Cesarean Section. Impact on Postpartum Recovery, Subsequent Pregnancy and Delivery.

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2021

Document Version:
Publisher's PDF, also known as Version of record

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Impact on Postpartum Recovery, Subsequent Pregnancy and Delivery

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Cesarean Section

Impact on Postpartum Recovery, Subsequent Pregnancy and Delivery

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LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Auditorium Dora Jacobsohn Beställ, Faculty of Medicine, Lund University. Date 19 March 2020 at 13:00.

Faculty opponent
Professor Ellika Andolf
Department of Obstetrics and Gynecology,
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Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION
	Date of issue MARCH 19, 2021
Author(s) EKATERINA NEDOPEKINA	Sponsoring organization EUROPEAN COMMISSION

Title and subtitle

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Abstract

Women are at increased risk of complications after Cesarean section (CS) postpartum and in subsequent pregnancy and delivery. The overall aim of the thesis was to evaluate complications after CS, outline options for their management and to assess strategies to increase the rate of vaginal deliveries after CS (VBAC).

Paper I was a prospective study where women were offered to have an additional appointment with an obstetrician supplemented by ultrasound 6-9 months after CS (n=147) to evaluate whether this appointment may reduce the levels of anxiety postpartum. In Paper II a case of a successful expectant management of Cesarean scar heterotopic pregnancy was reported. Paper III was a retrospective study included all cases of Cesarean scar and other non-tubal ectopic pregnancies managed between 2010-2018 (n=39) to evaluate the success rate and complications of different treatment regimens and to determine predictive factors for treatment failure. In Paper IV pregnant women with one previous CS in their first or third trimester participated in the study (n=87) to determine their level of knowledge regarding risks and benefits of CS and VBAC. Paper V included women with one previous CS who delivered during two periods: 2005-2008 (n=792) and 2013-2016 (n=1225), to compare the rate of VBAC, maternal and perinatal outcomes between the two cohorts.

Paper I, the appointment with the obstetrician supplemented by ultrasound significantly reduced the levels of anxiety in women after CS. In Paper II and III, it was shown that conservative treatment may be the first option for consideration in non-tubal ectopic pregnancies and even expectant management is possible in small non-viable Cesarean scar pregnancies. The presence of fetal heartbeat and β-hCG levels at diagnosis may be used for prediction of treatment failure. In Paper IV it was found that the level of knowledge about risks and benefits of VBAC increased in the third trimester of pregnancy compared to the first trimester. Nevertheless, women reported to get insufficient information even at the end of pregnancy. Paper V revealed that an appropriate management of women with one previous CS might increase VBAC rate without negative impact on maternal or perinatal outcomes.

The results of the research might help to develop educational programs for women with previous CS, establish clinical guidelines for management of complications after CS such as postpartum anxiety and Cesarean scar pregnancy, and improve the interaction between ultrasound department, antenatal units and delivery ward to provide better support to women.

Key words

Cesarean section, anxiety, Cesarean scar pregnancy, conservative treatment, knowledge about vaginal delivery after Cesarean, information pregnancy, vaginal birth after Cesarean section.

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN and key title 1652-8220; Lund University, Faculty of Medicine Doctoral Dissertation Series 2021:24		ISBN 978-91-8021-030-0
Recipient's notes	Number of pages 59	Price
	Security classification	

Signature Ekaterina Nedopekina Date 2021-02-11

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Cover photo by Robert Ersin.

Faculty of Medicine
Department of Clinical Sciences

ISBN 978-91-8021-030-0
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2021

To my beloved sister Marta

Table of Contents

Original Papers

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. Vikhareva O, Nedopekina E, Sjöström K. A supportive obstetrician consultation combined with ultrasound examination of Cesarean hysterotomy scar reduces anxiety in women postpartum. Submitted 2021.

II. Vikhareva O, Nedopekina E, Herbst A. Normal vaginal delivery at term after expectant management of heterotopic Cesarean scar pregnancy: a case report. J Med Case Rep. 2018 Jun 21;12(1):179.

III. Nedopekina E, Escura S, Cobo T, Hansson SR, Martinez JM, Figueras F, López M. Conservative treatment in non-tubal ectopic pregnancy and predictors of treatment failure. Eur J Obstet Gynecol Reprod Biol. 2021 Feb;257:6-10.

IV. Nedopekina E, Gómez S, Crespo E, Hansson SR, Palacio M, Gratacós E, Figueras F, López M. Knowledge about mode of delivery throughout pregnancy in women with previous Cesarean section. Submitted 2020.

V. Vikhareva O, Nedopekina E, Kristensen K, Dahlbäck C, Pihlsgård M, Skott Rickle G, Herbst A. Strategies to increase the rate of vaginal deliveries after Cesarean without negative impact on outcomes. Submitted 2020.

Paper not included in the thesis

Vikhareva O, Rickle GS, Lavesson T, Nedopekina E, Brandell K, Salvesen KÅ. Hysterotomy level at Cesarean section and occurrence of large scar defects: a randomized single-blind trial. Ultrasound Obstet Gynecol. 2019 Apr;53(4):438-442.

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Abbreviations

BDI-II	The Beck Depression Inventory-Second Edition
β-hCG	Human chorionic gonadotropin
BMI	Body mass index
CI	Confidence interval
CS	Cesarean section
CSP	Cesarean scar pregnancy
CSQ-8	The eight-item Client Satisfaction Questionnaire
ICD-10	International Classification of Diseases, version 10
KCl	Potassium chloride
MTX	Methotrexate
NICE	United Kingdom's National Institute for Health and Care Excellence
OR	Odds ratio
PAS	Placenta accreta spectrum
STAI, Form Y	Spielberger State-Trait Anxiety Inventory
TOLAC	Trial of labour after Cesarean
VB	Vaginal birth
VBAC	Vaginal birth after Cesarean

Introduction

Epidemiology

Cesarean section (CS) is one of the most common major surgical interventions in many countries. It is a life-saving operation for women and newborns when complications occur, such as fetal distress, malpresentation, labor dystocia, antepartum hemorrhage[1]. Over the last decades the rate of CS is constantly increasing in the most countries, with an average annual increase of about 4% worldwide[2, 3]. Based on the data from 169 countries it was estimated that 21% (29.7 million) of births occurred through CS in 2015[3].

In Sweden, the first rapid increase in the CS rate happened in 1970s. The increase was from 5% to 12% (data from the Swedish Medical Birth Register). Similar trends were also noted globally at that time. Between 1970-1978 the number of births by CS increased by 152% in Canada and tripled in the United States and Norway[4]. The second increase in the CS rate in Sweden was from 11% in 1990 till 17% in 2006 (data from the Swedish Medical Birth Register). Thereafter, the level remained stable and varied between 17.2-17.7% (Figure 1).

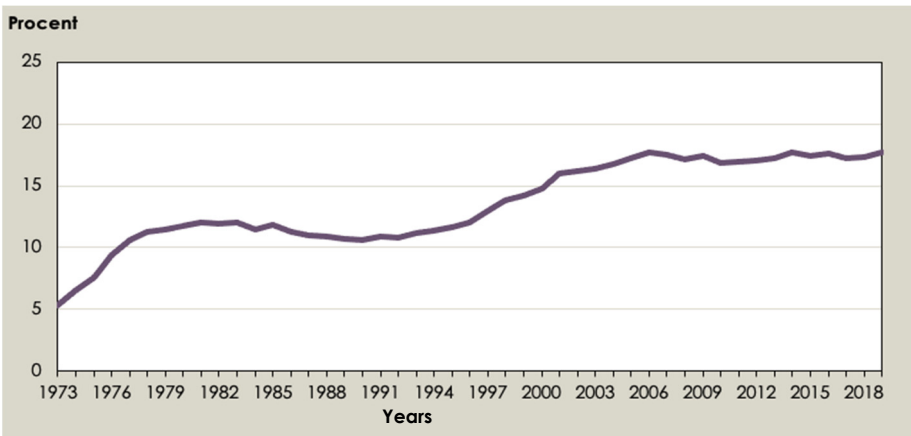


Figure 1. The total rate of Cesarean section in Sweden in 1973-2018 (the Swedish Medical Birth Register).

Various research works from North America and Europe hypothesized factors leading to such rise[4, 5]. Among those factors were rising maternal age; decline in fertility; changes in management of failure of progress at labor; increasing use of new technology in obstetrics, e.g., electronic fetal monitoring to detect fetal distress; fear of litigation; maternal request; growing reluctance to deliver fetuses in breech presentation; decrease in the level of the manual skills for vaginal delivery and as a result decrease in the number of operative VB[4-6]. For example, in Sweden the rate of CS in case of breach presentation increased from 14% in 1973 up to 60% in 1980 and reached 93% in 2005 (data from the Swedish Medical Birth Register). The increased number of primary CSs due to the forementioned factors has led to an increase in the rate of repeat CS in many countries and hospitals due to believe that "once a Cesarean always a Cesarean".

Benefits of CS

A growing number of women are requesting delivery by elective CS without medical indications[7]. This trend is partially due to the general perception among some women that CS is a safer mode of delivery for mother and/or child[8, 9]. Planned CS is associated with a reduced risk of vaginal injury, pelvic organ prolapse, early postpartum hemorrhage, and obstetric shock compared with planned vaginal birth (VB)[1, 10]. Abdominal and perineal pain during birth and three days postpartum was shown to be slighter less after CS compared to VB[10]. Reduced risk of urinary and anal incontinence after CS has also been found in the literature[11]. However, in a Cochrane review it was concluded that planned CS should not be considered as a prevention method for anal incontinence[12]. The risk of uterine rupture in planned repeat CS is less that 0.02% and is lower compared to planned trial of labor after Cesarean (TOLAC)[13].

Short-term and Long-term Risks after CS

Although CS has proven benefits, it is also associated with short-term and long-term health consequences, even life-threatening, both for mother and child. In general, the prevalence of maternal morbidity and maternal mortality is higher after CS than after VB[10].

Short-term risks for mother

The overall rate of maternal intraoperative complications was reported to be about 15%[14]. The most common serious intraoperative complications in CS are excessive blood loss and as a consequence increased risk of the need of transfusion; and lacerations of the uterine corpus[14, 15]. The other complication includes surgical injuries. The incidence of bladder injury was reported to be 0.1-0.3% and is more common in

low transverse abdominal incisions, repeat CSs and emergency CS due to fetal distress or placenta abruption[16-18]. Ureteral and bowel injuries are rare complications. However, the incidence increases after multiple CSs[14, 16, 18, 19].

The postoperative complications were reported to occur in 36% and were significantly higher in women undergoing emergency CS compared to those with elective CS[14]. The short-term risks associated with planned CS compared to VB include longer hospital stay, hysterectomy due to by postpartum hemorrhage and cardiac arrest[1]. However, it was mentioned by the UK's National Institute for Health and Care Excellence (NICE) that quality of the studies evaluating these risks was low or very low[1].

The overall risk of maternal death after CS is low in high-developed countries[12]. Several studies evaluating the risk of maternal mortality associated with elective CS compared to VB got controversial results[20-22]. However, the risk of maternal death was shown to be four times higher in case of emergency CS compared to VB[23-25]. Furthermore, the risk of death in subsequent delivery after CS increases with the number of CSs due to an increased risk of uterine rupture and abnormal placentation.

Long-term risks for mother

Cesarean scar syndrome was first described by Morris back in 1996[26]. This syndrome includes postmenstrual abnormal uterine bleeding, pelvic pain and infertility. These symptoms were studied in various research works and were considered to be associated with the defect in the hysterotomy Cesarean scar when incomplete or defective healing occur[27]. Postmenstrual abnormal uterine bleeding has also been found to correlate with the size of the defect[28]. According to the literature the prevalence of postmenstrual spotting varies between 20-29% in women with Cesarean scar defect[27, 28]. In Sweden, over a third of women reported minor or major problems associated with wound pain four to eight weeks after CS[29]. The incidence of chronic postsurgical pain after CS was revealed to range from 15% at 3 months to 11% at 12 months or longer after the operation[30].

Pelvic adhesions are common after CS but the risk is low after the first operation. However, the risk increases steadily with the number of subsequent CSs and can reach 24%, 43%, and up to 75% at the second, third, and fourth (or greater) CS, respectively[31, 32]. Pelvic adhesions may lead in its turn to small bowel obstruction, female subfertility, chronic pain, intestinal obstruction and complications in subsequent surgeries[33-35].

The psychological effects of CS have not been well studied. However, a significant worsening in postpartum self-reported general health status in women after CS has been found[36]. In a study by Ryding et al. psychological reactions of women after emergency and elective CS, instrumental and normal VB were compared[37]. The women reported the most negative birth experience after emergency CS. In addition, the prevalence of post-traumatic stress symptoms was higher after emergency CS compared to elective CS or normal VB. Another study compared depression, anxiety and anhedonia in women following VB, elective and emergency CS[38]. The highest levels of anxiety were

noted after elective CS, whereas anhedonia was more common after emergency CS. It was also shown that higher levels of anxiety may persist up to one year after CS[39]. Despite the evidence that mode of birth may influence the psychological well-being, there is limited information in the literature on how to process and enhance women's birth experience, particularly after CS. To the best of our knowledge, there is no studies evaluating the strategies to decrease anxiety in women after previous CS.

Risks in subsequent pregnancy

In a systematic review and meta-analysis which included 10 articles studying the impact of CS on subsequent pregnancies, it was shown that women who had undergone CS had a 9% lower subsequent pregnancy rate[40]. In two other studies, the risk of miscarriage following CS was reported to increase significantly by 22-32%[41, 42]. However, the results from other studies are controversial and the precise effect of CS to subsequent subfertility yet to be defined.

Another complication associated with previous CS is Cesarean scar pregnancy (CSP), a potentially life-threatening condition when a pregnancy partially or completely implants into the area of the hysterotomy Cesarean section scar[43]. In the last decades the number of reported cases increased significantly. This may be explained by the increased number of performed CSs and wider use of ultrasound diagnostic methods to diagnose such cases[43]. The rate was estimated to be 6% of all ectopic pregnancies in women with at least one previous CS or 1:1800 to 1:2200 of all pregnancies[43, 44]. However, the overall true rate may be underreported due to complexities of diagnosis[45].

Several strategies were proposed for the treatment of CSP, such as transcervically or transabdominally surgical evacuation of the pregnancy or conservative methods: medical therapy with systemic methotrexate (MTX), ultrasound-guided intrasaccular injection of MTX or potassium chloride (KCl), and expectant management[46-54]. However, the quality of evidence regarding management of CSP does not come from randomized controlled trials. The consensus regarding management of CSP has not been reached yet and specific guidelines are scarce. The overall success rate of different treatment regimens is reported to be 42-97%[55]. The complications related to treatment failure include loss of fertility, rupture of the site of the pregnancy, severe hemorrhage, need for hysterectomy and death[55, 56]. Thereby, more studies are needed to provide the best treatment option in each particular case and to determine possible predictive factors for treatment failure.

Placenta previa is the complete or partial covering of the internal cervical os with the placenta[57]. This condition prevents VB and requires delivery through CS. The risk of placenta previa is higher among women with previous CS, additional risk factors are advanced maternal age, multiple gestation, high parity, and drug use[58, 59]. The incidence of placenta previa increases from 10 in 1000 deliveries with 1 previous CS to 28 in 1000 with 3 and more CSs[60]. Placenta previa in its turn is a risk factor for postpartum hemorrhage, hysterectomy and placenta accreta spectrum[57].

Placenta accreta spectrum (PAS) is a pathologic placental invasion into the uterine wall[61]. The incidence of PAS increased significantly from 1 in 4000 deliveries in the 1970s[62] up to 1 in 533 deliveries by 2002[63]. The incidence of PAS is directly related to the increase in CS[64]. The main additional risk factor for placenta accreta after a previous CS is placenta previa. A multicenter cohort study has found that for women presenting with placenta previa and prior CS, the risk of accreta placentation increases form 3% after the first CS till 61% and more after the fourth and subsequent CSs[65].

Complete uterine rupture is a potentially life-threatening complication defined as tear through all three layers of the uterine wall, with communication between the uterine and abdominal cavities[66]. Most uterine ruptures occur in women with scared uterus undergoing TOLAC[67]. Several risk factors for uterine rupture were described in the literature, including short inter-delivery interval, advanced maternal age, obesity, lower prelabour Bishop score, labor induction with prostaglandins, oxytocin augmentation, macrosomia and decreased lower segment myometrial thickness assessed by ultrasound in the third trimester of pregnancy[13, 67]. Nevertheless, the overall rate of uterine rupture in women with one previous CS is low and varies between 0.2-0.5%[13].

Two systematic reviews have shown that pregnancy after CS is also associated with an increased risk of stillbirth by 23-27% and a 5-fold increase in the rate of spontaneous preterm delivery[62, 68].

The high-quality evidence for the short- and long-term risks and benefits of CS is essential. Interesting estimations about risks-benefit balance have been made in the recent systematic review and meta-analysis[62]. It was calculated that around 17 Cesareans would be needed to prevent one case of urinary incontinence. For every 1500 Cesareans performed, there would be nine additional cases of childhood asthma, in the subsequent pregnancies, an additional 166 women with subfertility, three women with placenta previa, two women with uterine rupture, 21 miscarriages and one stillbirth[62]. This information would help to discuss the preferable mode of delivery with women and may facilitate shared decision-making. In discussions, risks and benefits to not only the current birth but also future pregnancies and births should be considered[68]. This particularly concerns primiparous women, who are likely to want more children.

Delivery in pregnancy after CS

Women who have undergone CS and health care providers are faced with a difficult decision about a mode of delivery in subsequent pregnancies. The published guidelines recommend TOLAC as the first option for consideration in women with one previous CS[13, 69, 70]. The estimated success rate of vaginal birth after CS (VBAC) is high and varies between 72-75%[13]. Nevertheless, elective repeat CS still remains one of the main contributors to the overall CS rate in many countries and hospitals, as verified using the Ten Group Classification System[71-73]. In those countries where the rate of primary CS is low, the rate of repeat CS usually correlates and is also low. In contrast, if the primary CS rate is high then the rate of repeat CS tends to be also high. However, in some countries, such as Latvia, Lithuania, Slovenia, Belgium, France, the primary CS rates are low but the rate of repeat CS is higher than expected (Figure 2).

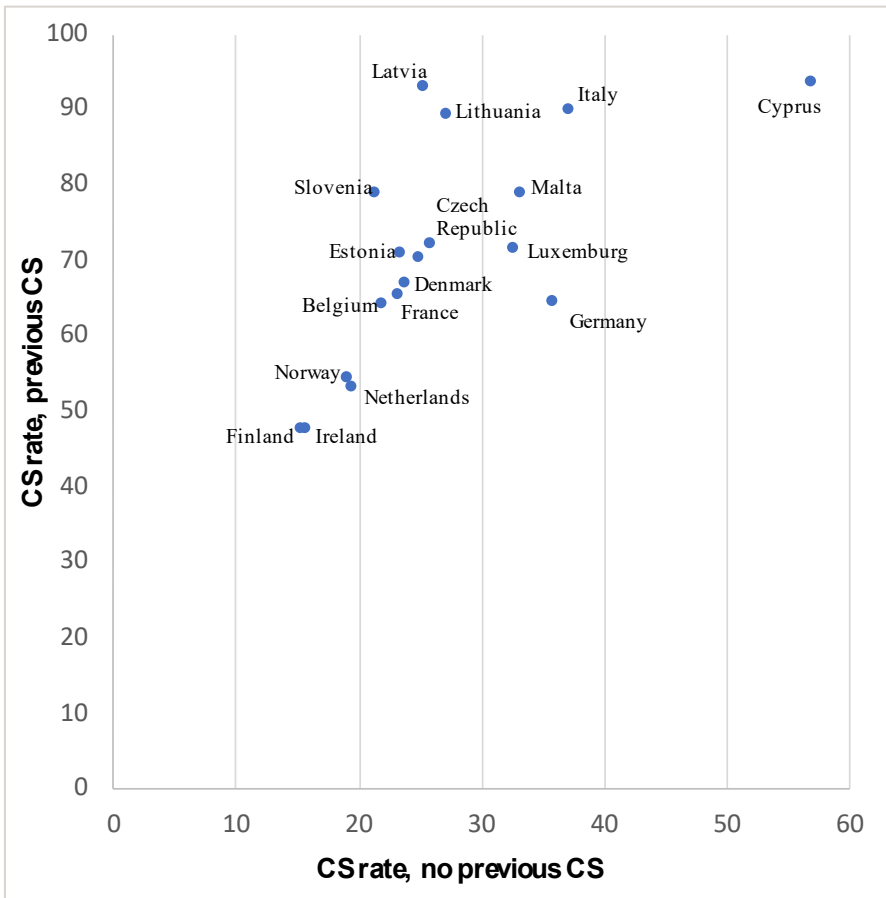


Figure 2. Comparison between the rates of Cesarean section in women with and without previous Cesarean section in European countries[72].

It was shown that socio-economic, cultural and religion factors may play a role in such differences between the countries[74, 75]. On a hospital level, among the variables which influence the rates of CS were the type of healthcare setting (public or private) and time of the day[76, 77]. The number of CS was significantly higher in private hospitals and at particular time points of the day.

Several strategies have been proposed in the literature to increase the rate of VBAC. Among them were use of pharmacological and non-pharmacological methods for labor induction, antepartum x-ray pelvimetry, external peer review, audit and feedback, existence of national and local guidelines, use of opinion leaders, individualized information to women, childbirth training workshops for mothers and psychoeducation[78-80]. However, the systematic review and meta-analysis evaluating the clinical interventions found low to very low certainty in the body of evidence. It was concluded that there is insufficient data to choose an optimal clinical intervention to increase the rate of VBAC in women with one previous CS[80]. The other articles also have shown controversial results. There is still a need for high-quality evidence-based strategies to increase the rate of VBAC.

Objectives

The overall aim of the thesis was to evaluate the impact of CS on postpartum recovery, subsequent pregnancy and delivery; and to assess strategies to increase the level of vaginal deliveries after CS.

Specific objectives were:

- To evaluate whether an appointment with a senior obstetrician combined with an ultrasound examination reduces levels of anxiety in women after CS, which factors influence on the anxiety levels and to assess women's satisfaction with the appointment.
- To assess the rate of failure of different primary treatment regimens, complications and additional interventions in non-tubal ectopic pregnancies.
- To find a possible tool for prediction of failure of conservative treatment of non-tubal ectopic pregnancies.
- To determine the level of knowledge about the mode of delivery in women with one previous CS and to evaluate its differences throughout pregnancy.
- To compare the rate of VBAC and maternal and perinatal outcomes in two historical cohorts before and after the implementation of certain changes in clinical practice and establishment of the antenatal research clinic for women with previous CS.

Study Populations

The studies described in this thesis are based on two populations: a Swedish (n=2165) and a Spanish (n=126). Study I, II and V were conducted at Skåne University Hospital, Malmö/Lund, Sweden. The Hospital handles approximately 8000-9000 deliveries per year with an overall CS rate around 17% (Figure 3). The VBAC rate in women with one previous CS varied between 52-54% in 2014-2018 (data from the official annual reports of Skåne University Hospital).

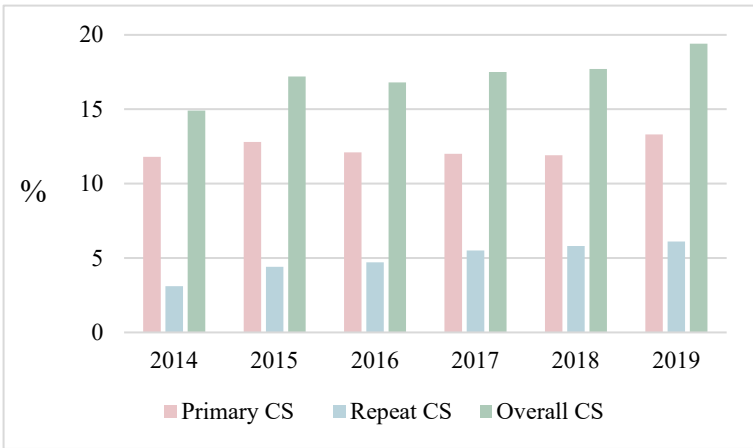


Figure 3. The primary, repeat and overall Cesarean section rates in Skåne University Hospital, Sweden (data from the official annual reports of Skåne University Hospital).

Studies II and III were conducted in BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine, Barcelona, Spain, a tertiary hospital having about 4000 births per year. Interestingly, that in contrast to the worldwide tendency, the rate of CS has been decreasing constantly from 2017 (Figure 4). Between 2011-2015 the rate of successful VBAC was estimated to be around 40%[81]. In 2018 the rate of VBAC was 33% and it reached up 44% in 2020 (data from the official annual reports of BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine).

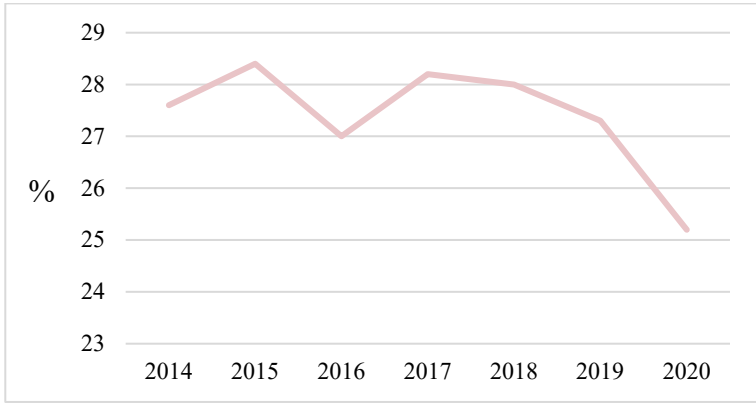


Figure 4. The Cesarean sections rates in BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine (data from the official annual reports of BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine).

The recruitment period was between January 2017 and October 2019. A schematic overview of the study populations, country, number of women included in each study, number of previous CSs and the primary outcomes are shown in the Figure 5.

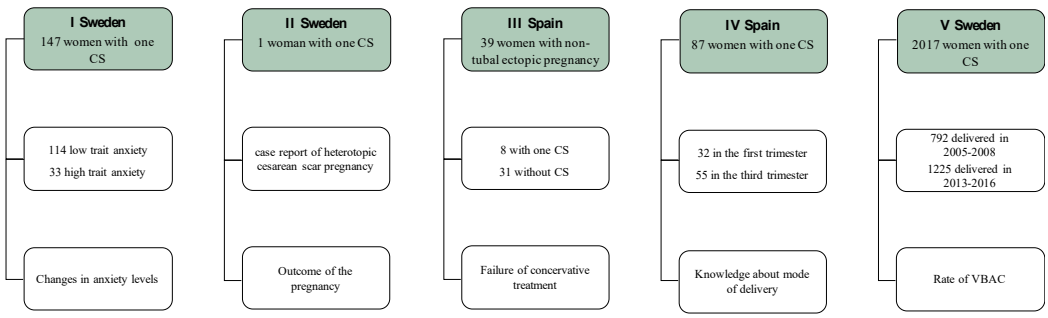


Figure 5. The overview of the populations chosen for the five papers.

Study Design

Paper I was a prospective observational study, which included women who delivered by their first CS. Six to nine months after the first CS, the women had an appointment with an experienced obstetrician supplemented by ultrasound examination of the uterus with particular assessment of the Cesarean scar area. Before the appointment, the women were asked to fill in the state and trait subscales of the Spielberger State-Trait Anxiety Inventory to evaluate the anxiety level and Beck's Depression Inventory to detect symptoms of severe depression. After the appointment, the participants filled in the state scale once more and the Client Satisfaction Questionnaire was distributed. The main outcome was changes in the state anxiety levels.

Paper II, a case report of successful expectant management of a heterotopic CSP observed at Skåne University Hospital, Sweden.

Paper III was designed after publishing a case report about heterotopic CSP and identifying the scarce of existing information regarding conservative treatment options and uncertainty in prognostic factors of treatment failure. Since CSP is a very rare condition we expanded the study population and included all cases of non-tubal ectopic pregnancies. *Paper III* was a retrospective analysis of the cases of non-tubal ectopic pregnancies managed during nine-year period in a tertiary hospital in Barcelona, Spain. Cases were retrieved from the hospital electronic patients' record system using the International Classification of Diseases, version 10 (ICD-10) related to ectopic pregnancy (633.10, 633.11, 633.20 633.80, 633.81, 633.90). Clinical characteristics, the rate of failure, complications and need for additional interventions of the different primary treatment regimens in non-tubal ectopic pregnancies were assessed. The main outcomes were success of the primary treatment and the need for additional interventions. Possible predictor factors for primary treatment failure, such as maternal age, gestational age, size of gestational sac, levels of human chorionic gonadotropin (β-hCG) at diagnosis, and presence of cardiac activity were assessed using logistic regression analysis.

Paper IV, a cross-sectional study which included Spanish-speaking pregnant women in the first and third trimester of pregnancy who had only one previous CS and had no medical indications for repeat CS. The women's knowledge about the risks of CS and the benefits of VBAC were evaluated using a structured questionnaire. The questionnaire consisted of closed and open questions and the different sections addressed to: I) background characteristics, including circumstances for their previous CS, II) general knowledge about CS and VBAC and III) personal view and request for

information. Thereafter, the level of knowledge was determined and was compared between women being in the first and third trimester of pregnancy.

Paper V was a retrospective cohort study comparing the rate of VBAC, maternal and perinatal outcomes between two particular periods of time: before and after the implementation of specific changes in the clinical practice. The changes were implemented between 2008 and 2013 and they were: (1) Lactate blood samples from presenting part for intrapartum fetal monitoring as a complement to cardiotocography (CTG) was implemented. (2) Changes in local clinical guidelines for induction of labor were made and prostaglandins were replaced by Foley's catheters for women with a previous CS. (3) A team of midwives providing psychological support for women with fear related to childbirth expanded their activity and experience in this area. (4) An antenatal research clinic to follow-up women with previous CS was established in 2013 in collaboration between the antenatal units, the ultrasound department and the labor ward.

All women with one previous CS who delivered either in 2005-2008 or in 2013-2016, were included in the study. The primary outcome was VBAC. Secondary maternal outcomes were uterine rupture/dehiscence, hysterectomy and blood loss. To determine which factors were associated with VBAC both univariate and multivariate logistic regression analysis were performed.

Methods

Ethical Considerations

Studies I and V were approved by the Ethics Committee of the Medical Faculty of Lund University, Sweden. For the Paper II, the patient has given permission for publication of her case report in a scientific journal. Studies III and IV were approved by the Research Ethics Committee of Hospital Clínic of Barcelona, Spain.

Ultrasound examination

In Paper I, the ultrasound examinations were performed using GE Voluson E8 ultrasound system (General Electric, Zipf, Austria) equipped with a 2.8–10-MHz transvaginal transducer. The ultrasound images were evaluated during ultrasound examination and thereafter, representative images were stored in the digital image storing system Siemens Syngo® Dynamics, version 5.0 (Siemens Medical Solutions Health Services Corp., Malvern, PA, USA). A urine pregnancy test was taken in all participants to exclude any unexpected pregnancy before the ultrasound examination.

The ultrasound examination of the pelvic organs was performed. The examination was carried out with a woman in the lithotomy position with an empty bladder. The uterus was evaluated for the appearance of the Cesarean scar in the sagittal plane, both with and without saline contrast sonohysterography. If a defect in the Cesarean scar was present, the measurements of the defect were taken using the standardized approach described in the literature[82].

All women were informed about the results of the ultrasound examination. Any detected abnormal findings were managed in accordance with routine clinical guidelines.

Questionnaires

Questionnaires are a written self-report technique where participants are given a pre-set number of questions to respond to. Throughout the studies the following questionnaires have been used:

Spielberger State-Trait Anxiety Inventory (STAI, Form Y)

The STAI, Form Y was employed to measure anxiety is Paper I. This is a self-administered scale which consists of 40 statements[83]. The first 20 statements assess state anxiety, i.e., assess how a person feels at a particular moment or a chosen period. The women were asked to score their state anxiety in two particular points of time: once before and once after the appointment with the obstetrician. The subsequent 20 items assess trait anxiety, i.e., assess how a person generally feels and his/her general tendency to respond to situations which perceived as threatening. Trait anxiety is found to be very stable over time and was assessed only once, before the appointment. All items on the state and trait scales are rated on a 4-point Likert scale (e.g., from "almost never" to "almost always"). The scores range from 20 to 80 points. Higher scores indicate higher anxiety.

The Beck Depression Inventory-Second Edition (BDI-II)

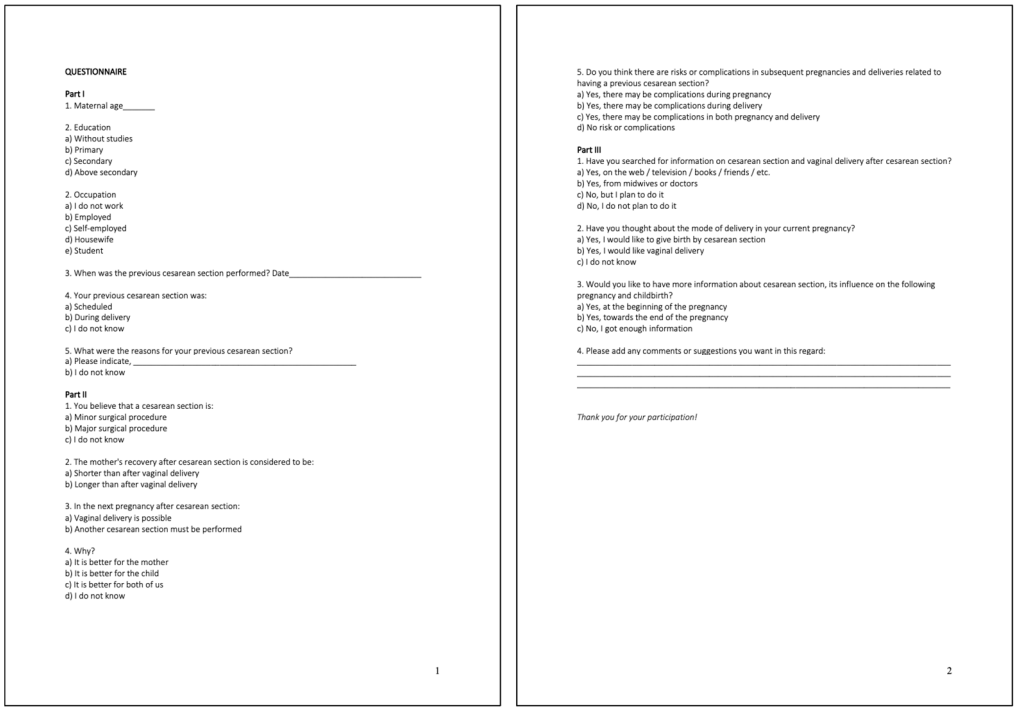
The BDI-II is one of the most widely used self-report measures of depression in both research and clinical practice[84]. The Second Edition (BDI-II) is the most recent version of the BDI[85]. The questionnaire consists of 21 items. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression and is rated from 0 = low to 3 = high. The total score ranges from 0 to 63. The women in Paper I were asked to answer the questionnaire before the appointment and reflect their feelings during the previous week.

The eight-item Client Satisfaction Questionnaire (CSQ-8)

The CSQ-8 is an eight-item standardized self-administered form to assess satisfaction with health services[86]. Responses are based on a four-point scale from 1 to 4, thus, the possible total scores range from 8 to 32. Higher scores correspond to higher satisfaction with the health services. The data from the CSQ-8 questionnaire was collected at the end of the appointment in Paper I.

Mixed developed questionnaire

A structured mixed questionnaire was used in Paper IV to determine the level of knowledge about mode of delivery in women with previous CS. The questionnaire consisted of closed and open questions and was divided into three different sections addressed to: 1) background characteristics, including circumstances for their previous CS; 2) general knowledge about CS and VBAC; and 3) personal view and request for information. The full questionnaire is presented in Figure 6.



QUESTIONNAIRE

Part I
1. Maternal age_____

2. Education
a) Without studies
b) Primary
c) Secondary
d) Above secondary

2. Occupation
a) I do not work
b) Employed
c) Self-employed
d) Housewife
e) Student

3. When was the previous cesarean section performed? Date_____

4. Your previous cesarean section was:
a) Scheduled
b) During delivery
c) I do not know

5. What were the reasons for your previous cesarean section?
a) Please indicate, _____
b) I do not know

Part II
1. You believe that a cesarean section is:
a) Minor surgical procedure
b) Major surgical procedure
c) I do not know

2. The mother's recovery after cesarean section is considered to be:
a) Shorter than after vaginal delivery
b) Longer than after vaginal delivery

3. In the next pregnancy after cesarean section:
a) Vaginal delivery is possible
b) Another cesarean section must be performed

4. Why?
a) It is better for the mother
b) It is better for the child
c) It is better for both of us
d) I do not know

1

5. Do you think there are risks or complications in subsequent pregnancies and deliveries related to having a previous cesarean section?
a) Yes, there may be complications during pregnancy
b) Yes, there may be complications during delivery
c) Yes, there may be complications in both pregnancy and delivery
d) No risk or complications

Part III
1. Have you searched for information on cesarean section and vaginal delivery after cesarean section?
a) Yes, on the web / television / books / friends / etc.
b) Yes, from midwives or doctors
c) No, but I plan to do it
d) No, I do not plan to do it

2. Have you thought about the mode of delivery in your current pregnancy?
a) Yes, I would like to give birth by cesarean section
b) Yes, I would like vaginal delivery
c) I do not know

3. Would you like to have more information about cesarean section, its influence on the following pregnancy and childbirth?
a) Yes, at the beginning of the pregnancy
b) Yes, towards the end of the pregnancy
c) No, I got enough information

4. Please add any comments or suggestions you want in this regard:
_____
_____
_____

Thank you for your participation!

2

Figure 6. The questionnaire used to determine the level of knowledge about mode of delivery in women with previous Cesarean section in Spanish population.

Data collection from medical records

Papers III and V were retrospective studies, hence it was particularly important to retrieve all the data with precise accuracy. The patients' detailed information was retrieved from the review of medical records and ultrasound images stored in the hospitals' computerized medical systems. If the patient was treated with surgical management or underwent CS, the surgical records were evaluated. The appearance of the lower uterine segment at CS was assessed. In cases where the description of the condition of the uterine wall was unclear or difficult to interpret, the surgeon who had performed the operation was personally inquired for details.

Statistics

Statistical analyses were carried out using the Statistical Package for the Social Sciences software version 24.0 (SPSS Inc., Chicago, IL, USA). Two-tailed p-values < 0.05 were considered statistically significant.

Differences between groups

In Papers I and III-V, the differences between groups in categorical data were studied using the chi-square test and the Fisher's exact test, as appropriate. The *chi-square test* applies an approximation assuming the sample is large, while the *Fisher's exact test* runs an exact procedure especially for small-sized samples[87].

Student's t-test is a technique to test a hypothesis on the basis of a difference between sample means and was used in Papers I and III-V for comparisons of continuously scaled normally distributed variables. *Mann-Whitney U* was used in Papers I and III to compare differences between two independent groups when the dependent variable was non normally distributed.

Paired sample t-test

The paired sample *t*-test is a statistical procedure used to determine whether the mean difference between two sets of observations is zero. In a paired sample t-test, each subject or entity is measured twice, resulting in pairs of observations. In Paper I the paired sample *t*-test was used to assess differences in state anxiety scores before and after the appointment in the study population.

Correlation analysis

Pearson correlation coefficient is a measure of the strength of a linear association between two variables and is denoted by *r*. The Pearson correlation coefficient, *r*, can take a range of values from +1 to -1. A value greater than 0 indicates a positive association; a value less than 0 indicates a negative association. If a value is equal to 0 this means that there is no association between the two variables. Pearson's correlation coefficient was performed to describe correlation between BDI, trait anxiety scores state anxiety scores in Paper I.

Logistic regression analysis

Logistic regression analysis is a statistical technique to evaluate the relationship between various predictor variables (either categorical or continuous) and an outcome which is binary (dichotomous)[88].

Univariate logistic regression analysis refers to the regression application with one dichotomous outcome and one independent variable; multiple logistic regression analysis applies when there is a single dichotomous outcome and more than one independent variable.

In Paper III, the possible predictive factors for the risk of failure of the primary treatment, such as maternal age, gestational age, size of gestational sac, β-hCG levels at

diagnosis, and presence of cardiac activity were evaluated using univariate logistic regression analysis with likelihood ratio test.

In Paper V, univariate logistic regression analysis was performed to determine which factors may influence the likelihood of TOLAC and VBAC followed by adjusted multiple logistic regression models.

Odds Ratio and Confidence interval

Odds ratio (OR) measures the association between an exposure and an outcome. An OR > 1.0 indicates that exposure associated with higher odds of outcome. OR=1 shows no effect of exposure on outcome.

The 95% confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR[89].

Results

Decrease in anxiety levels in women after CS

In total, 147 women were included in the study. Of these, 114 (78 %) had low trait anxiety scores and 33 (22 %) had high trait anxiety scores. There was a positive correlation between BDI, trait anxiety scores and state anxiety scores. The women with higher trait anxiety had significantly higher state anxiety scores both before and after the appointment in comparison with those with lower trait anxiety (Figure 7). Before the appointment, the state anxiety scores did not differ between the women who underwent emergency or elective CS (30.1±8.3 vs. 31.8±9.8, p=0.43). State anxiety scores among the unemployed women before and after the appointment were significantly higher compared to those employed (45.5±11.3 vs. 30.5±8.6, p=0.001 and 31.4 ±9.2 vs. 25.1±6.1, p=0.016, respectively).

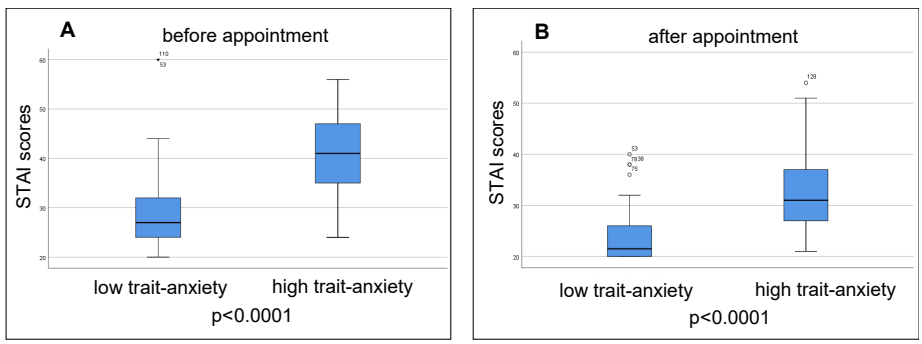


Figure 7. Differences in state anxiety scores between the low trait anxiety and high trait anxiety groups before (A) and after (B) the appointment.

After the appointment with the obstetrician the mean anxiety levels decreased significantly by 5.8±6.1 points in the overall population. The analysis of changes in state anxiety scores in the low and high trait anxiety groups is presented in Figure 8. Most of the women 133 (91%) were highly satisfied with the appointment as measured by CSQ-8.

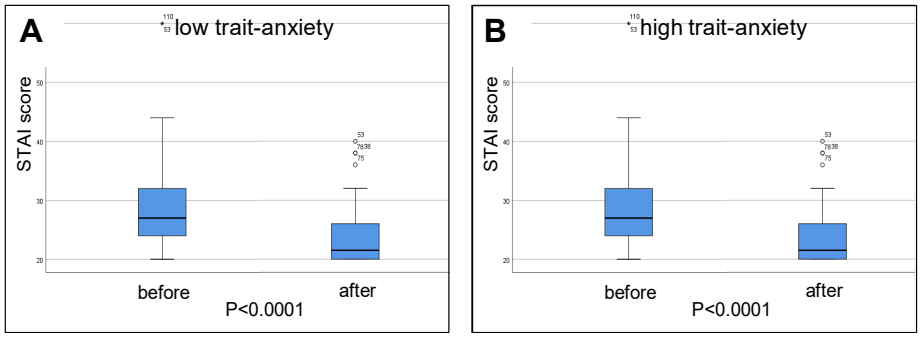


Figure 8. Changes in state anxiety scores before and after the appointment in the low trait anxiety (A) and high trait anxiety groups (B).

Conservative treatment of non-tubal ectopic pregnancies

In Paper III, a total of 39 cases were included. The cases were divided into two groups: (1) embryo heartbeat positive group (33%), and (2) embryo heartbeat negative group (67%). In the embryo heartbeat positive group, the most frequent treatment was intrasaccular ultrasound guided injection with MTX or KCl combined with systemic multiple dose MTX (69% of the cases). In the embryo heartbeat negative group systemic multiple dose MTX alone was the most prevalent treatment in 92% of the cases.

The rate of failure of the primary treatment was significantly higher in the group with presence of cardiac activity (46%) than in the embryo heartbeat negative group (15%), $p<0.0001$. Additional treatments, such as embolization, additional doses of MTX, intrasaccular injection of KCL, removal of retainers were needed in ten cases of treatment failure. None of the cases required hysterectomy or led to serious morbidity/mortality in women.

During the study period two interstitial heterotopic pregnancies were managed. Both ectopic pregnancies were viable with positive heartbeat. In the first case, due to ongoing miscarriage of the intrauterine pregnancy, ectopic pregnancy was managed with intrasaccular injection of MTX combined with systemic multi doses MTX. Curettage of the intrauterine pregnancy was performed. In the second case, the intrauterine pregnancy was viable. Therefore, the ectopic pregnancy was managed with ultrasound-guided injection of KCl. No complications were recorded. The intrauterine pregnancy continued to term gestation and a health neonate was born by CS due to failure of progress at labor.

Possible factors which could influence the success of the primary treatment in the whole population were evaluated using univariate analysis (Figure 9). Higher levels of β-hCG at the time of diagnosis and the presence of embryo heartbeat were associated with treatment failure.

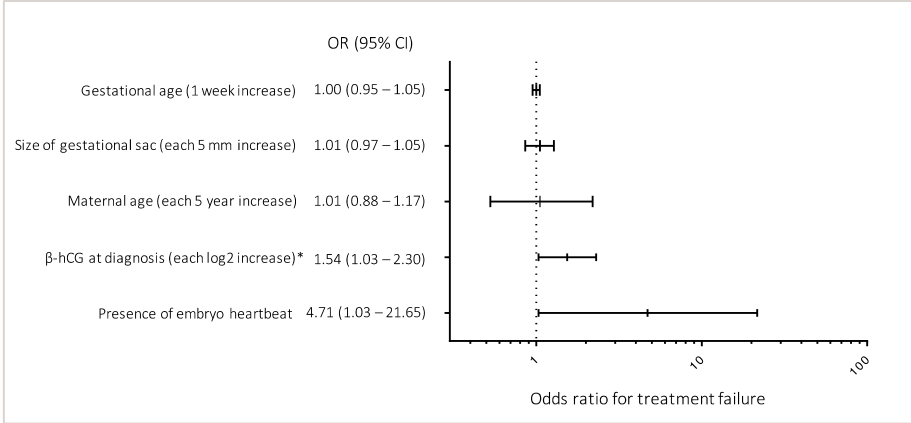


Figure 9. Forest plot showing the odds ratios for likelihood of the primary treatment failure.
OR – odds ratio, CI – confidence interval, β-hCG – human chorionic gonadotropin.
* Due to not normal distribution of levels of β-hCG at diagnosis the variable was transformed with a base-2 logarithm for logistic regression analysis.

Twenty women (69%) got pregnant after the case of ectopic pregnancy. The interpregnancy interval ranged between 6 to 80 months. No fetal congenital abnormalities were recorded.

Knowledge about mode of delivery in women with previous CS

In Study IV, the participants were divided into two groups: 32 women (36.8%) in the first trimester group (Trim I) and 55 (63.2%) in the third trimester group. The results of our study have shown that by the third trimester of pregnancy a larger number of women knew that VBAC is safer for both mother and child than elective repeat CS, $p<0.01$ (Figure 10 A). However, there were no differences in the level of knowledge about risks of CS between the two groups. In each group, 30% thought that there were no risks after CS neither for subsequent pregnancy no for subsequent delivery (Figure 10 B).

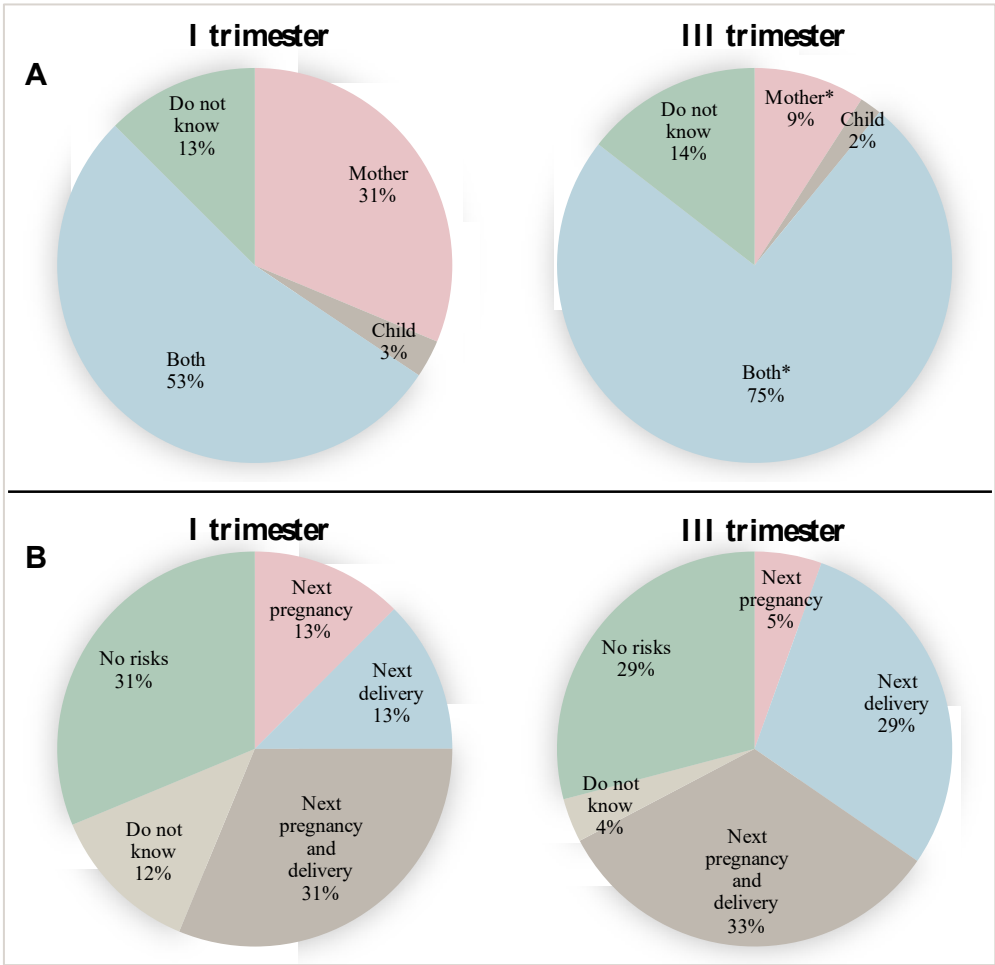


Figure 10. Distribution of the answers between the first and the third trimester groups for the question: (A) For whom vaginal delivery after Cesarean section is better? (B) Are there risks after Cesarean section? * $p<0.05$

In the third trimester of pregnancy, a significantly higher number of women got the information about risks and benefits of VBAC from the medical staff compared to the first trimester group. There was a reduction in the number of women who wanted to have more information in the third trimester compared to the first trimester (Figure 11). Nevertheless, over a half of the women still asked for more information even in the third trimester of pregnancy and after signing the informed consent on the planned TOLAC.

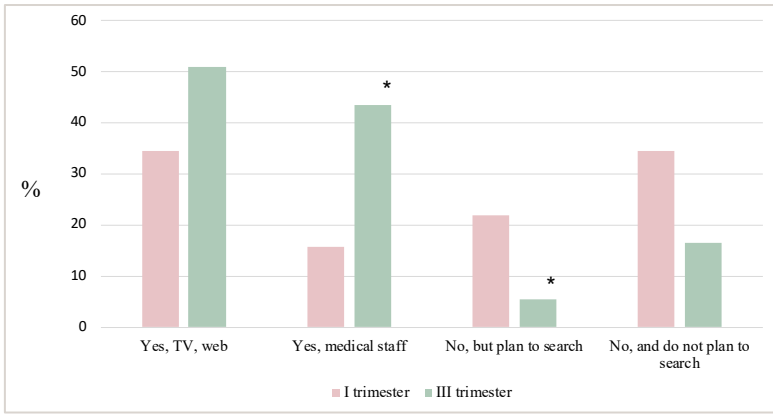


Figure 11. The comparison of answers for the question: Have you searched for information on Cesarean section and vaginal delivery after Cesarean section? * p<0.05

Strategies to increase VBAC rate

In Paper V a total of 2017 women were included: 792 patients who delivered in 2005-2008 (Group I) and 1225 women who delivered in 2013-2016 (Group II). The rate of TOLAC was 65.0% and 76.9% in Group I and Group II, respectively (OR 1.79; 95% CI 1.47-2.18; p<0.0001). The VBAC rate was 49.8% and 62.0% in Group I and Group II, respectively (OR 1.65, 95% CI 1.38-1.98, p<0.0001). No significant differences between the groups regarding maternal complications were found. In women who underwent TOLAC, the rate of newborns with arterial pH <7.05 was significantly lower in Group II (1.3 %) than in Group I (2.2%), p<0.02.

The significant differences found between the groups regarding background characteristics, characteristics of labor and indications for CS in the current delivery are presented in Table 1. It was found that in Group II number of inductions by prostaglandins reduced dramatically, but the rate of successful inductions did not change. Simultaneously oxytocin and epidural anesthesia were used more frequently during labor. There was an increase in the number of emergency CS due to failure of progress with the reduction in the rate of instrumental delivery.

Table 1. Significant differences noted between the two groups.

	Group I (n=792)	Group II (n=1225)	p-value
Background characteristics			
Height (cm)	165.1 ± 6.5	164.3 ± 6.9	<0.01
Prior vaginal deliveries	132 (16.7)	328 (26.2)	<0.0001
Characteristics of labor during study period			
Underwent TOLAC	515 (65.0)	942 (76.9)	<0.0001
Prostaglandin induction	97 (89.8)	35 (15.6)	<0.0001
Oxytocin augmentation	190 (36.9)	473 (50.2)	<0.0001
Duration of augmentation, hours	2.53 ± 2.33	3.53 ± 2.88	<0.0001
Epidural anesthesia	109 (21.2)	324 (34.4)	<0.0001
Instrumental delivery	55 (10.7)	75 (8.0)	0.04
Successful VBAC	394 (49.8)	760 (62.0)	<0.0001
Indication for CS			
Maternal request	170 (61.4)	146 (51.6)	0.02
Failure to progress	55 (45.5)	113 (62.1)	<0.01

Data are given as mean ± standard deviation or n (%).
TOLAC – trial of labor after Cesarean section, VBAC – vaginal delivery after Cesarean section, CS – Cesarean section.

The multivariate logistic regression analysis of odds ratio for women from Group II to undergo TOLAC and then to have successful VBAC was performed. It was revealed that the increase by 12% in the number of women who underwent TOLAC was the main contributor to the overall increase of the VBAC rate in Group II.

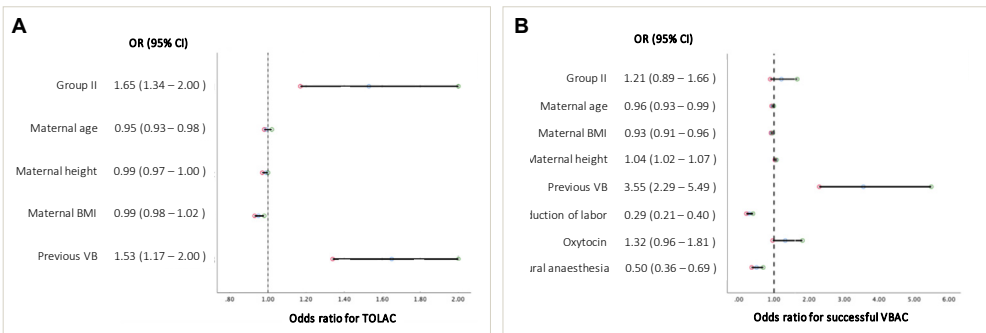


Figure 12. Forest plot showing odds ratio for women from Group II to undergo TOLAC (A) and to have successful VBAC (B) adjusted for other variables.
The reference group is Group I.
OR – odds ratio, CI – confidence interval, BMI – body mass index, VB – vaginal birth, TOLAC – trial of labor after Cesarean, VBAC – vaginal birth after Cesarean.

Discussion

Decrease in anxiety levels in women after CS

The results of our study found that the appointment with an obstetrician supplemented by ultrasound examination may decrease anxiety levels in women after CS, particularly in highly anxious patients. Several strategies to decrease the anxiety levels were proposed previously in different groups of patients, mostly before surgical procedures[90-95]. However, despite the existed evidence of the risks for prolonged anxiety associated with CS,[36-39, 96, 97] to the best of our knowledge, this is the first study conducted in the group of women after CS. Moreover, the need for greater attention to continuous assessment of psychological well-being among women who undergo CS has been recommended[98].

The appointment may be particularly important for such vulnerable groups of women as unemployed. Our results found that unemployed women had higher anxiety scores at the time of appointment. This is in agreement with the published articles where unemployment had a negative impact on mental health[99-101]. It was suggested that health care providers should pay attention and be able to identify women with the presence of symptoms of anxiety and that the women might need counselling and/or treatment in order to decrease their anxiety[101].

In several articles, women reported that they got insufficient and/or not clear information before and after giving birth as well as during the subsequent pregnancy[102, 103]. A high proportion of women undergoing CS asks for more information on what constitutes a 'normal' post-operative recovery, the healing process of the uterine Cesarean scar and advice regarding subsequent pregnancies and deliveries[104, 105]. A large proportion of misunderstanding exists among women regarding the indications for the previous CS[103]. Women undergoing emergency CS are more likely to experience moderate or strong childbirth fear after CS and to prefer a CS in case of another birth[106]. A report from Denmark found that 80% of CSs performed due to maternal request were among multiparous with a previous traumatic delivery[107]. Therefore, it is extremely important to give good professional service to women experienced dramatic circumstances. The supportive appointment with an obstetrician combined with an ultrasound examination of the uterine scar may be given to discuss the circumstances of the previous Cesarean delivery and the uterine healing process. During those appointments an advice according future pregnancies and options for the mode of delivery in a positive manner towards VBAC might also be given. This might enhance the postpartum care and women's overall birth experience as well as increase the

proportion of women preferring VBAC as the mode of birth in the next pregnancy[104, 108]. This is in line with the current guidelines and published articles which emphasized the importance of relevant information for women and their partners in the postpartum period[13, 108, 109].

Interestingly, how differences in culture and in general obstetric approach may influence the results. The current and one recent study[37] evaluating the level of anxiety in women after CS were conducted in Sweden. In both of these studies no differences in the anxiety levels after emergency or planned CS have been found. However, in a study conducted in Italy[38], it was shown that women tend to have higher anxiety levels after emergency CS compared to planned CS. When evaluating the differences between the countries, it was found that in Sweden VBAC is considered to be the first and obvious alternative if no medical indications for CS present[75]. All health care providers including midwives and obstetricians would play as one team with one opinion. In Italy, in contrast, a woman may get different opinions from different doctors/ midwives in addition to the opinion translated in media and from family and friends[75]. By the end of the pregnancy the woman in Italy may become overwhelmed and anxious when thinking about the mode of delivery due to diversity of the opinions and suggestions. This is in agreement with the other articles that higher anxiety before CS may lead to higher anxiety after CS, especially when the expectations about the preferred mode of delivery have not been met[110, 111]. Hence, it emphasizes the importance of teamwork of all departments taking care of a pregnant women, particularly when it comes to VBAC, which has been also confirmed previously by several studies[112, 113].

Conservative treatment of non-tubal ectopic pregnancies

The results of the study have shown that conservative treatment may be the first option for consideration in management of non-tubal ectopic pregnancies. The overall rate of successful treatment was similar to the previous articles[114-116]. Conservative treatment had a low level of failure and allowed to preserve fertility in these women. Our study supported the idea that even cases with the presence of embryo heartbeat may be treated conservatively. However, intrasaccular injection of MTX/ KCl should be performed promptly in such cases. Our results are in line with the published article[117] that intrasaccular injection combined with systemic MTX may be a highly effective approach for the management of viable ectopic pregnancies despite high initial β-hCG values. In addition, the importance to have an established protocol for management of such conditions was emphasized. In BCNatal, Barcelona Center for Maternal-fetal and Neonatal Medicine there were no clinical guidelines before 2018, which probably have led to the failure of primary treatment and the need of additional interventions in some cases.

Two heterotopic pregnancies were managed during the study period. The correct management of this condition is still unclear. Mostly case reports are described in the literature. The data from this study and our previously published case report[118] show

that heterotopic pregnancies may be managed successfully with preservation of the intrauterine pregnancy and delivery at term. However, in the lack of strong clinical guidelines to manage heterotopic pregnancies, each woman diagnosed with such condition should receive an individual approach.

Higher levels of β-hCG at the time of diagnosis and the presence of embryo heartbeat were associated with treatment failure in our study. These findings are in accordance with other data in the literature[119-122]. However, there is still no consensus on a threshold value of β-hCG that best predicts failure of the conservative treatment regimen and more studies are needed[123]. The predictive markers may help the physicians in the decision-making and would allow for a safer patient counselling.

Our findings add information to the existing limited data about management options for women with non-tubal ectopic pregnancy. Use of evidence-based guidelines and protocols for standardized management of rare diagnosis is necessary to individualize and optimize the treatment of the patients.

Knowledge in women with previous CS

The results of the present study show that there is an improvement in knowledge about the benefits of VBAC in the third trimester of pregnancy compared to the first trimester. However, there were no differences in the level of knowledge regarding the risks of CS. Probably there are still some women who see CS as a safer mode of delivery for both their baby and/or for themselves. This pattern has also been described in the previously published studies[8, 9]. Moreover, about 20% in each group wanted to undergo elective repeat CS other than TOLAC. It was reported that factors which influence the women's decisions-making include previous birth experience, concerns about the risks of vaginal birth, evaluation of a mode of birth, current pregnancy situation, information resources and health insurance[124]. Consequently, our results support the importance of providing up-to-date, comprehensive information regarding the risks and benefits of CS and VBAC from caregivers to women in an accessible manner at all stages of pregnancy.

Understanding of the initial level of knowledge, expectations and fears among women is important for improving the healthcare for women with a previous CS. This might become the first step in development of informational materials about the risks of scarred uterus and the mode of delivery for women and their partners in post-partum, in preconception counselling, and in the subsequent pregnancy. Furthermore, it was noted that women with higher educational level were better informed and preferred to get the information from health care providers other than from TV, internet and friends. Therefore, a more individual approach might be needed, considering social and educational determinants.

The present study supports the idea that the information should be provided by health care professionals to women with previous CS as early in pregnancy as possible, both

as written information and orally during the antenatal visits. The adequate and early information may help to prepare woman for TOLAC, having enough time to know about previous delivery, solve doubts, and discuss the preferable mode of delivery at the end of the pregnancy. The approach was also recommended by the guidelines[13, 69, 70].

Strategies to increase the VBAC rate

There was a significant increase in the rate of TOLAC and VBAC in Group II without increasing in the rate of adverse outcomes. This is in agreement with the recent articles and guidelines that VBAC after one previous CS is a safe alternative to elective repeat CS both for mother and infant[13, 69].

Extended use of lactate blood samples from presenting part probably has led to decrease in the number of emergency CSs due to fetal distress and to the lower number of newborns with acidosis. The use of lactate blood samples as a complement to CTG is among clinical guidelines[125] today and was proven to significantly reduce the rate of unnecessary CSs[126].

Induction of labor with prostaglandins in women with scared uterus is associated with a higher risk of uterine rupture and a higher risk of perinatal death due to uterine rupture[127]. Therefore, another method of induction, such as an intracervical Foley catheter was considered. Interestingly, the rate of uterine rupture did not change between Group I and Group II. Probably the discrepancies between the current and previous studies are due to differences in sample sizes or obstetric approaches. To determine the influence of prostaglandins induction on the rate of uterine rupture was not the aim of our study and more research may be needed. Nevertheless, the success rate of induction did not change, which is in agreement with the other articles that Foley catheter might be as effective as prostaglandins[128, 129].

In our study in Group II there was a significant reduction in the number of elective repeat CS due to maternal request and larger number of women underwent TOLAC in the second cohort. In Sweden women are routinely treated for childbirth fear within multidisciplinary teams[130, 131]. It was shown previously that the women who received the psycho-education had better birth experience and would prefer a vaginal birth other than elective CS[130, 132].

An antenatal research clinic to follow-up women with previous CS was established in 2013 and helped to spread the latest information and knowledge regarding risks and benefits of TOLAC and VBAC among women and medical staff and allowed to accumulate experience that may have contributed to the increase in the overall VBAC rate.

In addition to changes in the clinical practice, the obstetric population has changed. In Group II the women tend to be shorter in heights and more often had one or more previous VB. Previous VB is a well-known prediction factor for successful VBAC in

subsequent pregnancies[13, 69, 133]. Thus, a higher number of women with previous vaginal deliveries in Group II might have contributed to higher VBAC rate.

It was concluded that an appropriate management of women with one previous CS and teamwork might increase VBAC rate without a negative impact on outcomes.

Conclusions

- The supportive appointment with an obstetrician combined with an ultrasound examination of the uterine scar may decrease anxiety levels in women after Cesarean section, particularly in highly anxious women. This would enhance the postpartum care and women's overall birth experience.
- Expectant management under close monitoring can be appropriate in small non-viable Cesarean scar pregnancies.
- Conservative treatment is a safe option for treatment of non-tubal ectopic pregnancies. The presence of embryo heartbeat and β-hCG levels at diagnosis may be used as predictive factors of treatment failure. The use of evidence-based guidelines and protocols and individualized approach would optimize the treatment for the patients and allow to lower the rate of complications.
- The study showed an increase in the knowledge about the benefits of VBAC in the third trimester of pregnancy compared to the first trimester. Nevertheless, women still reported the need for more information even after having signed an informed consent for VBAC at the end of pregnancy. A more comprehensive and personalized written information may be crucial to encourage women for TOLAC and to improve the overall birth experience.
- Appropriate management of women with one previous CS might increase the VBAC rate without a negative impact on outcomes. The antenatal teamwork has the greatest contribution to VBAC rate by increasing the number of women undergoing TOLAC.

Future Directions

Based upon the data presented in the thesis, several directions are suggested for the future research.

- There is a need for more studies on the short- and long-term medical and psychological consequences of CS both for mother and child with a specific focus on what factors may increase the risk of psychological disorders postpartum and in subsequent pregnancy. It would be also of great interest to conduct further research on how to prevent the increased levels of anxiety and depression disorders postpartum. Probably the best way to do this would be a prospective study evaluating different strategies for women during their pregnancy.
- There is still scarce of high-quality evidence about management of Cesarean scar pregnancies with the minimum risk of complications and preserving fertility. More research is required to establish international guidelines for treatment of such pregnancies with high level of evidence, ideally coming from randomized controlled trials.
- Strategies to improve women's knowledge about the risks and the benefits of CS and VBAC are necessary to be evaluated. Previous articles regarding women-centred interventions to help women to make an informed decision regarding mode of delivery in subsequent pregnancy did not prove to have a significant effect. Another field of interest might be evaluating the cultural differences and how they influence on women's decision regarding the preferred mode of delivery in the pregnancy after CS. This would help to adjust the existing guidelines and to provide the best possible options for each particular country and hospital.

Populärvetenskaplig Sammanfattning

Bakgrund

Idag är mödrar och barns hälsa över hela världen i fokus. Moderns hälsa är avgörande för både barnets och moderns välmående. Naturlig (vaginal) förlossning förordas i de flesta kliniska riktlinjerna. Trots detta ökar andelen kejsarsnitt (KS) ständigt. Faktum är att KS är ett av de vanligaste kirurgiska ingreppen i många länder. Det är en livräddande operation för kvinnor och nyfödda när komplikationer uppstår. Det är dock också förknippat med kortvariga och långsiktiga hälsokonsekvenser, till och med livshotande, både för mor och barn. Riskerna ökar dessutom med antalet efterföljande KS.

Inte bara fysiskt välbefinnande utan också psykisk hälsa och välmående måste vägas in. Postpartumdepression börjar ofta innan förlossning. Två tredjedelar av alla mödrar kämpar med svår depression med symptom som börjar redan under graviditet och fortsätter postpartum. Bland de viktigaste och mest återkommande psykologiska symptomen hos gravida och nyförlösta kvinnor är depression, låg självkänsla, kroppsuppfattnings problematik och en känsla av att inte ha kontroll. När en kvinna inser att det finns stöd och hjälp att få tenderar hennes symptom att minska och till och med avta i många fall.

Det är viktigt för kvinnor att de under graviditeten och senare i föräldraskapet kan vara trygga i sig själva och i sin roll som mamma.

Syfte och Metoder

Det övergripande syftet med avhandlingen var att utvärdera effekterna av KS med avseende på återhämtning efter förlossningen, vid efterföljande graviditet och förlossning, och att undersöka vilka strategier som bör användas för att öka antal vaginala förlossningar efter KS med en minimal risk för mor och barn.

Det första målet med studie I var att utvärdera om ett extra möte med en erfaren förlossningsläkare kompletterat med ultraljudundersökning av ärret, 6–9 månader efter en KS kan minska nivåerna av ångest inför en ny förlossning. Kvinnornas ångestnivåer bedömdes före och efter möten med hjälp av Spielberger state-trait ångest frågeformulär.

Studie II, en fallrapport som beskriver en framgångsrik hantering av en heterotop graviditet i ett sectioärr. Studien gav upphov till nya frågeställningar som syftade till att bredda kunskapen inom detta område. I studie III utvärderades därför

lyckandefrekvensen för olika behandlingar och komplikationer i graviditeter vid sectioärr och andra utomkvedshavandeskap. Alla fall av utomkvedshavandeskap, inklusive CS-ärrgraviditeter som hanterats under en nioårsperioden samlades in och analyserades. Nya effektivt biomarkörer för prediktion av misslyckande vid konservativ behandling identifierades.

I studie IV syftade till att undersöka hur informerade gravida kvinnor var om risker och fördelar med KS respektive vaginal förlossning efter ett tidigare KS.

Målet med sista studien V, var att jämföra resultat av graviditet och förlossningen hos kvinnor med tidigare KS under två olika tidsperioder, före och efter implementeringen av specifika förändringar i de kliniska rutinerna. Vi inkluderade och utvärderade resultaten av alla omföderskor vid Skånes universitetssjukhus mellan åren 2005-2008 eller 2013-2016.

Resultat

Resultaten i studie I visades att ett extra möte med en erfaren förlossningsläkare, kompletterat med ultraljudundersökning av ärret, minskade ångestnivån signifikant.

Studie II och III visade att expekterande behandling vid små icke-livsdugliga graviditeter i sectioärr kan vara optimalt vid utomkvedshavandeskap. Förekomsten av fosterhjärtslag och höga β-hCG-nivåer vid diagnos kan användas som prediktiva biomarkörer för misslyckande med primär behandling. I studie IV var de viktigaste resultaten att kvinnor i allmänhet var medvetna om möjligheten till vaginal födelse efter KS i en efterföljande graviditet och att majoriteten föredrog vaginal förlossning istället för ett upprepat KS.

Trots detta, svarade ändå en del kvinnor att de inte hade tillräckligt med information och att de ville ha mer information för att ta beslut angående förlossningssätt. Studie V visade att det är möjligt att öka antal vaginala förlossningar efter tidigare KS utan en negativ inverkan på mor eller barn. Det viktigaste bidraget till en lyckad vaginal förlossning efter tidigare KS var ett kollektivt arbete av medicinsk personal i form av information och noggrann förberedelse av kvinnan.

Slutsats

Resultaten av studierna som ingår i denna avhandlingen har gett nya vetenskapliga bevis avseende återhämtning efter förlossningen med KS, efterföljande graviditet och förlossningssätt i nästkommande graviditet. Resultaten av forskningen kan användas för att ge ett bättre stöd för kvinnor, minska deras risker och samtidigt förbättra deras övergripande förlossningsupplevelse. Nya frågeställningar för vidare forskning inom dessa områden har också identifierats.

Acknowledgements

First of all, I would like to thank my supervisor **Olga Vikhareva** for her support throughout my PhD studies. I am thankful for her endless patience, even when I did the wrong things, her advice and inspiration. Thank you for sharing with me your deep clinical and scientific knowledge and showing what it means to work hard with your own example. This thesis would not have been possible without you.

Stefan Hansson, my supervisor, thank you for welcoming me in your research group. I am grateful for your constant support, for being always ready to discuss any issue or concern and for your valuable input to the manuscripts and this thesis.

Marta López, my supervisor at the University of Barcelona, thank you for making my stay in Spain one of the best experiences during the PhD studies. I really appreciate your support, our interesting scientific discussions and that you have always given me time and constructive comments.

Karin Sjöström, for introducing me a new field of psychology and contribution to the research and article.

Mats Pihlsgård, for statistical support and paper review.

All the co-authors in Sweden **Andreas Herbst, Karl Kristensen, Charlotte Dahlbäck, Gisela Skott Rickle**, for your review and comments on the paper.

Maria Walles, for creating a friendly atmosphere and for her administrative support.

Anette Saltin, for the help with the documents and patience when I was late with deadlines.

All **colleagues** and **staff** at the Skåne University Hospital for helping me with the daily routines. Special thanks to **Eva Löfström** for the help with scheduling ultrasound examinations.

I would also like to thank my colleagues at the Fetal Medicine Research Center, Barcelona where I spent my mobility period:

Francesc Figueras, for creating a productive and friendly environment and for reviewing and commenting on the manuscripts.

Eduard Gratacós, for taking your time to welcome me in Spain and for valuable contribution to the article.

All the co-authors in Spain **Silvia Gómez, Montse Palacio, Silvia Escura, Teresa Cobo, Josep Maria Martinez, Esther Crespo,** for your important contribtuion to the research and manuscripts.

Maite Aguilera, for your administrative support.

The European Commission, for providing me with a scholarship of Erasmus Mundus Joint Doctorate Program in Fetal and Perinatal Medicine.

Special thanks to my family and friends:

My dearest parents **Elena** and **Kamil**, for always supporting me in any life situations and for your valuable advice.

Natalia Girchik, for opening Sweden to me, for caring and being ready to help at any time, for our dinners and interesting conversations.

My friend in my home city Kazan, **Alina**, you always believed in me and have taken you time talking to me when I had moments of despair.

My husband **Aydar**, for being ready to follow me to Sweden, support and patience when I was busy during many evenings and weekends. You have made my life much easier and cheerful when I had difficult times.

My son **Albert**, for the joy you brought into my life and for understanding when I did not have enough time to spend with you.

Finally, **all women** who participated in the studies and made it all possible both in Sweden and Spain.

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Paper I

A supportive obstetric consultation combined with Ultrasound Examination of hysterotomy scar reduces anxiety in women after Cesarean section.

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ABSTRACT

Objective: To evaluate whether an appointment with a senior obstetrician combined with an ultrasound examination reduces levels of anxiety in women after Cesarean section. Factors influencing anxiety levels were also analyzed. Women's satisfaction with the appointment was evaluated.

Methods: A prospective observational study was conducted between January 30th 2018 and January 30th 2019 at Skåne University Hospital, Malmö/Lund in Sweden. Women underwent an appointment with a senior obstetrician 6 to 9 months after their first Cesarean section. Before the appointment, women were asked to fill in the state and trait subscales of the Spielberger State-Trait Anxiety Inventory (Form Y) and the Beck's Depression Inventory. The women's experience of the childbirth was discussed and an ultrasound examination with saline contrast sonohysterography was performed to assess the appearance of the hysterotomy scar. The obstetrician conveyed a positive view on future pregnancy and labor. After the appointment, the participants filled in the state scale and the Client Satisfaction Questionnaire (CSQ-8). A cut-off limit of ≥ 40 was used to detect clinically significant trait anxiety on the STAI scale. The study group was divided into low trait anxiety (< 40) and high trait anxiety (≥ 40) groups for comparisons.

Results: 147 women were included in the study. Of those, 114 (78%) had lower trait score <40 (mean 29.2±5.4) and 33 (22%) had higher trait score ≥ 40 (mean 47.4±6.5). Mean difference of state score in the lower trait anxiety group before and after the examination was 4.8±5.6 (95% CI 7.20 to 11.97, p<0.0001). In the higher trait anxiety group, mean difference of state score was 9.2±6.5 (95% CI 3.77 to 5.82, p<0.0001). Most of the women, 133 (91 %), were highly satisfied with the appointment.

Conclusions: A supportive obstetric consultation combined with an ultrasound examination of the uterine scar decreased anxiety levels in women after Cesarean section, particularly in patients with higher anxiety.

Keywords: Cesarean section, ultrasound, uterine scar, STAI

INTRODUCTION

There is a difference in postpartum self-reported general health status scores between women who delivered vaginally and by CS [1]. One study found a significant worsening in physical and mental health, increase of bodily pain and fewer daily activities in women after CS [1]. After CS, women have a higher risk of anxiety disorders, depression and post-traumatic stress symptoms [1-4]. One study found that anxiety and depression symptoms persisted up to one year after an elective CS (ELCS), particularly in women who were highly worried or depressed before delivery [4]. A negative birth experience is more common after emergency CS (EMCS) [5]. A bad experience of labor may negatively influence women's perception of parenthood as well as their attitude towards subsequent pregnancies and deliveries [6], which in turn may be related to an increasing awareness of the increased risks of CS postpartum and in subsequent deliveries [7-9].

It is reported that women receive insufficient information after their CS [10, 11]. According to our experience, women worry about the condition of the uterine wall after a CS. The routine postpartum follow-up consultation by a midwife is mostly about parenting issues and does not usually cover women's concerns about the uterine healing process and the circumstances surrounding their previous CS.

The appearance of the uterine scar can non-invasively and successfully be evaluated by ultrasound [12, 13]. Transvaginal ultrasound examination with or without saline contrast sonohysterography is reported to be a well-validated technique to assess uterine scar after CS in non-pregnant women [12, 13].

The literature on how to help women process and facilitate their birth experience is scarce, particularly after a CS. An opportunity to discuss circumstances of the previous CS, getting information about condition of the uterine scar with advice on the following pregnancies may thus be essential to reduce mental distress and improve psychological well-being after CS.

The aim of the study was to evaluate whether an appointment with a senior obstetrician combined with an ultrasound examination, may reduce levels of anxiety in women six to nine months after their CS. Factors known to influence anxiety were analyzed and satisfaction with the appointment was evaluated.

METHODS

The study was performed at Skåne University Hospital, Malmö/Lund in Sweden. In 2018, there were 8848 deliveries and 1566 (18%) of these were CS. In the CS group of women, 1051 underwent their first CS. The recruitment period was between January 30th 2018 and January 30th 2019. All women who had their first CS between 37^{+0} and 41^{+6} weeks of gestation, irrespective of the indication for CS, were asked to participate in the study six to nine months after their study. The inclusion criteria were: non-pregnant women, and speaking and reading Swedish fluently. We searched for eligible women in the hospital patient records system. To those who fulfilled the inclusion criteria, letters of invitation to participate in the study with detailed information about the study procedure were sent by post. About 50 letter per month were sent to 550 women. The response rate was 60 to 70 %. Of those who responded about 50 % were eligible for the study which resulted in 151 women. Women, who agreed to participate, signed a written informed consent and were given an appointment time.

Before the appointment, women were asked to fill in the Spielbergers´ State-Trait Anxiety Inventory (STAI, Form Y) [14] to assess their levels of anxiety and Beck's Depression Inventory (BDI) [14] to detect levels of depressive symptoms. The women were given privacy to fill in all questionnaires, having a possibility to ask for clarification if any of the questions was felt unclear. After the forms were completed, information of current contraception, breast-feeding and day of menstrual cycle were registered in a standardized research protocol. A urine pregnancy test on all participants was taken to exclude any unexpected pregnancy before the ultrasound examination. A senior obstetrician with experience of ultrasound examinations of Cesarean hysterectomy scar conducted a semi-structured interview with open-ended questions related to the circumstances of the previous CS. The women got the opportunity to speak freely about any concerns regarding the previous CS delivery and their fear of possible influences on future pregnancies. A follow-up from an early stage of the subsequent pregnancy were offered to all women. Before the appointment, the obstetrician was prepared for the conversation by scrutinizing women’s details of the previous CS. Psychiatric and obstetric history that potentially could influence anxiety were investigated in all women. Gestational age, indication for the CS, cervical dilatation at the operation, duration of active labor, blood loss and complications were registered. All information, including biological and social background data, was obtained from the hospital data records and registered in the standardized research protocol.

The same obstetrician who conducted the semi-structured interview performed an ultrasound examination. The examination was carried out with the women in the lithotomy position with an empty bladder using a GE Voluson E8 ultrasound system (General Electric, Zipf, Austria) equipped with a 2.8–10-MHz transvaginal transducer. The uterus wall was evaluated for the appearance of the Cesarean scar,

with and without saline contrast sonohysterography, with the same method as described in previous studies [12, 15]. The ultrasound images were evaluated during the ultrasound examination and representative images were stored in the digital image storing system Siemens Syngo® Dynamics, version 5.0 (Siemens Medical Solutions Health Services Corp., Malvern, PA, USA). All women were informed about the ultrasound examination results. Based on the current knowledge, it is not possible to state whether a defect in the hysterotomy scar detected by ultrasound in non-pregnant women may influence the outcome in subsequent pregnancy and delivery [16]. Therefore, a supportive stance concerning subsequent pregnancy and delivery was conveyed to the women, regardless of the appearance of the uterine scar area. Any abnormal findings detected besides the uterine scar were managed in accordance with routine clinical guidelines. Immediately after the appointment, the participants filled in the STAI -state scale once more and the Client Satisfaction Questionnaire (CSQ-8) was distributed.

The STAI (Form Y) consists of 40 statements and is a well-established self-rating scale with high stability and validity often used in surgical, gynecological, medical and psychiatric clinical anxiety research [17-21]. The first 20 statements assess state anxiety i.e. assess how a person feels at a particular moment or a chosen period. The state anxiety scale is highly sensitive in measuring acute anxiety. In this study, subjects were asked to rate their anxiety before the examination, that is "right now, at this moment." The subsequent 20 items assess trait anxiety; i.e. the relatively stable anxiety proneness or how the individual generally perceives stressful situations as dangerous or threatening. Persons with higher trait anxiety respond to stressful situations with higher elevations in intensity of their state anxiety. Trait anxiety has been found to be very stable over time with a test–retest reliability range from 0.73 to 0.86 in a normative sample [14]. Answers are given on a 4-point Likert scale. Scores on the state and trait scales range from 20 to 80 points respectively, with higher scores indicating higher levels of anxiety symptoms. The state and trait anxiety scales usually strongly correlate (r= 0.70) [14]. In large normative samples of female working adults and college students, 19 to 39 years of age, the mean values of state and trait anxiety range from 35.2 to 38.8, and 34.8 to 40.4, respectively. A cut-off $\geq$ 40 has been suggested to detect clinically significant anxiety symptoms for the trait anxiety scale. The study population was divided into two groups of low trait anxiety (< 40) and high trait anxiety ($\geq$ 40) for comparisons.

The Beck Depression Inventory Second Edition (BDI-II) is one of the most widely used self-report measures of depression in both research and clinical practice, with high validity and good psychometric properties [22]. This inventory does not measure clinical depression but rather different levels of depressive symptoms. The questionnaire consists of 21 items and answers are rated on a four-point scale from 0 = low to 3 = high. The total score ranges from 0 to 63. For persons clinically examined for depression, scores from 0-13 represent minimal depressive symptoms, scores of 14-19 indicate mild, scores of 20-28 indicate moderate, and scores of 29-

63 indicate severe depressive symptoms. In this study, a cut-off ≥ 20 defined high depressive scores. The BDI questionnaire was used in this study to detect women with higher depressive scores that may be related to anxiety symptoms.

The eight-item Client Satisfaction Questionnaire (CSQ-8), Swedish version, is a validated eight question self-administered form to assess satisfaction with health services [23, 24]. Responses are based on a four-point scale from 1 to 4. Total scores range from 8 to 32 with higher values corresponding to higher satisfaction with treatment. Scores of 8-20 represent dissatisfaction, 21-24 as mildly satisfied, 25-28 as satisfied and 29-32 highly satisfied. Items include satisfaction with appointment, satisfaction with consultation provided at the appointment, and a question of whether the respondent would recommend the same appointment to a friend.

An ethical approval for the study was obtained from the Ethics Committee of the Medical Faculty of Lund University, Sweden, reference number 2018/432.

The statistical software package SPSS 24.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. Statistical power for the STAI state subscale was estimated to, using a two-sided Students *t* test with a 5% significance level and a mean (SD) of 35 (10) and a sample size of 100 women, have a power of 99% to detect a difference of ten points. Differences in categorical data were analyzed using chi-square and Fisher's exact tests. Student's t-test was used for comparisons for continuous normally distributed variables and Mann-Whitney U test was used for skewed data. An analysis of state anxiety before and after the consultation was performed in women with different employment status. Paired *t* -tests were used to assess differences in state anxiety scores before and after the appointment. Pearson's correlation coefficient was used to analyse correlations between continuous variables. The level of significance was set at $p < 0.05$, two-tailed.

RESULTS

151 women agreed to participate and filled out the forms. Three women were excluded because of missing data on the STAI trait scale and one woman because of missing data on the BDI. Thus, 147 women were included in the study. Of these, 114 (78 %) had low trait anxiety scores and 33 (22 %) had high trait anxiety scores. In total, there were 90% (132/147) women with BDI score indicating minimal depressive symptoms, 6% (9/147) with mild depressive symptoms and 4% (6/147) with scores, indicating moderate to severe depressive symptoms. There was a positive statistical correlation between BDI scores and trait anxiety scores ($r = 0.65$, $p<0.0001$); between BDI scores and state anxiety scores ($r = 0.60$, $p<0.0001$); and between trait and state anxiety scores ($r=0.73$, $p<0.0001$). Background characteristics for the low and high trait anxiety groups and the total sample are presented in Table 1. In the group of women with high trait anxiety scores, the mean

BDI scores and the mean state anxiety scores were statistically significantly higher both before and after the appointment, compared to women with low trait anxiety (Table 2). In both low and high trait anxiety groups, state anxiety scores decreased significantly after the appointment, $p<0.001$ (Figure 1).

In 11 of 147 (8%) women, state anxiety scores remained or increased after the appointment. We found that all women had either pre-existing psychiatric comorbidity or previous dramatic obstetric circumstances (Figure 2).

No differences in trait or state anxiety levels were found between different occupational categories (Table 1). We found a non-significant trend between groups of low and high trait- anxiety for women unemployed. Comparison showed that unemployed women (n=8), had higher mean trait anxiety scores compared to the women employed (n=139), (40.5±11.6 vs. 32.9±9.2, p=0.03). State anxiety scores before and after appointment were similarly higher in the women unemployed (45.5±11.3 vs. 30.5±8.6, p=0.001 and 31.4 ±9.2 vs. 25.1±6.1, p=0.016, respectively).

There were no statistically significant differences in trait anxiety and BDI scores between women who had an EMCS or ELCS (31.8±8.7 vs. 34.0±9.8, p=0.16 and 5.8±4.4 vs. 6.7±6.3, p=0.77 respectively). Neither did state anxiety scores differ significantly between groups of EMCS and ELCS before and after the appointment (30.1±8.3 vs. 31.8±9.8, p=0.43 and 24.4±4.7 vs. 26.0±7.1, p=0.44, respectively).

Satisfaction with the appointment was assessed in 145/147 because of missing data in two cases. Most of the women 133 (91%) were highly satisfied with the appointment, eight (5%) were satisfied and four (3%) were mildly satisfied. None of the women reported to be unsatisfied with the appointment. In the group of 11 women with equal or higher state anxiety scores after the appointment, CSQ-8 score showed that they were satisfied or very satisfied with their medical appointment.

DISCUSSION

The results of the present study showed that anxiety scores were lower after the appointment with an obstetrician supplemented by an ultrasound examination in women 6-9 months after a CS. The higher the state anxiety before the appointment the more effect of the appointment was noted. Previous studies showed that women considered that they had received insufficient information about circumstances and indications for the CS. Moreover, the women worried about the healing process and the anatomical condition of the uterus after surgery [9, 10]. The ultrasound examination may give the obstetrician an opportunity to discuss and explain the uterine healing process more thoroughly. Furthermore, an obstetrician may give a more detailed information regarding the circumstances of the previous CS compared

to a midwife at the postnatal visit. This information may have contributed to the decrease in the state anxiety levels. During the appointment, an advice regarding future pregnancies and options for the mode of delivery in a positive manner towards vaginal birth after CS might already be given. Speculatively, it could be suggested that this type of early information to women also may contribute to an increase in the rate of vaginal deliveries after a CS.

In those women where anxiety levels increased after the appointment there were preexisting mental conditions and obstetric traumatic events (Figure 2). In ten out of eleven women this information was partially missed by the obstetrician in the preparation stage before the appointment. This suggest that a thorough preparation including not only obstetrical and gynecological history but also psychological comorbidities is required. This approach together with a reassuring ultrasound examination may help to process previous trauma and create a more positive attitude towards subsequent pregnancies and deliveries.

There were no statistical significant differences in background characteristics between women with low and high state anxiety levels, but a trend was found between groups of employed and unemployed women. A separate analysis revealed that unemployed women had higher trait and state anxiety scores than those employed. Women who were unemployed seemed to be a socially vulnerable group with higher anxiety. This result is in agreement with many published studies where unemployment showed to have a negative impact on mental wellbeing [25]. In this study, women were less anxious than the normative sample for Spielberger´s reference values for women [14]. Furthermore, their mean depressive scores were low. This means that it is unlikely that the study population as a whole differed from a normal population regarding mental illnesses.

We did not find any statistical significant differences in anxiety between women receiving an EMCS or an ELCS. The state scores were somewhat higher in the ELCS group, but did not reach statistical significance. Probably, it may be so that women are more worried about the scar and the healing process than the type of CS, whether it was elective or emergent. This is in agreement with one other Swedish study [3], where the authors did not find any differences of mental distress in women having an EMCS or an ELCS. However, in one other study it was shown that anxiety scores were statistically significantly higher in a group of women after an ELCS compared to a vaginal delivery and an EMCS [26]. The discrepancies may be explained by differences between populations and obstetrical approach in different countries. The work by both Ryding et al. [3] and current study are based on Swedish populations, whereas another study [26] was performed in Italy. Differences in cultural perspectives on vaginal birth between Sweden and Italy have been described previously [27].

To the best of our knowledge, this is the first study evaluating the impact of an appointment with the purpose to reduce anxiety in women after a CS by a supportive ultrasound examination.

The limitation of the study is that a psychiatrist using a clinical examination did not examine an eventual diagnosis of depression or anxiety. However, it is considered that an experienced obstetrician has knowledge enough to detect severe depression or psychological instability. In this study, women were less anxious than the normative sample for Spielberger´s reference values [14]. It may suggest that the risk for not detecting any serious mental condition was low. Another limitation is that no control group was used in the study. It was methodologically difficult because routine midwife postpartum visits take place at 8-10 weeks postpartum, whereas in this study appointments were arranged at 6-9 months after CS. Moreover, the midwives' antenatal clinics are geographically dispersed and also belong to a separate organization. However, the psychological rating scales used in this study are well validated among many different groups of patients and are widely used in both clinical practice and research [18-20, 28]. The rating scales may hence be used alone for measures of anxiety and depression.

The findings of the study emphasize the importance of special consideration for women after CS, particularly who are socially or constitutionally more vulnerable or have experienced trauma in relation to their CS. This is in line with the current guidelines and published data, which emphasizes the importance of relevant information for women and their partners in the postpartum period [10, 11, 29].

CONCLUSIONS

A supportive obstetric consultation combined with an ultrasound examination of the uterine scar may decrease anxiety levels in women after CS, particularly in patients with high trait anxiety and in vulnerable groups.

Table 1. Background characteristics for the total sample and in low and high trait anxiety groups.

Characteristics	Total population N=147	Low trait anxiety < 40 n=114	High trait anxiety ≥ 40 n=33	P-value
Age, years	30.37±3.04	30.4±3.1	30.3±3.0	0.79[1]
Occupation				
Professional	69 (46.9)	56 (49.1)	13 (39.4)	0.33
Technician	27 (18.4)	21 (18.4)	6 (18.2)	0.98
Managers, directors	12 (8.2)	11 (9.6)	1 (3.0)	0.30
Secretary	22 (15.0)	15 (13.2)	7 (21.2)	0.25
Unemployed	8 (5.4)	4 (3.5)	4 (12.1)	0.08
Student	9 (6.1)	7 (6.1)	2 (6.1)	1.00
Social satisfaction				
Satisfied	147 (100.0)	114 (100.0)	33 (100.0)	1.0
Partner				
Yes	145 (98.6)	112 (98.2)	33 (100)	1.0
No	2 (1.4)	2 (1.8)	0	
Parity				
1	120 (81.6)	96 (84.2)	24 (72.7)	0.20[2]
≥ 2	27 (18.4)	18 (15.8)	9 (27.3)	
Pregnancy				
Expected and welcome	140 (95.2)	107 (93.9)	33 (100.0)	1.0
Unexpected but welcome	7 (4.8)	7 (6.1)	0	
Gestational age, weeks	39.3±1.6	39.3±1.6	39.2±1.4	0.82[1]
CS				
ELCS	47 (32.0)	39 (34.2)	8 (24.2)	0.40[2]
EMCS	100 (68.0)	75 (65.8)	25 (75.8)	
Indication for CS				
Maternal request	13 (8.8)	10 (8.8)	3 (9.1)	1.0[2]
Failure to progress	35 (23.8)	28 (24.6)	7 (21.2)	0.82[2]
Non-cephalic, macrosomia or disproportion	35 (23.8)	30 (26.3)	5 (15.2)	0.25[2]
Fetal distress	44 (29.9)	31 (27.2)	13 (39.4)	0.20[2]
Placenta praevia	4 (2.7)	2 (1.8)	2 (6.1)	0.22[2]
Maternal conditions	13 (8.8)	10 (8.8)	3 (9.1)	1.0[2]
Foetal abnormalities	3 (2.0)	3 (2.6)	0	1.0[2]
Experience of CS				
Unstressful	48 (32.7)	38 (33.3)	10 (30.3)	0.74
Stressful but understandable	79 (53.7)	63 (55.3)	16 (48.5)	0.49
Stressful and not understandable	6 (4.1)	5 (4.4)	1 (3.0)	1.00
Extremely stressful	14 (9.5)	8 (7.0)	6 (18.2)	0.05
Previous psychiatric conditions				
Healthy	112 (76.2)	92 (80.7)	20 (60.7)	0.02
Depression	17 (11.5)	10 (8.7)	7 (21.2)	0.049
Anxiety	12 (8.1)	8 (7.0)	4 (12.1)	0.47
ADHD/ADD	2 (1.4)	2 (1.8)	0 (0.0)	1.00
Bipolar	2 (1.4)	1 (0.9)	1 (3.0)	0.40
Other	2 (1.4)	1 (0.9)	1 (3.0)	0.40

Data are given as mean ± SD or n (%) unless otherwise specified.
CS – Cesarean section, ELCS – elective Cesarean section, EMCS – emergency Cesarean section.
[1] Student's t-test
[2] Fisher's exact test

Table 2. Psychological variables for the total sample and in low and high trait anxiety groups.

Measurements	Total population N=147	Low trait anxiety < 40 n=114	High trait anxiety ≥ 40 n=33	P-value*
STAI trait anxiety	33.3±9.5 32 (20 – 62)	29.2±5.4 29.5 (20 – 39)	47.4±6.5 45 (40 – 62)	<0.0001
STAI state anxiety before the appointment	31.3±9.4 29 (20 – 60)	28.3±7.2 27 (20 – 60)	41.5±9.0 41 (24 – 54)	<0.0001
State anxiety after the appointment	25.5±6.4 23 (20 – 54)	23.5±4.5 21.5 (20 – 40)	32.3±7.5 31 (21 – 54)	<0.0001
Mean difference in state anxiety before and after the appointment	5.8±6.1 4 (-7 – 33)	4.8±5.6 4 (-6 – 33)	9.2±6.5 9 (-7 – 28)	<0.0001
BDI score	6.4±5.8 5.0 (0 – 30)	4.8±4.3 4 (0 – 23)	11.9±6.7 12 (0-30)	<0.0001
CSQ-8	30.9±1.9 32 (23 – 32)	31.2±1.6 32 (23 – 32)	29.9±2.4 31 (24 – 32)	<0.0001

Data are presented as mean±SD, median (range).
CSQ-8 - Client Satisfaction Questionnaire.
*Mann-Whitney U test.

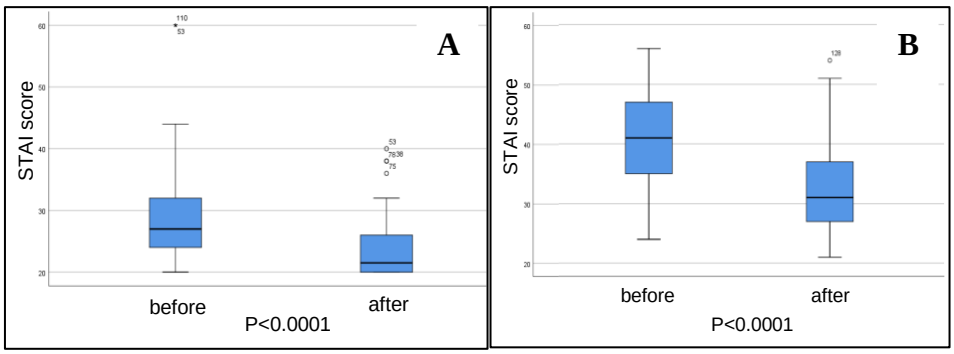

Figure 1. Spielberger state anxiety scores before and after the appointment in the low trait anxiety (A) and high trait anxiety (B) subgroups.

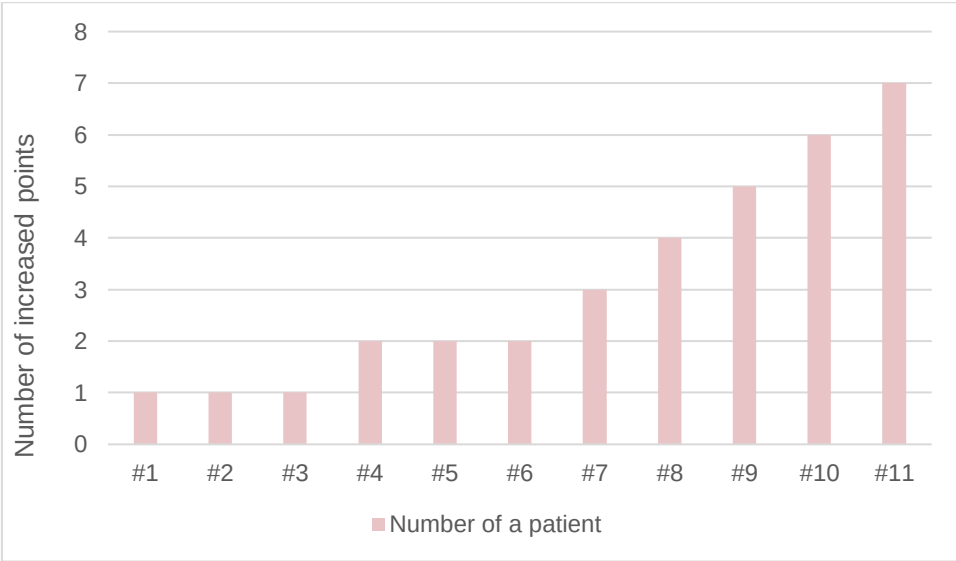

Figure 2. Increase in state scores after the appointment in 11 patients.
Background factors in women who had an increase in anxiety after appointment: #1 – diagnosed unplanned pregnancy at the appointment, #2-6 and #8-10 – highly traumatic birth experience, #7 – bipolar disorder type I, #11 – foetal death due to placenta abruption.

Acknowledgements

We are grateful to Dr. Eva Biringer at the Department of Research and Innovation, Helse Fonna HF, for her advice and support during the process of writing the present paper.

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Paper II

Vikhareva et al. Journal of Medical Case Reports (2018) 12:179
https://doi.org/10.1186/s13256-018-1713-0

Journal of Medical Case Reports

CASE REPORT Open Access

Normal vaginal delivery at term after expectant management of heterotopic caesarean scar pregnancy: a case report

Olga Vikhareva[1,2*], Ekaterina Nedopekina[1,2] and Andreas Herbst[1,2]

Abstract

Background: Heterotopic pregnancy with a combination of a caesarean scar pregnancy and an intrauterine pregnancy is rare and has potentially life-threatening complications.

Case presentation: We describe the case of a 27-year-old white woman who had experienced an emergency caesarean delivery at 39 weeks for fetal distress with no postpartum complications. This is a report of the successful expectant management of a heterotopic scar pregnancy. The gestational sac implanted into the scar area was non-viable. The woman was treated expectantly and had a normal vaginal delivery at 37 weeks of gestation.

Conclusion: Expectant management under close monitoring can be appropriate in small non-viable heterotopic caesarean scar pregnancies.

Keywords: Heterotopic caesarean scar pregnancy, Expectant management, Vaginal delivery

Background

Heterotopic caesarean scar pregnancy (CSP), in which one gestational sac is located in the caesarean scar area and the other one is a normal intrauterine pregnancy, is rare and may have potentially life-threatening complications. The correct management of this condition is unclear. It is a challenge to manage a heterotopic CSP with preservation of the intrauterine pregnancy minimizing the risks for mother and child.

Transvaginal sonography is a valuable diagnostic tool in the management of such pregnancies [1]. Currently, we offer women with one previous caesarean section participation in an ongoing study of transvaginal ultrasound examinations in each trimester. The study provides support to identify patients with high risk of uterine rupture/potential placental complications to make an individual plan for pregnancy surveillance and delivery.

We have not found previous reports on successful expectant management of spontaneous heterotopic CSP with the preservation of intrauterine pregnancy resulting in a normal vaginal delivery.

Case presentation

We describe the case of a 27-year-old white woman who had experienced an emergency caesarean delivery at 39 weeks for fetal distress with no postpartum complications. As part of our ongoing study "Vaginal delivery after caesarean section", she underwent saline contrast sonohysterography 6 months after the caesarean section. The caesarean scar had a small indentation and the remaining myometrium over the defect was 7.5 mm (Fig. 1a).

In the current pregnancy, she had a dating scan at around 11 weeks with no remarks. She came for a transvaginal ultrasound examination at around 13 weeks as part of our study. This scan revealed a duplex pregnancy with one viable intrauterine fetus with normal anatomy and placenta located high on the anterior wall and a small gestational sac (8 mm) with a yolk sac without embryo was located in the caesarean scar (Fig. 2a). There was no extensive vascularity surrounding the sac. One corpus luteum was found in each of the two ovaries. She was asymptomatic.

She was informed that not enough evidence existed to advise a specific management of this condition. After

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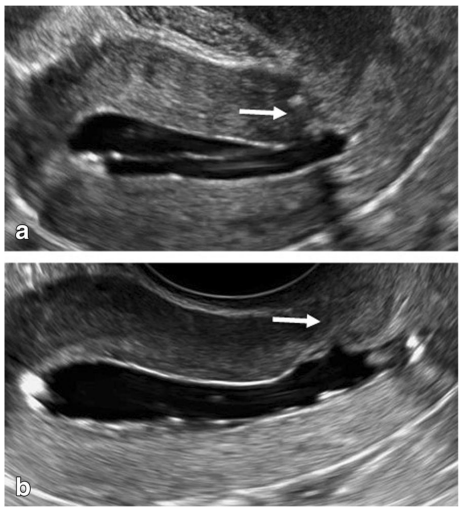

Fig. 1 Saline contrast sonohysterography images. The *arrows* indicate the caesarean section scar 6 months after the index caesarean (**a**) and 6 months after the end of the heterotopic caesarean scar pregnancy by vaginal delivery (**b**). The thickness of the remaining myometrium appeared almost unchanged

discussion with her and her husband, expectant management was chosen with a new ultrasound examination after 5 weeks.

She came to our ultrasound department at 18 weeks, 22 weeks, and 30 weeks of gestation. She remained asymptomatic. The ectopic gestational sac was not visualized with transvaginal or transabdominal scans at the 18 weeks examination (Fig. 2b). The niche in the scar and the thickness of the thinnest part of the remaining myometrium appeared unchanged at all visits. The intrauterine pregnancy developed normally with no signs of abnormal placentation. At 30 weeks of gestation the ultrasound appearance of the scar area did not indicate any contraindications for vaginal delivery. The thickness of the lower uterine segment (LUS) was 4.9 mm (Fig. 2c). In agreement with our patient, vaginal delivery was planned. The staff of the labor ward was fully informed.

She was admitted to the labor ward with irregular contractions in week 37 + 0. Her cervix dilated to 3 cm with no further progress. Due to that oxytocin augmentation was administered for 3 hours. The duration of active labor was 6.5 hours. A healthy male neonate weighing 2985 g was delivered, with Apgar scores 9–10 at 1 and 5 minutes and umbilical cord pH 7.27. The placenta delivered spontaneously and total blood loss was 250 ml. The postpartum period was without any complications, and she was discharged home the next day.

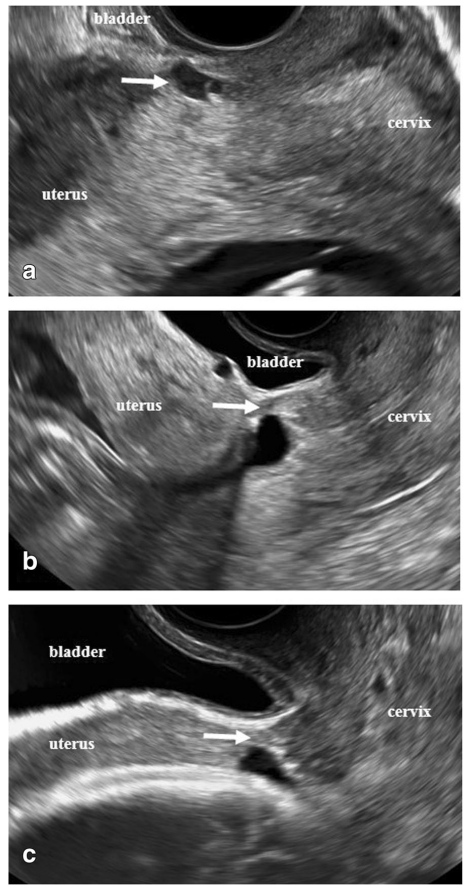

Fig. 2 Transvaginal sonographic images. The *arrows* indicate the appearance of the cesarean scar area at the presence of the scar pregnancy at 13 + 2 (**a**) and after reabsorption of the scar pregnancy at 22 + 0 (**b**) and at 30 + 2 (**c**) weeks of gestation

At a follow-up visit 6 months postpartum, saline contrast sonohysterography showed no signs of the previous CSP, and the remaining myometrium over the hysterotomy scar defect was 5.7 mm (Fig. 1b).

Ethical approval for the ongoing study was obtained by the Ethics Committee of the Medical Faculty of Lund University, Sweden, reference number 2013/176. Our patient has given permission for publication of this case report in a scientific journal.

Discussion and conclusions

Management of heterotopic CSP with an intrauterine gestation is a challenge. Treatment options for CSP include

expectant management, and medical or surgical termination [1–4].

The use of methotrexate has been reported in management of ectopic gestations, but in heterotopic pregnancies with preservation of intrauterine pregnancy this may cause a teratogenic effect with fetal anomalies [5, 6].

A few case reports have described treatment of heterotopic CSP viable pregnancies with local injection of potassium chloride. This method is commonly used for fetal reduction in multiple pregnancy [7–9]. Treatment with potassium chloride is associated with an increased risk of abdominal pain, pregnancy loss, excessive vaginal bleeding, prematurity, need for subsequent surgery, and spontaneous rupture of membranes and subsequent chorioamnionitis [1, 8–12].

Laparoscopic treatment can be an option for removal of an ectopic scar pregnancy, but there is increased risk of hemorrhage and miscarriage [7, 13–15].

Michaels *et al.* suggested that expectant management can be appropriate in early gestations with no heartbeat, often resulting in complete absorption of the trophoblast [10]. Our patient had no bleeding or abdominal pain. The gestational sac located in the scar was non-viable with no extensive vascularity.

It is difficult to study possible changes in the tissues of the caesarean scar area after reabsorption of CSP. With ultrasound one can appreciate the thickness of LUS during the pregnancy, but not the quality of the myometrium.

Interestingly, it was found that our patient had a small defect in the uterine scar detected at ultrasound 6 months after caesarean section. Jurkovic *et al.* reported 18 cases of CSP over a 4-year period [1]. They observed that the majority of scars were well-healed. These data suggest that the size of a defect in the scar does not increase the risk of CSP; however, more studies are needed.

Our patient had a "normal" dating scan at 11 weeks. The early diagnosis of a heterotopic CSP is easy to miss, in particular with presence of an intrauterine viable embryo. Serum human chorionic gonadotropin (hCG) is of little value as long as an intrauterine pregnancy is ongoing. Transvaginal ultrasound is the best tool for diagnosis and management of such pregnancies. In our ongoing study "Vaginal delivery after caesarean section" we assess multiple parameters: scar area/scar pregnancy/potential placental complications. These ultrasound characteristics and clinical evaluation together with close monitoring provide support for the obstetrician in management of these women.

The literature is sparse and we still lack evidence and strong clinical guidelines to manage heterotopic pregnancies. Each woman diagnosed with scar implantation should receive an individual approach.

Abbreviations

CSP: Caesarean scar pregnancy; hCG: Human chorionic gonadotropin; LUS: Lower uterine segment

Availability of data and materials

Data are available in internal digitalized record systems of Skåne University Hospital.

Authors' contributions

All authors EN, AH, and OV contributed to the analysis and interpretation of the data. The first draft was written by EN and OV and all the authors revised it critically and approved the final version to be published.

Ethics approval and consent to participate

Ethical approval was obtained by the Ethics Committee of the Medical Faculty of Lund University, Sweden, reference number 2013/176.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 13 February 2018 Accepted: 8 May 2018
Published online: 21 June 2018

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Paper III

European Journal of Obstetrics & Gynecology and Reproductive Biology 257 (2021) 6–10

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Conservative treatment in non-tubal ectopic pregnancy and predictors of treatment failure

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ARTICLE INFO

Article history:
Received 19 August 2020
Received in revised form 24 November 2020
Accepted 27 November 2020
Available online xxx

Keywords:
Non-tubal ectopic pregnancy
Conservative treatment
Failure of treatment
Intrasaccular injection

ABSTRACT

Objectives: To find possible predictive factors to predict the failure of conservative treatment of non-tubal ectopic pregnancy. For that purpose, we assessed the rate of failure, complications and need for additional interventions of the different primary treatment regimens in non-tubal ectopic pregnancies that occurred in our center.

Study design: Retrospective single-center study conducted at Hospital Clínic of Barcelona (Spain). Conservative treatment regimens included medical (systemic single or multiple dose methotrexate; ultrasound-guided intrasaccular injection of methotrexate or chloride potassium; surgical (oophorectomy in case of ovarian ectopic pregnancy, surgical curettage). The main outcome measures were success of primary treatment and the need for additional interventions. The secondary outcomes were success rate of conservative treatment, incidence of complications, days to discharge from the hospital, days until negative β-hCG, days until complete resolution of the process. Possible predictor factors for primary treatment failure were assessed.

Results: A total of 39 cases were included. Primary treatment was successful in 74 % (29/39). The rate of failure of primary treatment was higher in the group with presence of embryo heartbeat than in the group without, 46 % vs. 15 % respectively ($p < 0.0001$). Among the cases that required additional treatments, none of them required hysterectomy. Presence of embryo heartbeat significantly increased the likelihood of failure of the primary treatment (OR 4.71, 95 % CI 1.03–21.65, $p < 0.05$). Every doubling of the β-hCG levels increased the risk of treatment failure by 54 % (OR 1.54, 95 % CI 1.03–2.39, $p < 0.05$).

Conclusions: Conservative treatment is a safe option for treatment of non-tubal ectopic pregnancy. The presence of embryo heartbeat and β-hCG levels at diagnosis may be used as predictive factors of failure of conservative treatment.

Introduction

Non-tubal ectopic pregnancies refer to the implantation of an embryo in the cervix, interstitial portion of the tube, Cesarean scar, ovary or abdominal cavity. It occurs in about 10 % of all ectopic pregnancies and is associated with maternal morbidity and mortality [1,2]. The incidence of non-tubal ectopic pregnancies has increased in the recent years due to a rise in the frequency of Cesarean sections (CS) and assisted reproductive techniques [3,4].

Classical treatment of uterine ectopic pregnancy used to require hysterectomy with the subsequent permanent loss of fertility. Nevertheless, different conservative strategies have been developed to preserve fertility and to avoid severe complications. The options for conservative treatment include: medical therapy with systemic methotrexate, ultrasound-guided intrasaccular aspiration and injection of methotrexate or potassium chloride (KCl), surgical curettage or other minor surgical treatments preserving the uterus, selective artery embolization and expectant management [1–7]. However, specific guidelines for management of non-tubal ectopic pregnancies are scarce, and there is low level of

Abbreviations: CS, Cesarean section; KCl, potassium chloride; β-hCG, human chorionic gonadotropin.

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https://doi.org/10.1016/j.ejogrb.2020.11.067
0301-2115/

evidence for the treatment strategies in use [8]. Reported success rate of conservative treatment ranges from 62 to 89 % [1,5,6]. The complications, rather spontaneous or related to treatment failure include, rupture of the site of the pregnancy, severe hemorrhage, loss of fertility, need for hysterectomy and death [1,2].

The predictive factors that determines the outcome of conservative treatment of ectopic pregnancies that previously have been evaluated are serum human chorionic gonadotropin (β-hCG) levels, the diameter of the gestational sac, gestational age, presence of embryo heartbeat and crown-to-rump length [9–12]. Nevertheless, the results are controversial and more studies are needed. Identifying reliable predictive factors would help to identify the women that are likely to benefit from conservative treatment while minimizing the adverse outcomes.

The aim of our study was to find possible predictive factors to predict the failure of conservative treatment of non-tubal ectopic pregnancy. For that purpose, we assessed the rate of failure, complications and need for additional interventions of the different primary treatment regimens in non-tubal ectopic pregnancies that occurred in our center.

Materials and methods

This was a retrospective single-center study conducted at Hospital Clínic of Barcelona, Spain. The inclusion period was from January 2010 to December 2018. Cases were retrieved from the hospital electronic patients' record system using the International Classification of Diseases related to ectopic pregnancy (633.10, 633.11, 633.20 633.80, 633.81, 633.90). All the records were checked manually. Cases with ectopic tubal pregnancies and pregnancies of unknown localization that turned out to be intrauterine pregnancies were excluded. Ethical approval for this study was obtained from the Research Ethics Committee of Hospital Clínic of Barcelona reference number HCP/2019/0831.

The patients' detailed information was retrieved from the review of clinical reports, medical records and ultrasound images. Demographics, gynecological and obstetrics history, previous surgical interventions were collected. Concerning the characteristics of the non-tubal ectopic pregnancies, we examined the dates of admission and discharge from the hospital, initial level of β-hCG and the date of negative β-hCG (<20 mIU/mL), ultrasound and magnetic resonance images, presence of embryo and cardiac activity, mode of treatment, complications, readmission to the hospital, outcomes and the date of complete resolution of the process. If the patient was treated with surgical management, the surgical records were evaluated. Cases were classified according to the site of the pregnancy: cervical, interstitial, Cesarean scar and ovarian. The heterotopic pregnancies were classified according to the location of the ectopic pregnancy.

There was not an established clear protocol for the treatment of non-tubal ectopic pregnancies until 2018, thus, we used general published recommendations for management of such cases. Conservative regimens included two main options: medical or surgical (oophorectomy in case of ovarian ectopic pregnancy and surgical curettage). Medical regimens were the following: systemic multiple-dose methotrexate, systemic single-dose methotrexate and ultrasound-guided intrasaccular injection of methotrexate or KCl. The options were used alone or in its combination. Multiple doses methotrexate was administered intramuscularly 4 times every 48 h followed with folic acid rescue. The dose for systemic

Table 1
Baseline and clinical characteristics of the study groups.

Characteristic	Embryo heartbeat positive (n = 13)	Embryo heartbeat negative (n = 26)
Age (years)	35.5 ± 3.2	35.4 ± 6.0
Smoking	2 (15.4)	3 (11.5)
Endometriosis	1 (7.7)	2 (7.7)
Salpingectomy	4 (30.8)	5 (19.2)
History of ectopic pregnancy	3 (23.1)	7 (26.9)
History of abdominal surgery	7 (53.8)	11 (42.3)
Previous caesarean section	2 (15.4)	6 (23.1)
Previous miscarriage	5 (38.5)	9 (34.6)
Previous termination of pregnancy	3 (23.1)	5 (19.2)
Previous curettage	3 (23.1)	4 (15.4)
Conceive		
Spontaneous	8 (61.5)	20 (76.9)
IVF	5 (38.5)	6 (23.1)
Heterotopic pregnancy	2 (15.4)	0
Localization of pregnancy		
Cervical	3 (23.1)	8 (30.8)
Interstitial	6 (46.2)	12 (46.2)
CSP	2 (15.4)	5 (19.2)
Ovarian	2 (15.4)	1 (3.8)
Gestational age at diagnosis (weeks)	7.0 ± 2.1	7.1 ± 2.2
Symptoms		
Pain	5 (38.5)	4 (15.4)
Metrorrhagia	3 (23.1)	14 (53.8)
Both	2 (15.4)	5 (19.2)
Asymptomatic	3 (23.1)	3 (11.5)
Gestational age at symptoms		
pain	7.2 ± 3.0	5.7 ± 1.2
metrorrhagia	6.0 ± 0	7.3 ± 2.3
both	6.0 ± 0	8.4 ± 2.3
asymptomatic	8.3 ± 2.1	5.3 ± 0.6
Size of gestational sac (mm)	31.0 (13.0–86.0)	17.0 (4.5–80.0)
Embryo presence	13 (100.0)	6 (23.1)
CRL (mm)	6.0 (2.0–55.0)	5.0 (1.0–7.0)
β-hCG at diagnosis (mIU/mL)	43 608 (2 447–287 587)	4 620 (218–33 398)

Data are presented in n (%), mean ± SD.
IVF – in-vitro fertilization, CSP – caesarean scar pregnancy, CRL – crown-rump length, β-hCG - human chorionic gonadotropin.

multiple dose methotrexate was calculated based on 1 mg/kg and dose for a single administration of methotrexate was 50 mg/m^2. Folic acid rescue was administered 24 h after methotrexate in a dose of 1 mg/kg. When embryo cardiac activity was present, intrasaccular injections were performed under ultrasound guidance and either 50 mg methotrexate or 2 ml (30 mmol/mL) KCl was used. Follow-up after treatment included β-hCG levels and ultrasound examination every 48 h until negative β-hCG. An ultrasound scan was performed every fourth week until full resolution of the process was confirmed. In addition, we conducted personal interviews with all women to assess their subsequent pregnancies, and perinatal outcomes.

The main outcomes were success of the primary treatment and the need for additional interventions. The primary treatment was defined as the treatment planned for at the time for diagnosis. Any other interventions or additional treatment ordinated later were defined as secondary. The primary treatment was defined as successful if no other intervention was needed and no complications occurred. The secondary outcomes were the success rate of conservative treatment, incidence of complications, days to discharge from the hospital, days until negative β-hCG, days until complete resolution of the process (asymptomatic woman with normal menses, negative β-hCG and stable/residual ultrasound image). Severe bleeding was defined as estimated blood loss over 1000 ml or bleeding with signs of hemodynamic instability.

The statistical software package SPSS 24.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Differences in categorical data were studied using the chi-square test and Fisher's exact test. Student's *t*-test was used for comparisons for continuous normally distributed variables and Mann-Whitney *U* test was used for not normally distributed variables. To determine which factors predicted success of the primary treatment we performed univariate logistic regression analysis with the likelihood ratio test. P-value <0.05 was considered statistically significant.

Results

A total of 41 women were managed with non-tubal ectopic pregnancy at Hospital Clínic of Barcelona between 2010 and 2018. One case was excluded due to loss of follow-up. One patient had been referred from another hospital after the failure of the primary treatment of suspected miscarriage. This case was also excluded from the final analysis due to the initial inaccuracy of the diagnosis.

Therefore, 39 cases of non-tubal ectopic pregnancy were included for the final analysis. Out of which 18 (46 %) were interstitial, 11 (28 %) cervical, 7 (18 %) Cesarean scar and 3 (8%) ovarian pregnancies. The cases were divided into two groups (1) embryo heartbeat positive group, there were 13 cases (33 %) with positive cardiac activity and (2) embryo heartbeat negative group, included 26 (67 %) cases without heartbeat (with or without embryo). The background characteristics of the groups are presented in the Table 1. There were no differences in demographics characteristics, medical history, presence of symptoms and gestational age at the time of diagnosis or particular localisation of the ectopic pregnancy between the groups.

In the embryo heartbeat positive group, the most frequent treatment was intrasaccular ultrasound guided injection with methotrexate or KCl combined with systemic multiple dose methotrexate [69 % (9/13)]. In the embryo heartbeat negative group systemic multiple dose methotrexate alone was the main treatment [92 % (24/26)]. Laparoscopic oophorectomy was performed in the three cases of ovarian pregnancy. No adverse effects were observed related to methotrexate. The primary treatment was successful in 74 % (29/39), which included 26 cases of medical and all 3 cases using surgical regimens. The rate of failure of the primary treatment was significantly higher in the group with presence of cardiac activity than in the embryo heartbeat negative group, 46 % vs. 15 % respectively, $p < 0.0001$ (Table 2). Ten cases required additional treatments (Table 3) and conservative treatment was finally successful in all cases. None of them required hysterectomy or led to serious morbidity/mortality. The reasons for secondary treatment were maternal complications in 5 cases (mainly severe pain or bleeding), and insufficient treatment in the other 5 cases (persistence of high β-hCG level or positive heartbeat).

There were five cases of moderate to severe bleeding. In two cases, the bleeding stopped without any medical intervention. Two out of five cases required blood transfusion. In the first case bleeding occurred before the initiation of treatment. Therefore, it was not related to the prescribed treatment. In the second case, bleeding occurred after the primary treatment failure and required embolization of the uterine arteries as well as surgical removal of

Table 2
Treatment strategy and outcomes among study groups.

Characteristic	Embryo heartbeat positive (n = 13)	Embryo heartbeat negative (n = 26)	P-value
Primary treatment			
ISI + systemic methotrexate	9 (69.2)	1 (3.8)	< 0.0001
Methotrexate	1 (7.7)	24 (92.3)	< 0.0001
ISI KCl	1 (7.7)	0	0.33
Surgical	2 (15.4)	1 (3.8)	0.25
Days to discharge	8 (1–12)	7 (1–8)	< 0.02
Days to negative β-hCG	83 (35–138)	53 (6–231)	< 0.02
Days to resolution of the process	124 (35–261)	58 (6–231)	0.05
Success of primary treatment	7 (53.8)	22 (84.6)	< 0.04
Need of secondary treatment*	6 (46.2)	4 (15.4)	< 0.04
ISI KCl	3 (23.1)	0	0.2
Mefepriston	0	1 (3.8)	0.4
Methotrexate extra dose	2 (15.4)	1 (3.8)	1.0
Embolization	2 (15.4)	1 (3.8)	1.0
Surgical removal of necrotic mass	1 (7.7)	1 (3.8)	1.0
Complications	5 (38.5)	1 (3.9)	0.11
Severe pain	1 (7.7)	0	0.33
Bleeding	4 (30.8)	1 (3.9)	0.35
Need for transfusion	2 (15.4)	0	0.12

Data are presented in n (%), mean ± SD or median (minimum-maximum), otherwise other specified.
ISI – intrasaccular injection, KCl - potassium chloride.
* More than 1 treatment in two cases.

Table 3
Characteristics of the cases which required additional treatment or intervention after the failure of the primary treatment.

case	localisation	gestational age	initial β-HCG	heartbeat	primary treatment	reason for retreatment	secondary treatment
1	CSP	12 + 0	287 587	positive	intrasaccular injection of KCL & systemic methotrexate*	severe pain	embolization
2	CSP	6 + 0	46 280	positive	systemic methotrexate	positive heartbeat, persistence of high β-HCG level	intrasaccular injection of methotrexate & methotrexate 1 extra dose 6 days after the injection
3	cervical	6 + 0	20 493	positive	intrasaccular injection of KCL & systemic methotrexate	persistence of high β-HCG level	systemic methotrexate 2 extra doses
4	cervical	6 + 4	16 897	positive	intrasaccular injection of KCL & systemic methotrexate	metrorrhagia and pain	embolization & removal of retainers
5	interstitial	5 + 6	22 696	positive	intrasaccular injection of methotrexate & systemic methotrexate	positive heartbeat	intrasaccular injection of KCL
6	interstitial	6 + 0	14 162	positive	intrasaccular injection of methotrexate & systemic methotrexate	positive heartbeat	intrasaccular injection of KCL
7	CSP	10 + 5	2 036	negative	systemic methotrexate	excessive vascularization	mifepristone
8	cervical	6 + 3	6 494	negative	systemic methotrexate	presence of hematoma	removal of retainers
9	cervical	7 + 0	23 189	negative**	systemic methotrexate	metrorrhagia	embolization
10	interstitial	7 + 1	33 398	negative**	systemic methotrexate	persistence of high β-HCG level	systemic methotrexate 1 extra dose

β–HCG – human chorionic gonadotropin, CSP – caesarean scar pregnancy, KCL- potassium chloride.
* Systemic methotrexate treatment always included 4 doses every 48 h complemented with 4 doses of folinic acid rescue.
** No embryo in the gestational sac.

hematoma. In one patient, bleeding occurred during the oophorectomy and balloon tamponade with ligation of the epigastric vessels was required.

In the study population there were two heterotopic pregnancies. In both cases, the ectopic pregnancies were viable both with positive heartbeat and interstitial localization. In the first case, ultrasound-guided injection of KCl was performed into the ectopic pregnancy without any complications. The intrauterine pregnancy continued to term gestation and the patient was delivered with CS due to failure of progress of labor. In the second case, an intrauterine miscarriage was diagnosed together with an ongoing interstitial gestation. A curettage was performed and ectopic pregnancy was managed with intrasaccular injection of methotrexate combined with systemic multi doses methotrexate.

We evaluated the possible predictive factors for the risk of failure of the primary treatment: maternal age, gestational age, size of gestational sac, β-hCG levels at diagnosis, and presence of cardiac activity (Fig. 1). Two factors significantly predicted failure of primary treatment: the presence of ultrasound verified heartbeats and the initial β-hCG levels at time of diagnosis. The presence of embryo heartbeat increased the likelihood of failure of the primary treatment by almost by 4 times (OR 4.71, 95 % CI 1.03–21.65, $p < 0.05$). The levels of β-hCG were not normal distributed and varied from 218 to 287587 mIU/mL. In this case, to perform univariate logistic analysis the variable was transformed with base-2 logarithm. The analysis showed that for each doubling of the β-hCG level significantly increased the risk of treatment failure by 54 % (OR 1.54, 95 % CI 1.03–2.39, $p < 0.05$). No correlation was found between the initial β-hCG level or embryo heartbeat and the time for discharge from the hospital, time until negative β-hCG or time until full resolution of the process.

Twenty-nine women (74 %) tried to conceive again after the case of non-tubal ectopic pregnancy. Out of them 20 (69 %) achieved pregnancy. The median interpregnancy interval was 13

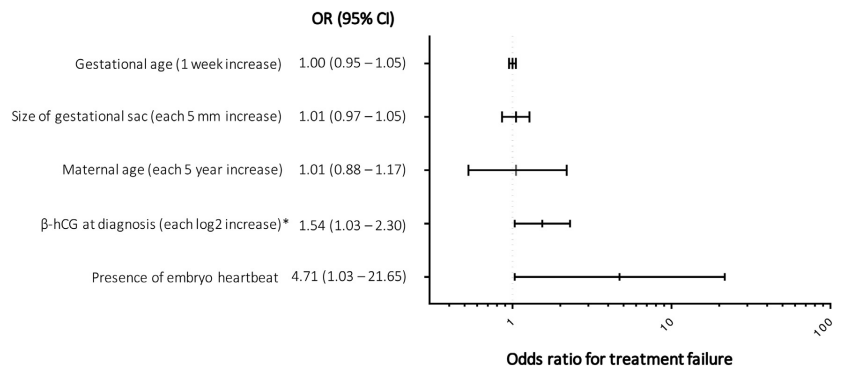

Fig. 1. Forest plot showing the odds ratios for likelihood of the primary treatment failure.
OR - odds ratio, CI – confidence interval, β-hCG - human chorionic gonadotropin.
*Due to not normal distribution of levels of β-hCG at diagnosis the variable was transformed with a base-2 logarithm for logistic regression analysis.

months and ranged between 6–80 months from the ectopic pregnancy. In this group, 2 performed elective termination, 2 had miscarriages, 8 delivered vaginally and 8 underwent CS. No fetal congenital abnormalities were recorded.

Discussion

Our results show that in the management of non-tubal ectopic pregnancies conservative treatment can be a safe option with a high rate of success, particularly in the case of negative EHR. Therefore, conservative strategies should be the first therapeutic option given the fertility preservation and the low rate of severe maternal complications.

The overall rate of successful treatment was comparable with previously published case series [5–7]. In 26 % of the cases additional treatment was needed, however hysterectomy could be avoided in all cases without any additional maternal complications. Major surgical interventions such as laparoscopic cornual resection were also avoided. Among the ten cases of primary treatment failure, only two required further minor surgical procedures.

Possible factors which could influence the success of the primary treatment in the whole population were evaluated using univariate analysis. It was shown that the presence of embryo heartbeat increases the risk of treatment failure. Of note, one case of Cesarean scar pregnancy with presence of cardiac activity was initially only treated with systemic methotrexate, but intrasaccular injection was then needed due to treatment failure. Two other cases also required a second intrasaccular injection of KCl due to presence of heartbeat. Additional interventions may have been needed in some cases because of the lack of a detailed internal clinical protocol which then was established in 2018. Nevertheless, all cases with treatment failure were managed conservatively with preserved fertility.

Embryo heartbeat does not contraindicate conservative treatment, but intrasaccular injection of methotrexate/KCl should not be delayed in these cases. Use evidence-based guidelines and protocols for standardized management of unusual diagnosis is necessary to individualize and optimize the treatment for the patients.

Higher levels of β-hCG at the time of diagnosis and the presence of embryo heartbeat were also associated with treatment failures. These findings are in accordance with other published data, however, these publications only refer to a specific location of the ectopic pregnancy [9–12]. A higher level of β-hCG implies a higher trophoblastic activity and vascularization, so it is entirely plausible that the level of β-hCG affects the efficacy of treatment. Nevertheless, in the published case series of non-tubal ectopic pregnancies in different localisations [5], the β-hCG levels did not make a significant contribution in the prediction of success rate. Differences in sample size and in clinical management may explain the contradictory findings.

Regarding further reproductive results, half of the women conceived after the ectopic pregnancy in our population. Maternal periconceptional exposure to methotrexate may be associated with subsequent fetal congenital defects [13,14]. Currently there is no consensus regarding the appropriate interval time between methotrexate administration and subsequent pregnancy. At our hospital it is recommend to wait for at least 6 months, which might be an appropriate time, as there were no fetal abnormalities recorded in our cohort.

Our findings add information to the existing limited data about management options for women with non-tubal ectopic pregnancy. The predictive markers may aid the physicians in the decision-making and allow for a safer patient counselling. Conservative treatment should be considered as the primary choice for such pregnancies.

The strengths of the study include the large period of a single center experience in non-tubal ectopic pregnancy regarding conservative treatment. The limitations include the retrospective design and the small sample size. The sample size prevented us from performing multivariate analyses: in particular, whether positive embryo heartbeat and β-hCG levels independently add in the prediction of failure rate could not be tested. The absence of a comprehensive clinical protocol before 2018, which could be considered as a limitation, also helps to reflect the importance of homogeneity in management approaches.

Conclusion

Conservative treatment is a safe option in the management of non-tubal ectopic pregnancy, particularly in the absence of embryo heartbeats. The β-hCG levels at the time of diagnosis and presence of embryo heartbeat may be used as a predictor of failure of the primary treatment.

Funding

No financial support had been received for this study.

Declaration of Competing Interest

The authors report no declarations of interest.

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Paper IV

Knowledge about mode of delivery throughout pregnancy in women with previous Cesarean section.

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Number of words in the manuscript: 2327.

ABSTRACT

Objectives: To determine the level of knowledge about the mode of delivery in women with one previous Cesarean section (CS) and to evaluate differences throughout pregnancy.

Materials and Methods: A cross-sectional study conducted in a tertiary hospital in Barcelona, Spain, from June until September 2019. Pregnant, Spanish-speaking women with one previous CS and with no indications for repeat CS were eligible for the study. Participants were divided into two groups according to the trimester of pregnancy: the first trimester group (Trim I) and the third trimester group (Trim III). A structured questionnaire was used to record information on women's experience of the previous CS and their attitude towards vaginal birth after Cesarean (VBAC) in the subsequent pregnancy.

Results: A total of 87 women were included in the study: 32 women (36.8%) in Trim I and 55 (63.2%) in Trim III. There was a significant increase in the number of women well informed about the benefits of VBAC (53.1% vs 74.6% in Trim I and Trim III respectively, p=0.004). There were no differences in the knowledge about risks of CS, and 30% in each group thought that there were no risks after CS. Overall, 66.7% of the women felt that they needed more information.

Conclusions: The study showed an increase in knowledge about the benefits of VBAC in the third trimester compared to the first trimester. Nevertheless, women still expressed need for more information, suggesting that more comprehensive written information may be crucial to improve empowering and their birth experience.

Key words: Vaginal delivery after Cesarean section, VBAC, Cesarean section, knowledge about vaginal delivery after Cesarean, information in pregnancy.

INTRODUCTION

Cesarean section (CS) is associated with higher risk of short- and long-term complications both for the mother and the child [1-3]. Nevertheless, the rate of CS has been increasing in many countries [4]. In the next pregnancy women are faced with the difficult decision regarding mode of delivery. According to the existing evidence and to most international guidelines, vaginal delivery after CS (VBAC) is a safe option, with a success rate of 72–75% [5, 6]. However, repeat CS remains to be one of the largest contributors to the overall CS rate [7, 8]. The perinatal risks in subsequent pregnancies increase with the number of CS [1]. Repeat CS is associated with higher risk of scar pregnancy, abnormal placentation, uterine rupture, hysterectomy due to postpartum hemorrhage, prolonged hospitalization and post-traumatic stress disorders [1-3].

Several strategies have been shown to be helpful to increase the rate of VBAC: receiving consistent information from supportive clinicians, knowing the advantages of VBAC and getting the relevant information as early in pregnancy as possible [9, 10]. Previous studies revealed that women felt like “groping through the fog”, when trying to receive information about VBAC from professionals. The main problems were insufficient and sometimes controversial information, both during pregnancy and at delivery [11, 12]. Several women-centred interventions have suggested to help women to make an informed decision and thereby increase the VBAC rate, but none of them proved to have any significant effects [13, 14]. The limitations of the published reviews are that they were based on just three studies from English-speaking counties: UK, Australia and Canada [15 -17]. The authors highlighted the need of more research from different countries and with different clinical approaches.

Understanding the initial level of knowledge, expectations and fears among women is important for improving the care of women with a previous CS and to increase VBAC. To the best of our knowledge there are no studies on women's knowledge about CS and their attitude towards VBAC in the Spanish population. The aim of the study was to determine the level of knowledge about the mode of delivery in women with one previous CS and to evaluate its differences throughout pregnancy.

METHODS

This cross-sectional study was conducted at BCNatal, Barcelona Center for Maternal-fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Deu, Barcelona, Spain), from June until September 2019. Women were recruited from the facilities of Hospital Clínic. A structured questionnaire was used to record information on women's experience with the previous CS and their attitude towards VBAC in their subsequent pregnancy. The inclusion criteria were women with a singleton pregnancy, being in their first or third trimester, with one previous CS, fluently speaking and reading Spanish. The exclusion criteria were having more than one previous CS and presence of medical indications for elective repeat CS (ERCS). The ethical approval was obtained from the Research Ethics Committee of Hospital Clínic of Barcelona reference number HCB/2019/0553.

The women were offered to participate in the study at their visit to the hospital for their routine antenatal controls. At the time of the visit, they were informed about the study orally and with written information. If they decided to participate an informed consent form was signed and the questionnaire answered. The full questionnaire is available as supplementary material (Supplement 1). Women were given privacy to answer the questionnaire, the researcher waited nearby and could be reached at any time in case of questions. The questionnaire consisted of closed and open questions and the different sections addressed: I) background characteristics, including circumstances for their previous CS, II) general knowledge about CS and VBAC and III) personal view and request for information. Regarding the previous CS, information was specifically obtained for the indication and whether it was emergency or elective. The answers given to these two questions were compared with the records made by the physician who performed the first CS to determine the accuracy of the women's understanding regarding the indication for CS. If the answer to one or both questions not coincide with medical records the understanding of the circumstances of the previous CS was defined as poor. It was assumed that the woman were adequately informed if the answers were in concordance with the records. At the end, there was one open question allowing them to add any additional relevant information or suggestions.

The detailed demographics and medical information regarding the gynecological and obstetrics history was retrieved from the clinical and medical records. The perinatal outcomes, including mode of delivery, were also collected for both groups. Elective repeat CS was defined as planned and expected (by the woman and the health professionals) to occur on a scheduled date, before onset of labour, whereas all unscheduled CSs were defined as emergency CS. High educational level was defined as passed more or equal to secondary levels.

The statistical software package SPSS 24.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. Differences in categorical data were studied using

the chi-square test and Fisher's exact test as appropriate. Student's t test was used for comparisons for continuous normally distributed variables. P-value <0.05 was considered statistically significant.

RESULTS

A total of 87 women agreed to participate in the study. The participants were divided into two groups: 32 women (36.8%) in the first trimester group (Trim I) and 55 (63.2%) in the third trimester group (Trim III). The mean gestational age was 11.9±2.24 and 34.9±2.10 weeks, in Trim I and Trim III respectively. There were no differences in the background characteristics between the groups (Table 1). The majority were White-European, employed with a high educational level.

Regarding the circumstances for the previous CS, full information was obtained from the hospital records for 53% (46/87) of women. Of them, 21.7% (10/46) did not know the reason for the previous CS or misunderstood the indication. The results from the questionnaire are presented in Table 2. In general, the majority of women considered CS as a major operation, knew that VBAC is an option for giving birth after CS and that the recovery after vaginal deliveries is faster than after CS. A significantly higher number of the women with high educational level knew that VBAC is better for both mother and child (76% vs. 50%, p=0.01), preferred to get the information from medical staff other than media (44% vs. 16%, p<0.01) and tended to have a higher rate of trial of labor after CS (TOLAC) (57% vs. 35%, p=0.05) compared to women with primary and secondary education.

In the Trim III group, a larger number of women knew that VBAC is safer for both mother and child than ERCS, compared with the Trim I group (Figure 1). Significantly fewer women thought that VBAC is safer just for mother. Remarkably, even in the third trimester, about 30% of the participants believed that there were no risks associated with previous CS for the subsequent pregnancy or delivery (Table 2). In Trim III, a significantly higher number of women got the information about risks and benefits of VBAC from the medical staff compared to the Trim I group. There was a reduction in the number of women who wanted to have more information in the third trimester compared with the first trimester. Nevertheless, still more than a half of the women in the Trim III group wanted to get additional information. Regarding the time point to receive the information, about half of the participants asked to get the information in the beginning of the pregnancy and the other half wanted to have it closer to the end.

Twenty-four (43.6%) women had already signed an informed consent on the planned TOLAC at the time of responding the questionnaire. Of them, a 56% (14/24) wanted to have more information. In 6 cases, the mode of delivery was

changed from VBAC to ERCS later in pregnancy due to medical reason in 2 cases and for maternal request in 4 cases.

Overall, 59.8% of the women wanted to deliver vaginally. Among the women who preferred to have VBAC (52/87), 57.7% (30/52) delivered vaginally, 25.0% (13/52) had elective CS, 11.5% (6/52) underwent emergency CS and 5.8% (3/55) were lost to follow-up.

DISCUSSION

The results in the present study show that there is an improved knowledge about the benefits of VBAC in the third trimester of pregnancy compared to the first trimester. Nevertheless, women in this study still revealed that they felt there was a lack of information even in the third trimester and after they had signed an informed consent for VBAC.

Almost all women, regardless of the group, knew that VBAC was an option after previous CS and that the recovery time normally is faster after vaginal deliveries compared to CS. Women in the third trimester had a higher and more accurate level of knowledge regarding benefits of VBAC compared to the women in the first trimester. A higher number of women in the third trimester knew that VBAC was better, not only for the mother, but also for their offspring. However, there were no differences in the level of knowledge regarding the risks of CS. About 70% of the women in each group were under a delusion regarding this issue. Our study shows that there are still some women that view CS as a safer mode of delivery for both their baby and/or for themselves, which is in agreement with previously published studies [18, 19]. To determine the reasons for such misinterpretation of the risks after CS, more studies looking at different aspects would be needed. Furthermore, one-fifth of the participants did not know the exact reason why the previous CS had been performed. A large proportion of misunderstanding exist among women regarding the indications for previous CS, a fact that has been reported previously [20]. The combined data show that the information provided to women before and after CS, as well as during the subsequent pregnancy, still is insufficient and/or not clear for women. Future studies may evaluate the true reasons why women are not able to accept and understand the information given by medical staff as well as to find relevant points for improvement.

Although the need for obtaining more information decreased in the third trimester, still 58.2% of the women asked for more information to make an informed decision about the mode of delivery when they reached third trimester. Moreover, even among those who had already sighed an informed consent for TOLAC, more than a half of them were not satisfied with the information provided. These findings are in agreement with other published articles and systematics reviews [9-12]. In the

situation of scarce information provided by the health care workers, women reported to search on the Internet or to discuss their fears and expectations with friends and family [21, 22]. In fact, the internet searches on the topic 'Cesarean section' increased dynamically from 2004 [21]. Furthermore, interest for the topic 'Cesarean section' has a positive association with the current increasing CS rate worldwide [21]. Several studies were conducted to evaluate the quality and completeness of web-based resources. It was reported that the information found on the Internet regarding the risks and benefits of CS/ VBAC was poor and often controversial [22].

Almost 20 % of the study population could not specify any preferable mode of delivery and 20% wanted to deliver by ERCS. Several factors have been reported to be important for women to choose VBAC, including the need for a shorter recovery, recommendations and adequate information from health care providers and the contact with midwives during pregnancy [9, 10, 23-25]. These factors might be addressed at the antenatal visits using optimized antenatal information programs. Of note, we observed that women with higher educational level were better informed and preferred to get the information from health care providers. Therefore, a more individual approach might be needed, considering social and educational determinants to provide health knowledge, adequate support and more information from caregivers.

The main strength of the present study is that, to the best of our knowledge, this is the first study of this type performed in a Spanish speaking country. Although limitation is the small sample size but still it is representative enough to get a general idea of the level of knowledge in women with previous CS. Yet another limitation may be that we did not evaluate the changes in knowledge for each individual woman throughout the study, rather included different women in the two groups. Nevertheless, if we would have included and followed-up the same women during the whole pregnancy we could have deliberately pushed them to actively search for more information or discuss these issues with their health care providers after the survey in the first trimester in order to be better prepared for the future survey. That could bias the results, limiting the external validation of the study.

The present study supports the idea that the information about the risks in the subsequent pregnancy and the options for the mode of delivery should be provided by health care professionals to women with previous CS as early in pregnancy as possible, both as written information and orally during the antenatal visits [23, 24]. This may decrease the level of misunderstandings of the information that they might have found on the internet. From a clinical point of view, this way of giving information may help to prepare woman for TOLAC, having enough time to know about previous delivery, solve doubts, and discuss the preferable mode of delivery at the end of the pregnancy.

CONCLUSION

In conclusion, the present study shows that the knowledge about the benefits of VBAC is higher in women in the third trimester compared to the first trimester. Nevertheless, there is still a lack of information even after having signed an informed consent for VBAC in the third trimester. Providing a written comprehensive and personalized information could be key to increase awareness and empower women in their decision towards VBAC, thereby reducing risks and improving their overall birth experience.

Table 1. Background characteristics of the groups and the total population.

Characteristics	All women (n=87)	Trim I (n=32)	Trim III (n=55)	P-value
Age, years	35.4±4.7	34.8±4.9	35.8±4.5	0.35
Origin				
Caucasian	48 (55.2)	19 (59.3)	29 (52.7)	0.55
Latino-American	19 (21.8)	8 (25.0)	11 (20.0)	0.59
Asian	7 (8.0)	2 (6.3)	5 (9.1)	1.00
Others*	13 (15.0)	3 (9.4)	10 (18.2)	0.27
Education				
Primary	9 (10.3)	3 (9.4)	6 (10.9)	1.00
Secondary	23 (26.4)	9 (28.1)	14 (25.5)	0.79
Above secondary	55 (63.2)	20 (62.5)	35 (63.6)	0.92
Occupation				
Employed	56 (64.4)	22 (68.8)	34 (61.8)	0.52
Self-employed	7 (8.0)	1 (3.1)	6 (10.9)	0.20
Unemployed	14 (16.1)	6 (18.8)	8 (14.5)	0.61
Housewife	10 (11.5)	3 (9.4)	7 (12.7)	0.64
Previous vaginal deliveries	14 (16.1)	6 (18.8)	8 (14.5)	0.61

Data are presented in n (%), mean±SD.
*Others include: Black, Berbers, Arabian.

Table 2. Questions and the distribution of answers between the groups and in the total population.

Question	All women (n=87)	Trim I (n=32)	Trim III (n=55)	P-value
CS is major operation	78 (89.7)	31 (96.9)	47 (85.5)	0.15
After vaginal delivery recovery is faster than after CS	78 (89.7)	28 (87.5)	50 (90.9)	0.72
VBAC is possible	80 (92.0)	28 (87.5)	52 (94.5)	0.42
VBAC is better for:				
Mother	15 (17.2)	10 (31.3)	5 (9.1)	0.02
Baby	2 (2.3)	1 (3.1)	1 (1.8)	1.00
Both	58 (66.7)	17 (53.1)	41 (74.6)	0.04
Do not know	12 (13.8)	4 (12.5)	8 (14.5)	1.00
There are risks after CS for				
Next pregnancy	7 (8.1)	4 (12.5)	3 (5.5)	0.4
Next delivery	20 (23.0)	4 (12.5)	16 (29.1)	0.11
Next pregnancy and delivery	28 (32.2)	10 (31.3)	18 (32.7)	1.00
No risks	26 (29.9)	10 (31.3)	16 (29.1)	1.00
Do not know	6 (6.9)	4 (12.5)	2 (3.6)	0.19
Searched for the information*				
Yes, TV, web	39 (44.8)	11 (34.4)	28 (51.0)	0.18
Yes, medical staff	29 (33.3)	5 (15.6)	24 (43.6)	0.01
No, but plan to search	10 (11.5)	7 (21.9)	3 (5.5)	0.03
No, and do not plan to do so	20 (23.0)	11 (34.4)	9 (16.4)	0.07
**more that 1 answer was possible*				
Want more information				
Yes	58 (66.7)	26 (81.2)	32 (58.2)	0.04
When would you like to get more information, n=58				
At the beginning of the pregnancy	32 (55.2)	14 (53.8)	18 (56.2)	0.86
Towards the end of the pregnancy	26 (44.8)	12 (46.2)	14 (43.8)	
As a mode of delivery prefer				
VBAC	52 (59.8)	18 (56.3)	34 (61.8)	0.66
CS	19 (21.8)	6 (18.8)	13 (23.6)	0.79
Do not know	16 (18.4)	8 (25.0)	8 (14.5)	0.26
Current delivery				
VBAC	33 (37.9)	10 (31)	23 (41.8)	0.33
Elective CS	41 (47.1)	15 (46)	26 (47.3)	0.97
Emergency CS	6 (6.9)	2 (6.3)	4 (7.3)	0.86
Missing data	7 (8.0)	5 (15.6)	2 (3.6)	0.05

Data are presented in n (%).
CS – Cesarean section, VBAC – vaginal delivery after Cesarean.

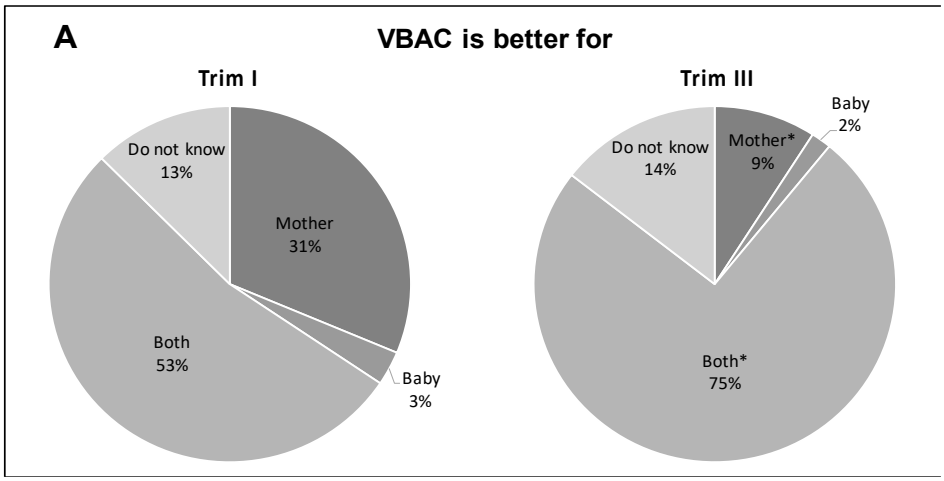

Figure 1.
Distribution of the answers between the Trim I and Trim III groups for the question: For whom VBAC is better?
* p<0.05
VBAC – vaginal delivery after Cesarean section.

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Paper V

Strategies to increase the rate of vaginal deliveries after Cesarean without negative impact on outcomes.

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Conflict of Interest

None declared.

Ethical Approval

The study was approved by the ethics committee of the Medical Faculty of Lund University, Sweden, reference number 2017/417.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABSTRACT

Objective: To compare the rate of vaginal birth after Cesarean section (VBAC), including the maternal and perinatal outcomes, in two historical cohorts before and after the implementation of specific changes in the clinical practice.

Design: A retrospective cohort study.

Setting: Skåne University Hospital in Malmö, Sweden.

Participants: All women with one previous Cesarean section (CS), who delivered during two 4-year periods: 2005-2008 (Group I) and 2013-2016 (Group II).

Methods: Medical records were retrieved from the hospital's computerized medical system. The surgical reports of all women delivered by repeat CS were reviewed and the appearance of the lower uterine segment at CS was assessed. The primary outcome was VBAC. Secondary maternal outcomes were uterine rupture/dehiscence, hysterectomy and blood loss. The secondary perinatal outcomes were cord blood pH < 7.05 and perinatal mortality rate. Differences for categorical data were studied using the chi-square test and Fisher's exact test. To assess differences for continuous data t-tests were used. To determine which factors predicted VBAC both univariate and multivariate logistic regression analysis with the likelihood ratio test were performed. A two-tailed P-value <0.05 was considered statistically significant

Findings: 2017 patients were included to the study: 792 patients in Group I and 1225 in Group II. The rate of trial of labor after Cesarean (TOLAC) was 65.0% and 76.9% and the VBAC rate was 49.8% and 62.0% in Group I and II respectively ($p<0.0001$). Maternal and perinatal adverse outcomes were not statistically different between the two groups.

Key conclusions and implications for practice: Appropriate management of women with one previous CS might increase the VBAC rate without a negative impact on maternal or perinatal outcomes. The antenatal teamwork has the greatest contribution to VBAC rate by increasing the number of women undergoing TOLAC.

Key words: Cesarean section, trial of labor after Cesarean, vaginal birth after Cesarean, uterine rupture.

INTRODUCTION

The rate of Cesarean section (CS) has been increasing in most countries over decades [1-4]. CS is associated with risks both for mother and child. [2-5] Women with one previous CS and obstetricians are faced with difficult decisions regarding mode of delivery in a subsequent pregnancy. According to the published guidelines, trial of labor after CS (TOLAC) is a safe option for consideration. The rate of successful vaginal delivery after Cesarean section (VBAC) is 72–75% [6]. However, repeat CS remains to be the largest contributor to the overall CS rate and its relative contribution may reach 46% [7,8]. Repeat CS is associated with higher risk of complications compared to TOLAC [5,9-10].

Previously, several strategies to increase the rate of VBAC have been studied, but the majority of them had no significant influence or very low level of evidence. At Skåne University Hospital has there always been a policy that one previous CS is not an indication for elective repeat Cesarean section (ERCS). Moreover, the clinical management of women with previous CS has been a topic for an ongoing and broad research agenda for many years. Between 2008 and 2013 several changes were made in the obstetric clinical routines to decrease the level of CS and increase the VBAC rate.

The objective of this study was to compare the rate of VBAC and maternal and perinatal outcomes in two historical cohorts before and after the implementation of changes in clinical practice and establishment of the antenatal research clinic for women after CS.

METHODS

This was a single center retrospective cohort study at Skåne University Hospital, Sweden. The department handles approximately 5000 deliveries per year with an overall CS rate around 15%. All women with one previous CS who delivered during either of the two time periods: 2005-2008 (Group I) or 2013-2016 (Group II) were included in the study. Those two periods were chosen to evaluate the influence of the strategies and changes in the obstetric clinical practice implemented between 2008 and 2013. (1) Lactate blood samples from presenting part for intrapartum fetal monitoring as a complement to cardiotocography (CTG) was implemented. (2) Changes in local clinical guidelines for induction of labor were made and prostaglandins were replaced by Foley's catheters for women with a previous CS. (3) A team of midwives proving psychological support for women with fear related to childbirth expanded their activity and experience in this area. (4) An antenatal research clinic to follow-up women with previous CS was established in 2013, in collaboration between the antenatal units, the ultrasound department and the labor

ward. Women included in this research project were offered to have an additional appointment with an experienced obstetrician supplemented by ultrasound in postpartum period, after their first CS, and during subsequent pregnancy.

Detailed information about demographic characteristics and maternal obstetric history was retrieved retrospectively. Delivery records were obtained from the hospital's computerized medical system. If women were delivered by repeat CS the surgical reports were reviewed. The appearance of the lower uterine segment at CS was assessed. In cases where the description of the condition of the uterine wall was unclear or difficult to interpret, the surgeon who had performed the operation was personally inquired for details. The indications for repeat CS were investigated and stratified as follows: maternal request, non-cephalic, macrosomia or disproportion, fetal distress, abnormal location/adhesion of placenta, maternal conditions (preeclampsia, previous anal sphincter injury, extragenital pathology which required delivery by CS) and previous uterine operations other than low transverse CS. In several cases a diagnosis registered as a primary indication for CS was in fact a secondary one. Therefore, medical records were scrutinized by two experienced obstetricians to determine the correct diagnosis as indication for the operation. Women who delivered vaginally were not routinely examined by exploration of the uterine cavity to detect uterine rupture or dehiscence. Manual exploration was only performed in case of severe bleeding or removal of retained placental products.

The primary outcome was VBAC. Secondary outcomes were TOLAC and maternal outcomes: uterine rupture/dehiscence, hysterectomy and blood loss. Uterine rupture was defined as tear through all layers of the uterine wall, with communication between the uterine and abdominal cavities. Uterine dehiscence was defined as a subperitoneal separation of the uterine scar with the chorioamniotic membrane being visible through the peritoneum [11]. The secondary perinatal outcomes were cord blood pH < 7.05 at birth and neonatal mortality (death within 28 completed days of birth). If both cord artery and cord vein blood had been assessed, the arterial pH value (the lowest of the two) was included. If only one blood sample was analyzed, this value was included regardless whether the sample was being reported as cord artery or cord vein.

The statistical software package SPSS 24.0 (SPSS Inc., Chicago, IL) was used to perform statistical analyses. Differences in categorical data between the periods were studied using the chi-square test and Fisher's exact test. To assess differences for continuous data, t-tests were used. To determine which factors were associated with TOLAC and VBAC both univariate and multivariate logistic regression analysis with the likelihood ratio test were performed. A two-tailed P-value <0.05 was considered statistically significant and was a prerequisite for including a variable in a logistic regression model.

The ethical approval was obtained from the Ethics Committee of the Medical Faculty of Lund University, Sweden, reference number 2017/417.

FINDINGS

A total of 2017 women were included: 792 patients in Group I and 1225 in Group II (Figure 1). The rate of TOLAC was 65.0% and 76.9% in Group I and Group II, respectively (OR 1.79; 95% CI 1.47-2.18; p<0.0001) and the VBAC rate was 49.8% and 62.0% (OR 1.65, 95% CI 1.38-1.98, p<0.0001). The number of women who underwent ERCS was significantly lower in the second cohort (23.1%) than in the first cohort (35.0%; p<0.0001). The number of EMCS was also lower in the second cohort (19.3 %) than in the first (23.5 %), but the difference was not statistically significant (p=0.06).

The background characteristics for both groups are presented in Table 1. In Group II women were marginally shorter, more often had one or more previous vaginal births, and the previous CS was more often an emergency CS (EMCS). Only women from Group II had the possibility to participate in the antenatal research clinic: 219 women had had an appointment with an experienced obstetrician supplemented by ultrasound for assessment of the Cesarean scar area in subsequent pregnancy.

Induction of labor with prostaglandins was reduced by 83 % in Group II (Table 1). Oxytocin augmentation during labor was used more frequently in Group II compared to Group I (Table 1). Nevertheless, the rate of successful VBAC decreased significantly among women who had oxytocin augmentation in labor during more than 4 hours (Figure 2). Epidural anaesthesia was used more frequently in Group II, whereas the rate of successful VBAC in women with epidural anaesthesia did not change (Figure 2).

The changes in indications for ERCS and EMCS for both cohorts are presented in Table 2. In Group II fewer CS were performed due to maternal request. There were also fewer CS performed due to fetal distress, but a higher rate of EMCS performed due to failure of progress, particularly at fully dilated cervix (Table 2).

Outcomes and complications in women who underwent TOLAC are presented in Figure 1. No significant differences between the groups regarding maternal complications were found. Uterine rupture occurred in 8 patients in group I (1.0 %), and 12 patients in group II (1.0%). There were also no clinical signs of uterine rupture observed after VBAC. A total of nine and eight manual explorations of the uterine cavity were performed due to retained placental tissue in Group I and Group II respectively. No anatomical defects of the uterine wall were noted. Two patients (1.9%) in Group I and seven patients (3.1%) in Group II had uterine rupture after induction of labor (p=0.51). No association was found between uterine rupture and method of induction. None of the cases with uterine rupture or dehiscence required hysterectomy. Adverse perinatal outcomes are presented in Figure 1. In in women who underwent TOLAC the rate of newborns with arterial pH <7.05 was significantly lower in Group II (1.3 %) than in group I (2.2%; p<0.02). There were

no neonatal deaths in any of the groups. There were no intrapartum deaths in both groups.

In univariate analysis the odds of TOLAC was affected positively by maternal height and previous vaginal delivery, and negatively by maternal age. Variables which increased the likelihood of VBAC were maternal height and prior vaginal delivery, whereas the odds decreased significantly with maternal age, maternal BMI, labor induction, oxytocin augmentation and epidural anesthesia. These all variables were all included in the multivariate analysis. A multivariate logistic regression analysis adjusted for confounders showed odds ratio 1.62 ($p<0.0001$) for TOLAC between Group II and Group I (Table 3). A similar analysis with VBAC as outcome applied to patients with TOLAC, which in addition was adjusted for labor induction, oxytocin augmentation and epidural anesthesia revealed no significant effect between the groups (Table 4). Thus, the higher rate of TOLAC by 11.9% was a large contributor to the overall increase in VBAC rate in Group II (Figure 1).

DISCUSSION

There was a significantly higher rate of VBAC in Group II without increasing in the rate of adverse outcomes. This is in line with the literature reporting that VBAC after one previous CS is a safe alternative to ERCS both for mother and infant [6,12].

Changes in the background characteristics were noted between the two groups. These might be partly explained by large immigration from Middle East countries. According to a literature review, non-European women tend to have shorter average heights but higher fertility rate compared to Europeans [13,14]. A higher number of women with previous vaginal deliveries in Group II might contribute to higher VBAC rate. This is in agreement with other publications, which have shown that previous vaginal deliveries increase the rate of successful VBAC [15].

Differences in number of EMCS due to fetal distress between Group I and Group II could be explained by the broad implementation of fetal scalp blood (FSB) lactate analysis in addition to cardiotocography for fetal monitoring. FSB lactate analysis may reassure medical staff of a fetal well-being and this might also explain significant reduction in the number of newborns born with acidosis after TOLAC in the second cohort. On the other hand, the proportion of EMCS due to failure of progress, particularly the number of CS performed at fully dilated cervix doubled. Delivery at fully dilated cervix often requires advanced obstetrical skills. The tendency of increasing number of such CSs might be explained by an increased fear of litigation among the staff, which was reported to be a factor influencing the decision to perform a CS in many countries [16,17]. Another reason might be that during period of the second cohort there was a shortage of experienced obstetricians. This might have led to decrease in the level of the manual skills for vaginal delivery,

particularly in management of women with previous CS. This dangerous trend, which increases the overall rate of CS, was also reported by several studies [18,19].

According to the publications advanced age, obesity, shorter heights and no previous vaginal delivery are risk factors for failure of VBAC. Nevertheless, in our study there was a significant increase in the number of VBAC in these particular groups of women. This might be explained by accumulation of experience by our medical staff in management of labor in women with previous CS with such risk factors. In Group II the induction of labor with prostaglandins was replaced by the Foley's catheter due to previously published literature that the induction with prostaglandins may be associated with uterine rupture [20]. The success rate of induction did not change, which is in agreement with the others [21,22]. However, the rate of uterine rupture was not decreased either. The present study was not aimed or powered to analyse the association between induction methods and risk of uterine rupture.

In Group II the frequency and duration of oxytocin augmentation in labor increased without increasing adverse outcomes such as uterine rupture/dehiscence. The more extensive use of oxytocin may be explained by regularly update of the personal about the risks and rate of adverse outcomes after TOLAC. Medical staff became more experienced and felt more confident in management of women with previous CS. On the other hand, proportion of women successfully delivered vaginally decreased significantly in those with oxytocin augmentation more that 4 hours in Group II. This suggests that prolonged oxytocin augmentation should be used only when the likelihood of safe vaginal delivery is high, and monitoring of adequate progress of labor is very important in such cases. This is in agreement with the published Cochrane review that oxytocin augmentation does not increase the rate of vaginal deliveries [23]. A Norwegian study reported that more strict use of oxytocin increased the number of successful vaginal birth and decreased the rate of instrumental delivery without increase in CS rate [24]. This might suggest the importance of accurate following the protocols for oxytocin augmentation, particularly in women with previous CS, with a closed monitoring of progress of labor. In the second cohort epidural anesthesia was also used more frequently. This did not contribute to the rate of successful VBAC in Group II. Moreover, in the whole population, epidural anesthesia was shown to be a negative predictor factor for VBAC, which is controversial to other studies [25]. Nevertheless, adequate pain relief might be helpful in encouraging women to choose TOLAC and further for labor analgesia or if it comes to operative delivery. The rate of uterine ruptures was similar to the study by Rozenberg et al. [26] but higher than reported by other authors in developed countries [27-30]. This discrepancy may be explained by underreported uterine ruptures, which has been published previously [31].

During the period of the second cohort, we could subjectively evaluate the positive influence of the established research antenatal clinic both for women and obstetricians. The ongoing research in women with previous CS, started at our

Department in 2013, has allowed us to accumulate experience that may have contributed to the increase in the overall VBAC rate. Even though not all women participated in the study this helped to spread the latest information and knowledge regarding risks and benefits of TOLAC and VBAC among women and medical staff. It also helped to justify the direction for further studies in this area.

The antenatal clinic in collaboration with the special team of midwifes caring for women with fear related to childbirth could also have contributed to the decrease in number of ERCS due to maternal request and helping prepare a larger number of women for TOLAC. Significant increase in the number of women who underwent TOLAC by 12% was the main contributor to the overall VBAC rate. The high level of successful vaginal deliveries may also form more positive attitude to VBAC in the society. Women exchange their experience about VBAC and transfer a positive attitude towards vaginal delivery to other women and their partners.

Meta-analysis of hospital-based interventions to reduce the rate of CS revealed that clinical audit is one of the most effective methods [32]. This detailed analysis of work and results helps to evaluate weak and strong points in obstetrical approach. This in turn helps to adjust directions for training of the personal, organizational activities and to update clinical policies.

The strength of this study is that all medical records and surgical descriptions were manually scrutinized by experienced obstetricians to avoid underestimation and mistakes in clinical interpretation, since the rate of uterine rupture/dehiscence might be underreported [31]. Another strength is that the policy "one previous CS is not an indication for ERCS" has been kept during the whole period of study. Thus, we could define the impact of other changes in the clinical practice. In addition, the two periods were long enough to be able to compare the results and all changes in clinical practice occurred between these two periods. One limitation of the study is its retrospective design. A second limitation is that there were differences in the study populations due to migration which might influence the results. A third limitation is the possibility of undetected asymptomatic cases of uterine rupture after VBAC. Such cases might complicate future pregnancies, but there is not enough evidence to perform a routinely manual exploration of the uterus in asymptomatic women to rule out uterine rupture [33]. Moreover, diagnosed asymptomatic uterine ruptures may lead to increase in unnecessary interventions.

CONCLUSION

Appropriate management of women with one previous CS might increase VBAC rate without a negative impact on outcomes. The antenatal teamwork has the greatest contribution to VBAC rate by increasing the number of women undergoing TOLAC.

Table 1. Demographic background variables and results of univariate logistic analysis.

	Group I (n=792)	Group II (n=1225)	Odds ratio	95% CI	p-value
Background characteristics					
Age, years	32.2 ± 4.8	32.3 ± 4.9	1.00	0.99-1.02	0.59
BMI (kg/m^2)	25.9 ± 5.4	26.0 ± 4.9	1.00	0.98-1.02	0.83
Height (cm)	165.1 ± 6.5	164.3 ± 6.9	0.98	0.97-0.99	<0.01
Prior vaginal deliveries	132 (16.7)	328 (26.2)	1.83	1.46-2.30	<0.0001
Index CS ELCS EMCS Unknown	 236 (29.8) 538 (67.9) 18 (2.3)	 302 (24.7) 880 (71.8) 43 (3.6)	 1.28	 1.05-1.56	 0.02 0.11
Characteristics of labor during study period					
Gestational age at delivery (weeks)	38.9 ± 1.8	39.0 ± 1.8	1.05	0.99-1.10	0.08
Birth weight (g)	3532 ± 572	3528 ± 578	1.00	1.00-1.00	0.90
Induction of labor Success of induction* Prostaglandin induction	108 (21.0) 70 (64.8) 97 (89.8)	225 (23.9) 134 (59.6) 35 (15.6)	1.17 0.80 0.01	0.90-1.52 0.50-1.29 0.01-0.03	0.23 0.36 <0.0001
Oxytocin augmentation Duration of augmentation, hours	190 (36.9) 2.53 ± 2.33	473 (50.2) 3.53 ± 2.88	1.68 1.17	1.35-2.10 1.09-1.27	<0.0001 <0.0001
Epidural anesthesia	109 (21.2)	324 (34.4)	1.89	1.47-2.43	<0.0001
Instrumental delivery due to fetal distress due to failure to progress unknown indication	55 (10.7) 32 (59.3) 20 (37.0) 2 (3.7)	75 (8.0) 49 (66.2) 25 (33.8) 0 (0)	0.68 1.33 0.83	0.47-0.98 0.65-2.75 0.40-1.72	0.04 0.44 0.61 0.18 **

Data are given as mean ± standard deviation or n (%), unless otherwise specified.
OR – odds ratio, CI – confidence interval, BMI – body mass index, CS – Cesarean section, ERCS – elective repeat Cesarean section, EMCS – emergency Cesarean section, TOLAC – trial of labor after Cesarean section, VBAC – vaginal delivery after Cesarean section.
* Success of induction was defined as induction resulted in VBAC.
** Fisher´s exact test.

Table 2. Indications for Cesarean section in women without TOLAC and after TOLAC.

Characteristic	Group I (n=792)	Group II (n=1225)	p-value
CS without TOLAC	277 (35.0)	283 (23.1)	<0.0001
Indications:			
Maternal request	170 (61.4)	146 (51.6)	0.02
Non-cephalic, macrosomia or disproportion	52 (18.8)	57 (20.1)	0.68
Fetal distress	24 (8.7)	24 (8.5)	0.94
Placenta praevia*	7 (2.5)	11 (3.9)	0.79
Maternal conditions***	18 (6.5)	36 (12.7)	0.01
Previous uterine operation	6 (2.2)	9 (3.2)	0.46
CS after TOLAC	121 (23.5)	182 (19.3)	0.06
Indications:			
Failure to progress, total	55 (45.5)	113 (62.1)	0.006
at cervical dilatation > 9 cm	7 (12.7)	26 (23.2)	0.11
Fetal distress	60 (49.6)	63 (34.6)	0.01
Suspected uterine rupture	2 (1.7)	1 (0.6)	0.57 *
Maternal conditions***	4 (3.3)	1 (0.6)	0.09 *
Non-cephalic presentation or macrosomia	0	4 (2.2)	0.15*

Data are given as mean ± standard deviation or n (%), unless otherwise specified.
CS – Cesarean section, TOLAC – trial of labor after Cesarean section.

Table 3. Results of multivariate logistic regression: Odds ratio for women from Group II to undergo TOLAC adjusted for other variables.

Characteristics	TOLAC		
	Odds Ratio	95% CI	P-value
Group II	1.65	1.34 – 2.00	<0.0001
Maternal age	0.95	0.93 – 0.98	<0.0001
Maternal height	0.99	0.97 – 1.00	0.29
BMI	0.99	0.98 – 1.02	0.88
Previous vaginal delivery	1.53	1.17 – 2.00	0.02

The reference group is Group I.
TOLAC – trial of labor after Cesarean section; VBAC – vaginal birth after Cesarean section;
CI – confidence interval; BMI – body mass index

Table 4. Results of multivariate logistic regression: Odds ratio for women from Group II to have VBAC, adjusted for other variables.

Characteristics	VBAC		
	Odds ratio	95% CI	P-value
Group II	1.21	0.89 – 1.66	0.22
Maternal age	0.96	0.93 – 0.99	<0.01
Maternal BMI	0.93	0.91 – 0.96	<0.0001
Maternal height	1.04	1.02 – 1.07	<0.0001
Previous vaginal delivery	3.55	2.29 – 5.49	<0.0001
Induction of labor	0.29	0.21 – 0.40	<0.0001
Oxytocin	1.32	0.96 – 1.81	0.09
Epidural anaesthesia	0.50	0.36 – 0.69	<0.0001

The reference group is Group I.
TOLAC – trial of labor after Cesarean section; VBAC – vaginal delivery birth after Cesarean section; CI – confidence interval; BMI – body mass index.

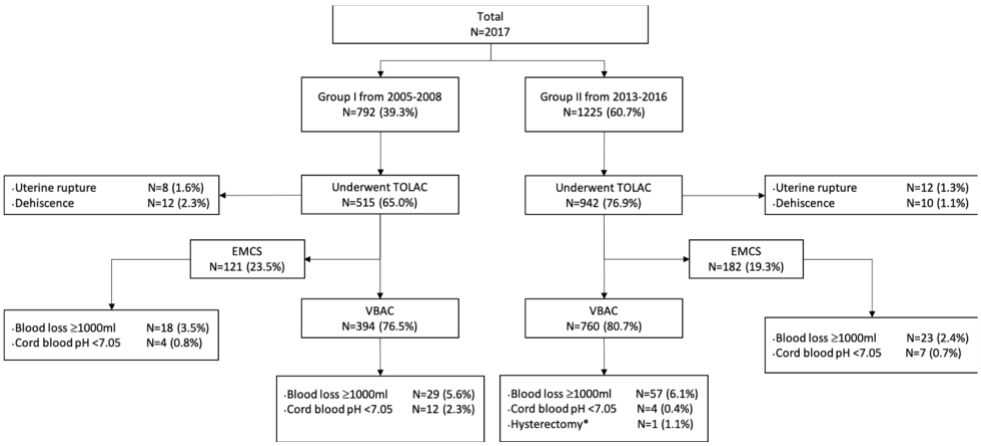

Figure 1. Flow chart describing two cohorts of women with one previous Cesarean section who underwent TOLAC and analysis of outcomes and complications.
TOLAC – trial of labor after Cesarean section; EMCS – emergency Cesarean section; VBAC – vaginal birth after Cesarean section.
* Hysterectomy was due to atonic bleeding but not due to uterine rupture/dehiscence.

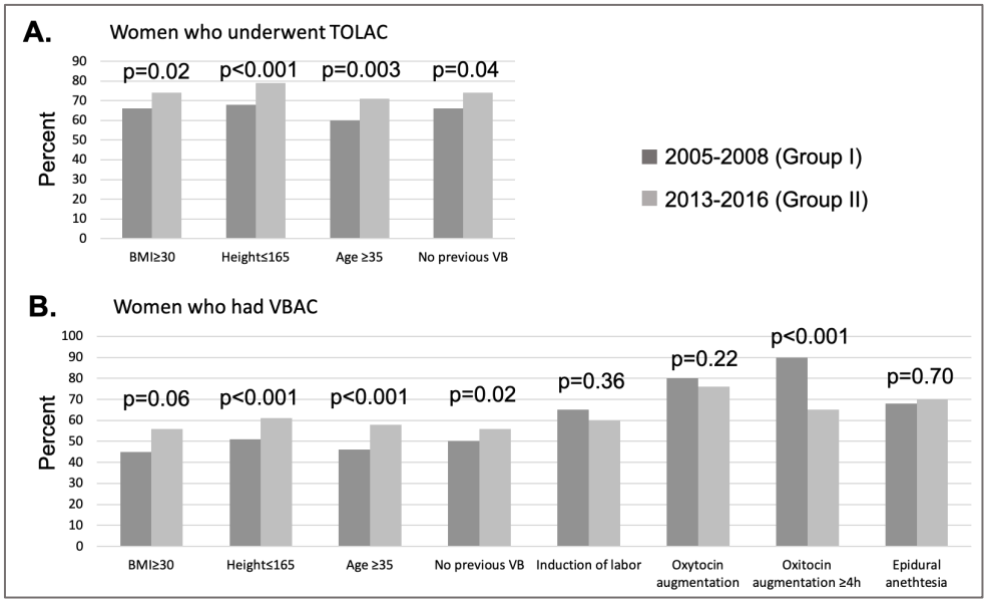

Figure 2. Comparison of TOLAC and VBAC rates in particular groups of women between the groups.
A. Percentage of women who underwent TOLAC from particular group: high BMI, short heights, advanced age and without previous vaginal births.
B. Percentage of women who had successful VBAC in the same groups of women as from A plus induction of labor, oxytocin augmentation and epidural anesthesia.
BMI – body mass index, VB – vaginal birth, h – hour.

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Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:4
ISBN 978-91-8021-030-0
ISSN 1652-8220