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Scarred Uterus: Subsequent Pregnancy and Delivery

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Risk assessment previous CD

Scarred Uterus:

Subsequent Pregnancy and Delivery

Anton Baranov

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DOCTORAL DISSERTATION

which, by due permission of the Faculty of Medicine at Lund University,

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in Lecture Hall at the Department of Obstetrics and Gynaecology,

Skåne University Hospital, Malmö

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Scarred uterus: subsequent pregnancy and delivery

Abstract

The aim of the work presented in this thesis was to address the problems associated with the management of pregnancy and delivery after Caesarean delivery (CD), with emphasis on ultrasound diagnostics. The prognostic value and utility of serial ultrasound examinations of Caesarean hysterotomy scars in the non-pregnant state and during pregnancy subsequent to CD were studied. This thesis includes 5 publications, and is based on 3 study populations.

The first study population (Paper I) included women who had undergone repeat CD at the University Hospital in Malmö (Sweden) during the period 2005-2009. It was found that the true incidence of complete uterine rupture was higher than previously reported. The incidence of uterine dehiscence was also determined.

The second study population (Papers II-IV) included women with one previous CD, recruited in a prospective cohort study at the Skåne University Hospital (Sweden). These women had undergone CD during the period from March 2013 to May 2015. The participants underwent serial ultrasound examinations in the non-pregnant state, 6-9 months after CD (transvaginal conventional ultrasound examination and saline contrast sonohysterography), and, in those who became pregnant, in the subsequent pregnancy (transvaginal and transabdominal examinations). The results presented in Paper II show that sonographic measurements of Caesarean hysterotomy scars in non-pregnant women were reliable and can be used in clinical practice. The results presented in Paper III demonstrated that the appearance of hysterotomy scars was similar in the non-pregnant state and in a subsequent pregnancy at 11-14 weeks. A cut-off value for Caesarean hysterotomy scar thickness measurement was established to predict scars with a large defect. Based on the results presented in Paper IV it was concluded that a previously published model for the prediction of successful vaginal birth after CD (VBAC), based on sonographic measurements of Caesarean hysterotomy scars, had limited utility in the Swedish population.

The third study population (Paper V) included women who had trial of labour after CD at the University Hospital in Barcelona (Spain) during the period 2011-2015. The results demonstrated that the previously published model, based on maternal non-sonographic characteristics, had reasonable accuracy in the prediction of successful VBAC in women with one previous CD and singleton pregnancy.

Key words: Caesarean hysterotomy scar, ultrasonography, reliability, Caesarean delivery, vaginal birth after Caesarean delivery, prediction model

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Scarred Uterus:

Subsequent Pregnancy and Delivery

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"Medicine is a science of uncertainty and an art of probability."

Sir William Osler

Abstract

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AUC	Area under the receiver-operating characteristics curve
BMI	Body mass index
CD	Caesarean delivery
CSP	Caesarean scar pregnancy
CI	Confidence interval
ERCD	Elective repeat Caesarean delivery
EPRS	Electronic patient record system
ICD-10	International Classification of Diseases, version 10
ICC	Intraclass correlation coefficient
IR	Interquartile range
MRI	Magnetic-resonance imaging
MTS	Myometrial thickness adjacent to the scar
ROC	Receiver-operating characteristics
RMT	Remaining myometrial thickness over the defect
SCSH	Saline contrast sonohysterography
ST	Scar thickness
TOLAC	Trial of labour after Caesarean delivery
VBAC	Vaginal birth after Caesarean delivery
WHO	World Health Organization

Original publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis. All papers were reprinted with permission of the publishers.

I.   Fogelberg M, Baranov A, Herbst A, Vikhareva O
        Underreporting of complete uterine rupture and uterine dehiscence in women with previous Cesarean section
        J Matern Fetal Neonatal Med. *Accepted in September 2016*

II.   Baranov A, Gunnarsson G, Salvesen KÅ, Isberg PE, Vikhareva O
        Assessment of Cesarean hysterotomy scar in non-pregnant women: reliability of transvaginal sonography with and without contrast enhancement
        Ultrasound Obstet Gynecol. 2016 Apr;47(4):499-505

III.   Baranov A, Salvesen KÅ, Vikhareva O
        Assessment of Cesarean hysterotomy scar before pregnancy and at 11-14 weeks of gestation: a prospective cohort study
        Ultrasound Obstet Gynecol. *Accepted in July 2016*

IV.   Baranov A, Salvesen KÅ, Vikhareva O
        Validation of a prediction model for successful vaginal birth after Cesarean delivery based on sonographic assessment of a hysterotomy scar
        Ultrasound Obstet Gynecol. *Accepted in February 2017*

V.   Baranov A, Gratacós E, Vikhareva O, Figueras F
        Validation of the prediction model for success of vaginal birth after Cesarean delivery at the University Hospital in Barcelona
        J Matern Fetal Neonatal Med. *Accepted in December 2016*

Preface

The dramatic increase in the number of women with a scarred uterus in the population during recent decades has led to greater attention being paid to the problem of the clinical management of pregnancy and delivery after previous Caesarean delivery (CD).

Pregnancy and childbirth after CD are associated with an increased risk of complications. Among them are scar pregnancy, placental complications and, the most feared one, uterine rupture. In order to make pregnancy and childbirth in women with a scarred uterus safer, obstetricians need tools which can accurately and reliably estimate the risk of adverse outcomes for each individual woman. This is the cornerstone of the most optimal delivery plan. The more accurate evaluation and prediction we are able to make – the better clinical management we can offer to women.

Several studies have shown that ultrasound may have clinical utility in refining the care of women with previous CD. Possibly, this method can provide additional important information. The prognostic value and applicability of ultrasound should, therefore, be studied further.

Content

Introduction

Caesarean delivery

Caesarean delivery (CD) is a common obstetric operation today, and dates back to ancient times, when it was performed as an acute intervention on dying mothers, in an attempt to save the child. However, with advance in modern medicine (the introduction of aseptics, anaesthesia, safe suture materials, antibiotics, blood transfusions and standardization of surgical techniques), the outcome of CD has been greatly improved (1). Indications for CD have been considerably expanded in modern times. The current list of widely accepted indications includes not only immediate maternal and foetal life-threatening conditions and diseases, but also those that can potentially have adverse short- or long-term impact on the health of the mother and/or the child. It is sometimes difficult to determine the risk–benefit balance of CD versus vaginal delivery.

It is estimated that 22.9 million women had CDs worldwide in 2012 (2). On average, every third pregnant woman in the United States and every fourth pregnant woman in Europe undergoes CD (3, 4). According to the worst case scenario in a forecast presented in 2011, if the current trend persists, the rate of CD in the United States will reach up to 56% in 2020 (5). This may result in 4504 additional cases of placenta accreta, and may lead to an additional 130 cases of maternal mortality.

Is there an optimal CD rate? In 1985, the World Health Organization (WHO) stated that there was no justification for any region to have CD rates higher than 10-15% (6). For many decades this was regarded as the ideal CD rate. However, a recent analysis of data from all 194 WHO member states revealed that this recommendation should be reconsidered (2). Molina et al. found that national CD rates of up to approximately 19 per 100 live births were associated with lower maternal or neonatal mortality (2). The current CD rates in many countries are above this optimal level (2). However, high CD rates do not appear to be associated with a reduction in maternal and neonatal mortality (7). This leads to the conclusion that there is considerable overuse of CD in many countries.

Sweden has a low CD rate, which in 2012 was 16.3 per 100 live births (2). However, the recent massive inflow of refugees from countries with large families

and high CD rates (for example, Syria, where the CD rate was 26.4 per 100 live births in 2009), and the significant proportion of EU immigrants (for example, Romania, where the CD rate in 2011 per 100 live births was 36.3), possibly, may increase the number of women with a scarred uterus in the Swedish population.

What can be done to lower CD rates? In 2014, the American College of Obstetricians and Gynecologists (ACOG) issued guidelines "Safe Prevention of the Primary Cesarean Delivery" (8). These guidelines provide comprehensive clinical recommendations regarding the most common indications for primary CD. For instance, it was suggested that the definition of labour dystocia, the most common indication for primary CD (34% of all indications), should be reconsidered (9). This recommendation is based on the findings of a recent study by Zhang et al., which showed that contemporary labour in women with singleton pregnancy, spontaneous labour onset and cephalic presentation has much slower progress than postulated by Friedman in the 1950s (10, 11). Therefore, the definition of active phase arrest, which was traditionally defined as the absence of cervical change for 2 hours or more in the presence of adequate uterine contractions and cervical dilatation of at least 4 cm, should be revised. The fact that the maximal slope in the rate of change of cervical dilatation over time often did not start until at least 6 cm suggests that neither active phase protraction (slower progress than normal) nor labour arrest (complete cessation of progress) should be diagnosed before 6 cm dilatation. Some maternity hospitals in the US, including the Mayo Clinic, have already introduced this new recommendation into their clinical routines.

Another ACOG recommendation was to improve and standardize foetal heart rate interpretation and appropriate management. Non-reassuring foetal status was second on the list of indications for primary CD, and was encountered in 23% of cases (9). It was emphasized that foetal scalp probes should only be used in case of abnormal or non-reassuring foetal heart patterns.

In addition to greater expectant management, the ACOG recommended other practices. For instance, obstetricians were encouraged to improve their skills in instrumental vaginal deliveries (vacuum or forceps), to use external cephalic version for breech presentation more often, and to offer trial of labour after CD (TOLAC) to women with twin pregnancy, when the first twin is in cephalic presentation.

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Complications in pregnancy after CD

No pregnancy nor childbirth is risk-free. However, several complications are more likely and some completely attributable to previous CD (7). These are Caesarean scar pregnancy (CSP), abnormal placentation (placenta previa and placenta accreta) and uterine rupture.

Caesarean scar pregnancy

CSP, or pregnancy implanted into a Caesarean hysterotomy scar, is a serious, but rare, condition. Very few cases have been reported in the literature, and the true incidence of CSP is unknown. It has been estimated that the incidence of CSP among women attending an early pregnancy assessment unit is 1:1800 (12). CSP may lead to profuse uncontrollable bleeding, invasion into surrounding organs, miscarriage, early preterm delivery, hysterectomy and loss of fertility (13). Therefore, the diagnosis of CSP is very important, and all CSP pregnancies should be treated as potentially dangerous, requiring careful clinical management.

The diagnosis of CSP is usually based on a positive pregnancy test and the following transvaginal sonographic criteria (14): visualization of an empty uterine cavity as well as empty endocervical canal; detection of the placenta and/or a gestational sac embedded in the hysterotomy scar; in early gestation (≤8 weeks), a triangular gestational sac that fills the niche of the scar, at ≥8 postmenstrual weeks this shape may become rounded or even oval; a thin (1-3 mm) or absent myometrial layer between the gestational sac and the bladder; a closed and empty cervical canal; the presence of embryonic/foetal pole and/or yolk sac with or without heart activity; the presence of a prominent, and at times rich, vascular pattern at or in the area of a hysterotomy scar. Diagnosis is often difficult, and differential diagnoses of CSP, cervical pregnancy, abortion in progress and intrauterine gestational sac implanted low in the uterus may be needed.

In a recent publication, Timor-Tritsch et al. described a sonographic method for differential diagnosis between CSP and intrauterine pregnancy in early gestation (15). It was suggested that the location of the centre of the gestational sac relative to the midpoint of the axis of the uterus, measured between the external cervical os and the fundus, can be used for the diagnosis of CSP at 5-10 gestational weeks.

Abnormal placentation

Placenta previa is the condition in which the placenta partially or totally covers the internal cervical os. Placenta previa complicates about 1 in 200 deliveries (16). It is the leading cause of vaginal bleeding in the second and third trimesters. In a large study, Gurol-Urganci et al. demonstrated that women with CD have an increased risk of placenta previa in the subsequent pregnancy (8.7 per 1000 births), in comparison with women who have previously had vaginal delivery (4.4 per 1000 births) (17).

The diagnosis of placenta previa is usually based on sonographic findings: i.e. the placenta is seen to overlap the internal cervical os. In some cases, diagnosis in early gestation may be not reliable, due to subsequent placental migration during pregnancy. Mustafa et al. showed that when the lower placental edge overlapped the internal cervical os by 23 mm at transvaginal ultrasound scan at 11-14 weeks, the probability of placenta previa at term was 8%, with a sensitivity of 83.3% and specificity of 86.1% (18). Naji et al. found no significant difference in placental migration patterns between women with and without previous CD in cases of low-lying placenta (19).

Placenta accreta is a serious obstetrical complication described as an inability of part of the placenta, or the entire placenta, to be separated from the uterine wall (20). It occurs when a defect in the decidua basalis enables the direct apposition of chorionic villi to the myometrium. When chorionic villi invade only the myometrium, the condition is called placenta increta. If the chorionic villi invade through the myometrium and serosa with possible invasion into adjacent organs, the condition is called placenta percreta. The incidence of placenta accreta has increased over the past 20 years, in conjunction with increasing CD rates, and has been reported to occur in 1 out of 533 pregnancies (21).

Placenta accreta is a life-threatening complication, which can lead to massive bleeding, coagulopathy and severe surgical complications, such as injury to the bladder, ureters or bowel. Women with placenta accreta require special medical care during delivery, which may include the involvement of specialized surgical teams, blood transfusions, and admission to the intensive care unit. Adequate diagnosis and follow-up are thus extremely important. Silver et al. emphasized that women with placenta accreta should be delivered at medical centres with multidisciplinary expertise, including expertise in placenta accreta management (22).

The vast majority of cases of placenta accreta occur in women with placenta previa, and the risk increases significantly with the number of previous CDs. According to Silver et al., the risk of placenta accreta in women with placenta

previa was 3%, 11%, 40%, 61% and 67% for the first, second, third, fourth and fifth or more repeat CDs, respectively (23). Therefore, the possibility of placenta accreta should be thoroughly considered in all cases of placenta previa. However, the absence of placenta previa does not exclude placenta accreta.

Prenatal diagnosis of placenta accreta may involve ultrasound and magnetic resonance imaging (MRI). It appears that the sensitivity and specificity of these imaging methods are comparable. Greyscale sonography has a sensitivity of 77-87% and a specificity of 96-98%, while MRI has a sensitivity of 80-85% and a specificity of 65-100% (24). Although, MRI may be useful in the assessment of invasion into adjacent organs, in cases of placentation into the posterior uterine wall or non-informative ultrasound, it is still unclear whether the combination of MRI and ultrasound improves the diagnostic accuracy in comparison with ultrasound alone (24).

Collins et al. summarized the following descriptors of placenta accreta, using greyscale ultrasound: loss of the "clear zone", abnormal placental lacunae, bladder wall interruption, myometrial thinning, placental bulge and focal exophytic mass (25). Using colour Doppler ultrasound, the descriptors included: utero-vesical hypervascularity, sub-placental hypervascularity, bridging vessels and placental lacunae feeder vessels. At 3D ultrasound, intra-placental hypervascularity (power Doppler), placental bulge, focal exophytic mass, utero-vesical hypervascularity and bridging vessels were described.

Ultrasound, probably, may be useful in the diagnosis of placenta accreta even earlier in pregnancy. Stirneman et al. showed that the late first trimester scan may have potential value for screening and refining the care of women suspected of having placenta accreta (26).

Uterine rupture and uterine dehiscence

Uterine rupture is a disruption or tear of the uterine muscle and visceral peritoneum (27). It is an uncommon, although potentially catastrophic obstetrical complication, which occurs mainly during vaginal birth attempt after previous CD. A WHO systematic review by Hofmeyr et al. showed that the median incidence of uterine rupture is 0.05% among unselected pregnancies, and 1% in women with previous CD (28). However, since this review was based mainly on an analysis of data registered in electronic databases, the true incidence of uterine rupture may be different. This was confirmed by Al-Zirqi, who studied medical coding practices in Norway, and found that the diagnosis of uterine rupture was underreported in the Medical Birth Registry by about 37% (29). Thisted et al. found significant

misreporting of uterine rupture in the Danish Medical Birth Registry (30). Thus, there is a need for studies to determine the true incidence of uterine rupture.

Uterine rupture may have serious medical consequences for both mother and child, as well as professional liability actions against the attending obstetrician (31, 32). Concerns about this complication have contributed to the decline in the rate of vaginal birth after Caesarean delivery (VBAC), with a corresponding increase in CD rates during recent decades (32).

Uterine dehiscence is usually defined as a disruption of the uterine muscle with intact visceral peritoneum (27). It is difficult to estimate the overall incidence of uterine dehiscence due to differences in definitions and diagnostic criteria.

Macones et al. investigated demographic and clinical risk factors for uterine rupture in a study of 25,000 women (33). Although, univariable analysis showed that maternal age, ethnicity, prior vaginal delivery, gestational age at delivery, birth weight, the need for induction/augmentation and cervical dilatation at the time of admission were significantly associated with uterine rupture, they considered that combination of these factors had poor predictive ability.

Other studies have shown that ultrasound can be useful and can complement risk estimation (34, 35). Most studies have been performed in the late third trimester to establish a cut-off value for sonographic measurements of the lower uterine segment in order to predict uterine rupture during TOLAC. Jastrow et al. carried out a review in which they summarized the results of these studies (34). Although this review showed that the degree of lower uterine segment thinning is a strong predictor of uterine scar defect at delivery, no optimal cut-off value could be recommended due to the heterogeneity of the studies reviewed, regarding the measurement techniques (myometrial thickness/full thickness including the wall of the urinary bladder) and sonographic approaches (transvaginal/abdominal; full/half-full/empty bladder). It should also be noted that the clinical value of a late third trimester scan is limited, as the delivery plan has usually already been established.

Several authors have attempted to study the diagnostic value of ultrasound at earlier stages. Gotoh et al. performed prospective serial transvaginal ultrasound examinations between 19 and 39 gestational weeks in two groups of women; with and without previous CD (36). Almost all (11 out of 12) women with uterine dehiscence had lower uterine segment less than "the mean control - 1 SD" in the late second trimester.

Vikhareva et al. performed a study in non-pregnant women and found that large defects of Caesarean hysterotomy scars detected by transvaginal ultrasound in non-pregnant women are likely to be associated with the risk of uterine rupture/uterine dehiscence in subsequent delivery (37). If this finding can be

verified in larger studies, a model combining clinical factors and findings from a transvaginal ultrasound examination in the non-pregnant state may help identify women at a higher risk of uterine rupture/uterine dehiscence in subsequent pregnancies.

Before performing larger studies in this area, it is necessary to perform a reproducibility study to determine whether transvaginal ultrasound examinations performed by different examiners in non-pregnant women are reliable and the measurements are consistent.

Mode of delivery in pregnancy subsequent to CD

One of the major questions in a pregnancy subsequent to CD is the selection of mode of delivery: elective repeat Caesarean delivery (ERCD) or TOLAC. Both have risks and benefits. TOLAC is associated with uterine rupture (27) and a higher risk of major operative injuries if the TOLAC attempt fails (38, 39). Interestingly, almost all the demographic and clinical risk factors for uterine rupture, found in a study by Macones et al. (33) on a largest series of uterine ruptures during attempted TOLAC, were the same as the risk factors for failed TOLAC, found by Srinivas et al. in a study of 13,706 patients (40).

ERCD has a higher risk of operative complications, such as abdominal wound infection, puerperal fever and the need for blood transfusions (38, 39). In addition, women with multiple CDs have a higher risk of placenta previa and placenta accreta in subsequent pregnancies (23).

It is generally accepted that successful VBAC is associated with fewer severe complications than ERCD (32, 41). Therefore, women with high chances of successful VBAC should be encouraged to undergo TOLAC. However, a failed TOLAC attempt results in emergency CD, which is associated with higher maternal and neonatal morbidities, than those at ERCD (27, 39). Thus, accurate evaluation of a woman's chances of successful VBAC is crucial for selection of the most optimal mode of delivery.

Traditionally, the attending obstetrician clinically evaluates a woman's chances of achieving successful VBAC by considering her individual demographic and obstetric characteristics. There is a growing body of evidence showing that factors such as prior vaginal birth and spontaneous labour onset increase the probability of successful VBAC (32). On the other hand, recurrent indication for previous CD, increased maternal age, maternal obesity, short interpregnancy interval, etc., decrease the probability of successful VBAC (32). The individual risks and

benefits of different modes of delivery are discussed with the woman at prenatal counselling, in order to reach a reasonable decision.

Although such a clinical approach is widely used and has many merits, it only provides an approximate assessment of the woman's chances of successful VBAC. Sometimes, the balance between the risks and benefits may not be clear-cut. Moreover, in some situations, it may be difficult to reconcile the obstetrician's views and the mother's expectations without using strong, reliable arguments. Thus, there is a need for additional tools that can provide objective and reliable information concerning individual risk assessment.

Prediction models for successful VBAC

In the 1990s, several authors suggested the use of scoring systems for the prediction of successful VBAC in an attempt to facilitate the decision-making process and to reach more informed decisions concerning the mode of delivery (42, 43). However, these scoring systems were not widely adopted in clinical routines. Later, when receiver-operating characteristics (ROC) curve analysis and multivariable regression modelling obtained popularity in medical research, several mathematical models for the calculation of the individual probability of successful VBAC were suggested (44-49). All these models were based on characteristics obtainable at different stages of pregnancy, but, until recently, none of them included sonographic parameters of the hysterotomy scar.

In 2013, Naji et al. published a model for the prediction of successful VBAC which was based on sonographic measurements of the Caesarean hysterotomy scar in the first and second trimesters (50). The predictive ability of their model was higher than that of previously published models for the prediction of successful VBAC (area under the receiver operating characteristic curve was 0.94) (44-50). Such a high predictive ability must be confirmed in external validation studies, before the model can be recommended for use in other clinical settings. No external validation studies of this model could be found in the available literature.

Summary and framework of this thesis

There is a growing body of evidence showing that ultrasound is clinically useful for the assessment of the risk of complications in pregnancy subsequent to CD, and the prediction of successful VBAC. However, more studies were needed to

further investigate sonographic aspects with regard to possible complications and the outcome of pregnancy after previous CD.

The core of the work presented in this thesis is based on a cohort of women recruited shortly after their first CD, and prospectively followed up with serial ultrasound examinations until their next pregnancy and delivery. Such an observational design allowed the natural course of the pregnancy to be followed while obtaining sonographic data.

In addition, two research questions were studied on two separate populations of women: the true incidence of uterine rupture, and the accuracy of a model, based on non-sonographic characteristics, for the prediction of successful VBAC.

Aims

The overall aim of the work presented in this thesis was to address the problems associated with the management of pregnancy and delivery after Caesarean delivery (CD), with emphasis on ultrasound diagnostics. The specific aims were:

- To determine the true rate of uterine rupture, and to determine the rate of uterine dehiscence at repeat CD at the University Hospital in Malmö. (*Paper I*)

- To determine intra- and interobserver reliability in describing the appearance and the measurements of Caesarean hysterotomy scars at conventional transvaginal ultrasound and at saline contrast sonohysterography (SCSH) in non-pregnant women with one previous CD. (*Paper II*)

- To compare the sonographic appearance and measurements of Caesarean hysterotomy scars at SCSH in non-pregnant women and at transvaginal ultrasound at 11-14 weeks in a subsequent pregnancy. (*Paper III*)

- To carry out external validation of the model proposed by Naji et al., based on sonographic measurements of the Caesarean hysterotomy scar in the first and second trimesters, for the prediction of successful VBAC. (*Paper IV*)

- To perform external validation of the model proposed by Grobman et al., based on variables easily obtainable at the first antenatal visit for most women, for the prediction of successful VBAC. (*Paper V*)

Subjects

The studies described in this thesis are based on three study populations.

The first study population included 716 women delivered by repeat CD at the University Hospital in Malmö, Sweden, during 2005-2009 (*Paper I*).

The second study population (*Papers II-IV*) consisted of women with one previous CD performed at ≥37 gestational weeks at the Skåne University Hospital, during 2013-2015. These women had their first ultrasound examination of the Caesarean hysterotomy scar when not pregnant. They were then followed up with regard to a new pregnancy. Those who became pregnant were booked for ultrasound examinations of the Caesarean hysterotomy scar at 11+0 to 13+6, 19+0 to 21+6 and 35+0 to 38+6 gestational weeks. A flowchart showing the number of women included in each study is shown in Figure 1.

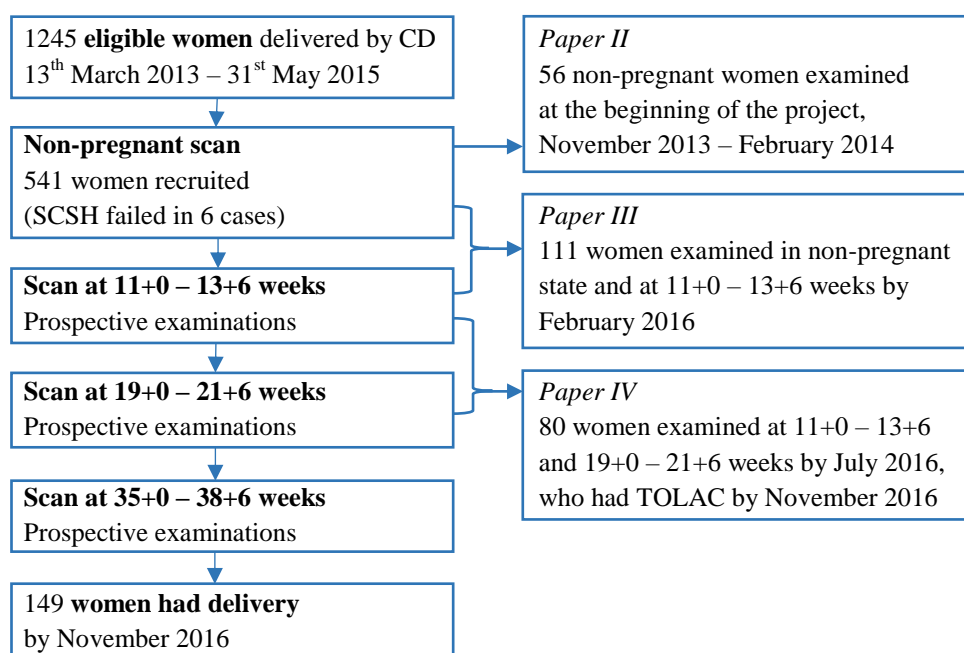|	
1245 **eligible women** delivered by CD 13th March 2013 – 31st May 2015	*Paper II* 56 non-pregnant women examined at the beginning of the project, November 2013 – February 2014
Non-pregnant scan 541 women recruited (SCSH failed in 6 cases)	*Paper III* 111 women examined in non-pregnant state and at 11+0 – 13+6 weeks by February 2016
Scan at 11+0 – 13+6 weeks Prospective examinations	
Scan at 19+0 – 21+6 weeks Prospective examinations	*Paper IV* 80 women examined at 11+0 – 13+6 and 19+0 – 21+6 weeks by July 2016, who had TOLAC by November 2016
Scan at 35+0 – 38+6 weeks Prospective examinations	
149 **women had delivery** by November 2016	

Figure 1. Flowchart describing the sampling of participants in the studies described in Papers II-IV.

The third study population included 630 women with a single live foetus in cephalic presentation with one previous low-transverse CD, who underwent TOLAC at ≥37 gestational weeks during 2011-2015, at the University Hospital in Barcelona (*Paper V*).

Methods

Paper I

No ethical approval was necessary for this study.

Patients' medical records were retrieved retrospectively from KIKA. KIKA is an electronic patient record system (EPRS) containing detailed clinical antenatal and perinatal information for all patients receiving maternity care at the University Hospital in Malmö, Sweden. It was developed as an in-house EPRS to reduce the manual clerical workload of medical teams, and to facilitate clinical data management. The system was introduced in 1998, and several years were required for it to become fully adapted to clinical routines. During the study period, the medical team managed the KIKA information system very well, the system was considered to be reliable, and only a few minor changes were made. Midwives and physicians attending a birth entered information about delivery in KIKA using both standardized forms and free text. Operation reports are described in detail, in free text by the operating surgeon. The diagnosis of complete uterine rupture was entered in KIKA with the two relevant International Classification of Diseases, version 10 (ICD-10) codes: O710 (uterine rupture before onset of labour) and O711 (uterine rupture during labour). ICD-10 does not contain a separate code for uterine dehiscence, and this diagnosis is therefore not reported in KIKA.

A new information system, Obstetrix (Siemens Healthcare, Upplands Väsby, Sweden), was introduced in 2010 to replace KIKA. ICD-10 codes were still used to enter diagnoses, but the programme interface was different. Some clinical information which was entered as free text in KIKA was managed in Obstetrix with standardized menu options. Structured templates are used for operation reports, with the possibility to skip some detailed descriptions. When operation reports were reviewed in Obstetrix, it was found that these changes made direct comparison of some medical data in Obstetrix and KIKA unreliable. Thus, the study was limited to the period from 2005 to 2009, when KIKA was used.

The study population consisted of women with repeat CD. It was not possible to directly retrieve this group from KIKA, but it could be derived from the group of multiparous women who were delivered by CD. When scrutinizing their medical records, it was found that a few of them were, in fact, primiparous, and were thus

incorrectly registered. Also, by chance, one woman was found who was registered in KIKA as having been delivered vaginally, while she had actually undergone CD. Therefore, to ensure that the data retrieved were reliable, the medical records of all women delivered at the University Hospital in Malmö, during the period 2005-2009 (n=21,420) were checked.

Sampling was performed as follows:

a) For the period 2005-2008

Medical records of all delivered women were reviewed and checked for registration inaccuracies regarding parity and history of previous CD. Misreported cases were corrected.

b) For 2009

From 2009, a mandatory question concerning previous uterine surgery was introduced in KIKA. If this question was answered positively, ICD-10 code O34.2 (maternal care due to uterine scar from previous surgery) was assigned. This provided the opportunity to check for the accuracy of registration with approximately the same reliability as manual reviewing of the medical records of the delivered women. Medical records of all women with ICD-10 code O34.2 were retrieved from KIKA and reviewed. It was found that in 2 cases this code was assigned because of previous myomectomy. In all other cases the reason for this code was previous CD. These cases were matched with cases from the group of women with repeat CD and a few missing cases were identified.

After identification of the study population, the operation reports of all women delivered by repeat CD were reviewed by experienced obstetricians. Pathological anatomical conditions of the lower uterine segment at CD were noted. If the operation report was unclear, or difficult to interpret, the surgeon who performed the CD was personally contacted and asked for details. Descriptions of uterine rupture or uterine dehiscence in operation reports were compared with the registered ICD-10 diagnosis for corresponding patients in KIKA.

The following definitions were used: complete uterine rupture, a disruption or tear of the uterine muscle and visceral peritoneum; uterine dehiscence, a disruption of the uterine muscle with intact visceral peritoneum (27). Uterine dehiscence was divided into two subgroups. The first subgroup was made up of cases with a clear diagnosis of uterine dehiscence. In the second subgroup, the diagnosis was uncertain, but highly suspected; the anatomical condition of the myometrium was extremely thin and described in operation reports as "thin as a leaf", "membranous" or "transparent".

Papers II-IV

Ethical approval was obtained from the Regional ethics committee. All participants signed informed written consent forms after the background of the study and all practical details had been fully explained.

Women were prospectively recruited after their first CD, performed at the Skåne University Hospital during the period from 13th March 2013 to 31st May 2015. The women recruited were followed up, and those who became pregnant were examined during the subsequent pregnancy.

Recruitment and follow-up procedures are described in detail below.

Invitation of eligible women

The hospital's register, Obstetrix, was prospectively searched every month to identify eligible women aged 18-35 years.

Inclusion criteria:

- ONE CD only,
- no other surgery on the uterus (conization and curettage were permitted) and
- CD carried out at ≥37 gestational weeks.

Exclusion criteria:

- previous CD other than low-transverse,
- moved away from the hospital's catchment area,
- unclear history regarding previous surgery on the uterus, or
- pregnant before non-pregnant scan.

The contact details of women eligible for the study were retrieved from the hospital's register, Obstetrix, and a letter inviting them to participate in the study was sent them. Those who accepted invitation were prospectively booked for ultrasound examination of the Caesarean hysterotomy scar 6-9 months after their CD.

Non-pregnant scan

Immediately before the examination a pregnancy test (urine hCG) was performed, and their medical history was recorded following a standardized research protocol, including information on parity, day of menstrual cycle (if resumed), breast feeding, contraceptives, earlier deliveries and gynaecological operations.

The women were examined with conventional transvaginal ultrasound in the lithotomy position with an empty urinary bladder. The uterus was scrutinized in the sagittal plane using a standardized approach to identify the Caesarean hysterotomy scar (51). SCSH was performed during the same visit, immediately after the conventional ultrasound examination. A polyethylene catheter (outer diameter 2.1 mm, inner diameter 1.7 mm) without an inflatable balloon (Prodimed, Neuilly-en-Thelle, France) was introduced into the uterine cavity through the cervical canal, and 10-20 ml saline was infused in order to delineate the borders of the scar area. No premedication or prophylactic antibiotics were given before performing the procedure.

Documentary images were obtained during conventional transvaginal ultrasound examination and SCSH, all of which were stored on the hospital's digital image storage system (Siemens Syngo Dynamics, version VA10B, Siemens Medical Solutions Health Services, USA, Inc.). Images were evaluated offline immediately after completion of the examinations. The following ultrasound features were noted: uterine position (anteflexion, retroflexion or midposition), visibility of a scar (clearly visible, barely visible or absent), presence of a scar defect (yes or no), and the shape of the scar defect (triangular, round, oval or total defect with no remaining myometrium over the defect). The Caesarean hysterotomy scar was defined as a hypo- or hyper-echoic line in the anterior uterine wall. Any indentation in the scar, however small, was classified as a scar defect. Myometrial thickness adjacent to the scar (MTS) was measured close to and fundal to the scar. If a scar defect was observed, the remaining myometrial thickness over the defect (RMT) was measured as the shortest distance between the apex of the scar defect and the lower boundary of the urinary bladder. A large scar defect was defined objectively, using cut-offs established in previous studies of women with only one CD, i.e. RMT $\leq$ 2.2 mm on conventional transvaginal ultrasound examination and $\leq$ 2.5 mm on SCSH (52, 53).

In order to evaluate the intra- and interobserver reliability of the measurements, women who were recruited at the beginning of the project, during the period from November 2013 to February 2014, were examined by two ultrasound observers. Each of the observers made every measurement three times with a 10-s interval. Women recruited after February 2014 were examined by one observer.

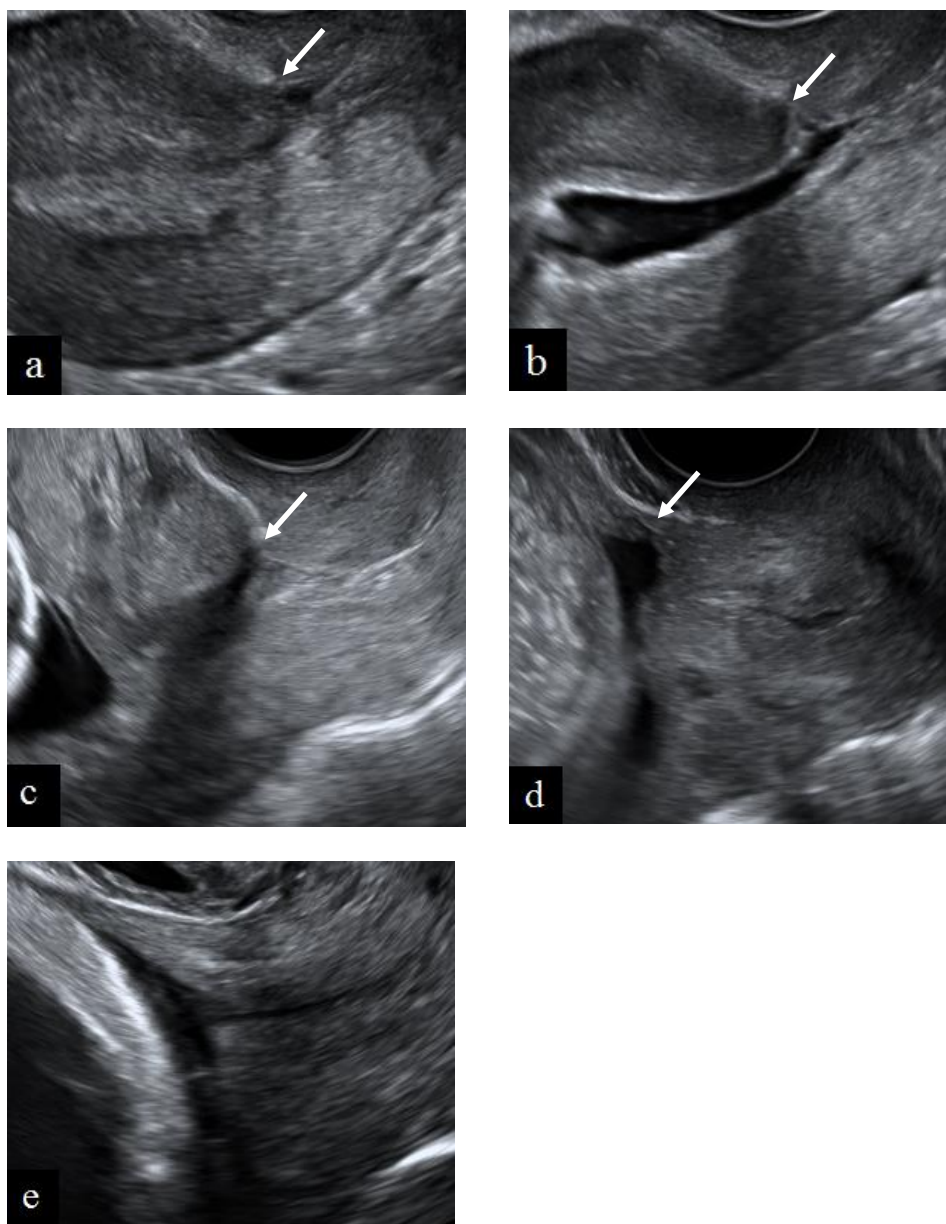Examples of prospective scans of the same woman are shown in Figure 2.

Figure 2. Transvaginal ultrasound images of the same woman obtained in: (a) the non-pregnant state using conventional ultrasound; (b) non-pregnant state using SCSH; (c) 13+0 gestational weeks; (d) 20+0 gestational weeks; (e) 37+1 gestational weeks. The arrow indicate Caesarean hysterotomy scar.

Ultrasound examinations in both the non-pregnant state and during subsequent pregnancy were performed with GE Voluson 730 or GE Voluson E8 expert ultrasound systems (General Electric, Zipf, Austria) equipped with a transvaginal probe RIC 5-9H or RIC 5-9-D, and with an abdominal probe, RAB 4-8L or RAB 4-8-D, respectively.

Follow-up

At the examination in the non-pregnant state the women were asked to contact personnel responsible for the study in the case of a new pregnancy, and to come for additional ultrasound examinations during the pregnancy. To minimize the dropout rate from the study, the maternity records of the recruited women were manually checked by personnel responsible for the study; every month in Obstetrix, and every 2-3 months in Melior (Siemens Healthcare, Upplands Väsby, Sweden). Women who became pregnant were contacted by telephone, and invited for prospective examinations during their pregnancy.

Scan at 11+0 – 13+6 weeks

Women were examined with transvaginal ultrasound with an empty urinary bladder. The uterine scar was identified in the sagittal plane with the same standardized approach as that used for the examination of non-pregnant women (51). The same ultrasound features as in the non-pregnant scan were noted. The scars were also subjectively classified as a scar with a large defect or a scar without a large defect. Subjective evaluation and sonographic scar measurements were used to establish an objective cut-off value for the definition of scars with large defects at this scan. MTS and RMT were measured, and a new parameter, the thickness of the myometrium in the scar area, called the scar thickness (ST) was introduced. This parameter combined both RMT and MTS; representing RMT when a scar defect was observed, and MTS when the scar was intact. We find it logical to believe that this parameter may play an important role in reflecting scar integrity during labour; a small ST, possibly, may indicate that the woman is more prone to uterine rupture. This is supported by findings reported by Naji et al. (50).

Scan at 19+0 – 21+6 weeks

Women were examined with both abdominal and transvaginal ultrasound, with a full and an empty urinary bladder. Only data from transvaginal ultrasound with an

empty urinary bladder are considered in this thesis. The uterus was scrutinized in the sagittal plane, and the ST was measured.

Scan at 35+0 – 38+6 weeks

Similarly to the scan at 19+0 – 21+6 weeks, women were examined with both abdominal and transvaginal ultrasound, with a full and an empty urinary bladder. The data obtained from this examination are not considered in this thesis.

Scrutiny of delivery reports

Management of pregnancy and delivery was carried out according to the hospital's policy and the discretion of the attending obstetricians, who were blinded to the results of the ultrasound examinations of the Caesarean hysterotomy scar.

After delivery, information about the pregnancy and delivery was retrieved from the EPRS, Obstetrix, for each woman participating in the study. The probability of successful VBAC was calculated for each woman according to the formula proposed by Naji et al. (50):

predicted individual probability of successful VBAC (%) = 1 / (1 + exp (−z))

where z=−0.77 − 0.29 (maternal age) / 5 + 1.44 (ST at second trimester scan) − 1.22 (change in ST between the first and second trimester) + 1.09 (prior VBAC). Successful VBAC was defined as a vaginal birth of the foetus (spontaneous or instrumental vaginal delivery).

Paper V

This study was carried out under the mobility period of the Erasmus Mundus Joint Doctorate in Fetal and Perinatal Medicine (FetalMed PhD), which is a mandatory part of the Joint Doctoral Degree Programme.

According to local regulations, no ethical approval was necessary for this study.

Women who had delivery at the University Hospital in Barcelona, Spain, during the period from 1st January 2011 to 31st December 2015 were retrospectively identified in the EPRS, SAP solution R/3 (SAP SE, Walldorf, Germany), using the online interface to access medical records to identify eligible women.

Inclusion criteria:

- undergone TOLAC,
- only ONE previous CD,
- delivery at ≥37 gestational weeks,
- singleton pregnancy, and
- cephalic presentation.

Exclusion criteria

- antenatal foetal demise,
- stillbirth,
- elective CD or emergency CD before TOLAC, or
- multiple pregnancy.

Among the eligible women, information concerning parity, number of previous CDs, gestational age at delivery, TOLAC in the current pregnancy and labour induction in the current pregnancy were double-checked by reviewing delivery summary reports, which were attached as an electronic document to all medical records for each woman.

To calculate the individual probability of successful VBAC, the following information was retrieved from the EPRS: parity, maternal age at delivery, maternal height and weight, prior vaginal deliveries, recurrent indication for prior CD (defined as arrest of dilatation or descent), mode of delivery in the current pregnancy (instrumental vaginal birth, non-instrumental vaginal birth, CD), indication for CD in the current pregnancy, and whether labour was inducted in the current pregnancy.

The probability of successful VBAC was calculated for each woman according to the formula proposed by Grobman et al. (46):

predicted individual probability of successful VBAC (%) = exp (w) / [1 + exp (w)]

where w = 3.766 – 0.039 (maternal age) – 0.060 (maternal body mass index (BMI)) – 0.671 (African American race) – 0.680 (Hispanic race) + 0.888 (any prior vaginal delivery) + 1.003 (prior VBAC) – 0.632 (recurring indication for prior CD). The variable "African American race" corresponds to sub-Saharan African ethnicity, and the variable "Hispanic race" to Latin America ethnicity.

Observed rates of successful VBAC were compared in each decile between groups of women in which labour had been induced and those with spontaneous labour.

Correlations between deciles and instrumental labour rate (forceps or vacuum) among women with VBAC, and the proportion of women with recurring indication for CD for arrested dilatation or descent were studied.

Statistical analyses

Continuous variables were compared between independent groups using the nonparametric Mann–Whitney U test. The chi-square test or Fisher's exact test were used for categorical data. Nonparametric tests were used to test statistical hypotheses for paired data: the Wilcoxon signed-rank test for continuous sonographic measurements, and McNemar's test for dichotomous categorical variables. Associations between variables were investigated with Spearman's rank correlation coefficient.

In the first study (*Paper I*), the sensitivity and specificity of the reported diagnosis of complete uterine rupture in the EPRS were calculated. Sensitivity refers to the ability of the information contained in the register to correctly detect women who had uterine rupture. Mathematically, this can be expressed as: sensitivity = number of true positives / (number of true positives + number of false negatives). Specificity relates to the ability of the register to correctly detect women who had no uterine rupture. Mathematically, this can be written as: specificity = number of true negatives / (number of true negatives + number of false positives). The accuracy of the data in an EPRS depends on the diagnostic codes available and the care with which the medical staff enter the data.

In the second study (*Paper II*), the reliability of sonographic scar measurements in non-pregnant women was assessed. Reliability refers to the consistency between measurements made at different times or by different observers. This should be distinguished from the validity, which describes how close the values are to the true state of the attribute. Intraclass correlation coefficients (ICCs) were used to assess intraobserver, interobserver and intermethod reliability (54). Mathematically, the ICC is the proportion of the total variance that is due to the variation between subjects. Calculations of the ICC were performed using two-way mixed single measures intraclass correlation coefficient (ANOVA) analysis. The following cut-off values were used for the interpretation of ICCs (55): <0.70 reflects very poor reliability; 0.70-0.90 poor; 0.90-0.95 moderate; 0.95-0.99 good, and >0.99 very good reliability. To assess interobserver variability, the smallest values of the three measurements made by each observer were compared. Intermethod reproducibility was assessed using the smallest values of the three measurements made by Observer 2. Bland–Altman plots were constructed to assess the limits of agreement of relative differences between measurements (56).

For categorical data the agreement was expressed as the percentage agreement, and Cohen's kappa was used to estimate the extent to which the percentage agreement exceeded that expected by random chance alone (57). Mathematically, this can be expressed as: kappa = (observed agreement – agreement expected by chance) / (1 – agreement expected by chance). The following values of Cohen's kappa were used (58): kappa <0.41 reflects poor strength of agreement between the observers, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.0 excellent agreement.

ROC curves were used in the third study (*Paper III*) to establish cut-off values for scar measurements for the classification of scars with large defects at the 11-14 weeks scan. ROC curves are commonly used in modern medical science to assess the limits of a test's ability to discriminate between alternative states of health over the complete spectrum of operating conditions (59). This statistical tool helps to choose a decision threshold by selecting the best cut-off value, i.e., an appropriate sensitivity/specificity pair with an optimal proportion of false negative and false positive results. The point located farthest from the reference line was selected as the best cut-off value.

The performance of two prediction models was assessed in the final two studies (*Papers IV* and *V*) using two traditional aspects: calibration and discrimination (60). Calibration is the assessment of agreement between predicted probabilities and observed outcome frequencies. In order to perform calibration analysis, the predicted probabilities of successful VBAC were categorized into ten deciles. Observed rates of successful VBAC were calculated for each decile, and compared with the corresponding decile. Discrimination is the ability of the model to distinguish between patients with different outcomes. This aspect is probably more important than calibration for the validation of a clinical prognostic model. It can be assessed quantitatively by calculating the area under the ROC curve (AUC) with its 95% confidence interval (CI). The closer the AUC is to '1', the higher the accuracy of the prediction model. An AUC of 0.8, for example, means that a randomly selected individual from the diseased group has a test value higher than that for a randomly chosen individual from the non-diseased group 80% of the time (59). It does not mean that a predicted result occurs with a probability of 0.80, nor that a positive result is associated with a disease 80% of the time.

The statistical calculations reported in *Paper I* were performed with the software package EpiInfo, version 7.1.5 (Centers for Disease Control and Prevention, Atlanta, GA, USA, www.cdc.gov/epiinfo). In *Papers II-V*, statistical analyses were performed using IBM SPSS Statistics, version 22 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

Results and Discussion

The true rate of uterine rupture and uterine dehiscence at repeat CD

The diagnoses of uterine rupture and uterine dehiscence are usually established at CD, when the integrity of the uterine wall can be examined directly. However, it cannot be excluded that there may be some cases of uterine rupture and uterine dehiscence after vaginal birth in asymptomatic women. The only way to verify the integrity of the uterine scar in this group of women is to perform manual exploration of the uterus. Since a risk of infection is associated with this procedure, such indication for manual exploration is currently considered unethical in many settings. Therefore, in practice, uterine rupture or uterine dehiscence in women with previous CD can only be verified at repeat CD.

In order to determine the true incidence of uterine rupture and uterine dehiscence, a study group of multiparous women delivered by repeat CD was identified in KIKA (*Paper I*). In total, 1296 multiparous women delivered by CD (out of 21420 women who delivered at the University Hospital in Malmö) were identified during the study period. Among them, 716 women underwent repeat CD. Their operation reports were reviewed by experienced obstetricians and compared with registered ICD-10 diagnoses in an EPRS.

All 13 women with a registered diagnosis of uterine rupture had their diagnosis confirmed by the reviewers. Seven additional women were identified by the reviewers as having uterine rupture whose diagnosis had not been registered. Unadjusted uterine rupture rate was 1.8%, which is in agreement with the results of a large Swedish register-based study by Hesselman et al., who reported the uterine rupture rate among women who had TOLAC in a subsequent pregnancy after CD to be 1.3% (61). The diagnosis of uterine dehiscence was not registered in KIKA as there is no relevant diagnosis code in ICD-10. While reviewing the women's medical records, the obstetricians identified 33 cases of evident uterine dehiscence and 39 cases of extremely thin myometrium. Thus, the true incidence of complete uterine rupture and uterine dehiscence in women delivered by repeat CD was 2.8% and 10.1%, respectively. The sensitivity of EPRS with regard to the detection of complete uterine rupture was 65%, and the specificity 100%.

These results are in agreement with the findings of Al-Zirqi et al., who found that the diagnosis of uterine rupture was underreported in the Norwegian Medical Birth Registry by about 37% (29). However, the real uterine rupture rate in the Norwegian population was found to be lower than in our study population: 0.6% among all women with a scared uterus (29). In a Danish study, Thisted et al. found that at least 16.2% of complete uterine ruptures had not been reported to the Danish Medical Birth Registry; and only 60.4% of women who were registered as having previous CD and uterine rupture, had uterine rupture (partial or complete) (30). The overall uterine rupture rate among women with previous CD in the Danish population was 0.8% (440/56332). However, caution should be exercised when comparing the uterine rupture rates from these two studies with the present findings, as different approaches were used for data collection and analysis in the Norwegian and Danish studies from those used in the present study.

The results of the present study provided additional scientific evidence that the incidence of uterine rupture is higher than previously described on the basis of population-based data (28). Thus, more women are affected by this complication, than previously thought. This emphasizes the importance of studies on the management of pregnancy after CD. There is also a need to improve diagnosis registration. A lack of information on previous uterine rupture may lead to suboptimal patient management during subsequent pregnancy and delivery. Fox et al. showed that patients with prior uterine rupture or prior uterine dehiscence can have excellent outcomes in a subsequent pregnancy if they are adequately managed, including CD before the onset of labour or immediately at the onset of spontaneous preterm labour (62). Similar results were reported by Lim et al. (63).

Several measures can be taken to decrease the number of mistakes in reporting diagnoses in EPRSs. Among them are the introduction of structured templates for operation reports with mandatory questions concerning uterine rupture or uterine dehiscence, and the introduction of an appropriate ICD diagnosis code for uterine dehiscence into new revision of ICD.

Intra- and interobserver reliability of ultrasound examinations of Caesarean hysterotomy scars in non-pregnant women

The ideal diagnostic method should be clinically useful, in the sense that it provides information that is important for patient management; and valid, in the sense that the measurements closely reflect the real state of the attribute. In

addition, the method should be reliable, which means that measurements made with the method are consistent.

In a previous study, Vikhareva et al. found that large defects of the Caesarean hysterotomy scar, detected by transvaginal ultrasound in non-pregnant women, are likely to be associated with the risk of dehiscence/uterine rupture in subsequent pregnancies (37). One of the further steps is assessment of intra- and interobserver reliability of these measurements. The aim of this study was thus to assess the intra- and interobserver reliability of sonographic measurements of Caesarean hysterotomy scars in non-pregnant women. The study was reported according to the Guidelines for reporting reliability and agreement studies (64). In total, 56 non-pregnant women were examined with transvaginal sonography, with and without saline contrast enhancement, 6 to 9 months after their CD (*Paper II*). During a single visit, two observers independently evaluated Caesarean hysterotomy scar appearance, and if a scar defect was observed, scar measurements (MTS and RMT) were made. SCSH was not possible in one woman due to a stenotic cervix. The results are presented in Table 1.

Analysis of the Bland–Altman plots showed that the 5th and 95th percentile limits of measurement differences for MTS ranged from -31.5 to +22.1% (median -2.7%) using conventional sonography, and from -23.6 to +33.5% (median 1.4%) using SCSH. Limits of measurement differences for RMT ranged from -56.9 to +45.6% (median -16.7%) with conventional sonography, and from -24.1 to +29.1% (median 0%) with SCSH. Intermethod estimated limits of agreement (5th and 95th percentiles) for MTS ranged from -23.3 to +34.4% (median 1.1%) and for RMT from -35.8 to +95.7% (median 14.4%).

Our results demonstrated that intraobserver reliability was good. The interobserver agreement regarding the appearance of the Caesarean hysterotomy scar (presence of a hysterotomy scar, presence of a scar defect and the shape of the defect) was excellent. The interobserver ICC for MTS and RMT with conventional sonography was poor. However, the 95% confidence interval (CI) varied from very poor to moderate. When using SCSH, the ICC was poor for MTS, with the upper limit of the 95% CI interpreted as moderate. The ICC for RMT was good, but the lower limit of the 95% CI was only moderate. With regard to the detection of large scar defects the kappa coefficient was excellent with both SCSH and conventional sonography. Thus, according to the formal criteria presented in the Methods section, the interobserver reliability varied for different measurements, and only the measurement of RMT using SCSH can be considered to have high interobserver reliability.

Table 1. Intraobserver, interobserver and intermethod reliability of transvaginal sonography with and without saline contrast enhancement

	Conventional sonography	SCSH
Intraobserver reliability		
ICC (95% CI) for Observer 1		
MTS	0.97 (0.95-0.98)	0.98 (0.98-0.99)
RMT	0.99 (0.98-1.0)	0.99 (0.98-1.0)
ICC (95% CI) for Observer 2		
MTS	0.98 (0.97-0.99)	0.98 (0.97-0.99)
RMT	0.99 (0.98-0.99)	0.99 (0.98-0.99)
Interobserver reliability		
ICC (95% CI)		
MTS	0.82 (0.72-0.89)	0.85 (0.76-0.91)
RMT	0.87 (0.68-0.95)	0.96 (0.93-0.98)
Agreement with regard to presence of large scar defect, % (n agreement/n total)	98.2 (55/56)[1]	98.2 (54/55)[2]
Kappa coefficient	0.85	0.92
Intermethod reliability		
ICC (95% CI)		
MTS	0.86 (0.78-0.92)	
RMT	0.89 (0.78-0.95)	
Agreement with regard to presence of large scar defect, % (n agreement/n total)	92.7 (51/55)[3]	
Kappa coefficient	0.57	

[1] Observer 2 classified the scar in one woman as intact or a small defect, whereas Observer 1 classified it as a large defect.
[2] Observer 2 classified the scar in one woman as intact or a small defect, whereas Observer 1 classified it as a large defect.
[3] Scars in four women were classified as intact, or small defects at conventional sonography, whereas at SCSH they were classified as large defects.

Several authors have studied the reliability of sonographic measurements of Caesarean hysterotomy scars in the late third trimester. Jastrow et al. found interobserver agreement in sonographic transvaginal measurements of the lower uterine segment in the late third trimester with 2D ultrasound to be good (65). However, the transabdominal approach demonstrated poor to moderate agreement. Martins et al. evaluated the reliability of both 2D and 3D ultrasound between 36 and 39 weeks of gestation, and also confirmed that the transvaginal approach had a greater reliability than the abdominal approach (66). They also found that 3D ultrasound was more reliable than 2D ultrasound. In contrast to the study by Martins et al., Cheung et al. considered that abdominal 3D sonography measurements of the lower uterine segment were not more reliable than transvaginal 2D measurements (67). In two studies, involving independent delayed evaluation of images and video clips by a second observer, Boutin et al. demonstrated that both 2D and 3D ultrasound had excellent intra- and interobserver reliability in the late third trimester (68, 69).

Naji et al. evaluated the reproducibility of measurements of Caesarean hysterotomy scars with transvaginal ultrasound in a prospective cohort study of 320 consecutive pregnant women at 11-13, 19-21 and 34-36 gestational weeks (70). They concluded that agreement between observers was good in the first trimester, but only moderate in the second and third trimesters.

In a recent study, Glavind et al. investigated the reliability of 3D transvaginal ultrasound of Caesarean hysterotomy scars in non-pregnant women (71). They found that it was unclear whether 3D ultrasound had a clinical advantage over 2D ultrasound due to wide limits of agreement.

To the best of our knowledge, the present study was the first to describe the intra- and interobserver reliability of transvaginal 2D examination of Caesarean hysterotomy scars in non-pregnant women. The findings of this study provide a scientific basis for the management of pregnancy and delivery after CD, and justify further studies concerning the clinical significance of large defects in the Caesarean hysterotomy scar. If further studies confirm an association between large defects of the Caesarean hysterotomy scar in the non-pregnant state and scar integrity during subsequent labour, it may be possible to use the results of transvaginal ultrasound examination together with clinical factors to identify women with previous CD who are at higher risk of severe complications. Appropriate training of ultrasound examiners to perform examinations of Caesarean hysterotomy scars correctly is an important component of reliable risk estimation.

Sonographic appearance of Caesarean hysterotomy scars in non-pregnant women and in a subsequent pregnancy

Prospective serial ultrasound examinations of women after CD led to the subjective impression that the appearance of Caesarean hysterotomy scars in the first trimester was not significantly different from that in the non-pregnant state. A search was carried out in PubMed with the keywords "Cesarean", "uterine scar" and "ultrasonography", and no studies were found in which scar appearance in the non-pregnant state had been compared with that during subsequent pregnancy. Moreover, no studies were found among the published articles that suggested a cut-off value for the classification of large defects of the Caesarean hysterotomy scar using transvaginal ultrasound in the late first trimester. Therefore, the sonographic data collected in the prospective study were used to elucidate these research questions.

By February 2016, 159 pregnancies had occurred in the cohort of women followed up over a period of 1 to 25 months after examination in the non-pregnant state (541 participants, with successful SCSH in 535 women). Ultrasound examination was not possible in some of these pregnancies due to pregnancy termination, withdrawal from the study or unavailability of the patient for scan booking.

The study sample included 111 women who had undergone two scans: a non-pregnant scan with SCSH and a conventional scan at 11-14 gestational weeks (*Paper III*). Caesarean hysterotomy scars were visualized in all women at all examinations. The median ST measurement at the non-pregnant scan was 6.1 mm (interquartile range (IR) 3.7-8.0). The median ST measurement at the 11-14-week scan was also 6.1 mm (IR 3.8-8.6). The median difference in paired ST measurements between scans at 11-14 weeks and the non-pregnant state was 0.1 mm (IR -0.7-1.6) (p = 0.09).

An ROC curve was constructed for ST measurements at 11-14 weeks to determine the cut-off for large scar defects. The AUC was 0.98 (95% CI, 0.95-1.0). The best cut-off value for ST to predict a scar with a large defect was 2.85 mm. This cut-off had 90% sensitivity (18/20), 97% specificity (88/91) and 95% accuracy (106/111).

The agreement between SCSH in the non-pregnant state, and scan at 11-14 weeks in detecting scars with a large defect was high (108 of 111 women) (Table 2). In the non-pregnant state large scar defects were found in 18 (16%) women, and all of them were confirmed at the 11-14-week scan. In addition, large defects were found in 3 women, who did not have large defects in the non-pregnant state.

Table 2. Agreement between SCSH in the non-pregnant state and transvaginal scan at 11-14 weeks with regard to the detection of a scar with a large defect

	Large defect at 11-14-week scan[1]		Agreement (% (n))	p-value
	No	*Yes*		
Large defect at SCSH[1]				
No	90	3	97 (108/111)	0.250
Yes	0	18		

[1] According to objective classification, using ST cut-off values of 2.5 and 2.85 mm for SCSH and the 11-14-week scan, respectively.

The main findings of the present study were that the appearance of the Caesarean hysterotomy scar was similar in the non-pregnant state and in a subsequent pregnancy at 11-14 weeks. This study provided new scientific evidence concerning natural changes in the appearance and dimensions of Caesarean hysterotomy scars between the non-pregnant state and subsequent pregnancy. This study complements data recently published by Naji et al., in which changes in the Caesarean hysterotomy scar dimensions during pregnancy were described (72).

Two points should be considered regarding the practical value of these new findings. The first is that in a previous study by Vikhareva et al. it was found that large defects in the Caesarean hysterotomy scar detected at transvaginal sonography 6-9 months after CD may have clinical significance with regard to the prediction of uterine rupture/dehiscence in a subsequent pregnancy (37). However, women are usually not planning their next pregnancy and delivery 6-9 months postpartum. Despite our subjective feeling that scanning non-pregnant women provided some reassurance at an early stage to those women considering vaginal birth in a subsequent pregnancy, counselling on mode of delivery is important early in a subsequent pregnancy. The findings of the present study suggest that a scan in the late first trimester might have similar prognostic value to the non-pregnant scan. However, larger studies involving pregnancy outcomes are needed to confirm this hypothesis.

The second point is that a scan at 11-14 weeks already provides information that is important for pregnancy management. Such a scan is widely used, especially in high-resource settings, to confirm the viability of the foetus, to establish the gestational age, determine the number of foetuses, assess chorionicity and amnionicity in multiple pregnancies, to detect gross foetal anomalies, and to assess

the risk of aneuploidy (73). Stirnemann et al. suggested that a scan at 11-14 weeks can help to stratify the risk of placenta accreta in women with previous CD, and in drawing up a follow-up plan for high-risk patients (26). It therefore appears that a late first trimester scan may have even broader clinical utility than presently believed, and may also include Caesarean hysterotomy scar assessment as part of the complex evaluation of risks in pregnancy.

Validation of the model for the prediction of successful VBAC, based on sonographic measurements of the Caesarean hysterotomy scar

In this study, some practical aspects of serial prospective ultrasound examinations of women with a scarred uterus were evaluated. In the available literature only one study, by Naji et al., was found that described a model for the prediction of successful VBAC, based on sonographic assessment of Caesarean hysterotomy scars at 11-14 and 19-21 gestational weeks (50). Such a model may have clinical value for refining the antenatal care of women with previous CD, provided it has a high predictive accuracy. Although the model demonstrated very high predictive accuracy, no external validation was performed. Therefore, the validity of the model was investigated in an external population, as described in *Paper IV*.

By November 2016, 120 women in the recruited cohort of 541 women had complete sonographic data from the first and second trimester scans, and had subsequently given birth to a child. Among these, 80 (67%) underwent TOLAC, with VBAC in 70 (88%) cases. All women who underwent TOLAC had a singleton pregnancy in cephalic presentation.

To ensure a blind study design, the attending obstetricians were not informed about the results of the ultrasound examinations of the Caesarean hysterotomy scar. The management of pregnancies and deliveries in this study cohort seem to be representative of management in the general population of women delivered at the Skåne University Hospital in 2014; the vaginal delivery rate in women with one previous CD at the Skåne University Hospital was 63% (209/332), versus 58% (70/120) in the study cohort.

Vacuum extraction was performed in eight women (11%), and manual exploration of the uterus was performed in two women (3%), due to postpartum bleeding. Emergency CD after attempted TOLAC was performed in ten women: five (50%) due to non-reassuring foetal status, and five (50%) due to arrest of labour. One woman had uterine rupture, and two women were diagnosed with uterine dehiscence (one had evident uterine dehiscence and one had an extremely thin

myometrium). All three had visible scars on ultrasound. In the woman with evident uterine dehiscence, the ST decreased from 7.2 mm at the first trimester scan to 2.8 mm at the second trimester scan. This woman had a predicted probability of successful VBAC of 2%. In the two women with uterine rupture and extremely thin myometrium, ST was thin at the first trimester scan and was unchanged at the second trimester scan (2.2 and 1.0 mm vs 2.0 and 1.0 mm, respectively). These women had predicted probabilities of successful VBAC of 50% and 22%, respectively.

The calculated individual probabilities of successful VBAC were divided into deciles, and compared with the observed VBAC rates (Table 3). Most of the observed VBAC rates did not correspond to the predicted deciles. Moreover, calculated individual probabilities had an uneven distribution over the range of probabilities. Most women had either a very low probability (0-9.9 decile) or a very high probability (90.0-100 decile) of successful VBAC. This was unexpected, as it could be anticipated that most of these women would have an intermediate probability of successful VBAC, since they were counselled by attending obstetricians before the decision concerning TOLAC was made.

Table 3. Predicted and observed VBAC rates in women with one previous CD who had TOLAC at the Skåne University Hospital

Predicted probability of VBAC deciles, %	All women who underwent TOLAC (n=80)		Women with sonographically visible scar (n=54)	
	N	*Observed VBAC rate, % (n)*	*N*	*Observed VBAC rate, % (n)*
0-9.9	22	95 (21)	14	93 (13)
10.0-19.9	5	80 (4)	2	100 (2)
20.0-29.9	5	80 (4)	2	50 (1)
30.0-39.9	6	83 (5)	5	80 (4)
40.0-49.9	3	100 (3)	2	100 (2)
50.0-59.9	2	50 (1)	2	50 (1)
60.0-69.9	7	86 (6)	5	80 (4)
70.0-79.9	1	100 (1)	0	-
80.0-89.9	6	100 (6)	2	100 (2)
90.0-100	23	83 (19)	20	90 (18)

The AUC was 0.44 (95% CI, 0.28-0.60) among all the women who underwent TOLAC, and 0.51 (95% CI, 0.32-0.71) among those with a sonographically visible scar at both scans. It was therefore concluded that the model presented by Naji et al. had poor accuracy in the prediction of successful VBAC in the Swedish population. This may have been because the regression coefficients in the prediction model were too large, or some important predictor variables were missing in the original model. The discrepancy between the model and the findings of the present study may be due to differences in obstetrical practice between hospitals. For example, there may be differences in hospital's policies regarding the selection of women suitable for TOLAC, differences in pregnancy and labour management, and differences in indications for emergency CD during TOLAC.

Although, the model presented by Naji et al. was not able to predict successful VBAC in the clinical setting in our study population, in the sense that it provided no useful additional information, we still believe that information obtained on Caesarean hysterotomy scars through sonographic investigation may play an important role in the prediction of successful VBAC. It can be expected that better healing of the Caesarean hysterotomy scar, as determined by ultrasound, would be associated with a higher probability of successful vaginal birth in a subsequent pregnancy.

Validation of the model for the prediction of successful VBAC, based on non-sonographic variables

A model proposed by Grobman et al. for the prediction of successful VBAC, based on maternal age, BMI, race and obstetrical history, is one of the models most frequently referred to in recent scientific literature (32, 46). Its popularity may be explained by the easy accessibility of the required variables and its applicability at the early stages of pregnancy. Another strong point of this model is that it was developed based on a large cohort of women from 19 medical centres across the United States. Contemporary regional CD rates across the United States vary from 23% to 40% (8). The multicentre design thus helped to control for confounders arising from differences in obstetrical practices between hospitals. The validity of this model has been studied in several external populations, demonstrating consistent results (44, 45, 74-79). However, no validation of this model was carried out in a Spanish setting. The model proposed by Grobman et al. was therefore validated during the author's mobility period at the University Hospital in Barcelona.

During the period from 1st January 2011 to 31st December 2015, 724 women who fulfilled the inclusion criteria underwent TOLAC at the University Hospital in Barcelona. During the same period, 420 women with similar characteristics underwent ERCD. Thus, the TOLAC rate was 63.3% (724/1144).

In total, 630 women who underwent TOLAC had all the information required for analysis, and were included in the study (*Paper V*). Among them, 450 (71.4%) women had successful VBAC. The observed successful VBAC rates were within the ranges predicted for the corresponding deciles, except in the decile 20.0-29.9, in which there were only two cases, and the calculations for this decile therefore had a high degree of uncertainty. A comparison of the results is presented in Table 4.

In the predicted successful VBAC rate range from 50 to 80%, women in whom labour was induced had successful VBAC significantly less often than women with spontaneous labour onset, and their observed rate of successful VBAC was lower for more than 10% for every corresponding decile. The instrumental VBAC rate was poorly correlated with the predicted probability of successful VBAC (correlation coefficient 0.41, p=0.320). The rate of emergency CD due to arrested dilatation or descent, the most common indication in the current study, decreased with increasing probability of successful VBAC (correlation coefficient -0.98, p<0.001).

The AUC was 0.70 (95% CI, 0.66-0.74). It was therefore concluded that this model can provide insight into the probability of successful VBAC at an early stage of pregnancy, and has a reasonable predictive accuracy in a Spanish population.

According to the findings of the present study, the predictive ability of the model developed by Grobman et al. was similar to that in their original study, and was in agreement with other external validation studies performed in the US, Canada, Sweden, the UK, Italy, the Netherlands and Japan (44, 45, 75-79).

Since studies in different settings have shown similar and consistent results, it appears that the variables in the model developed by Grobman et al. are well-balanced. However, possibly, prediction models including sonographic parameters of the hysterotomy scar together with these variables may be able to provide more accurate estimates of the individual probability of VBAC. This might further facilitate the decision-making process, and help to reach a more informed decision about the mode of delivery.

Table 4. Predicted and observed VBAC rates in women with one previous CD who had TOLAC at the University Hospital in Barcelona

Predicted probability of VBAC deciles, %	Women undergoing TOLAC, n	Observed VBAC rate, % (n)	Women with labour induction, % (n)	VBAC after labour induction, % (n)	VBAC after spontaneous labour, % (n)	p-value	Instrumental VBAC rate, % (n)	CD for arrested labour, % (n)
0-9.9	0	-	-	-	-	-	-	-
10.0-19.9	0	-	-	-	-	-	-	-
20.0-29.9	2	50.0 (1)	50.0 (1)	0 (0)	100.0 (1)	1.0	0 (0)	50.0 (1)
30.0-39.9	17	35.3 (6)	41.2 (7)	28.6 (2)	40.0 (4)	1.0	11.8 (2)	41.2 (7)
40.0-49.9	29	48.3 (14)	55.2 (16)	37.5 (6)	61.5 (8)	0.198	17.2 (5)	31.0 (9)
50.0-59.9	96	52.1 (50)	25.0 (24)	29.2 (7)	59.7 (43)	0.009	16.7 (16)	22.9 (22)
60.0-69.9	135	69.6 (94)	25.9 (35)	45.7 (16)	78.0 (78)	<0.001	20.0 (27)	16.3 (22)
70.0-79.9	217	76.0 (165)	33.6 (73)	58.9 (43)	84.7 (122)	<0.001	21.2 (46)	9.2 (20)
80.0-89.9	62	85.5 (53)	29.0 (18)	77.8 (14)	88.6 (39)	0.427	17.7 (11)	12.9 (8)
90.0-100	72	93.1 (67)	16.7 (12)	91.7 (11)	93.3 (56)	1.0	2.8 (2)	0 (0)

Concluding remarks

The findings of the research presented in this thesis have provided new scientific evidence concerning some aspects of the management of pregnancy after CD, and have identified directions for further research in this area. This project was carried out within the framework of the Erasmus Mundus Joint Doctorate Programme, and was based on study populations in Sweden and Spain.

Bearing in mind the low incidence of complications and adverse outcomes in women with a scarred uterus related to previous CD, it is suggested that the recruitment and follow-up of women in a Swedish prospective study be continued to obtain a sufficient number of women for further analysis based on this cohort.

Conclusions

The reliability of data concerning uterine rupture and uterine dehiscence registered in an EPRS was checked. The main finding was that:

- the incidence of uterine rupture and uterine dehiscence in women with previous CD was higher than described previously.

The diagnostic utility of serial ultrasound examinations of Caesarean hysterotomy scars was studied, and it was concluded that:

- transvaginal ultrasound examination of the Caesarean hysterotomy scar in non-pregnant women was a reliable method that can be used in clinical practice,

- Caesarean hysterotomy scar appearance was similar in the non-pregnant state and in a subsequent pregnancy at 11-14 weeks, providing knowledge on the natural course of the sonographic appearance of the hysterotomy scar,

- an objective cut-off value for ST for the classification of large Caesarean hysterotomy scar defects at an 11-14-week scan was found to be 2.85 mm; this cut-off can be used in further studies to investigate the role of ultrasound in the prediction of uterine rupture and uterine dehiscence during labour, and

- the only available prediction model based on sonographic parameters of a hysterotomy scar had limited utility in the Swedish population for the prediction of successful vaginal birth after CD.

A previously published model predicting the success of vaginal birth after CD, based on non-sonographic variables easily obtainable at the first antenatal visit for most women, was validated in a Spanish population, and it was concluded that:

- the model had reasonably good accuracy in the prediction of successful vaginal birth after CD.

Future perspectives

Two main directions are suggested for further research: the assessment of the risk of possible complications, and the prediction of successful VBAC. These are highly related, as the probability of successful VBAC is dependent on the risk profile of each individual woman.

The relation between the sonographic characteristics of Caesarean hysterotomy scars and the success of labour should be further investigated to develop a universal prediction model for successful VBAC. Ideally, such a model should not only predict the probability of successful VBAC, but also accurately identify women at increased risk of failed TOLAC. Findings in the present thesis indicated that obstetrical practice may have significant influence on the performance of a prediction model. Therefore, future studies should preferably include several centres to develop a "one size fits all" prediction model, applicable to various populations. Such studies should be large enough to have sufficient statistical power to address relevant scientific questions.

Studies should also be carried out on the assessment of the risk of complications in women with previous CD. The role of large defects of the Caesarean hysterotomy scar, detected using ultrasound in the non-pregnant state and at early stages of pregnancy, in the prediction of uterine rupture/uterine dehiscence during TOLAC should be further investigated. Bearing in mind the relatively low incidence of these complications, such studies should include large numbers of participants to allow sound scientific conclusions to be drawn concerning the clinical significance of large defects of the Caesarean hysterotomy scar.

Further studies concerning the role of ultrasound in the prediction of placental complications (placenta previa and placenta accreta) in women with previous CD are also justified.

Populärvetenskaplig sammanfattning på svenska

Kejsarsnitt är en förlossningsmetod som används då vanlig förlossning av någon anledning inte är möjlig eller önskvärd. Det är ett bukkirurgiskt ingrepp som leder till ärr i livmoderväggen som kan orsaka allvarliga komplikationer vid påföljande graviditet och förlossning, t.ex. uterusruptur, placentakomplikationer och graviditet i kejsarsnittsärr. Dessa tillstånd är fortfarande ovanliga, men eftersom kejsarsnittfrekvensen ökar i många länder kan det medföra en ökning av dessa komplikationer.

Några studier har visat att ultraljud har klinisk nytta för bedömning av risken för komplikationer i graviditet efter kejsarsnitt och för att förutse möjlighet till lyckad vanlig förlossning. Det behövs dock fler studier för att studera sonografiska aspekter ytterligare när det gäller eventuella komplikationer och resultatet av graviditet efter tidigare kejsarsnitt.

Denna avhandling innehåller fem publikationer som är baserade på tre studiepopulationer. En stor del av denna avhandling bygger på en kohort av kvinnor som rekryterades efter sina första kejsarsnitt. Kvinnorna följdes upp prospektivt med ultraljudsundersökningar fram till sina nästa graviditeter och förlossningar (*studierna II-IV*). En sådan observationsstudiedesign tillät det naturliga förloppet av graviditeten att följas och samtidigt erhålla sonografiska data. Dessutom har två forskningsfrågeställningar studerats på två separata populationer av kvinnor: den sanna frekvensen av uterusruptur (*studie I*), och noggrannheten av en modell som bygger på icke-sonografisk maternella karakteristika, för att förutse lyckad vanlig förlossning (*studie V*).

Efter genomgång av patienternas journaler är slutsatsen att:

- incidensen av uterusruptur och fenestrering hos kvinnor med tidigare kejsarsnitt är högre än tidigare beskrivet i registerdata.

Det prognostiska värdet och nyttan av ultraljudsundersökningar av kejsarsnittsärr vid icke-gravida tillstånd och under graviditeten efter kejsarsnitt studerades och det visades att:

- transvaginal ultraljudsundersökning av kejsarsnittsärr hos icke-gravida kvinnor är en tillförlitlig metod som kan användas i klinisk praxis,

- kejsarsnittsärr befanns vara likartade vid undersökning hos icke-gravida och i påföljande graviditet vid 11-14 veckor; detta ger kunskap om det naturliga förloppet av sonografiskt utseende av kejsarsnittsärr,

- preciserad cut-off värde (2,85 mm) för kejsarsnittsärrstjocklek (scar thickness) för klassificering av stora defekter i kejsarsnittsärret fastställdes i graviditetsvecka 11-14; detta cut-off värde kan användas i framtida studier för att undersöka samband mellan stora defekter och risk för uterusruptur eller fenestrering i samband med förlossning,

- den enda publicerade prediktiv modellen baserad på ultraljudsparametrar hos kejsarsnittsärr har begränsad användbarhet i en svensk population för att förutse lyckad vanlig förlossning efter kejsarsnitt.

En publicerade modell baserad på icke-sonografiska variabler för att förutse lyckad vanlig förlossning hos kvinnor med tidigare kejsarsnitt var validerad i en spansk population. Det visades att:

- en modell baserad på maternella karakteristika har en relativt god prediktiv förmåga för att förutse lyckad vanlig förlossning efter kejsarsnitt.

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Thesis at a glance

Paper	Design	Participants	Main finding
I	Population-based study	716 women who underwent repeat CD	Diagnosis of complete uterine rupture is underreported, and diagnosis of uterine dehiscence was missing in an electronic patient record system.
II	Reproducibility study	56 women with one previous CD	Sonographic measurements of Caesarean hysterotomy scars in non-pregnant women are reliable, and can be used in clinical practice.
III	Prospective cohort study	535 women with one previous CD, of which 111 were examined at 11-14 weeks	Caesarean hysterotomy scar appearance is similar in the non-pregnant state and in a subsequent pregnancy at 11-14 weeks.
IV	Prospective cohort validation study	80 pregnant women with one previous CD and complete sonographic data who underwent TOLAC	A model based on sonographic measurements of Caesarean hysterotomy scars has low accuracy in the prediction of successful VBAC in a Swedish population.
V	Retrospective validation study	630 pregnant women with one previous CD who underwent TOLAC	A prediction model based on non-sonographic variables, easily obtainable at the first antenatal visit for most women, can provide insight into the probability of successful VBAC.

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