this is also discussed in countries with high CS rates. Also, the risk of uterine rupture is often named in the consulting room; this is 0.5-1.5% in the general population in case of TOL after one previous CS. [60, 61] In a select group of women with a large niche defined as RMT/AMT ratio of ≤0.5 (24%)[62, 63], this risk is possibly even higher, but this has not yet been established. We assume that the risk of niche development (24-75%) and related symptoms (abnormal uterine bleeding, dysmenorrhea and subfertility) are rarely told due to relative obscurity, but we have the opinion that all women should be informed about its risk during counseling of mode of delivery; and especially the women with the preference of a scheduled CS without medical indication. The content of this counseling depends on the moment of counseling during pregnancy or labor; understandably, counseling of an emergency CS will not include all risks and possible complications due to the lack of time. Therefore, it is also important that women are explained about gynecological symptoms during follow-up after a pregnancy resulting in a CS to achieve awareness.

The disadvantage of informing patients about niche presence may be that symptoms are wrongly attributed to niche presence. Recently, more consensus on the distinction between the sonographic findings of a niche and associated symptoms has been described. A Delphi study introduced the 'Cesarean Scar Disorder' (CSD) as a new term for the condition in which a niche is determined in combination with at least one primary or two secondary symptoms. [64] Primary symptoms include postmenstrual spotting, pain during bleeding, secondary unexplained subfertility with intrauterine

fluid, and secondary symptoms include dyspareunia, chronic pelvic pain, and secondary unexplained infertility. This condition may help practitioners to discriminate between a sonographic finding and a relevant condition that impacts the quality of life and, therefore, avoid overdiagnosis. Screening all women with a previous CS is not advisable if they are asymptomatic.

Cost-effectiveness of niche therapies

The cost-effectiveness of niche treatment still needs to be evaluated. Hormonal therapy (oral or intrauterine device (IUD)) may be cost-effective, given its low costs, but this has never been studied, just as the cost-effectiveness of laparoscopic or hysteroscopic niche resection has not. You could imagine that if the quality of life improves after niche resection, fewer women need medical care, lowering healthcare costs in both primary and secondary care. Also, if LNR is proven to increase implantation rates, this could reduce the costs of fertility treatment. A trial with this aim is currently being conducted (LAPRESS study, NL57660.029.16). Proper counseling about a CS may reduce the number of elective CSs and increase the number of vaginal deliveries, including associated costs, but probably only in the future; at present, this number will not yet outweigh the number of women with a previous CS who opt for a CS in their subsequent pregnancy. The immediate birth costs for a vaginal delivery have been reported to be lower than for a requested CS, but this difference may be smaller if urinary incontinence, seen more often after vaginal delivery, is taken into account. [42] There is no significant cost-effectiveness difference between successful TOL and a repeat CS. [42]

CSP screening in early pregnancy?

The incidence of CSP is low (1:1800) in the general population[65, 66] and therefore it is not necessary to discuss with all women who have previously undergone a CS. However, most CSPs are missed as they often end in miscarriage, so the risk of CSP is probably higher in the presence of a niche. To what extent niche size (volume) influences the risk of CSP is still unclear and needs to be determined in future research. Therefore, screening before pregnancy to estimate the risk of CSP is neither possible nor advisable.

Standard assessment of the CS scar during subsequent pregnancy at the moment a vitality scan is made may be considered. In the Netherlands, more than 160,000 women give birth each year, of which roughly 29,000 women (18%) receive a CS (a first CS or repeat CS). We know that over half of them develop a niche and are probably more at risk for related obstetric complications, including CSP or PAS. The development of PAS has been linked to (surgical) damage (CS, curettage, manual removal of the placenta and postpartum endometritis) in which the uterine endometrium and myometrium are disrupted. [67] In the absence of endometrial re-epithelialization of the scar area,

the trophoblast and villous tissue can invade deeply within the myometrium, including its circulation, and reach the surrounding pelvic organs. [67] Early detection of a CSP in pregnancy may decrease the number of cases of PAS in advanced pregnancy, including its complications. The first trimester is the best (and perhaps only) moment to evaluate the pregnancy location and, if located low (or in the niche), anticipate placental problems (PAS) later in pregnancy. It is known that evaluation of a CSP becomes more difficult as pregnancy progresses, and a low-implanted pregnancy can be missed if it progresses into an intrauterine pregnancy later in pregnancy. Women with multiple (≥2) CSs possibly have a higher risk of CSP as they have a higher risk of PAS. [68-70]

Nowadays, ultrasound in early pregnancy is performed quite often, without medical indication but requested by patients. Today, the costs of an early ultrasound are between 25 and 40 euro. If we would start with routine screening of all women with a previous CS, this would probably slightly increase the number of early ultrasounds, including its costs. The (cost-) effectiveness of screening on CSP should be determined in a future study because we must be aware that we do not unnecessarily medicalize women and terminate intrauterine-located pregnancies. Also, the clinical relevance of the different CSP types and therapeutic management needs to be analyzed. We propose to do a cohort study in which women with a previous CS are offered an ultrasound at 6-7 weeks GS, which is determined as the best moment to determine the location of the pregnancy by the expert panel, with PAS as primary outcome. Furthermore, pregnancy location at 10 weeks GA, which is included in standard care, could be compared with this early ultrasound to determine the change of location.

We have the opinion that, at present, we should not routinely screen all pregnant women with a previous CS early in the first trimester for pregnancy location, but if ultrasound is performed early in the first trimester for another indication (i.e. in case of previous miscarriage, term discussion or on request of the patient) or if there is an indication to exclude CSP (previous CSP or PAS, multiple CSs), one should specifically determine and report niche presence and any CSP. As described earlier, care should be taken with the classification in the context of treatment and referral to an expert clinic should be easily accessible. Most importantly, as stated before, health professionals involved in early pregnancies should be aware of CSP occurrence.

FUTURE PERSPECTIVES

Our practical guideline concerning niche evaluation in non-pregnant women and CSP can be used in future research on treating niche-related symptoms, surgical indication

and management in case of CSP. Uniform standardized evaluation of the uterine CS scar will allow future studies to be comparable, which may lead to better interpretation of data and possible adjustment of the (inter)national guidelines. However, evaluating the clinical value of the sonographic features used in the Delphi studies is important. This can be achieved gradually by assessing whether future studies with equal outcome measures and using our guidelines report similar results. Furthermore, the determination of the relevance of sonographic features of related gynecological symptoms (CSD, see earlier), subfertility or prediction of obstetric complications in a subsequent pregnancy, such as CSP and PAS, uterine rupture and successful TOL, needs to be elucidated. If found relevant, the next steps are to determine whether it is of additional value to screen women after previous CS on niche presence and perform niche measurements before the next pregnancy and develop prediction models for CSP and successful TOL in subsequent pregnancy.

Also, the relevance of the different CSP types needs further assessment, which can be accomplished by recording the same features in future studies and registering CSP cases in one database. Our reporting system has already been shown useful in determining therapy on the success rate of the chosen therapy. In a retrospective cohort study (n=63) LNR was performed successfully in case of a CSP crossing the serosal line of the uterus or if initial treatment (expectant management, methotrexate, or curettage) failed. [21]

Recommendations on how to evaluate the CS scar in the second and third trimester of pregnancy were outside the scope of this thesis and should be determined in future research, including niche measurements relevant to obstetric outcomes (i.e. uterine rupture). Furthermore, we could not determine the best moment in pregnancy to evaluate the CS scar (RMT) concerning these outcomes, which also requires defining the cut-off value of RMT, to develop prediction models for a successful trail of labor and uterine rupture.

Although we confirmed distortion of uterine peristalsis features in women with a niche compared to women without a CS scar, it is uncertain whether it is the niche itself or the CS scar that causes the disturbance and what is its underlying mechanism. Knowledge of the underlying pathway may be useful in the search for possible prevention or therapy and is needed to elucidate in future studies. If the niche itself is causing disturbed uterine peristalsis and not the CS scar, then we should evaluate uterine peristalsis in women after LNR with a 'healed' scar. However, if the disruption of the (endo) myometrium (the CS scar) is causing the abnormal peristalsis, then further research into surgical techniques to improve healing of the endo-/myometrium may need to

be done. As an example, a current study is evaluating the effect of 4Dryfield. This powder transforms into a viscous gel after adding water and functions as a temporary mechanical barrier separating surgically traumatized tissue and ensuring the healing of the respective surfaces (4DryField study, NL72538.029.20). The underlying theory is that 4DryField will prevent adhesion formation, and as a result may decrease niche presence. This may be effective for the healing of the endo-/myometrium in general. Furthermore, adenomyosis is often seen in women with a CS scar; a CS has been described as one of exogenous traumatic damage that may contribute to adenomyosis fibrosis. [71] Adenomyosis is also related to lower implantation rates after IVF, like a niche. [72] Due to thickening and architectural changes in the subendometrial layer (junctional zone), which is often seen in case of adenomyosis, it may also lead to abnormal uterine peristalsis. [73] However, proper objective analysis, like speckle tracking, has never been performed in women with adenomyosis. Therefore, the exact influence of a CS scar or a niche whether in combination with adenomyosis, on uterine peristalsis needs further assessment.

LNR has been shown to positively affect on the RMT and number of uterine dehiscence during subsequent pregnancy. LNR is currently only performed in the Netherlands in a research setting in women with gynecological symptoms related to the presence of a niche. No evidence underlines the need for an LNR to improve fertility or obstetrical outcomes. We suggest a randomized controlled trial to study the effect of LNR in women with a large niche and include the patient symptoms and the cut-off value of RMT as outcome data.

In the prevention of niche development, we have shown that the number of uterine layers (single or double) during CS is not of influence. Since this has been studied sufficiently, this does not need to be further explored. Also, the used suture type (monofilament, multifilament, barbed or chromic suture) has not shown to influence the niche presence. [74] What does need our attention is the fact that experience with surgical closure of the uterus seems to be related. All surgeons probably have slightly different techniques, but if we can specify which surgical aspects are important for adequate wound healing, this can be added in the training of residents.

CONCLUSION

Niches have shown to be quite prevalent and can be visualized by TVUS. With this thesis we added the first practical guidelines on niche evaluation in non-pregnant women and in early pregnancy to detect CSP. They can be used in daily clinical practice

and will hopefully establish uniformity in future niche studies and increase awareness for the existence of CSP amongst all sonographers performing ultrasound in early pregnancy after CS. During evaluation, it should be considered that niche presence and features change over time after CS. Niche presence disturbs uterine peristalsis, possibly causing niche-related symptoms and subfertility, but this must be further assessed. Its presence does not appear to be affected by uterine closure technique, although the learning curve of uterine closure does seem important. LNR increases RMT, which is favorable during subsequent pregnancy; future research will have to focus on the improvement of obstetric outcomes by LNR. As a CS cannot be prevented in obstetric policy, proper counseling of women with or without medical indication for a CS should be part of daily practice, including niche-related symptoms. This should be done before but otherwise during follow-up after the CS. Furthermore, recognizing these symptoms in primary care will lead to a sense of understanding in women and not cause an unnecessary delay in therapeutic management.

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CHAPTER 11

SUMMARY

SAMENVATTING

SUMMARY

Nowadays, the cesarean section (CS) is one of the most common surgeries performed in the world with an average rate of 21% globally and the number is still rising. No evidence is available that a CS rate above 10% improves mortality rates; the risk of maternal and perinatal mortality and morbidity increases. In addition, women with long-term gynecological and obstetrical complications after CS, including the presence of a uterine CS scar defect or "niche", is of importance is often under reported/neglected. The definition of a niche has been determined in this thesis (chapter 2) as an indentation at the site of a CS scar, with a depth of at least 2 mm.

The primary aim of this thesis was to investigate how to evaluate a niche after a previous cesarean section (CS) and during subsequent pregnancy by using ultrasound. Furthermore, we aimed to develop a uniform reporting system to reduce variation in clinical practice and future research, and ultimately to determine prevention and treatment options. This chapter summarizes the results of the research we conducted.

Chapter 1 provides a general introduction to the clinical consequences and diagnostics of a niche. Currently, there is no research on the most effective methods for diagnosing and treating women with niche-related symptoms, because a standardized definition of a niche is lacking. Gynecological symptoms (i.e. postmenstrual spotting, dysmenorrhea) and subfertility have been reported in literature to be related with a niche. Also, the prevalence of related obstetric complications, including a cesarean scar pregnancy (CSP), is important to evaluate for proper counseling of patients, but this is unclear, again, due to the lack of a uniform definition and reporting system. The niche can be detected with ultrasound. To prevent niche development and related symptoms, knowledge of the underlying mechanism and influence of surgical technique is important. In this thesis, we determined the definition of a niche and provided two reporting systems for both a niche and CSPs. We evaluated niche presence and its change over time after CS and during subsequent pregnancy, and the influence of uterine closure technique on niche development.

PART 1: SONOGRAPHIC NICHE EVALUATION

This part of the thesis focuses on the development of sonographic definitions and reporting systems of a niche and CSP, and the effect of the niche on the uterine peristalsis, evaluated with ultrasound.

Chapter 2 presents the recommendations of detailed uterine niche evaluation in non-pregnant women by using transvaginal ultrasound (TVUS). A panel of twenty European gynecological experts participated in a modified Delphi study. In this study, 42 relevant items on niche measurement (definitions, relevance, method of measurement and tips for visualization of the niche) were predetermined based on relevant literature and recommendations of a focus group. After three Delphi rounds, consensus was reached for all 42 items. Based on the consensus findings, we formulated a definition for the uterine niche, see above, and produced guidance for its various ultrasound measurements, which can be used in daily clinical practice. In addition, we aim that the recommendations will contribute to standardized niche measurement in future studies.

In **chapter 3**, the results of a prospective cohort study are presented in which uterine motion was analyzed and the effect of a niche on uterine peristalsis was evaluated by using dedicated speckle tracking. High amplitudes are associated with lower implantation rates and possibly with gynecological symptoms. We included 31 women with a niche and 11 controls (women without previous CS). Primary outcome of this study was the amplitude of subendometrial peristalsis (see Figure 3 in chapter 1). The amplitude was significantly higher in women with a niche compared to controls (8.5% (SD ±4.2) and 2.9% (SD ±1.3), respectively, $p<0.001$), independent of the menstrual phase. Also, a positive correlation was found between niche sizes (depth and length) and amplitude. These findings support the hypothesis that uterine peristalsis is disturbed in women with a niche, which could lead to postmenstrual spotting due to suboptimal menstrual outflow and lower implantation rates.

In **chapter 4**, we present the recommendations regarding the sonographic evaluation and reporting of a CSP in the first trimester of pregnancy. A modified Delphi procedure was conducted, in which sixteen international experts in obstetric and gynecological sonography participated. Based on a literature search, a list of 58 items were determined to be relevant for definition, detection and evaluation of CSP. After four Delphi rounds, consensus was reached for all items. The definition and classification of a CSP was formulated, concluding first that a CSP can occur only when a niche is present, and not in relation to a *healed* CS scar, which is an important proposition in the evaluation of the literature. The classification of a CSP was divided into three types depending on the location of the GS; whether or not its largest part protrudes towards the uterine cavity, and whether or not it crosses the outer contour of the cervix or uterus. A reporting system for CSP was proposed, differentiated between basic measurements to be performed in general practice and advanced measurements for expert centers or for research purposes. Although the clinical relevance of our classification and reporting system needs to be evaluated, it can be used internationally to enable consistent data

collection regarding treatment outcomes of CSP and develop evidence-based guidelines in the future including preferential treatment and follow-up.

Two e-learning modules have been developed after our Delphi studies, which are freely available for all interested, see www.gynaecologyonline.com

PART 2: NICHE DEVELOPMENT AND CHANGES OVER TIME AFTER CS

In this part of the thesis we focused on (the moment of) niche presence and its changes over time after previous CS and in subsequent pregnancy. Furthermore, the effect of laparoscopic niche resection (LNR) on the residual myometrial thickness (RMT) in subsequent pregnancy was studied. It is known that the RMT is of prognostic value in the prediction of obstetric complications (uterine rupture or dehiscence), and niche presence is often difficult to visualize as the pregnancy progresses.

Chapter 5 describes the results of a prospective cohort study evaluating the change of niche prevalence and RMT in the first year after a CS, using both TVUS and gel installation sonohysterography (GIS). Twenty women after one previous CS were included. A statistically significant decrease of RMT was found at 12 months after CS compared to 2 months after CS (6.5 mm and 11.9 mm, respectively, $p<0.001$). Also, the ratio between RMT and adjacent myometrium with GIS decreased from 0.80 at 2 months to 0.54 at 12 months ($p=0.002$). Niche prevalence did not change, independent of the assessment with TVUS or GIS. Although the small sample size, we were able to conclude that niche size change over time.

With the aim to identify the best moment to evaluate a niche after CS according to niche presence and its change, we reviewed available evidence. **Chapter 6** presents the results of this systematic review and meta-analysis. Fourteen studies, reporting on niche presence and features (length, depth, width and RMT), and evaluating the CS scar at least twice in the period after CS or in subsequent pregnancy using TVUS, were included; seven studies in non-pregnant women and seven in pregnant women. Although meta-analysis showed no significant change in niche presence between six weeks and two years after CS, an increase was found during the first two months and it seemed to stabilize at six months after CS. A slightly decrease over time was seen in RMT ($p=0.017$); niche depth remained similar ($p=0.158$). In subsequent pregnancy after previous CS, niche presence and RMT decreased as the pregnancy progressed, but meta-analysis could not be performed due to the low number of reporting studies

and the lack of crucial data. We concluded that the best moment to evaluate the CS scar seems to be six months after CS, because of an increase of the assessed presence of a niche and stabilization seen at 6 months. Furthermore, we showed that niche presence and RMT also change as pregnancy progresses. The best moment of niche evaluation during (or before) pregnancy to predict obstetric outcomes (uterine rupture or dehiscence) was not within the scope of this study.

LNR, performed in case of gynecologic symptoms, has already shown to increase the RMT six months after surgery and to improve these symptoms. Obstetric outcomes after LNR are unknown. **Chapter 7** presents the effect of LNR on the RMT during subsequent pregnancy, studied in a prospective cohort study. Two groups of pregnant women with a previously diagnosed niche were included; 61 with a large symptomatic niche (RMT <3 mm) followed by LNR (LNR group), and 39 without LNR (expectant group). Niche measurements in first, second and third trimester of pregnancy were performed according to the standardized method in non-pregnant women, described in chapter 2. The change in RMT from baseline value before LNR to the third trimester of pregnancy was +2.0 mm in the LNR group versus −1.6 mm in the expectant group ($p<0.001$). Furthermore, although RMT was thinner at baseline in the LNR group, it was thicker in the LNR group than in the expectant group during all trimesters: 3.2 mm ($p<0.001$) in the first trimester, 2.5 mm ($p<0.001$) in the second trimester, and 1.8 mm ($p=0.001$) in the third trimester of pregnancy. No uterine rupture was reported. Uterine dehiscence was more prevalent in the expectant group compared to the LNR group (7/36 (19%) and 1/50 (2%), $p=0.007$) and related to the RMT in the second trimester of pregnancy. On the other hand, per-section blood loss was higher in the LNR group. In conclusion, LNR has a positive effect on the RMT before and during the entire pregnancy and may decrease the prevalence of uterine dehiscence. However, LNR is currently performed to improve gynecologic symptoms and future research is needed to study its effect on reproductive outcomes.

PART 3: INFLUENCE OF SURGICAL CLOSURE TECHNIQUE ON NICHE DEVELOPMENT

In this part of the thesis we focused on the effect of uterine closure techniques during a CS on eventual niche development after CS.

To identify a possible optimal uterine closure technique, we conducted a systematic review and meta-analysis. The results are presented in **chapter 8**. Twenty studies were included on three variations in closure technique; single-layer versus double-

layer closure; locked versus unlocked closure; and in- versus exclusion of the decidua (inner layer of the uterus). All reported on operative, sonographic and/or clinical outcomes. Both double-layer closure and unlocked closure resulted in a thicker residual myometrium compared to single-layer closure and locked closure ($p<0.001$). Furthermore, a lower prevalence of large niches were found if the decidua was included in uterine closure, compared to exclusion of the decidua (25.7% and 36.1%, respectively; RR 1.71; $p=0.002$), but this was based on two small studies. Based on our findings, we concluded that double-layer unlocked uterine closure, including the decidua could possibly result in more beneficial sonographic outcomes (thicker RMT and lower prevalence of large niches). However, we were not able to draw firm conclusions as to which surgical technique is preferable, due to the overlap between the three variations in techniques, severe methodological limitations of the included studies and confounding factors (i.e. inclusion of women with a previous CS).

Because large (randomized) trials evaluating the effect of uterine closure techniques on gynecological symptoms, including cost-effectiveness, were lacking, we decided to conduct a randomized controlled trial (RCT). In **chapter 9**, the study protocol is described of a multicenter, double blinded RCT – the 2Close study – to evaluate the (cost-)effectiveness of double-layer versus single-layer uterine closure after a first CS. A superiority design was chosen since our systematic review found possibly more favorable sonographic outcomes after double-layer closure, despite a longer operative time. We included women over 18 years who underwent a first CS, either scheduled or unscheduled, and randomized the participants for double-layer unlocked closure including the decidua (intervention group), or single-layer unlocked closure, with the decidua in- or excluded in the suture, based on the preference of the gynecologist (control group). Our calculation showed that 2290 women should be included to find a difference in number of days with postmenstrual spotting (primary outcome) of 15% at nine months of follow-up. Important secondary outcomes were sonographic features of the CS scar, for which all participating women received TVUS at three months after CS to assess the uterine scar. If necessary saline infusion sonohysterography (SIS) or gel instillation sonohysterography (GIS) will be added to the examination. To ensure standardized intervention and sonographic evaluation, a mandatory instruction video and e-learning were developed for all participating doctors and sonographers. Other secondary endpoints were perioperative outcomes, menstrual disorders, quality of life, sexual functioning, reproductive outcomes and cost-effectiveness from societal perspective.

Finally, **chapter 10** concludes with a general discussion summarizing the main findings of this thesis, including the comparison with the literature, and answering the research

questions. Also, methodologic considerations of the studies are discussed. We explain the importance of using our guidelines concerning niche evaluation in non-pregnant women and in early pregnancy in clinical daily practice, namely to raise awareness and properly counsel patients. The clinical value of the sonographic features, used in our Delphi studies, should still be evaluated in future studies. Furthermore, future research should focus on the underlying mechanism of disturbed uterine peristalsis in women with a niche, to finally search for possible preventive or therapeutic strategies. The performed uterine closure technique (single- or double-layer) has been shown to be not to have an influence on niche presence, but surgical experience may have and needs further assessment. To implement LNR to improve obstetric outcomes (uterine rupture) more studies are needed, but the results of this thesis suggest that this surgery is promising.

SAMENVATTING

De keizersnede is tegenwoordig een van de meest uitgevoerde operaties ter wereld met een gemiddelde van 21% wereldwijd en dit percentage stijgt nog steeds. Er is geen bewijs dat een keizersnede-percentage van meer dan 10% de sterftecijfers verbetert; het risico op maternale en perinatale sterfte en morbiditeit neemt zelfs toe. Bovendien worden vrouwen met gynaecologische en verloskundige complicaties na de keizersnede op de lange termijn, waaronder de aanwezigheid van een defect in het litteken van de baarmoeder ofwel "niche", vaak onder gerapporteerd of niet herkend. Een niche is in dit proefschrift (hoofdstuk 2) gedefinieerd als een indeuking ter plaatse van het keizersnede litteken in de baarmoeder, met een diepte van minimaal 2 mm.

Het belangrijkste doel van dit proefschrift was om te onderzoeken hoe een niche na een eerdere keizersnede en tijdens de daaropvolgende zwangerschap kan worden geëvalueerd met behulp van echografie. Daarnaast wilden we een uniform rapportagesysteem ontwikkelen om variatie te verminderen in de klinische praktijk en toekomstig onderzoek, en uiteindelijk om preventie- en behandelmogelijkheden te bepalen. In dit hoofdstuk zijn de resultaten samengevat van het onderzoek dat wij hebben uitgevoerd.

Hoofdstuk 1 geeft een algemene introductie op de klinische consequenties en diagnostiek van een niche na een keizersnede. Momenteel is er geen onderzoek voorhanden met de meest effectieve methode voor het diagnosticeren en behandelen van vrouwen met niche-gerelateerde symptomen, omdat een gestandaardiseerde definitie van een niche ontbreekt. Uit de literatuur is wel bekend dat gynaecologische symptomen (o.a. post-menstrueel bloedverlies, dysmenorroe) en subfertiliteit gerelateerd zijn aan een niche. Ook is de prevalentie van gerelateerde verloskundige complicaties, waaronder een zwangerschap in het keizersnedelitteken, belangrijk om te evalueren om patiënten goed te kunnen counselen, maar dit is wederom onduidelijk vanwege het ontbreken van een uniforme definitie en rapportagesysteem. Een niche kan worden gedetecteerd met behulp van echografisch onderzoek. Om niche ontwikkeling en gerelateerde symptomen te voorkomen, is kennis van het onderliggende mechanisme en de invloed van chirurgische techniek belangrijk. In dit proefschrift hebben we de niche gedefinieerd en twee rapportagesystemen voor zowel een niche als een zwangerschap in het keizersnede litteken ontworpen. Verder hebben we de aanwezigheid van een niche en de verandering ervan in de loop van de tijd na een keizersnede en tijdens de daaropvolgende zwangerschap geëvalueerd, en de invloed van de hechttechniek van de baarmoeder op de ontwikkeling van een niche onderzocht.

DEEL 1: ECHOGRAFISCHE BEOORDELING VAN EEN NICHE

Dit deel van het proefschrift richt zich op de ontwikkeling van echografische definities en rapportagesystemen van een niche en een zwangerschap in het keizersnedelitteken, en het effect van de niche op de peristaltiek van de baarmoeder, beoordeeld met behulp van echografisch onderzoek.

Hoofdstuk 2 presenteert de aanbevelingen van gedetailleerde niche evaluatie bij niet-zwangere vrouwen met behulp van transvaginale echografie. Een panel van twintig Europese gynaecologische experts nam deel aan een gemodificeerde Delphi-studie. In dit onderzoek zijn 42 relevante items over het meten van een niche (definities, relevantie, meetmethode en tips voor visualisatie van de niche) vooraf bepaald op basis van relevante literatuur en aanbevelingen van een focusgroep. Na drie Delphi rondes werd consensus bereikt voor alle 42 items. Op basis van deze bevindingen hebben we een definitie van de niche geformuleerd, zie hierboven, en richtlijnen opgesteld voor de verschillende echometingen, die kunnen worden gebruikt in de dagelijkse klinische praktijk. Daarnaast streven we dat de aanbevelingen zullen bijdragen aan gestandaardiseerde nichemetingen in toekomstige studies.

In **hoofdstuk 3** worden de resultaten van een prospectieve cohortstudie gepresenteerd waarin de peristaltiek van de baarmoeder werd geanalyseerd en het effect van een niche op die peristaltiek werd onderzocht door gebruik van zogenoemde 'speckle-tracking'. Hoge amplitudes zijn geassocieerd met lagere aantallen van innesteling van een bevruchte eicel en mogelijk ook met gynaecologische symptomen. We includeerden 31 vrouwen met een niche en 11 controles (vrouwen zonder eerdere keizersnede). De primaire uitkomst van deze studie was de amplitude van subendometriale peristaltiek (zie Figuur 3 in hoofdstuk 1). De amplitude was significant hoger bij vrouwen met een niche vergeleken met de controles (respectievelijk 8.5% (SD ±4.2) en 2.9% (SD ±1.3), $p<0.001$). Dit was onafhankelijk van de menstruatiefase. Ook werd een positieve correlatie gevonden tussen afmetingen van de niche (diepte en lengte) en amplitude. Deze bevindingen ondersteunen de hypothese dat de peristaltiek van de baarmoeder verstoord is bij vrouwen met een niche, wat zou kunnen leiden tot post-menstruele spotting als gevolg van een suboptimale uitstroom tijdens de menstruatie en een lager aantal innestelingen van een zwangerschap.

In **hoofdstuk 4** presenteren we de aanbevelingen met betrekking tot de echografische evaluatie en rapportage van een zwangerschap in het keizersnedelitteken, in het eerste trimester van de zwangerschap. Er werd een gemodificeerde Delphi procedure uitgevoerd, waaraan zestien internationale experts op het gebied van verloskundige

en gynaecologische echografie deelnamen. Op basis van een literatuuronderzoek werd een lijst van 58 items opgesteld, die relevant waren bevonden voor de definitie, detectie en evaluatie van een zwangerschap in het keizersnedelitteken. Na vier Delphi-rondes was er voor alle items consensus bereikt. De definitie en classificatie van een zwangerschap in het keizersnedelitteken werd geformuleerd, waarbij allereerst werd geconcludeerd dat een zwangerschap in het keizersnedelitteken alleen kan optreden als er een niche aanwezig is, en dus geen relatie heeft met een *genezen* keizersnedelitteken. Dit laatste is een belangrijke stelling voor evaluatie van de literatuur. De classificatie van een zwangerschap in het keizersnedelitteken was verdeeld in drie typen afhankelijk van de locatie van de vruchtzak; of het grootste deel van de vruchtzak al dan niet uitsteekt in de richting van de baarmoederholte, en of de vruchtzak al dan niet de buitencontour van de baarmoederhals of baarmoederholte overschrijdt. Er werd een rapportagesysteem voor een zwangerschap in het keizersnedelitteken ontwikkeld, waarbij onderscheid werd gemaakt tussen basismetingen die kunnen worden uitgevoerd in de dagelijkse klinische praktijk, en geavanceerde metingen voor expertisecentra of voor onderzoeksdoeleinden. Hoewel de klinische relevantie van dit classificatie- en rapportagesysteem moet worden geëvalueerd, kan het internationaal worden gebruikt om consistente gegevensverzameling over behandelresultaten van zwangerschappen in het keizersnedelitteken mogelijk te maken en in de toekomst 'evidence-based' richtlijnen te ontwikkelen, inclusief behandeling en follow-up.

Er zijn twee e-learning modules ontwikkeld naar aanleiding van onze Delphi studies. Deze zijn gratis beschikbaar voor alle geïnteresseerden, zie www.gynaecologyonline.com

DEEL 2: NICHE ONTWIKKELING EN VERANDERING IN DE LOOP VAN DE TIJD NA KEIZERSNEDE

Dit deel van het proefschrift had als doel om (het moment van) de aanwezigheid van een niche en de veranderingen ervan in de loop van de tijd te evalueren, na eerdere keizersnede en tijdens de daaropvolgende zwangerschap. Verder werd het effect van laparoscopische nicheresectie op de dikte van de overgebleven baarmoederwand in een volgende zwangerschap bestudeerd. Het is bekend dat de dikte van de overgebleven baarmoederwand van prognostische waarde is bij het voorspellen van verloskundige complicaties (ruptuur of –dehiscentie van het keizersnedelitteken), en de aanwezigheid van een niche vaak moeilijk te visualiseren is naarmate de zwangerschap vordert.

Hoofdstuk 5 beschrijft de resultaten van een prospectieve cohortstudie waarin de verandering van prevalentie van een niche en de dikte van de overgebleven

baarmoederwand in het eerste jaar na een keizersnede werden geëvalueerd, gebruikmakend van zowel transvaginale echografie als gel contrast echografie. Er werden twintig vrouwen geïncludeerd die één eerdere keizersnede hadden ondergaan. Er werd een statistisch significante afname van de dikte van de overgebleven baarmoederwand gevonden 12 maanden na de keizersnede in vergelijking met 2 maanden na de keizersnede (respectievelijk 6.5 mm en 11.9 mm, $p<0.001$). Ook nam de verhouding af tussen de dikte van de overgebleven baarmoederwand en de (aan de niche) aangrenzende baarmoederwand van 0.80 na 2 maanden tot 0.54 na 12 maanden ($p=0.002$), beoordeeld met gel contrast. De prevalentie van een niche veranderde niet, onafhankelijk van de beoordeling met transvaginale of gel contrast echografie. Ondanks de kleine studiegroep konden we concluderen dat de afmetingen van de niche in de loop van de tijd verandert.

Met het doel om het beste moment te identificeren om een niche na keizersnede te evalueren op basis van niche aanwezigheid en de verandering ervan, hebben we het beschikbare bewijs beoordeeld. **Hoofdstuk 6** presenteert de resultaten van deze systematische review en meta-analyse. Veertien onderzoeken werden geïncludeerd, waarin niche aanwezigheid en zijn kenmerken (lengte, diepte, breedte en dikte van de overgebleven baarmoederwand) werden gerapporteerd, en waarin het keizersnede litteken ten minste twee keer in de periode na keizersnede of in de daaropvolgende zwangerschap werd geëvalueerd met transvaginale echografie; dit waren zeven onderzoeken met niet-zwangere vrouwen en zeven met zwangere vrouwen. Hoewel de meta-analyse tussen zes weken en twee jaar na keizersnede geen significante verandering liet zien in niche aanwezigheid, werd er een toename gevonden tijdens de eerste twee maanden en dit leek te stabiliseren vanaf zes maanden na de keizersnede. Er werd een lichte daling gezien van de dikte van de overgebleven baarmoederwand in de loop van de tijd ($p=0.017$); de diepte van de niche bleef gelijk ($p=0.158$). Tijdens de volgende zwangerschap na eerdere keizersnede namen de niche aanwezigheid en de dikte van de overgebleven baarmoederwand af naarmate de zwangerschap vorderde, maar meta-analyse kon niet worden uitgevoerd vanwege het lage aantal studies die deze uitkomsten rapporteerden en het ontbreken van cruciale gegevens. We concludeerden dat zes maanden na keizersnede het beste moment lijkt te zijn om het keizersnedelitteken te evalueren, vanwege een toename van de beoordeelde aanwezigheid van een niche en stabilisatie na 6 maanden. Verder toonden we aan dat niche aanwezigheid en de dikte van de overgebleven baarmoederwand ook veranderen naarmate de zwangerschap vordert. Het beste moment van niche evaluatie tijdens (of vóór) de zwangerschap om verloskundige uitkomsten (ruptuur of –dehiscentie van het keizersnedelitteken) te voorspellen, viel buiten het doel van deze studie.

Het uitvoeren van een laparoscopische nicheresectie bij gynaecologische klachten heeft al aangetoond dat het zes maanden na de operatie een toename geeft van de dikte van de overgebleven baarmoederwand en deze klachten verbetert. Verloskundige uitkomsten na laparoscopische nicheresectie zijn onbekend. **Hoofdstuk 7** presenteert het effect van laparoscopische nicheresectie op de dikte van de overgebleven baarmoederwand tijdens een volgende zwangerschap, onderzocht in een prospectieve cohortstudie. Twee groepen zwangere vrouwen met een eerder gediagnosticeerde niche werden geïncludeerd; 61 met een grote symptomatische niche (dikte van de overgebleven baarmoederwand <3 mm) gevolgd door laparoscopische nicheresectie (de LNR-groep), en 39 zonder laparoscopische nicheresectie (de controle groep). Er werden nichemetingen uitgevoerd in het eerste, tweede en derde trimester van de zwangerschap volgens de gestandaardiseerde methode bij niet-zwangere vrouwen, beschreven in hoofdstuk 2. De verandering in de dikte van de overgebleven baarmoederwand vanaf de uitgangswaarde vóór de laparoscopische nicheresectie tot het derde trimester van de zwangerschap was +2.0 mm in de LNR-groep versus −1.6 mm in de controle groep ($p<0.001$). Bovendien was de overgebleven baarmoederwand dikker in de LNR-groep dan in de controle groep gedurende alle trimesters, ondanks dat de uitgangswaarde lager was in de LNR-groep, namelijk: 3.2 mm ($p<0.001$) in het eerste trimester, 2.5 mm ($p<0.001$) in de tweede trimester en 1.8 mm ($p=0.001$) in het derde trimester van de zwangerschap. Er werd geen ruptuur van het keizersnedelitteken gemeld. Dehiscentie van het keizersnedelitteken kwam vaker voor in de controle groep in vergelijking met de LNR-groep (7/36 (19%) en 1/50 (2%), $p=0.007$) en was gerelateerd aan de dikte van de overgebleven baarmoederwand in het tweede trimester van de zwangerschap. Aan de andere kant was het bloedverlies tijdens de keizersnede hoger in de LNR-groep. Concluderend heeft een laparoscopische nicheresectie een positief effect op de dikte van de overgebleven baarmoederwand voor en tijdens de gehele zwangerschap en kan de prevalentie van dehiscentie van het keizersnedelitteken verminderen. Laparoscopische nicheresectie wordt momenteel echter uitgevoerd om gynaecologische symptomen te verbeteren en toekomstig onderzoek is nodig om het effect ervan op resultaten ten aanzien van voortplanting te bestuderen.

DEEL 3: INVLOED VAN OPERATIEVE HECHTTECHNIEK OP NICHE ONTWIKKELING

In dit deel van het proefschrift hebben we ons gericht op het effect van hechttechnieken van de baarmoeder tijdens een keizersnede op de uiteindelijke niche ontwikkeling na de keizersnede.

Om een mogelijke optimale techniek voor het sluiten van de baarmoeder te identificeren, hebben we een systematische review en meta-analyse uitgevoerd. De resultaten worden gepresenteerd in **hoofdstuk 8**. Twintig studies werden geïncludeerd met drie variaties in hechttechniek; enkellaags versus dubbellaags hechten; gefestoneerd versus niet-gefestoneerd hechten; en excluderen versus includeren van het endometrium (binnenbekleding van de baarmoeder). Alle studies rapporteerden operatieve, echografische en/of klinische uitkomsten. Zowel dubbellaags hechten als niet-gefestoneerd hechten resulteerden in een dikkere overgebleven baarmoederwand in vergelijking met enkellaags hechten en gefestoneerd hechten ($p<0.001$). Verder werd een lagere prevalentie van grote niches gevonden als het endometrium was geïncludeerd in het hechten van de baarmoeder, in vergelijking met exclusie van het endometrium (respectievelijk 25.7% en 36.1%; RR 1.71; $p=0.002$), maar dit was gebaseerd op twee kleine studies. Op basis van onze bevindingen concludeerden we dat dubbellaags, niet-gefestoneerd hechten van de baarmoeder, met inclusie van het endometrium, mogelijk zou kunnen leiden tot gunstigere echografische resultaten (dikkere overgebleven baarmoederwand en lagere prevalentie van grote niches). We konden echter geen harde conclusies trekken betreft welke chirurgische techniek de voorkeur heeft, vanwege de overlap tussen de drie variaties in technieken, ernstige methodologische beperkingen van de geïncludeerde studies en verstorende factoren (bijv. inclusie van vrouwen met een eerdere keizersnede).

Vanwege het ontbreken van grote (gerandomiseerde) onderzoeken naar het effect van hechttechnieken van de baarmoeder tijdens een keizersnede op gynaecologische symptomen, inclusief kosteneffectiviteit, besloten we om een gerandomiseerde gecontroleerde studie (RCT) uit te voeren. In **hoofdstuk 9** wordt het onderzoeksprotocol beschreven van een multicenter, dubbelblinde RCT – de 2Close studie – met als doel om de (kosten)effectiviteit van dubbellaags versus enkellaags hechten van de baarmoeder na een eerste keizersnede te evalueren. Er werd gekozen voor een superioriteitsdesign, omdat wij in onze systematische review mogelijk gunstigere echografische resultaten vonden na dubbellaags hechten, ondanks een langere operatietijd. We includeerden vrouwen ouder dan 18 jaar die een eerste keizersnede ondergingen, gepland of ongepland, en randomiseerden de deelneemsters voor dubbellaags niet-gefestoneerd hechten, met inclusie van het endometrium (interventiegroep), of voor enkellaags niet-gefestoneerd hechten, met in- of exclusie van het endometrium, op basis van de voorkeur van de gynaecoloog (controlegroep). We hadden vooraf berekend dat 2.290 vrouwen geïncludeerd zouden moeten worden om een verschil van 15% in aantal dagen met post-menstrueel bloedverlies (primaire uitkomst) te vinden, na negen maanden follow-up. Belangrijke secundaire uitkomsten waren echografische kenmerken van het keizersnedelitteken, waarvoor alle deelnemende vrouwen drie

maanden na keizersnede een transvaginale echo kregen om het keizersnedelitteken te beoordelen. Indien nodig wordt een aanvullende water of gel contrast echo uitgevoerd. Om gestandaardiseerde interventie en echografische evaluatie te garanderen, werden een verplichte instructievideo en e-learning ontwikkeld voor alle deelnemende artsen en echoscopisten. Andere secundaire uitkomsten waren perioperatieve uitkomsten, menstruatiestoornissen, kwaliteit van leven, seksueel functioneren, uitkomsten ten aanzien van voortplanting en kosteneffectiviteit vanuit maatschappelijk perspectief.

Ten slotte wordt in **hoofdstuk 10** afgesloten met een algemene discussie waarin de belangrijkste bevindingen van dit proefschrift worden samengevat, inclusief de vergelijking met de literatuur, en waarin de onderzoeksvragen worden beantwoord. Ook worden methodologische overwegingen van de studies besproken. We leggen het belang uit van het gebruik van onze richtlijnen met betrekking tot niche evaluatie bij niet-zwangere vrouwen en vroeg in de zwangerschap in de klinische dagelijkse praktijk, namelijk om het bewustzijn te vergroten en patiënten goed te counselen. De klinische waarde van de echografisch kenmerken, die in onze Delphi studies worden gebruikt, moet in toekomstige studies nog worden geëvalueerd. Verder zou toekomstig onderzoek zich moeten richten op het onderliggende mechanisme van verstoorde peristaltiek van de baarmoeder bij vrouwen met een niche, om uiteindelijk op zoek te gaan naar mogelijke preventieve of therapeutische behandelingen. Er is aangetoond dat de hechttechniek van de baarmoeder (enkel- of dubbellaags) geen invloed heeft op de aanwezigheid van een niche, maar mogelijk heeft chirurgische ervaring dat wel en behoeft verder onderzoek. Om de laparoscopische nicheresectie te implementeren om de verloskundige uitkomsten (ruptuur van het keizersnedelitteken) te verbeteren, zijn meer studies nodig, maar de resultaten van dit proefschrift suggereren dat deze operatie veelbelovend is.

APPENDICES

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LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
AMT	Adjacent myometrial thickness
BROK	Basic course Regulations and Organisation for Clinical researchers
CD	Cesarean delivery
CI	Confidence interval
CRF	Case report form
CS	Cesarean section
CSD	Cesarean scar disorder
CSP	Cesarean scar pregnancy
D/RMT ratio	Depth of niche–to–residual myometrial thickness ratio
eCRF	Electronic case report form
ESHRE	European Society of Human Reproduction and Embyology
GA	Gestational age
GCP	Good clinical practice
GIS	Gel installation sonography
GP	General practitioner
GS	Gestational sac
ICER	Incremental cost-effectiveness ratio
iMCQ	iMTA Medical Consumption Questionnaire
iMTA	Institute for Medical Technology Assessment
iPCQ	iMTA Productivity Cost Questionnaire
IQR	Interquartile range
IUD	Intrauterine device
IVF	In vitro fertilization
LNR	Laparoscopic niche resection
LUS	Lower uterine segment
MEC	Medical ethics committee
MRI	Magnetic resonance imaging
NRS	Non-randomised study
OC	Oral contraceptives
OR	Odds ratio
PAS	Placenta accreta spectrum
PEE	Pooled effect estimates
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY	Quality adjusted life years
QOL	Quality of life
RCT	Randomized controlled trial
RMT	Residual myometrial thickness
RoA	Rate of agreement
RR	Risk ratio / Relative risk
SAE	Serious adverse event
SD	Standard deviation
SHG	Sonohysterography
SIS	Saline infusion sonography
SL	Serosal line
TOL	Trial of labor (after CS)
TV(U)S	Transvaginal ultrasound / sonography
UCL	Uterine cavity line
UP	Uterine peristalsis
VAS	Visual analogue scale
VBAC	Vaginal birth after cesarean section
VV fold	Vesicovaginal fold
WMD	Weighted mean difference

PORTFOLIO

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- Oral: Beoordeling SC litteken / niche in de zwangerschap 2019
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- Oral: Standardised ultrasound evaluation of a niche: consensus statement and e-learning platform of the niche taskforce group 2019
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- Oral: Changes of uterine niche during pregnancy after laparoscopic niche resection in comparison to controls without niche surgery
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- Poster: Sonographic evaluation of the uterine Cesarean scar in 1st trimester and classification of a Cesarean scar pregnancy
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OVER DE AUTEUR

Inge Jordans is geboren in Haarlem op 28 januari 1986 en groeide daar op samen met haar ouders en twee broers. Na de middelbare school in 2004, startte ze met haar studie Geneeskunde aan de Universiteit van Amsterdam. Al van jongs af aan droomde ze om kinderarts te worden (in het AMC) en met dat doel voor ogen ging zij de opleiding door. Na het behalen van de eerste vier jaar, besloten zij en haar vriend Tim de studie voor een jaar te onderbreken om de wereld te verkennen. Samen reisden ze enkele maanden langs de Frans-Atlantische kust met tent en surfplank, en trokken ze al backpackend door Zuidoost Azië. Tijdens de coschappen werd het voor Inge duidelijk dat haar hart bij de gynaecologie lag en gooide ze haar plannen om.

Na haar afstuderen, begon zij in 2012 haar medische carrière als ANIOS Verloskunde in Ziekenhuis Amstelland, in Amstelveen. Een jaar later kon zij verder doorgroeien op de afdeling Verloskunde en Gynaecologie in het Meander Medisch Centrum in Amersfoort (dr. M.J. Duk). Na een korte periode als ANIOS in VU medisch centrum in Amsterdam vanaf eind 2014, werd ze aangenomen als arts-echoscopist bij de afdeling Prenatale diagnostiek van het VUmc in juni 2015. Tegelijkertijd begon ze haar promotietraject bij de afdeling Verloskunde en Gynaecologie, onder begeleiding van prof. dr. J.A.F. Huirne, prof. dr. C.J.M. de Groot en dr. R.A. de Leeuw, wat heeft geleid tot dit proefschrift. In juli 2020 is ze begonnen aan de opleiding tot gynaecoloog in het Spaarne Gasthuis in Haarlem (dr. J. Gianotten). Inmiddels heeft zij haar derde opleidingsjaar voortgezet in het Amsterdam UMC (dr. A.W. Valkenburg).

Inge woont in Haarlem, samen met Tim en hun twee zoons, Jesse en Sven.