Tampere University

RIITTA ANTILA

Cesarean Scar Defect

Prevalence, Risk Factors and Clinical Outcome

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology of Tampere University
for public discussion at Tampere University,
on 12th of June 2020, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Department of Obstetrics and Gynecology

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Cover design: Roihu Inc.

ISBN 978-952-03-1556-6 (print)
ISBN 978-952-03-1557-3 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1557-3

PunaMusta Oy – Yliopistopaino
Tampere 2020

To Selma, Noel and Emil

ACKNOWLEDGEMENTS

This study was carried out at the Department of Obstetrics and Gynecology, Tampere University Hospital, and the Faculty of Medicine and Health Technology, Tampere University.

I wish to express my deepest gratitude to my supervisor Professor Johanna Mäenpää for her support and patience during these years. I admire her dedication to research and profound knowledge of medicine. Her extensive experience in scientific research has truly helped me with this work.

I am deeply and forever thankful to my second supervisor, Docent Synnöve Staff. Her kind, always optimistic and encouraging attitude has winged me through this work. Since I performed my first Cesarean section under her guidance in the summer of 2004, I have truly admired her positivity, humanity and intelligence. It has been an enormous privilege to be able to work with her.

I warmly thank Heini Huhtala, M.Sc. for her skilled and kind guidance in the world of statistics throughout these years. She has always had time for my questions, however silly they were. Moreover, we not only discussed statistics and science, but also life itself.

I also want to express my appreciation to my co-author, Docent Eija Tomás for her positive support and assistance in this project.

I am very grateful to the official reviewers of this thesis, Professor Leea Keski-Nisula and Professor Kaarin Mäkikallio, for their professional and enthusiastic evaluation, valuable comments and detailed corrections, which have all improved the final result. I am also most profoundly grateful to Professor Oskari Heikinheimo for agreeing to act as the opponent at the public defense of this thesis.

I warmly thank Docent Kati Tihtonen and Docent Annika Auranen, members of the follow-up group in this work, for their interest in my pursuits.

Special thanks go to my chiefs at the Department of Obstetrics and Gynecology at Tampere University Hospital, Kari Nieminen and Kirsi Kuismanen, and deputy chief Riikka Niemi for their encouraging attitude and for allowing me to combine both research and clinical work. Sami Saarelainen kindly helped me with the practice of ultrasonography in the first steps of this project, for which I am profoundly thankful.

My sincere gratitude goes to both former and present colleagues, co-workers, nurses and midwives for providing an encouraging atmosphere for both my clinical and scientific work. It has been an honor to be able to work with you all. The patients who took part in my studies deserve my special gratitude. Without their contribution this study would never have been possible.

I wish to thank all of my friends for their great affection. You are each unique in my heart. Special thanks to Sanna Saariaho for priceless mental support. I also thank the ladies at "the literature club", Anita Virtanen, Anu Aalto, Kadri Lill, Kristina Veskimäe, Mari Kalamo, Marian Jaalama, Noora Kaartinen and Tea Kuittinen for such fun-filled meetings, countless laughs, deep conversations and unforgettable journeys.

Warmest thanks to my dear parents Kristina and Matti Antila who have always supported me and believed in me. Thank you for your wise guidance and help in my life and for being such awesome grandparents!

Finally, and most eminently I thank my beautiful children, the wise Selma, the funny Noel and the cheerful Emil for making my life meaningful and delightful. You are certainly my biggest achievements ♥♥♥

This study was financially supported by The Finnish Medical Foundation, Competitive State Research Funding of Tampere University Hospital, The Scientific Foundation of the City of Tampere, Tampere University Hospital Support Foundation and the Doctoral Programme of Tampere University.

ABSTRACT

Cesarean delivery is the most frequently performed obstetric procedure, and millions of women undergo this procedure every year. It may be a life-saving operation if performed for the right indications. Nevertheless, as a consequence, hundreds of millions of women carry a scar in their uterus. Approximately half of the scars are known to heal incompletely, resulting in a scar defect, also called isthmocele. Isthmocele is feared to predispose a woman to uterine rupture in subsequent pregnancy. Moreover, it has been suggested to cause gynecological symptoms such as bleeding disorders or pain and has even been associated with infertility or sub-fertility.

The aim of this study was to investigate prospectively the prevalence, risk factors and clinical outcome of isthmocele. The study population consisted of 401 women who delivered by Cesarean section at Tampere University Hospital between January 2016 and January 2017. Six months after delivery, the women were examined by means of ultrasonography in order to diagnose possible isthmocele at the site of the Cesarean scar. The women were followed by means of electronic questionnaires one year after the Cesarean delivery in order to collect data on gynecological symptoms. Thereafter, data on subsequent pregnancies were collected from hospital medical records.

In the first study we compared two different methods to diagnose an isthmocele in nonpregnant women. Sonohysterography, in which contrast-enhancement is used, turned out to be superior compared with unenhanced transvaginal ultrasonography. It was shown that half of cases of isthmocele remain undiagnosed in connection with pure unenhanced ultrasonography. The prevalence of isthmocele was 22.4% in transvaginal ultrasonography and 45.6% in sonohysterography.

In the second study we investigated the risk factors for the development of isthmocele. Type of surgery (elective versus emergency Cesarean delivery), maternal background variables, and factors related to pregnancy, labor and post-operative recovery were analyzed in relation to isthmocele. High maternal body mass index and gestational diabetes were found to be independent risk factors for isthmocele. Additionally, the risk of isthmocele increased with the growing number of previous Cesarean deliveries. These findings concerning the role of obesity and diabetes are

new. This association may become even more important because the prevalence of obesity and gestational diabetes in women of childbearing age has increased tremendously all over the world.

In order to explore the clinical outcome of isthmocele, we conducted an electronic follow-up inquiry, which was carried out one year after the Cesarean delivery. The presence of gynecological symptoms, such as abnormal uterine bleeding and dysmenorrhea, was surveyed. We achieved a high response rate of 88%. Postmenstrual spotting was reported by 20.0% of women with isthmocele, and by 25.9% of women with a large isthmocele, compared with 8.3% in women without isthmocele ($p=0.004$ and $p<0.001$, respectively). Moreover, postcoital bleeding was associated with isthmocele ($p=0.026$).

As regards long-term outcome we collected clinical information on subsequent pregnancies. During the follow-up period (28–41 months) 91 pregnancies and 72 deliveries occurred. Interestingly, massive hemorrhage (≥1000 ml) at delivery was more common in women in whom an isthmocele had been diagnosed earlier (37.5% vs. 16.7%, $p=0.050$). There were no cases of uterine rupture, and otherwise, pregnancy-related complications were rare. Moreover, adverse events in early pregnancy were not associated with isthmocele. All in all, in spite of isthmocele, pregnancy and delivery can be regarded as safe, considering both the newborn and the mother.

In conclusion, isthmocele is a common phenomenon after Cesarean delivery. An overweight condition, gestational diabetes and repeated Cesarean sections increase the risk of isthmocele. Isthmocele may predispose a woman to postmenstrual spotting but nevertheless the majority of women with isthmocele are free from bleeding disorders. Similarly, the presence of isthmocele increases the risk of massive hemorrhage at subsequent delivery. However, isthmocele-related complications during pregnancy and delivery are rare.

TIIVISTELMÄ

Keisarileikkaus on yleisin synnytysopillinen toimenpide. Vuosittain miljoonat naiset synnyttävät keisarileikkauksella. Se voi olla hengenpelastava toimenpide tietyissä tilanteissa, mutta toisaalta, keisarileikkauksen seurauksena kohtuun tulee pysyvä arpi. Noin puolet kohtuun tehdyistä keisarileikkaushaavoista parantuu epätäydellisesti johtaen arpipuutoksen kehittymiseen. Arpipuutoksen on ajateltu altistavan kohdun repeämiselle seuraavassa raskaudessa. Lisäksi, on saatu viitettä sen aiheuttamista gynekologisista oireista, kuten vuotohäiriöistä ja kivuista. Arpipuutoksen on ajateltu myös vaikuttavan naisen hedelmällisyyteen.

Tämän tutkimuksen tarkoitus oli selvittää etenevässä tutkimusasetelmassa kohdun arpipuutoksen esiintyvyyttä, riskitekijöitä sekä vaikutusta lisääntymisterveyteen. Tutkimusaineisto koostui 401 naisesta, jotka synnyttivät keisarileikkauksella Tampereen yliopistollisessa sairaalassa tammikuun 2016 ja tammikuun 2017 välisenä aikana. Kuuden kuukauden kuluttua keisarileikkauksesta heidät kutsuttiin ultraäänitutkimukseen, jossa selvitettiin kohtuarven paranemista. Vuoden kuluttua keisarileikkauksesta naisille lähetettiin sähköinen oirekysely, jossa selvitettiin arpipuutokseen mahdollisesti liittyvien oireiden esiintyvyyttä. Myöhempien raskauksien tiedot kerättiin sähköisestä potilastietojärjestelmästä.

Väitöskirjan ensimmäisessä osatyössä vertailimme kahta eri tutkimusmenetelmää, jolla kohtuarven paranemista voidaan selvittää ei-raskaana olevalla naisella. Sonohysterografia, jossa emättimen kautta tehtävään ultraäänitutkimukseen liitetään tehosteaineenkäyttö, osoittautui paremmaksi tavalliseen emättimen kautta tehtyyn ultraäänitutkimukseen verrattuna. Puolet sonohysterografiassa todetuista arpipuutoksista jäi toteamatta, kun tehosteainetta ei käytetty. Arpipuutoksen esiintyvyys ultraäänitutkimuksessa oli 22.4% ja sonohysterografiassa 45.6%.

Toisessa osatyössä selvitimme arpipuutoksen muodostumiseen vaikuttavia tekijöitä. Keisarileikkauksen kiireellisyysluokitus (suunniteltu vs. kiireellinen), äidin taustatiedot, raskauden ja synnytyksen aikaiset tapahtumat sekä leikkauksen jälkeiseen toipumiseen liittyvät tekijät otettiin huomioon mahdollisina riskitekijöinä. Ylipainon sekä raskausdiabeteksen todettiin olevan arpipuutoksen itsenäisiä riskitekijöitä. Lisäksi, arpipuutoksen kehittymisen riski oli sitä suurempi, mitä enemmän aikaisempia keisarileikkauksia naisella oli. Tutkimustulokset ylipainon ja

raskausdiabeteksen vaikutuksesta ovat uusia. Niiden merkitys saattaa jatkossa vielä korostua, sillä synnytysikäisten naisten ylipaino ja raskausdiabetes yleistyvät maailmanlaajuisesti.

Arpipuutoksen kliinistä merkitystä selvitettiin sähköisellä oirekyselyllä, joka lähetettiin tutkimuspotilaille vuoden kuluttua keisarileikkauksesta. Siinä selvitettiin gynekologisten vaivojen, kuten vuotohäiriöiden ja kuukautiskipujen esiintyvyyttä. Vastausprosentti oli korkea, 88.4%. Naisista, joilla arpipuutos oli todettu, 20.0% ilmoitti kärsivänsä kuukautisten jälkeisestä tiputteluvuodosta, ja naisista, joilla oli todettu iso arpipuutos, tiputteluvuotoa raportoineiden osuus oli 25.9% ($p=0.004$ ja $p<0.001$). Lisäksi, yhdynnän jälkeisen verisen vuodon esiintyminen oli yhteydessä arpipuutokseen ($p=0.026$).

Pitkäaikaisseurantaa varten keräsimme tutkimuspotilaiden seuraavien raskauksien ja synnytysten tiedot sähköisestä potilastietojärjestelmästä. Seuranta-ajan (28–41 kk) kuluessa todettiin 91 raskautta ja 72 synnytystä. Runsas verenvuoto synnytyksessä (≥1000 ml) oli yleisempää arpipuutos-ryhmässä (37.5% vs. 16.7%, $p=0.050$). Tutkimuskohortissa ei todettu kohdun repeämisiä, ja muutkin komplikaatiot olivat vähäisiä. Alkuraskauden häiriöt eivät lisääntyneet arpipuutokseen liittyen. Kaiken kaikkiaan, raskaus ja synnytys todettiin turvalliseksi sekä äidin että vastasyntyneen kannalta huolimatta arpipuutoksesta.

Yhteenvetona voidaan todeta, että kohdun arpipuutos on yleinen keisarileikkauksen seuraus. Ylipaino, raskausdiabetes sekä toistuvat keisarileikkaukset lisäävät sen esiintyvyyttä. Arpipuutos altistaa kuukautisten jälkeiselle tiputteluvuodolle, vaikkakin suurin osa naisista on oireettomia. Arpipuutos myös lisää runsaan verenvuodon riskiä seuraavassa synnytyksessä. Muutoin, arpipuutokseen liittyvät komplikaatiot raskauden ja synnytyksen aikana ovat harvinaisia.

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ABBREVIATIONS

AMT	Adjacent myometrial thickness
AUB	Abnormal uterine bleeding
BA	Bland–Altman
BMI	Body mass index
CD	Cesarean delivery
CSP	Cesarean scar pregnancy
GDM	Gestational diabetes
HSC	Hysteroscopy
IUD	Intrauterine device
MRI	Magnetic resonance imaging
NICU	Neonatal intensive-care unit
RCT	Randomized controlled trial
RMT	Residual myometrial thickness
SHG	Sonohysterography
TVUS	Transvaginal ultrasonography
US	Ultrasonography/ultrasonographic
3D-US	Three-dimensional ultrasonography

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to by the Roman numerals I–IV as assigned below.

I Antila-Långsjö R, Mäenpää J, Huhtala H, Tomás E, Staff S. Comparison of transvaginal ultrasound and saline contrast sonohysterography in evaluation of cesarean scar defect. A prospective cohort study. Acta Obstetrica et Gynecologica Scandinavica 2018 97(9):1130-1136

II Antila-Långsjö R, Mäenpää J, Huhtala H, Tomás E, Staff S. Cesarean scar defect: A prospective study on risk factors. American Journal of Obstetrics and Gynecology 2018 219:458.e1-8

III Antila R, Mäenpää J, Huhtala H, Tomás E, Staff S. Association of cesarean scar defect with abnormal uterine bleeding; the results of a prospective study. European Journal of Obstetrics & Gynecology and Reproductive Biology 2020 244:134-140

IV Antila R, Mäenpää J, Huhtala H, Tomás E, Staff S. Association of post-cesarean isthmocele in non-pregnant women with subsequent pregnancy outcome. Submitted.

 In addition, some unpublished data are presented.

1 INTRODUCTION

Cesarean delivery (CD) is the most frequently performed obstetric procedure (Rutkow, 1997). Every year, millions of women undergo this operation. CD is potentially a life-saving procedure for both mother and newborn when some complications come up during pregnancy or labor. However, a large proportion of all CDs is performed because of non-obstetric reasons, for example maternal request. The CD rate has increased worldwide in recent decades. In the United States of America almost 1.3 million CDs were performed in 2014, representing 32.2% of all deliveries (Hamilton et al., 2015). In China, the annual number of CDs has been over 5 million for many years, which corresponds to a CD rate of 35% (Li et al., 2017). According to the World Health Organization there are countries in which the CD rate has increased up to 56% (*WHOstatistics*, n.d.). As the CD rate increases, complications related to CD also increase. Besides the short-term complications related to the procedure itself, attention should be paid to the long-term complications of CD. One of these complications is Cesarean scar defect, also known as isthmocele, pouch or niche in the literature. Isthmocele reflects inadequate healing of the myometrium at the site of Cesarean incision. It has been proposed to be associated with various obstetric and gynecological problems (Bij de Vaate et al., 2014; Monteagudo, Carreno, & Timor-Tritsch, 2001; Tower & Frishman, 2013; Uppal, Lanzarone, & Mongelli, 2011; L F van der Voet, Bij de Vaate, Veersema, Brolmann, & Huirne, 2014; Olga Vikhareva Osser & Valentin, 2011; Wang et al., 2009). These include complications related to a subsequent pregnancy, such as Cesarean scar pregnancy (CSP), morbidly adherent placenta, and dehiscence or rupture of a CD scar, which may have life-threatening consequences (Timor-Tritsch, Monteagudo, Cali, Palacios-Jaraquemada, et al., 2014; Olga Vikhareva Osser & Valentin, 2011). These conditions are fortunately rare. Nevertheless, bleeding disorders and menstrual pain are thought to be fairly common complaints related to isthmocele (Bij de Vaate et al., 2011, 2014; Uppal et al., 2011; L F van der Voet, Bij de Vaate, et al., 2014; Wang et al., 2009). Isthmocele may also increase the risk of complications during gynecological procedures such as application of an intrauterine

device (IUD), evacuation and embryo transfer (Patounakis et al., 2016; Tower & Frishman, 2013).

In previous studies the prevalence of isthmocele has varied considerably, between 6.9–88% depending on the study population (Osser, Jokubkiene, & Valentin, 2009; Wang et al., 2009). The great variability may be the result of various definitions of isthmocele, and different study designs and diagnostic methods. Because not all women with a CD scar in their uterus develop a scar defect, the predisposing risk factors have been investigated. A history of multiple CDs is generally considered as a major risk factor of isthmocele (Armstrong, Hansen, Van Voorhis, & Syrop, 2003; Ofili-Yebovi et al., 2008; Wang et al., 2009). However, data on other risk factors is conflicting.

In recent years, numerous studies have been published on scar defect and the results are heterogeneous. Various diagnostic methods have been used for assessing an isthmocele. In most of the studies the population has been selected, i.e. symptomatic patients have been enrolled. Additionally, prospective studies are scarce. In spite of previous studies, the impact of isthmocele on subsequent pregnancy and delivery is unclear. Moreover, it is not obvious whether a scar classified as deficient in ultrasonography is associated with gynecological complications such as menstrual problems, subfertility and scar pregnancy. Although large prospective trials concerning the clinical outcome of isthmocele are lacking, symptomatic women with isthmocele are frequently treated by means of invasive surgical techniques.

The present work was aimed at studying the prevalence, risk factors and clinical outcome of isthmocele prospectively in an unselected population. Identifying the risk factors of isthmocele would be helpful in developing preventive strategies for reducing these risks. Moreover, better understanding of the clinical outcome of isthmocele may improve management and follow-up of women, thus overcoming possible adverse outcomes and unnecessary interventions.

2 REVIEW OF THE LITERATURE

2.1 Cesarean delivery

Cesarean delivery is a major surgical procedure. In the United States 1.3 million CDs are performed annually (Hall, DeFrances, Williams, Golosinskiy, & Schwartzman, 2010; Martin, Hamilton, Osterman, Driscoll, & Drake, 2018). The CD rate has continued to rise for decades and this has become a global trend. Rates up to 50% have been reported in developed countries (Betrán et al., 2016). CD may potentially decrease both maternal and infant mortality and morbidity. However, CD is also significant as regards a woman´s reproductive and future health. The growing CD rate can consequently lead to morbidity and an increasing number of complications. Short-term complications include infections, anesthesia-related complications, massive bleeding, bladder or bowel lacerations, utero-cervical lacerations, thromboembolisms and need of hysterectomy (Zelop & Heffner, 2004). Long-term complications are mainly related to the scar in the uterus. These include Cesarean scar defect (isthmocele), ectopic scar pregnancy, placental abruption, placenta previa, abnormally adherent placentation, scar dehiscence and uterine rupture, which may potentially have catastrophic consequences (S L Sholapurkar, 2014; Zelop & Heffner, 2004).

2.2 Definition and characteristics of isthmocele

Isthmocele represents defective healing of a uterine scar after CD. It is a pouch-like defect in the lower uterine segment. Alternative terms for isthmocele are Cesarean scar defect, niche, pouch and diverticulum. Most commonly, isthmocele is triangular or semicircular in shape (Figure 1) (Bij de Vaate et al., 2011). In a case of total defect, there is no remaining myometrium over the defect. Isthmocele may also have branches, which are thinner parts of the main isthmocele. There is no generally accepted definition for isthmocele. Typically, isthmocele is defined as an anechoic structure (with or without fluid) at the presumed site of uterine incision communicating with the endometrial cavity. At the mildest, any visible indentation,

however small, has been considered as isthmocele (Ofili-Yebovi et al., 2008; Osser et al., 2009; Osser, Jokubkiene, & Valentin, 2010). More commonly, isthmocele is defined as an anechoic area at the site of the Cesarean scar with a depth of at least 1–2 mm (Bij de Vaate et al., 2011; L F van der Voet, Bij de Vaate, et al., 2014). Recently, a European guideline suggested a definition in which the depth of isthmocele is at least 2 mm (Jordans et al., 2018). In the literature, isthmoceles have often been subdivided to large or small. There is no objective cut-off level of the depth to define isthmocele as large (Jordans et al., 2018). In a few papers, the thickness of residual myometrium (RMT) has been used to define an isthmocele. Osser et al. used different cut-off values of RMT depending on the method of examination. In unenhanced ultrasonographic examination, a large isthmocele was defined as RMT ≤2.2 mm. In sonohysterography (SHG) a large isthmocele was defined as RMT ≤2.5 mm (O Vikhareva Osser & Valentin, 2010). Van der Voet et al. defined isthmocele as large if the RMT was <50% of adjacent myometrium thickness (AMT) (L F van der Voet, Bij de Vaate, et al., 2014). In histologic specimens of isthmocele the following findings have been reported: congested endometrium, lymphocytic infiltration, capillary dilatation, polyp formation, residual suture material with a foreign-body giant-cell reaction, free red blood cells in the endometrial stroma (suggesting recent hemorrhage), fragmentation and breakdown of the endometrium, and iatrogenic adenomyosis (Morris, 1995).

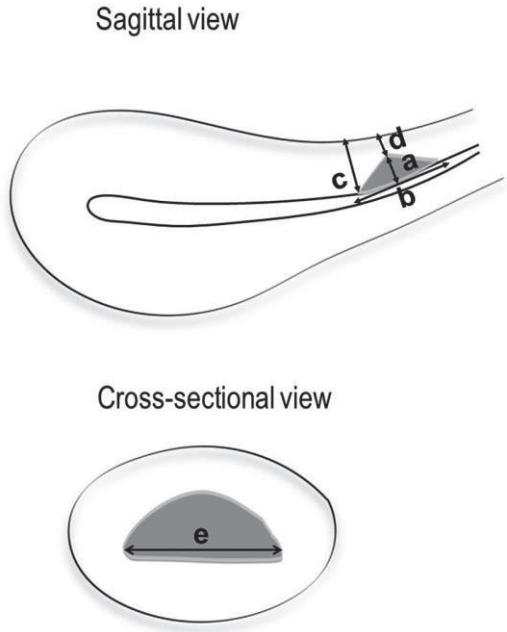

Figure 1. Schematic presentation of isthmocele (gray area) demonstrating the measurements: a. depth, b. width, c. adjacent myometrial thickness, d. residual myometrial thickness, e. length of isthmocele

2.3 Diagnostics

Various methods to detect and measure the size of isthmocele have been described. Studies published between 1960–1988 have involved imaging isthmocele by hysterography, which is based on radiology (Roberge et al., 2012). Since then, hysterography has been replaced by modern imaging techniques, mainly ultrasonography (US). In European guidelines evaluation of isthmocele is recommended at the earliest at three months after CD (Jordans et al., 2018). On the other hand, the wound-healing process is suggested to take up to at least six months, which points towards a later evaluation time (Dicle, Küçükler, Pirnar, Erata, & Posaci, 1997). RMT and AMT values have been noticed to become reduced in serial measurements when CD scars were screened at two and 12 months after CD. Also,

the ratio between RMT and AMT values was reduced. However, the prevalence and the depth of isthmocele did not change between serial measurements in that particular study (Lucy F van der Voet, Jordans, Brölmann, Veersema, & Huirne, 2017).

The best time for evaluation of isthmocele during the menstrual cycle has not yet been elucidated. In the follicular phase of the menstrual cycle, a possible early pregnancy is avoided. On the other hand, in the mid-follicular phase the possible presence of intrauterine fluid may facilitate the diagnostics (Jordans et al., 2018). The scan can be performed during the mid-follicular phase if effective contraception is used (Ludwin, Martins, & Ludwin, 2018).

2.3.1 Transvaginal ultrasonography

Transvaginal ultrasonography (TVUS) has been used in the diagnosis of isthmocele since 1990 (Roberge et al., 2012; Tower & Frishman, 2013). It is a dynamic process in which the use of pressure with the probe and variation of the position of the probe (anterior or posterior fornix) can affect visualization of isthmocele. TVUS is performed with the woman lying in the lithotomy position with an empty bladder. A possible isthmocele is detected as a hypoechoic shadow at the anterior wall in the uterine isthmus. An isthmocele should be measured in three dimensions. In the sagittal plane, the width and depth of isthmocele, and RMT and AMT are measured. The length of isthmocele is measured in the transverse plane (Figure 1). Length, depth and width should be measured in the plane in which they are the largest; RMT should be measured in the plane where it is the smallest. AMT should be measured as close to the isthmocele as possible, where the myometrium is at its thickest. If visible, branches of isthmocele should also be measured and reported (Jordans et al., 2018; Naji et al., 2012).

2.3.2 Sonohysterography

The evaluation of isthmocele by means of contrast-enhanced SHG (also called hydrosonography or hysterosonography) is of additional value (Jordans et al., 2018). It is considered to be a first-line imaging method when assessing isthmocele. SHG is fast, inexpensive, easily performed and well tolerated by the patients (Dueholm, Laursen, & Knudsen, 1999) Sterile saline or gel is typically used as the contrast medium. It enables better visualization and demarcation of isthmocele. Additionally,

isthmoceles are more often detected by means of SHG compared with TVUS (Osser et al., 2010; Rasheedy, Sammour, Elkholy, & Fadel, 2019). When performing SHG, a catheter is inserted inside the uterus via the cervix, sterile contrast medium is flushed inside the uterine cavity and transvaginal sonography is performed simultaneously (L F van der Voet, Bij de Vaate, et al., 2014). A maximal contrast-medium volume of 10–20 ml is typically sufficient. The best location of the catheter is just in front of the isthmocele or, if possible, cranial to the isthmocele at the beginning, then pulling the catheter slowly backwards until it reaches the base of the isthmocele. If fluid is present in the uterine cavity, additional saline instillation is not necessary (Jordans et al., 2018). The same parameters as with TVUS are then measured. In the detection of isthmocele by means of SHG, interobserver reliability is reported to be high (100% agreement between observers). Also, in the measurement of RMT interobserver reliability is reported to be high with SHG (correlation coefficient 0.96). Interobserver reliability in general is considered better with SHG compared with TVUS (Baranov, Gunnarsson, Salvesen, Isberg, & Vikhareva, 2016).

2.3.3 Three-dimensional ultrasonography

The use of three-dimensional ultrasonography (3D-US) may improve the assessment of isthmocele (Ludwin et al., 2018). In particular, the coronal plane, which cannot be obtained using two-dimensional US, may provide additional information on isthmocele. Moreover, with 3D-US it is possible to reconstruct and display chosen sections within the volume dataset off-line (Naji et al., 2012). However, even with 3D-US the measurements remain subjective, and both interobserver and intraobserver variability is high (Glavind, Madsen, Uldbjerg, & Dueholm, 2016). Contrast-enhancement is also recommended with 3D-US because it enables better tissue contrast (Ludwin et al., 2018; Naji et al., 2012). The use of 3D-US requires a longer examination time, specific training, and machinery with a 3D-US application (Naji et al., 2012).

2.3.4 Hysteroscopy

Isthmocele can also be visualized by means of hysteroscopy (HSC). Often, a gap or disruption of the endometrium or myometrium is observed (Figure 2). There may be a ring-shaped flap or fibrotic tissue below the pouch which may impair the

drainage of menstrual blood through the cervix (Fabres et al., 2005; Fernandez, Fernandez, Fabres, & Alam, 1996). In general, there is no hysteroscopic classification for isthmocele (L. L. F. van der Voet et al., 2017). In a prospective study of asymptomatic women with at least one previous CD undergoing hysteroscopic sterilization, isthmocele was observed in 75% of cases. In the study, isthmocele was defined as any defect in the anterior wall of the uterus at the level of the isthmus. In the isthmocele the investigators noticed polyp-like structures, cyst-like formations, visible serosa (total defect), fibrotic tissue, abnormal vascular patterns, lateral branches, mucus production and bleeding inside the defect (L. L. F. van der Voet et al., 2017). Moreover, intrauterine adhesions may be detected (El-Mazny, Abou-Salem, El-Khayat, & Farouk, 2011).

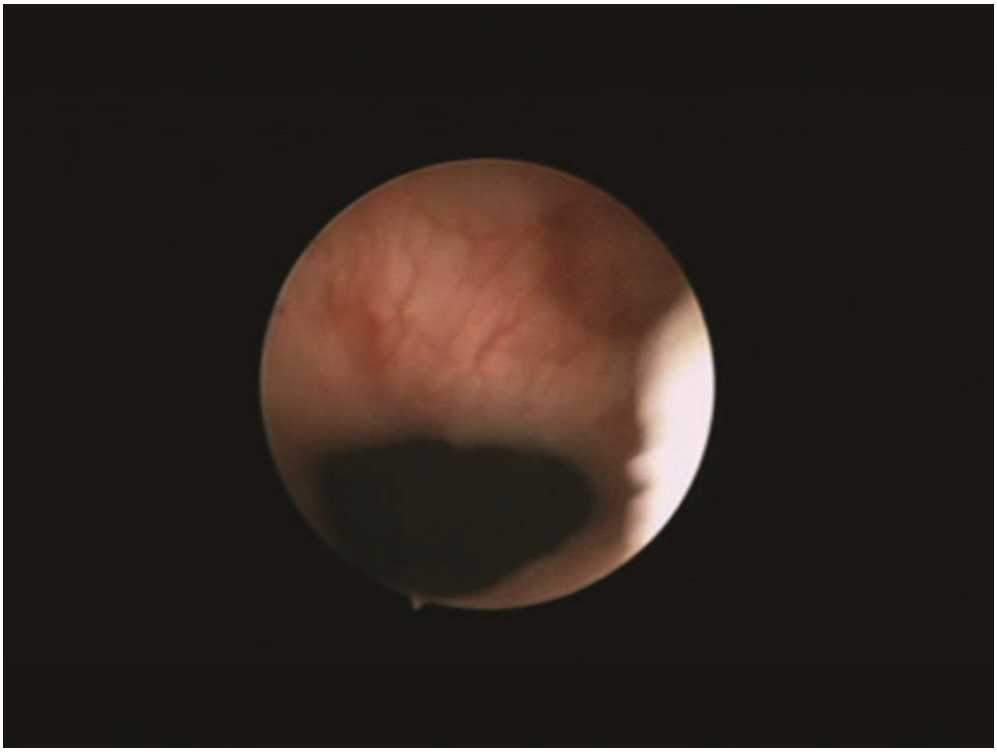

Figure 2. Hysteroscopic image of isthmocele, which appears as a dome-like pouch at the anterior uterine wall. Courtesy of Dr. Reita Nyberg

2.3.5 Magnetic resonance imaging

Magnetic resonance imaging (MRI) relies upon the magnetic properties of living tissue. MRI detects the magnetic moment created by single protons in hydrogen atoms. Superior soft-tissue contrast and multiplanar imaging capabilities are the advantages of MRI. It is an expensive and time-consuming imaging method and often not easily available. Thus, it is less frequently used in clinical practice. However, isthmocele can be detected by means of MRI (Figure 3) (Wong & Fung, 2018). Its diagnostic accuracy is comparable to that of TVUS (Liu, Yang, & Wu, 2018). The use of MRI may be considered when certain complications such as CSP are suspected (Huang, Zhang, & Zhai, 2014).

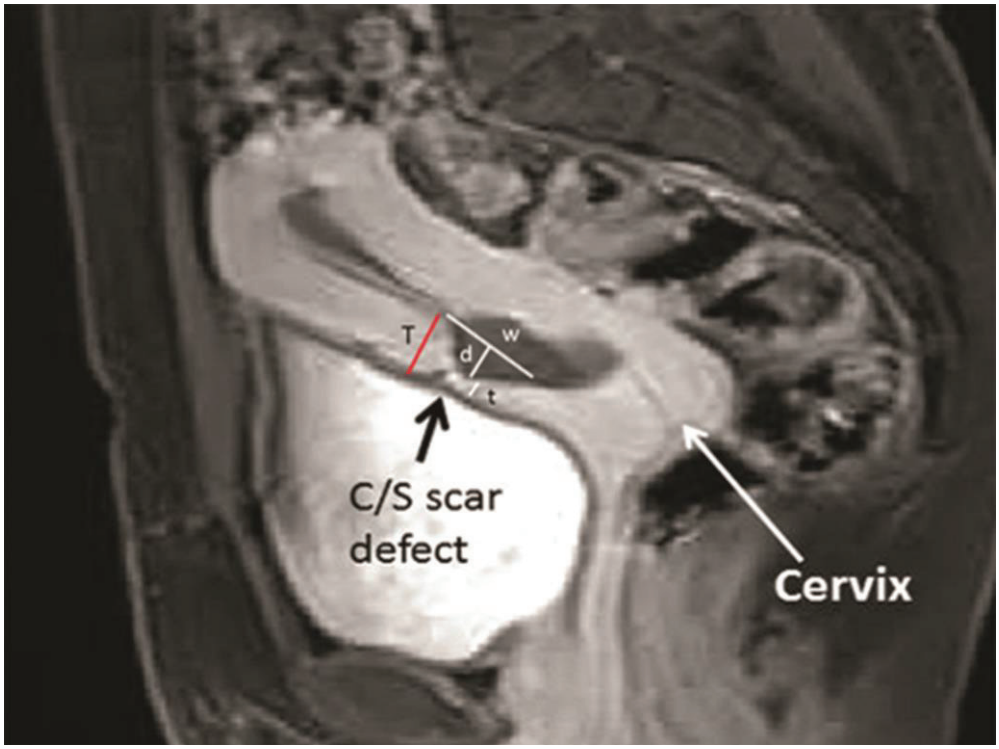

Figure 3. Magnetic resonance imaging measurement of isthmocele: d = depth; w = width; t = residual myometrial thickness; T = adjacent myometrial thickness. Reprinted from Gynecology and Minimally Invasive Therapy, Vol. 7, Wong et al. "Magnetic resonance imaging in the evaluation of Cesarean scar defect", pp.104-10. Copyright, with permission from Wolters Kluwer

2.4 Prevalence

The reported prevalence rate of isthmocele has varied between 7% and 88% (Table 1) (Chang, Tsai, Long, Lee, & Kay, 2009; Rasheedy et al., 2019; Wang et al., 2009). There are many studies in which the study population has been selected, for example, studies including women who were referred because of gynecological symptoms. Additionally, methods used to detect possible isthmocele and the definition of isthmocele have varied. Mainly, TVUS and SHG have been used. A few studies have involved detection of isthmocele by means of HSC, but these studies have included only symptomatic patients (Borges, Scapinelli, de Baptista Depes, Lippi, & Coelho Lopes, 2010; El-Mazny et al., 2011; Fabres et al., 2003). The prevalence rates in unselected populations have varied between 24% and 70% when TVUS has been used and between 56% and 84% with SHG.

2.5 Risk factors

Various risk factors associated with the development of isthmocele have been investigated. These can be divided into subgroups: demographic factors, factors related to the current pregnancy and delivery, and factors related to wound healing (Table 2).

2.5.1 Demographic factors

The effect of maternal age and previous vaginal births on the development of isthmocele has been investigated in various studies. Neither of these factors has been found to be associated with isthmocele (Hayakawa et al., 2006; Ofili-Yebovi et al., 2008; O Vikhareva Osser & Valentin, 2010). There appears to be no study on the effect of smoking on isthmocele development.

Table 1. Prevalence of isthmocele in relation to diagnostic method in a population of women with a history of Cesarean delivery

Study	Design	Selected/ Unselected	n	Population	Definition of isthmocele	Prevalence %		
						TVUS	SHG	HSC
Menada Valenzano 2006	Case-control	Unselected	116	1 previous CD between 1995—2004	Triangular, anechoic area		60	
Bij de Vaate 2011	Prospective	Unselected	225	CD 6—12 months earlier	Anechoic area ≥ 1 mm	24	56	
Osser 2010	Prospective	Unselected	108	CD 6—9 months earlier	Any visible indentation	70	84	
Osser 2009	Case-control	Unselected	162	CD 6—9 months earlier	Any visible indentation	69		
Armstrong 2003	Case-control	Unselected	32	CD within preceding 5 years	Fluid within CD scar	42		
Regnard 2004	Prospective	Unselected	33	CD in history + pregnancy planning	Triangular, anechoic area		58	
Chen 1990	Prospective	Unselected	47	CD within preceding 8 years	Various patterns of CD scar defect			
Ofili-Yebovi 2008	Prospective	Selected	324	CD in history + various gynecological symptoms	Any detectable thinning	19		
El-Mazny 2011	Cross-sectional	Selected	75	CD in history + various gynecological symptoms	Triangular, anechoic area		27	31
Monteagudo 2001	Prospective	Selected	44	CD in history + SHG for various indications	Triangular, anechoic area		100	
Wang 2009	Cross-sectional	Selected	207	CD in history + TVUS for various indications	Hypoechoic area	7		
Uppal 2011	Prospective	Selected	71	CD in history + TVUS for various indications	Fluid-filled defect	40		
Chang 2009	Prospective	Selected	57	CD in history + postmenstrual spotting	Triangular, anechoic area	88		
Borges 2010	Prospective	Selected	43	CD in history + postmenstrual spotting	Cavity in HSC + superior/inferior fibrotic ring			88
Fabres 2003	Retrospective	Selected	92	CD in history + AUB (HSC: n=40)	A pouch at anterior wall of uterus	100% correlation with TVUS and HSC		

AUB = Abnormal uterine bleeding, CD = Cesarean delivery, HSC = Hysteroscopy, SHG = Sonohysterography, TVUS = Transvaginal ultrasonography

Table 2. Assessment of possible risk factors associated with the development of isthmocele in various study populations

	Osser 2010(O Vikhareva Osser & Valentin, 2010)	Hayakawa 2006	Ofili-Yebovi 2008	Yazicioglu 2006	Wang 2009	Armstrong 2003	Pomorski 2016
Number of patients	108	137	324	70	207	31	399
Number of previous CDs	1	1	≥1	1	≥1	≥1	≥1
Endpoint: Presence of isthmocele/Large isthmocele	Large	Presence	Presence	Presence	Large	Presence	Presence
Method of imaging	TVUS/SHG	TVUS	TVUS	TVUS	TVUS	TVUS	TVUS
Time point of imaging after CD	6–9 months	1 month	> 3 months	6 weeks	NA	< 5 years	6 weeks
Demographic factors							
Maternal age	yes	no	no	-	-	-	yes
Previous vaginal births	no	-	no	-	-	-	-
Factors related to current pregnancy and delivery							
Cervical dilatation	yes*	-	-	yes**	-	-	no
Position of the presenting part	yes	-	-	-	-	-	-
Duration of labor	yes	-	-	no	-	-	-
Location of a scar	yes	-	no	-	-	-	-
Oxytocin during labor	yes	-	-	-	-	-	-
Emergency CD	no	no	no	-	-	yes	no
Fetal weight	-	-	-	no	-	-	-
Multiple pregnancy	-	yes	no	-	-	-	no
Gestational age	yes	yes	no	no	-	-	yes
Premature rupture of membranes	-	yes	-	-	-	-	-

Preeclampsia	no	yes	-	-	-	-	-
Placenta previa	-	no	-	-	-	-	-
Factors related to wound healing							
Number of previous CDs	-	-	yes	-	yes	yes	no
Retroflex position of uterus	yes	-	yes	-	yes	-	no
Suturing technique [1]	no [1]	yes [2]	-	yes [3]	-	-	-
Surgical experience [4]	-	no	-	-	-	-	-
BMI	no	no	-	-	-	-	-
Intra-operative complication	no	-	-	-	-	-	-
Peri- and postpartum infection [5]	no	no	-	-	-	-	-
Operating time	-	-	-	no	-	-	-
Pfannenstiel or vertical incision	-	no	-	-	-	-	-

* More cervical dilatation, ** Less cervical dilatation
[1] Single-layer versus double-layer continuous sutures
[2] Single-layer myometrial closure increased the risk of isthmocele compared with double-layer closure or single-layer myometrial closure with decidual suture
[3] When excluding the endometrial layer the risk of isthmocele increased compared with sutures which included the endometrial layer
[4] Years of surgeon experience
[5] Including chorioamnionitis, wound infection, urinary-tract infection, endometritis, infection of unknown origin

BMI = body mass index, CD = Cesarean delivery, NA = not assessed, SHG = sonohysterography, TVUS = transvaginal ultrasonography

2.5.2 Factors related to current pregnancy and delivery

The stage of labor at the time of CD is associated with isthmocele development. Cervical dilatation and the position of the presenting fetal part are associated with the risk of large defects. In one study the risk increased dramatically if the duration of labor was ≥5 hours or cervical dilatation was ≥5 cm (O Vikhareva Osser & Valentin, 2010). In contrast, in a small study of women with only one previous CD the duration of labor did not increase the risk of isthmocele. Moreover, the investigators found that advanced cervical dilatation decreased the risk of isthmocele (F. Yazicioglu, Gökdogan, Kelekci, Aygün, & Savan, 2006).

The location of a scar in relation to the internal cervical os has not been regarded as a risk factor of isthmocele when any thinning of the myometrium has been considered as isthmocele (Ofili-Yebovi et al., 2008). However, large defects were located lower in the uterus than intact scars or small defects (O Vikhareva Osser & Valentin, 2010). Here, the authors suggested that in lower incisions, cervical tissue may be included in the scar, with less favorable healing properties.

Emergency CD and fetal weight have not been found to be associated with isthmocele (Hayakawa et al., 2006; Ofili-Yebovi et al., 2008; O Vikhareva Osser & Valentin, 2010). The effects of gestational age and multiple pregnancy on the development of isthmocele are unclear (Hayakawa et al., 2006; Ofili-Yebovi et al., 2008; O Vikhareva Osser & Valentin, 2010; H. F. Yazicioglu, Sevket, Ekin, Ozyurt, & Aygun, 2012).

2.5.3 Factors related to wound healing

Many studies have shown that a history of previous CD increases the risk of isthmocele (Armstrong et al., 2003; Ofili-Yebovi et al., 2008; Park, Kim, Lee, Gen, & Kim, 2018; Wang et al., 2009). The risk increases with the number of previous CDs (Ofili-Yebovi et al., 2008). It is suggested that repeated trauma could disrupt the normal healing process in the wound. Also, vascular perfusion in the scar tissue may be reduced, which may impair scar healing (Ofili-Yebovi et al., 2008; Wang et al., 2009).

Isthmoceles have been found to be more common in cases of retroflexed uterus (Wang et al., 2009). The chance of woman with a retroflexed uterus to end up with a deficient scar was more than twice that of a woman with an anteflexed uterus. It is

suggested that mechanical traction in the lower uterine segment may reduce vascular perfusion, impairing wound healing (Ofili-Yebovi et al., 2008; O Vikhareva Osser & Valentin, 2010)

The optimal way to suture the uterus after hysterotomy has been a matter of debate. In a prospective study a procedure consisting of a continuous suture with decidual closure, followed by an interrupted myometrial suture as well as double-layered interrupted sutures reduced the risk of isthmocele compared with single-layer closure with interrupted sutures (Hayakawa et al., 2006). In that particular study the scars were evaluated by TVUS one month after CD.

Bamberg et al. carried out a randomized controlled trial (RCT) in which single-layer continuous unlocked, single-layer continuous locked and double-layer sutures were compared. A total of 435 women were included. There were no significant differences between the groups at 6–24 months after CD concerning the prevalence or the depth of isthmocele. After double-layer suturing, there was a trend towards increased RMT (Bamberg et al., 2017). The same authors noticed that after double-layer closure, RMT was greater in primary (no previous CD) and elective CD patients at 6–24 months after CD compared with single-layer closure (Bamberg et al., 2018).

In a meta-analysis of RCTs including 3969 patients the groups of women with single-layer versus double-layer uterine closure showed a similar prevalence of isthmocele and there was no difference in the incidence of uterine dehiscence or rupture even though RMT was thinner after single-layer closure. The quality of evidence concerning uterine rupture was low because there were very few cases of uterine rupture (Di Spiezio Sardo et al., 2017). Sholapurkar suggested that there may be additional factors related to isthmocele formation, such as malapposition of myometrial layers, and inappropriate tightness of sutures, leading to ischemia and adhesions (Shashikant L Sholapurkar, 2018).

In summary, current evidence based on randomized trials does not support a specific type of uterine closure for optimal maternal outcomes and the data is insufficient to draw conclusions on the risk of uterine rupture.

Surgical experience, maternal body mass index (BMI), intraoperative complications, peri- or postpartum infections, operating time and Pfannenstiel/vertical incision have been found not to be associated with the risk of isthmocele development (Hayakawa et al., 2006; O Vikhareva Osser & Valentin, 2010; H. F. Yazicioglu et al., 2012). The effect of gestational diabetes (GDM) has not been analyzed. In only one study was GDM taken into account as a possible risk factor, but the number of cases was too small for statistical calculations (O Vikhareva Osser & Valentin, 2010).

2.6 Clinical outcome

There are several reports on isthmocele-related symptoms. Isthmocele can be considered to be a pouch-like reservoir where menstrual blood may accumulate and lead to bleeding disorders. Again, thin, weakened residual myometrium above isthmocele may predispose a woman to obstetric complications in subsequent pregnancies.

2.6.1 Gynecological symptoms and early pregnancy outcome

Various gynecological symptoms have been reported to be associated with isthmocele. The symptoms include abnormal uterine bleeding (AUB), prolonged periods, dysmenorrhea, chronic pelvic pain, subfertility and suprapubic pelvic pain (Bij de Vaate et al., 2011; Fabres et al., 2003; Gubbini, Casadio, & Marra, 2008; Gubbini et al., 2011; Tower & Frishman, 2013; Uppal et al., 2011; L F van der Voet, Bij de Vaate, et al., 2014; Wang et al., 2009). In the majority of studies reporting isthmocele-related symptoms, selection bias is likely to exist, as study participants have been referred for various gynecological indications. There are only a few prospective studies on isthmocele-related gynecological symptoms in unselected populations.

The incidence of postmenstrual spotting in women with isthmocele was 33.6% compared to 15.2% in women without isthmocele in a prospective study in which SHG was performed 6–12 months after CD. Also, intermenstrual bleeding was associated with isthmocele (30.0% vs. 10.3%) and the number of intermenstrual bleeding days was significantly higher in the isthmocele group (0.8 days vs. 0.3 days) (Bij de Vaate et al., 2011). Similarly, in another prospective study in which a possible isthmocele was evaluated much earlier (6–12 weeks after CD), the prevalence of postmenstrual spotting was 28.9% in the isthmocele group compared with 6.9% in women with no isthmocele (L F van der Voet, Bij de Vaate, et al., 2014). Prolonged periods or urologic symptoms were not associated with isthmocele in either of the studies.

In a meta-analysis of 24 prospective cohort studies, women with previous CD had increased odds for miscarriage (OR 1.17), ectopic pregnancy (OR 1.21) and stillbirth (OR 1.27) when compared with women with previous vaginal delivery (Keag, Norman, & Stock, 2018). However, there are no studies on the association between isthmocele and early pregnancy complications, such as miscarriage.

Ectopic CSP occurs when a gestational sac implants at the site of a previous hysterotomy scar. Its association with isthmocele has not been studied. It is a rare condition with a reported incidence of 1:1800 to 1:2200 pregnancies (Rotas, Haberman, & Levgur, 2006). Nevertheless, there is a substantial increase in the number of cases of CSP when the CD rate increases. It is diagnosed by TVUS. Ultrasonographic criteria for CSP are an empty uterine cavity and cervical canal with a clearly visualized endometrium, the presence of a gestational sac within the anterior portion of the lower uterine segment at the presumed site of the Cesarean scar and thinned or absent myometrium between the gestational sac and bladder (Osborn, Williams, & Craig, 2012). There is a risk of life-threatening complications such as uterine rupture, severe hemorrhage and need for hysterectomy, and thus pregnancy termination is generally recommended soon after the diagnosis (Ash, Smith, & Maxwell, 2007). Women with CSP are at risk of recurrence in the future, although a normal pregnancy after a CSP is also possible (Grechukhina et al., 2018). It is believed that CSP and a morbidly adherent placenta are early manifestations of implantation abnormalities, starting with CSP and progressing to deeper placental invasion as gestation advances (Timor-Tritsch, Monteagudo, Cali, Palacios-Jaraquemada, et al., 2014). A morbidly adherent placenta is a severe complication often leading to hysterectomy, permanent loss of fertility and increased morbidity (Kaelin Agten et al., 2017; Timor-Tritsch, Monteagudo, Cali, Vintzileos, et al., 2014).

2.6.2 Obstetric outcome

Isthmocele has been considered to predispose a woman to uterine rupture. Reports on uterine rupture are mainly case reports as it is a rare condition. In a Swedish register-based study among women who delivered by repeat CD, the incidence of uterine rupture was 2.8% and the incidence of uterine dehiscence was 10.1% (Fogelberg, Baranov, Herbst, & Vikhareva, 2017). In a small prospective study of 65 deliveries after at least one CD there was a probable association between large defects and uterine rupture or dehiscence in subsequent pregnancies. There were two cases of dehiscence and one case of uterine rupture in the group of women with large isthmocele, compared with one uterine rupture in a woman with a small isthmocele. The numbers were too small to reveal a statistically significant difference (Olga Vikhareva Osser & Valentin, 2011). The ratio between the depth of isthmocele and RMT could possibly be useful in predicting those patients who are at an elevated

risk of CD scar dehiscence (Pomorski, Fuchs, & Zimmer, 2014). Similarly, low RMT values (<3 mm) were associated with the risk of uterine rupture or dehiscence in a small study of 149 women (Risager, Uldbjerg, & Glavind, 2020).

2.7 Treatment of isthmocele

Hormonal therapy is the treatment of choice for a woman with symptomatic isthmocele causing AUB. The aim of hormonal therapy is to reduce menstrual bleeding. Combined hormonal therapies were successfully used in a preliminary report (Tahara, Shimizu, & Shimoura, 2006). Surgical management of symptomatic isthmocele should be reserved for situations in which hormonal therapy has been unsuccessful or is contraindicated. If surgery is considered, the indication should be based on symptoms, and other causes of AUB should be excluded first (L. L. F. van der Voet et al., 2017). Hysterectomy can be considered, but if a woman wishes to preserve fertility, less invasive surgical procedures should be considered. The aim of the treatments is to facilitate the drainage of menstrual blood, reduce in situ production of blood and reconstruct the uterine defect. Surgical treatment options are hysteroscopic resection and laparoscopic, vaginal or robotic repair (L F van der Voet, Vervoort, et al., 2014). Hysteroscopic resection is the least invasive of these techniques, but it requires a sufficiently thick residual myometrium. RMT ≥3 mm is usually a prerequisite (Vervoort et al., 2018). Hysteroscopic repair does not strengthen the uterine wall. If myometrial endurance is to be reinforced, a laparoscopic, vaginal and robotic repair is considered. Basically, the technique is to open the scar from one side to the other, excise the fibrotic tissue to access healthy myometrium and then resuture the scar (Donnez, Jadoul, Squifflet, & Donnez, 2008).

In a recent RCT among women with isthmocele and postmenstrual spotting, 52 women were randomized to hysteroscopic resection and 51 women to expectant management. The hysteroscopic procedure included resection of the lower rim of the isthmocele and superficial coagulation of the surface of the isthmocele with the use of a rollerball. After six months of follow-up the number of postmenstrual spotting days was reduced by three compared with the control group. The RMT at three months was not changed in comparison with the baseline measurement (Vervoort et al., 2018). In a systematic review of isthmocele treatments, hysteroscopic, vaginal and laparoscopic repair were reported to reduce bleeding disorders and pain. However, because of small sample sizes, low methodological

quality of the studies and incomplete long-term follow-up, the evidence is not sufficient to draw conclusions on the effectiveness of the interventions. High-quality comparative studies on different surgical methods are lacking (Setubal et al., 2018; L F van der Voet, Vervoort, et al., 2014).

3 AIMS OF THE STUDY

This study was undertaken to assess the prevalence, risk factors and clinical outcome of isthmocele. The specific aims were:

1. To assess the prevalence of isthmocele at six months after Cesarean delivery and to compare transvaginal ultrasonography and saline-contrast sonohysterography in the diagnostics of isthmocele.

2. To identify risk factors predisposing women to isthmocele.

3. To evaluate the relationship between isthmocele and gynecological symptoms (i.e. bleeding disorders, dysmenorrhea, dyspareunia) at one year after Cesarean delivery.

4. To investigate the clinical outcome of subsequent pregnancy and delivery in relation to isthmocele.

4 PATIENTS, MATERIALS AND METHODS

4.1 Study subjects

Four hundred and one women who delivered by Cesarean section at the Department of Obstetrics and Gynecology, Tampere University Hospital, Finland, between January 1, 2016 and January 31, 2017 were recruited in this study. The women were approached at the maternity outpatient clinic prior to elective CD or within three days of CD at the maternity ward. Exclusion criteria were age under 18, a known uterine anomaly and absence of a common language. All participants gave their written informed consent before enrollment. Clinical information concerning pregnancy, delivery, operation technique and post-operative recovery time was obtained from the electronic medical database.

4.2 Ultrasonographic assessment of isthmocele

Six months after CD, consenting women were invited to the gynecological outpatient clinic for US assessment. Current contraceptive use, menstrual cycle status, possible amenorrhea or breastfeeding, smoking habits and BMI were recorded. US assessment was performed by using Samsung WS80 Elite equipment (Samsung Medison Co., Ltd., Gangwon-do, Republic of Korea) and a volume transducer. Women without contraception were examined during the follicular phase of the menstrual cycle to avoid an eventual early pregnancy. Otherwise, a random phase of the menstrual cycle was accepted. Women who were pregnant at the time of US were excluded. The uterus was examined in a standardized way with the woman lying in the lithotomy position with an empty bladder. TVUS was performed first (Naji et al., 2012). The position of the uterus (anteverted or retroverted) and the Cesarean scar were identified. Possible isthmocele was defined as an anechoic defect in the anterior wall of the lower uterine segment. Isthmocele was classified as triangular, round, oval or a total defect. When an isthmocele was detected, it was measured first in the sagittal plane (depth, width, RMT, AMT) and then in the transverse plane (length) (Figure 1). If more than one defect was found, the largest

one was measured. For the definition of an isthmocele we used a published definition of a depth of a defect of at least 2.0 mm in the longitudinal plane (Jordans et al., 2018). Right after TVUS, SHG was performed. A small catheter (Insemination cannula standard, Laboratoire CCD, Paris, France) was inserted into the uterus via the cervix, and a maximum of 20 ml of sterile saline was flushed until the site of the Cesarean scar was visualized. The same measurements as with TVUS were recorded. The flushed saline volume was measured. All US assessments were performed by the author (R.A.) who was blinded to any clinical data concerning the pregnancy, delivery and CD. Women were not informed about the US findings.

4.3 Follow-up one year after Cesarean delivery

Gynecological symptoms were surveyed one year after CD. The participants were sent electronic questionnaires three times at one-month intervals. Each of the three questionnaires was identical and concerned the symptoms and bleeding pattern of the current month. If a woman answered the questionnaire more than once, all questionnaires were analyzed separately. In detail, we asked about menstrual bleeding and spotting days, and the presence of dysmenorrhea, dyspareunia or postcoital bleeding. Additionally, the use of painkillers for dysmenorrhea, and absence from work or other activities because of bleeding or dysmenorrhea were inquired about. Possible confounders, such as method of contraception, breastfeeding, possible amenorrhea, smoking habits and BMI were inquired about (Appendix). Postmenstrual spotting was defined as ≥2 days of brownish discharge after the end of menstrual bleeding, and the definition of intermenstrual bleeding was ≥1 days of bleeding starting within five days from the end of menstruation. For statistical analysis postmenstrual spotting and intermenstrual bleeding were combined, on the basis of the results of a previous prospective study (Bij de Vaate et al., 2011). Exclusion criteria were pregnancy at the time of inquiry, and miscarriage, induced abortion or extrauterine pregnancy during the previous two months.

4.4 Long-term follow-up

The primary aim of the long-term follow-up of study participants was to investigate the outcome of possible subsequent pregnancies and deliveries in relation to isthmocele. The data on subsequent pregnancies was obtained from hospital medical

records. In Tampere University Hospital, early pregnancy complications and induced abortions are documented in the same electronic records. All visits to the Department of Obstetrics and Gynecology during the follow-up period were documented. The medical staff involved in the clinical management of the participants, and participants themselves, had no knowledge of the results of the ultrasonographic examinations. The primary outcome was the outcome of subsequent pregnancy. In cases of repeat CD, detailed data on the operation and the possible presence of uterine rupture or dehiscence were obtained. Dehiscence was defined as subperitoneal separation of the uterine scar in the lower uterine segment, with the chorioamniotic membrane visible through the peritoneum. Uterine rupture was defined as complete separation of the uterine scar with communication between uterine and abdominal cavities (Olga Vikhareva Osser & Valentin, 2011). Other outcome measures included possible adverse events during pregnancy and delivery, amount of blood loss at delivery, neonatal birth weight, Apgar scores, umbilical artery pH, admission to a neonatal intensive-care unit (NICU), and incidence rates of miscarriage, induced abortion, CSP and ectopic pregnancy.

4.5 Statistical analyses

Statistical analyses were performed using SPSS version 22.0 software (IBM Corp, Armonk, NY). Student's independent *t*-test was used for comparison of continuous variables in cases of normal distribution. Otherwise, the non-parametric Mann–Whitney *U* test was used. The Chi-square test was used for categorized variables. When the expected frequency for any cell was less than five, Fisher´s exact test was used. Binary logistic regression was used to compare associations between isthmocele and continuous variables (risk factors). Logistic regression was used in multivariate analysis to assess the effect of statistically significant factors found in univariate analysis (Studies I & IV). In Study III, logistic regression was used to control for potential confounding factors.

In Study I, Bland–Altman (BA) plots were used to compare two different methods of imaging. The function of BA analysis is to show whether two methods of diagnostics agree sufficiently (Blandman & Altman, 1986). The 95% limits of agreement, estimated by mean ± 1.96 standard deviations of the differences, provide an interval within which 95% of differences between measurements in the two methods are expected to lie (Bland & Altman, 1999). In statistical analysis in Study

III, postmenstrual spotting was combined with intermenstrual bleeding, on the basis of the results of a previous prospective study (Bij de Vaate et al., 2011).

Sample size calculations were based on the assumptions that the prevalence of bleeding disorders among women with isthmocele is 30%, and the prevalence of isthmocele was estimated to be approximately 50% (Bij de Vaate et al., 2011). To achieve 80% power with a two-sided alpha value of 0.05, we needed to enroll 266 women in the study. Considering the drop-out rate, which we anticipated to be up to 30%, we planned to recruit 400 women.

4.6 Ethics

The study protocol was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R15104). A written informed consent document was obtained before enrolment. Women were invited to the outpatient clinic for US assessment. Participation was voluntary and women could choose not to attend. The participants were not informed about the US findings in order to avoid bias in reporting their symptoms. As the true clinical relevance of isthmocele is somewhat unclear, we considered this strategy ethical. The participants were advised to take a painkiller after SHG for abdominal pain if necessary. In cases of severe adverse effects, they were advised to call the emergency number at our department. If there were additional findings at sonography (for example ovarian cyst or pregnancy) they were referred. The electronic questionnaires were sent via e-mail to all women who took part in US assessment. It was voluntary to reply.

Table 3. Summary of Studies I–IV

	Study I	Study II	Study III	Study IV
N	401	371	313	91
Design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Study period	Jan 2016 — Sept 2017	Jan 2016 — Sept 2017	Jan 2016 — March 2018	Jan 2016 — Jun 2019
Inclusion criteria	Delivery by CD	Delivery by CD. SHG performed 6 months after CD	Delivery by CD. SHG performed 6 months after CD	Delivery by CD. SHG performed 6 months after CD. Subsequent pregnancy during follow-up period.
Exclusion criteria	Uterine anomaly, lack of common language, age <18		Current pregnancy or miscarriage at the time of questionnaire	
Main research question	Are TVUS and SHG comparable methods in the diagnostics of isthmocele?	What are the risk factors of isthmocele?	Are gynecological bleeding disorders related to isthmocele?	Is maternal and neonatal morbidity in subsequent pregnancy and delivery related to isthmocele?
Main outcome	Correlation of TVUS and SHG	Presence of isthmocele	Prevalence of postmenstrual spotting	Incidence of delivery complications
Data collection	Examination by TVUS/SHG	Hospital medical records	Electronic survey	Hospital medical records

CD, Cesarean delivery; TVUS, Transvaginal ultrasonography; SHG, Sonohysterography

5 RESULTS

5.1 Prevalence and characteristics of isthmocele (Study I)

In all, four hundred and one women were enrolled in the study. Later, twenty-six women refused to continue. Three women were excluded because of pregnancy at the time of scheduled US examination and one woman was excluded because of severe vulvodynia, which prevented SHG examination. Thus, the study cohort consisted of three hundred and seventy-one women. The mean age of the participants was 32.4 (range 19–46) years and mean gestational age at delivery was 39+2 (24–42 weeks). A total of 58.0% (n=215) of the participants had had no previous deliveries before the index Cesarean, 68.5% (n=254) had had no previous CDs, 22.6% (n=84) had had one previous CD, 6.7% (n=25) had had two previous CDs and 2.2% (n=8) had had three previous CDs. Of the CDs included in the study, 41.8% were elective and 58.2% were emergency CDs. This distribution corresponds to the rate of elective vs. emergency CDs in our hospital. A total of 364 participants received a low transverse incision. There was one vertical incision, four J-shaped incisions, one ruptured CD scar and one T-shaped incision. In total, 370 out of 371 received double-layer continuous closure of the uterine incision.

All 371 women were examined successfully by means of both TVUS and SHG, on average 6.7 months after CD (range 4.5–10.0 months). No complications during SHG occurred, and the procedure was well tolerated. The prevalence of isthmocele detected in TVUS was 22.4% and in connection with SHG it was 45.6%. Figure 4 represents an isthmocele which remained undiagnosed in TVUS. The sonographic characteristics are shown in Table 4. Most of the isthmoceles were triangular in shape (92%), while the rest were oval or round. The prevalence of isthmocele in the subgroups of elective and emergency CD did not differ significantly in connection with either TVUS or SHG (p=0.237 and p=0.898, respectively). The prevalence increased with an increasing number of previous CDs (in both TVUS and SHG). However, the difference in detection rate between TVUS and SHG remained. The prevalence rates of isthmocele diagnosed in TVUS and SHG were 18.9% and 35.4%

in women with no previous CD, 22.6% and 63.1% in women with one previous CD, and 48.5% and 78.8% in women with ≥2 previous CDs, respectively.

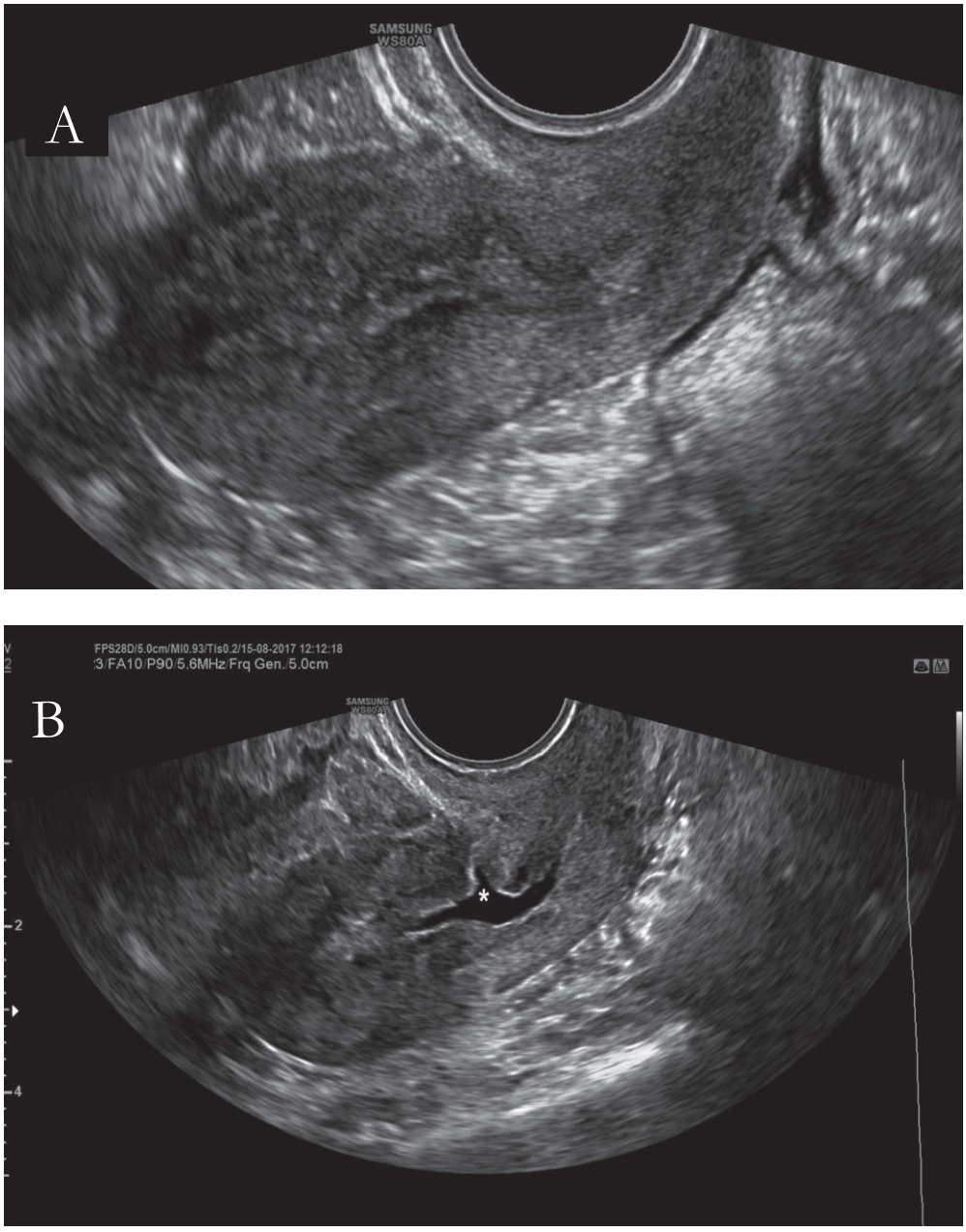

Figure 4. A) Transvaginal ultrasonography showed no visible anechoic defect at the uterine isthmus in a patient with one previous Cesarean delivery. B) After saline administration in sonohysterography, a triangular-shaped isthmocele was detected (asterisk)

Table 4. Findings detected by transvaginal ultrasonography (TVUS) and sonohysterography (SHG) in 371 patients six (4.5–10.0) months after Cesarean delivery

Depth of isthmocele, mm		
TVUS	0	(1.5)
SHG	1.8	(2.0)
Width of isthmocele, mm		
TVUS	0	(2.1)
SHG	3.1	(2.8)
Length of isthmocele, mm		
TVUS	0	(4.1)
SHG	6.4	(4.1)
RMT/AMT		
TVUS	0.56	(0.18)
SHG	0.60	(0.19)
Volume of flushed saline, ml	7	(5)
Position of uterus		
anteversion	70	
retroversion	23	
upright	7	
Shape of isthmocele		
triangular	92	
round	4	
oval	2	
total defect	2	

Values are median (SD) or percentages
AMT, adjacent myometrial thickness; RMT, residual myometrial thickness

5.2 Comparison of transvaginal ultrasonography and saline contrast sonohysterography in evaluation of isthmocele (Study I)

We used Bland–Altman (BA) plots to estimate the agreement between TVUS and SHG. In measurement of the depth of isthmocele, a BA plot showed an underestimation of 1.1 mm (range 0.0 to 7.9) for TVUS compared with SHG, with 95% limits of agreement from -1.9 to 4.1 mm (Figure 5). Considering RMT, the underestimation with TVUS was 0.3 mm compared with SHG (range 0.00 to 15.55) with 95% limits of agreement from -3.8 to 3.2 mm (Figure 6). For a low RMT, we used a cut-off point of 3.0 mm. Thus, with TVUS 59 (15.9%) of the participants had low RMT compared with 73 (19.7 %) with SHG. When SHG was considered as a reference method, sensitivity and specificity for TVUS were 50.7% and 92.6%,

respectively. Figure 7 represents an isthmocele which was detected equally well with both TVUS and SHG.

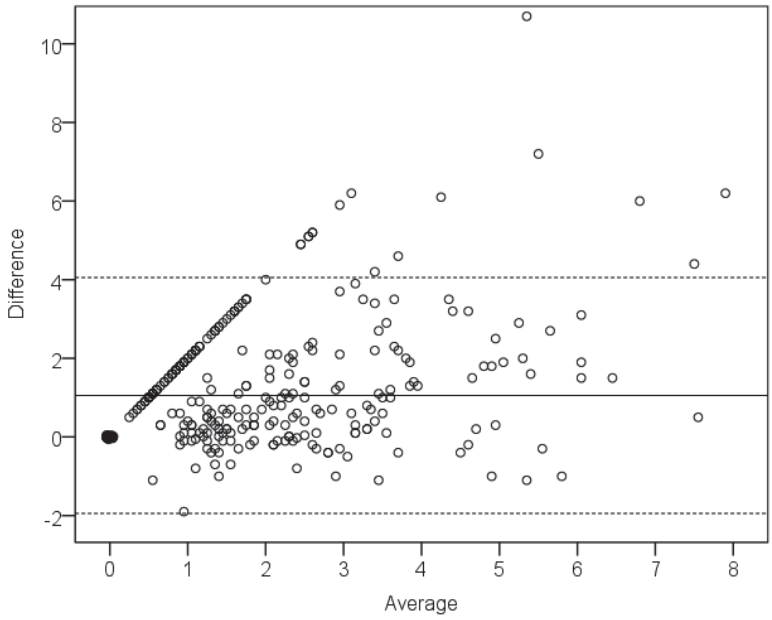

Figure 5. Bland–Altman plot for differences in depth of isthmocele measured by transvaginal ultrasonography and sonohysterography. Dashed lines represent the 95% limits of agreement for depth of isthmocele and the solid line represents the mean difference

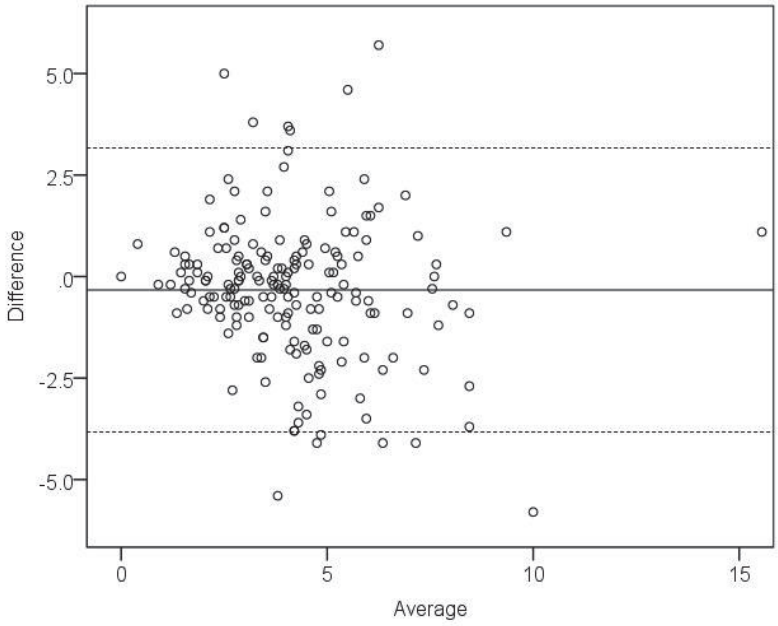

Figure 6. Bland–Altman plot for differences in residual myometrial thickness measured by transvaginal ultrasonography and sonohysterography. Dashed lines represent the 95% limits of agreement and the solid line represents the mean difference

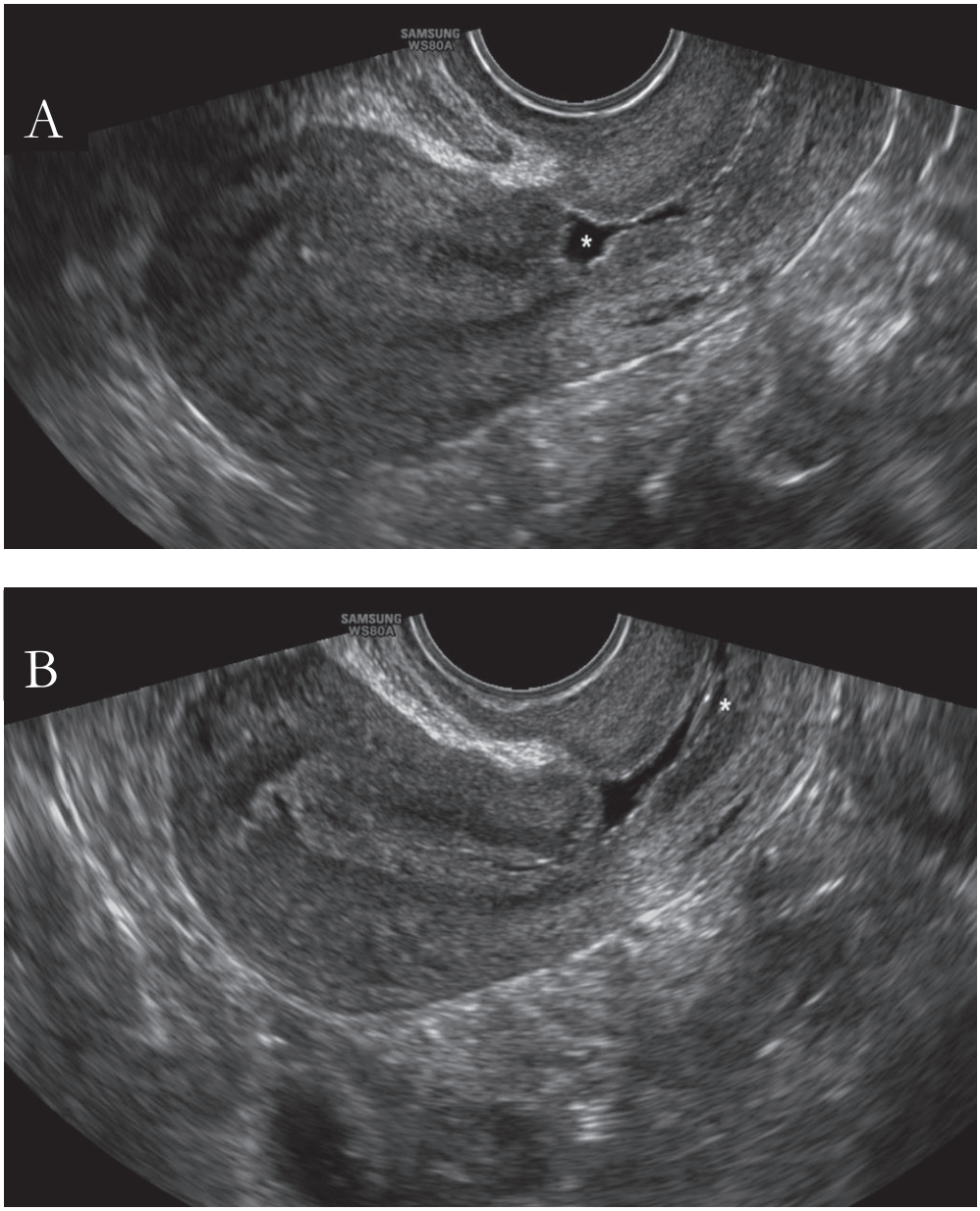

Figure 7. A) Triangular-shaped isthmocele in a woman with one previous Cesarean delivery detected by means of transvaginal ultrasonography (asterisk). B) After saline administration in sonohysterography the shape and size of the isthmocele remain. The hyperechoic tip of the catheter is visible left of the asterisk

5.3 Risk factors of isthmocele (Study II)

In the risk-factor study, our primary question was whether or not the urgency rating of CD (elective vs. emergency) has an influence on isthmocele development. For isthmocele we used a definition of a ≥2 mm-deep defect measured by means of SHG. The proportion of cases of elective CD was 41.8%, that of emergency CD 55.0% and that of emergency-crash CD (i.e. requiring immediate intervention) 3.2%. However, there was no significant difference in the presence of isthmocele between the groups of elective and emergency CD (p=0.898). A history of previous CD had a significant influence on isthmocele formation (p<0.001). Women who had no previous CD had a 35% chance of developing isthmocele, while after one, two or three previous CDs, the risks were 63%, 76% and 88%, respectively (Figure 8). Similarly, increased parity raised the risk of isthmocele (p<0.001). Both pre-pregnancy BMI and BMI at CD were associated with isthmocele (p=0.001 and p=0.002, respectively; Figure 9). The absolute change in gestational weight-gain was not associated with the risk of isthmocele. Women with GDM were more likely to have an isthmocele (p=0.002). However, type I diabetes did not increase the risk. A retroverted position of the uterus at US examination was associated with an increased risk of isthmocele (p=0.049). Background data of the participants and the results of risk-factor analysis are shown in Table 5.

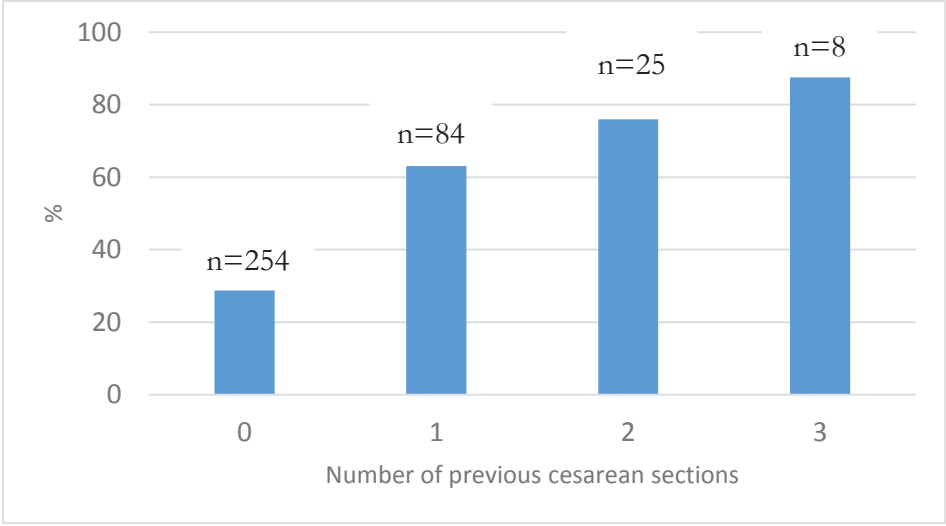

Figure 8. The prevalence of isthmocele in relation to the number of previous Cesarean sections. The number of women in each group is shown above the columns

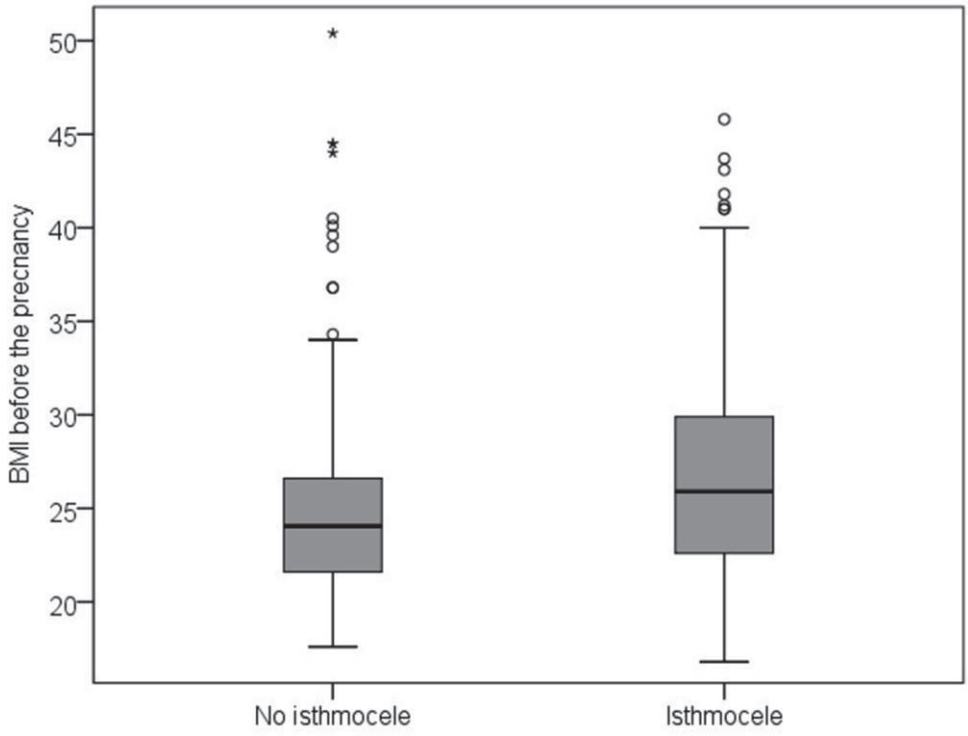

Figure 9. Median BMI before pregnancy in the non-isthmocele (n=202) and isthmocele (n=169) groups (p=0.001; Mann–Whitney U Test)

In a subanalysis of women who had undergone an emergency CD, previous CD (p=0.001), maternal age (p=0.032), GDM (p=0.046) and peripartal infections (p=0.035) were associated with the development of isthmocele. Additionally, the duration of active labor (i.e., number of hours with regular contractions) was longer in women who developed isthmocele, with a mean duration of 16.3 vs. 13.9 hours, respectively (p=0.039). Peripartal infections were diagnosed in 59 out of 371 women (15.9%). Diagnosed infections included postpartum wound infections, chorioamnionitis and endometritis. Cervical dilatation, the position of the presenting fetal part, multiple pregnancy, induction of labor, smoking during pregnancy or unsuccessful vacuum delivery prior to CD did not influence the risk of isthmocele.

In multivariate analysis including the whole study cohort, independent risk factors of isthmocele were the number of previous CDs, GDM and maternal BMI (OR 3.14, p<0.001; OR 1.73, p=0.042 and OR 1.06, p=0.012, respectively). In the subcohort

of emergency CD the duration of labor was found to be an independent risk factor of isthmocele ($p=0.032$).

Risk factors of reduced RMT (<3.0 mm) were peripartal infection ($p=0.008$) and advanced cervical dilatation ($p=0.045$). The number of previous CDs, and parity, were associated with large isthmocele defects ($p=0.002$ and $p=0.033$, respectively).

Table 5. Demographic background data and the results of univariate logistic regression analysis in relation to the presence of isthmocele

	No isthmocele n=202 (54.4%)	**Isthmocele** n=169 (45.6%)	OR	95% CI	p-value
Maternal age, years	32.1 (5.6)	33.1 (4.9)	1.04	1.00-1.08	0.074
Gestational age, weeks + days	39+2 (2.5)	39+2 (2.2)	1	0.92-1.09	0.947
Parity	0 (0–6)	1 (0–5)	1.54	1.22-1.93	0.001
Ever delivered vaginally	35 (17.3)	23 (13.6)	0.75	0.43-1.33	0.327
Ever delivered by CD	38 (18.8)	79 (46.7)	3.69	2.38-6.03	<0.001
Indication for CD					
Elective	85 (42.1)	70 (41.4)			0.898
Emergency	117 (57.9)	99 (58.6)	1.03	0.68-1.56	
Birth weight, grams*	3532 (705)	3595 (610)	1.02	0.98-1.05	0.375
Smoking during pregnancy	9 (4.5)	6 (3.6)	0.79	0.28-2.26	0.660
Gestational diabetes	49 (24.3)	66 (39.1)	2.00	1.28-3.12	0.002
Diabetes mellitus	6 (3.0)	6 (3.6)	1.20	0.38-3.80	0.753
BMI before pregnancy, kg/m²	25.1 (5.3)	27.1 (6.1)	1.07	1.03-1.11	0.001
BMI at CD, kg/m²	30.4 (5.3)	32.3 (5.9)	1.06	1.02-1.10	0.002
Change in maternal weight, kg	14.3 (6.2)	13.4 (6.0)	0.98	0.94-1.01	0.159
Uterine position in ultrasonography					
Anteversion	149 (73.8)	108 (64.3)			0.049
Retroversion	53 (26.2)	60 (35.7)	1.56	1.00-2.44	
Cervical dilatation at CD, cm					
0	95 (47.0)	82 (48.5)			0.071
1–4	62 (30.7)	36 (21.3)	0.67	0.41-1.12	0.125
≥5	45 (22.3)	51 (30.2)	1.31	0.80-2.16	0.284
Intrapartum or postoperative infection	26 (12.9)	33 (19.5)	1.64	0.94-2.88	0.083
Experience of CD operator					
Resident	133 (65.8)	110 (65.1)			0.879
Specialist	69 (34.2)	59 (34.9)	1.03	0.67-1.59	
Induction of labor**	59 (29.2)	38 (22.5)	0.63	0.37-1.10	0.103
Multiple pregnancy	12 (5.9)	8 (4.7)	0.79	0.31-1.97	0.609
Preeclampsia	15 (7.4)	8 (4.7)	0.62	0.26-1.50	0.288
Antenatal corticosteroid	16 (7.9)	10 (5.9)	0.73	0.32-1.66	0.453
Duration of labor, hours**	13.9 (6.7)	16.2 (7.6)	1.05	1.00-1.10	0.039
Oxytocin augmentation in labor**	70 (59.8)	68 (68.7)	1.00	0.99-1.01	0.530
Failed vacuum delivery prior to CD**	8 (6.8)	5 (5.1)	0.73	0.23-2.29	0.584
Position of presenting part**					
At or above pelvic inlet	105 (48.8)	85 (39.5)			0.494
Below pelvic inlet	12 (5.6)	13 (6.0)	1.34	0.58-3.09	

Values are mean (SD), mean (range) or number (%). BMI, Body mass index; CD, Cesarean delivery
* Twin pregnancies (n=20) excluded
** In the subgroup of emergency CD; n=117 (no isthmocele), n=98 (isthmocele)

5.4 Clinical outcome of isthmocele (Study III)

An electronic follow-up inquiry was sent to three hundred and seventy-one participants. Forty-three women were lost to follow-up (non-responders or incorrect e-mail address). In total, 328 (88.4%) of the participants completed the questionnaire. Later, 15 women were excluded (14 because of pregnancy and one because of recent miscarriage). In statistical analysis we included 313 women, resulting in a follow-up rate of 84.4%. Seventy-seven of them (24.6%) answered the inquiry once, 108 (34.5%) twice, and 128 (40.9%) completed all three questionnaires (Figure 10). There were no statistically significant differences between the study participants who completed the questionnaire and those who were lost to follow-up as regards age, parity, previous vaginal delivery, previous CD, induction of labor, BMI or the type of CD (elective versus emergency).

Background characteristics, reported symptoms and bleeding patterns are shown in Table 6. The prevalence of isthmocele among the women who answered the inquiry was 46.3%. In all, 13.7% of the responders reported postmenstrual spotting. In the isthmocele group the prevalence of postmenstrual spotting was 20.0% (29/145), compared with 8.3% (14/168) in women without an isthmocele ($p=0.004$). Additionally, postcoital bleeding was associated with isthmocele (8.3% vs. 2.4%, $p=0.026$). There was no difference between the isthmocele and non-isthmocele groups concerning the prevalence of dyspareunia, dysmenorrhea, prolonged periods, use of painkillers and absence from work or activities. In the whole study cohort, 80.2% of the women had no bleeding disorders. Moreover, 74.5% of the women with isthmocele did not suffer from any bleeding disorder.

Women in whom an isthmocele was detected had a hormone-releasing IUD more commonly than those without (Table 6). When these women were excluded (n=266), no significant association between isthmocele and postmenstrual spotting was found ($p=0.061$). However, when all women using hormonal contraception were excluded, the association between isthmocele and postmenstrual spotting remained statistically significant (n=209; $p=0.012$). Also, when women with amenorrhea were excluded, the association between postmenstrual spotting and isthmocele remained statistically significant (21.9% vs. 10.1%; $p=0.012$).

An association between postmenstrual spotting and the depth of isthmocele was found ($p=0.025$; Figure 11). In a sub-analysis of large isthmocele, the prevalence of postmenstrual spotting was 25.9%, compared with 9.5% in the no isthmocele/small isthmocele group ($p<0.001$). In nearly half of the women reporting postmenstrual spotting (47.8%) a large isthmocele was diagnosed.

None of the predefined confounding factors or baseline characteristics (BMI, age, method of contraception, breastfeeding, smoking) were related to postmenstrual spotting. There were no differences in pre-existing medical conditions possibly affecting bleeding patterns (celiac disease, hypothyreosis, inflammatory bowel disease) between women who suffered from AUB and those who did not. Moreover, no uterine pathologies (such as fibroids or polyps) possible causing AUB were found in SHG.

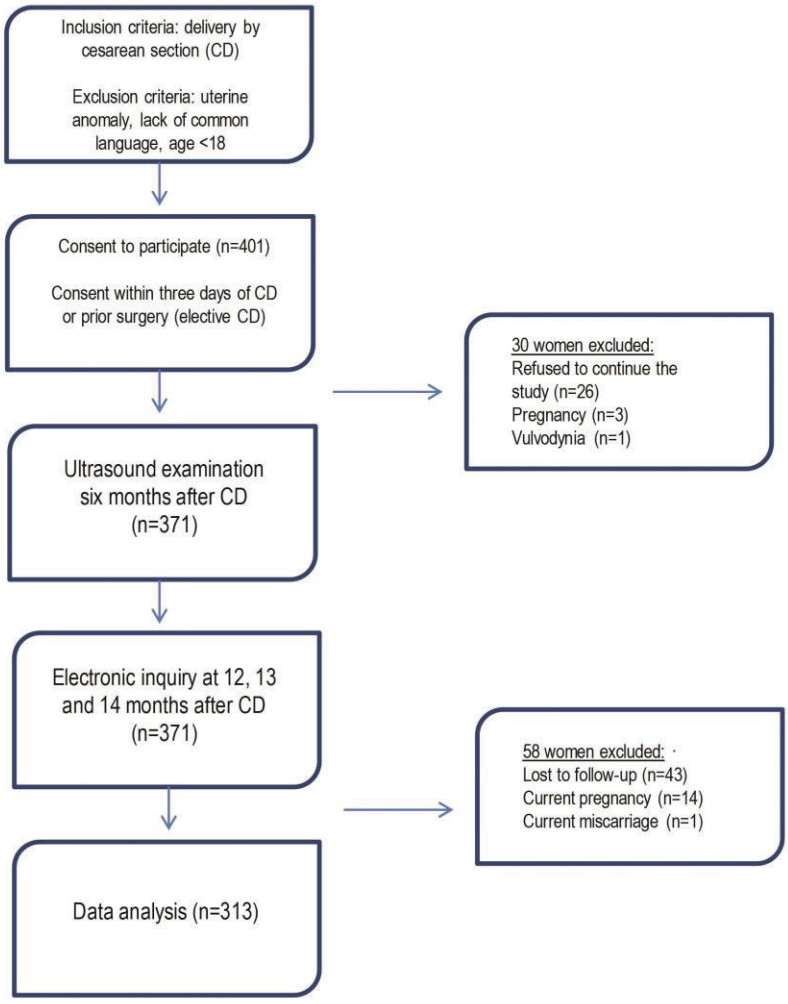

Figure 10. Flow chart of participants in Study III. CD, Cesarean delivery

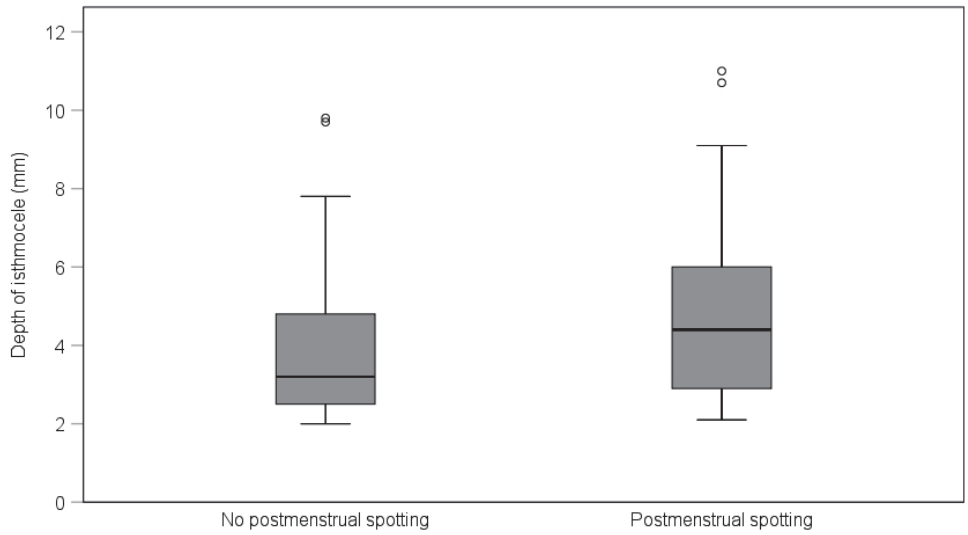

Figure 11. Median depth of isthmocele in women with no postmenstrual spotting (n=270) and in women with postmenstrual spotting (n=43)

Table 6. Baseline characteristics and symptoms reported one year after Cesarean delivery in relation to the presence of isthmocele

	Isthmocele (n=145)	No isthmocele (n=168)	p-value
Background characteristics			
Age, years	33.4 (4.7)	32.0 (5.5)	0.018
Parity	1.9 (2.0)	1.5 (0.8)	<0.001
Number of previous CDs	0.7 (0.8)	0.2 (0.5)	<0.001
Body mass index	27.9 (6.4)	25.5 (5.3)	0.001
Smoking	8 (5.5)	11 (6.5)	0.703
Contraception			0.002
No hormonal contraception	85 (58.6)	124 (73.8)	
Oral contraceptive pills	10 (6.9)	4 (2.4)	
Progestin-only pills	13 (9.0)	18 (10.7)	
Hormone-releasing IUD	32 (22.1)	15 (8.9)	
Copper IUD	5 (3.4)	4 (2.4)	
Contraceptive implant	0 (0.0)	3 (1.8)	
Bleeding patterns and symptoms			
Amenorrhea	31 (21.4)	29 (17.4)	0.370
Breastfeeding	45 (31.0)	48 (28.6)	0.634
Duration of menstruation, days	4.2 (2.9)	4.4 (2.5)	0.885
Prolonged periods (> 7 days)	10 (7.2)	12 (7.2)	0.998
Postmenstrual spotting	29 (20.0)	14 (8.3)	0.004
Dysmenorrhea	80 (55.2)	93 (55.4)	0.974
Dyspareunia	24 (16.6)	18 (10.7)	0.131
Postcoital bleeding	12 (8.3)	4 (2.4)	0.026
Need of painkillers	49 (34.0)	54 (32.1)	0.724
Absence from work	0 (0.0)	1 (0.6)	1.000
Absence from activities	2 (1.4)	7 (4.2)	0.188

Values are mean (SD) or number (%)

5.5 Long-term outcome (Study IV)

During the follow-up period (range 28–41 months) 86 out of 371 women became pregnant (Figure 12). Among these 86 women, there were 91 pregnancies and 72 deliveries. Eleven women experienced a total of 14 miscarriages and five women had an induced abortion. The prevalence of isthmocele in women with subsequent pregnancy was 34.9%. Women who became pregnant had lower parity and were younger compared with those who did not became pregnant. Additionally, most women who became pregnant had had only one previous CD (88.4% vs. 62.5%).

Background characteristics and those of subsequent delivery in relation to the presence of isthmocele are shown in Table 7. Statistical comparisons were performed between the groups of no-isthmocele versus isthmocele (of any size) and between the groups of large isthmocele versus no/small isthmocele. The combined data on the groups of no isthmocele & small isthmocele is not shown in the table. The proportion of cases of vaginal delivery was 43% (n=31). Three of these were vacuum-assisted. The proportion of cases of CD was 57%. Of these, 71% were elective and 29% emergency CDs (after trial of labor). Five women (7%) delivered preterm and 67 women (93%) delivered at term (≥37 weeks of gestation) (range 24+4 to 42+2 weeks). There were no scar pregnancies or other isthmocele-related complications during the pregnancies. Also, early pregnancy complications, such as miscarriage, were not associated with isthmocele. Among women who delivered by CD, two cases of uterine dehiscence were diagnosed at surgery (2.8%). One of these was diagnosed in a woman with a small isthmocele and the other one in a woman with an intact Cesarean scar. Thus, uterine dehiscence was not associated with isthmocele (p=1.000). No cases of uterine rupture were diagnosed in this study cohort. In the whole study population, there were two cases of placental abruption (2.8%). Neither of them was related to isthmocele (p=0.549). There were no placenta accreta or placenta previa cases in the study cohort. A total of 17 women out of 72 suffered from massive hemorrhage at delivery (≥1000 ml), which was statistically significantly associated with isthmocele (37.5% vs. 16.7%; p=0.050). Thirteen cases of massive hemorrhage occurred at CD (76%) and four cases at vaginal delivery (24%). Of these 17 cases, three were considered to have resulted from uterine atony, two from laceration at CD and two from laceration at vaginal delivery. In ten women (59%), there was no obvious reason for massive hemorrhage. Massive hemorrhage was more common in women who delivered by CD than in women who delivered vaginally. When the mode of delivery and the presence of isthmocele were entered in binary logistic regression analysis, the presence of isthmocele was associated with

an increased risk of massive hemorrhage of borderline significance (OR 3.00 [95% CI 0.98–9.21]; p=0.055). Five-minute Apgar scores were seven or more in all but one newborn and were not associated with the presence of isthmocele. Similarly, NICU admission was not related to isthmocele (p=0.708). All but one (71 out of 72) of the newborns had a normal umbilical-cord-blood pH of ≥7.1 (range 7.0–7.4).

The amount of blood loss was greater in women who presented with a large isthmocele compared with those in the no/small isthmocele group (p=0.017). Moreover, 41.7% (5/12) of women with a large isthmocele suffered from massive hemorrhage (>1000 ml), although the difference was statistically nonsignificant (p=0.139). There were no cases of placental abruption, uterine rupture or dehiscence related to large isthmocele.

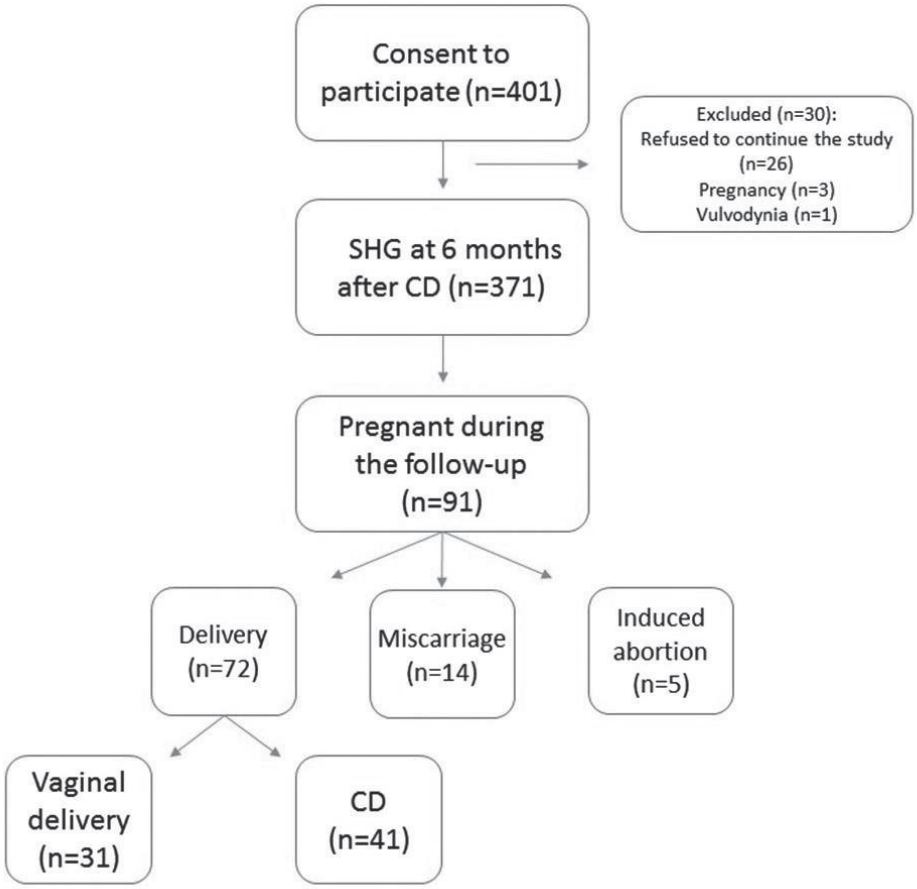

Figure 12. Flow chart of participants in Study IV. CD, Cesarean delivery; SHG, Sonohysterography

Table 7. Demographic characteristics and the outcome of subsequent delivery. Statistical comparison was performed between the women with and without isthmocele and between the women with and without large isthmocele. The data on the women without large isthmocele is not shown. Large isthmocele is a subgroup of the isthmocele-group

	No isthmocele (n=48)	Isthmocele (n=24)*	Large isthmocele (n=12)
Mother			
Age, years	32.0 (4.9)	32.4 (4.1)	30.7 (4.5)
Time between deliveries, months	25 (6)	25 (7)	24 (6)
Parity	2 (2–6)	2 (2–7)	2 (2–3)
Number of previous CDs			
1	46 (95.8)	18 (75.0)	10 (83.3)
2	2 (4.2)	5 (20.8)	2 (16.7)
3	0	1 (4.2)	0
Number of previous vaginal deliveries			
0	43 (89.6)	22 (91.7)	12 (100)
1	4 (8.3)	1 (4.2)	0
2	0	0	0
3	0	1 (4.2)	0
4	1 (2.1)	0	0
Current delivery			
Gestational age, weeks + days	39+2 (2.7)	38+5 (1.8)	38+3 (2.1)
Current delivery by CD	25 (52.1)	16 (66.7)	9 (75.0)
Uterine dehiscence at CD	1 (2.1)	1 (4.2)	0
Placental abruption	2 (4.2)	0	0
Uterine rupture at CD	0	0	0
Total bleeding, ml	678 (100–2500)	904 (100–2100)	1020 (350–2100)***
Massive hemorrhage (>1000 ml)	8 (16.7)	8 (37.5)**	5 (41.7)
Birth weight, grams	3486 (847)	3428 (673)	3315 (779)
Umbilical artery pH	7.3 (7.0–7.4)	7.3 (7.1–7.4)	7.3 (7.2–7.4)
NICU admission	7 (14.6)	2 (8.3)	2 (16.7)
Apgar score at 5 minutes	9 (4–10)	9 (4–9)	9 (4–9)

Values are mean (SD), mean (range) and number (%). CD, Cesarean delivery
* Includes all isthmoceles
** p=0.050 vs. No isthmocele
*** p=0.017 vs. No/small isthmocele

6 DISCUSSION

6.1 Prevalence and diagnostics (Study I)

The prevalence rates of isthmocele detected by means of TVUS and SHG at six months after CD were 22.4% and 45.6%, respectively. Specificity for TVUS was 100% but sensitivity was poor, 49.1%, when compared with SHG. Accordingly, half of the isthmoceles (50.9%) diagnosed in SHG remained undiagnosed when only TVUS was used. Interestingly, even large isthmoceles may remain undiagnosed without the use of contrast enhancement. Similarly, considering RMT, nearly half (49.3%) of women with low RMT values are missed with TVUS. This result is emphasized by BA analyses, which suggest that TVUS and SHG do not measure exactly the same phenomenon.

Bij de Vaate et al. reported similar prevalence numbers (24.0% with TVUS and 56.0% with SHG) in their prospective study (Bij de Vaate et al., 2011). They recruited participants up to nine months after CD and performed the US examinations 6–12 months after CD. In another prospective trial by the same study group, a clearly higher prevalence was found (49.6% with TVUS and 64.5% with SHG) (L F van der Voet, Bij de Vaate, et al., 2014). This difference may be explained by the much earlier time point of the examinations (6–12 weeks after CD), as the wound-healing process may still have been on-going (Dicle et al., 1997; Roberge et al., 2012). However, they later conducted a small proof-of-concept study in which the prevalence of isthmocele remained unchanged when scanned by means of TVUS and SHG at two months and at one year after CD (Lucy F van der Voet et al., 2017). We decided to perform the examinations six months after CD because it has been suggested that the Cesarean wound-healing process will take at least six months (Dicle et al., 1997; Roberge et al., 2012). On the other hand, we wanted to minimize the risk of subsequent pregnancy, which would have prevented us from performing SHG. For these reasons, we chose a particular time point for scans.

Mainly, US-based imaging methods are nowadays used in the diagnostics of isthmocele. Even though TVUS has been suggested to be a reliable method to diagnose isthmoceles, SHG has been reported to reveal more isthmoceles and

facilitate their measurement (Osser et al., 2009, 2010; Roberge et al., 2012; O Vikhareva Osser & Valentin, 2010). Moreover, SHG may ease the differentiation between isthmocele and, for example, cervical mucous cysts (Bij de Vaate et al., 2014; L F van der Voet, Bij de Vaate, et al., 2014). Another factor varying in previous studies is the definition of isthmocele. Often, any visible indentation, however small, has been regarded as an isthmocele (Ofili-Yebovi et al., 2008; Osser et al., 2009, 2010). We adopted a definition of an at least 2.0 mm-deep anechoic structure, which is also a recommended definition in the European Guideline of Isthmocele Evaluation (Jordans et al., 2018).

6.2 Risk factors (Study II)

Interestingly, besides the number of previous CDs, advanced maternal BMI, and GDM, were found to be independent risk factors of isthmocele. Both pre-pregnancy BMI, and BMI at the time of operation were associated with isthmocele. Although the result is novel considering the development of isthmocele, the effects of obesity and GDM in wound healing in general are not surprising. Both conditions are known to worsen the complex pathway of wound healing (Guo & DiPietro, 2010). Chronic low-grade inflammation, hyperglycemia and insulin-resistance are the suggested mechanisms (Baltzis, Eleftheriadou, & Veves, 2014; Pantham, Aye, & Powell, 2015).

Our study population may vary from previous study populations, at least when it comes to GDM. In Finland, there is an inclusive and complementary population-wide maternity healthcare system. Clear indications for glucose tolerance testing during pregnancy ensure that the majority of cases of GDM become diagnosed. Consequently, the incidence of GDM was high (31%) in the study cohort, which is not surprising, as GMD increases the risk of delivering by CD. The incidence of GDM in Finland was 19.2% in 2019 (thl.fi). Primary-care nurses weigh women regularly during their pregnancies, which provided us with reliable weight data.

The third independent risk factor of isthmocele was a history of previous CD. Even though the number of previous CDs is known to predispose women to isthmocele development, we showed a tremendous rise in the prevalence of isthmocele with a growing number of previous CDs. Without previous CD, the risk of isthmocele was 35%, while after one, two or three previous CDs the chances of isthmocele ascended to 63%, 76% and 88%, respectively. It is supposed that repeated trauma at the site of a Cesarean scar may impair wound healing by

generating avascular scar tissue and reducing vascular perfusion (Ofili-Yebovi et al., 2008).

In the subcohort of women who attempted a trial of labor, longer duration of active labor increased the risk of isthmocele. As far as we know, there are no previous studies on isthmocele risk factors including women who underwent a trial of labor before CD. A prolonged duration of labor may stretch the lower uterine segment and thus finally worsen healing of the myotomy. Also, the CD wound may be located lower in the uterus, or even in cervical tissue, which may have relatively weak healing properties (O Vikhareva Osser & Valentin, 2010). Additionally, advanced cervical dilatation and peripartal infections were risk factors of low RMT values. Infections in general are known to have a negative influence in wound healing. Various pro-inflammatory cytokines may prolong the inflammatory phase and thus the wound may fail to heal properly (Guo & DiPietro, 2010) An advanced stage of labor has previously been found to increase the risk of large isthmoceles (O Vikhareva Osser & Valentin, 2010). Low RMT, which we report here, represents a corresponding phenomenon, because in that particular study large isthmocele was defined by low RMT.

Numerous authors have reported risk factors of isthmocele. Previous reports are conflicting as regards maternal age, gestational age, duration of labor, cervical dilatation, location of the scar, multiple pregnancy and position of the uterus (Hayakawa et al., 2006; Ofili-Yebovi et al., 2008; Pomorski, Fuchs, Rosner-Tenerowicz, & Zimmer, 2016; O Vikhareva Osser & Valentin, 2010; Wang et al., 2009; H. F. Yazicioglu et al., 2012). The only generally accepted risk factor is the number of previous CDs (Armstrong et al., 2003; Ofili-Yebovi et al., 2008; Wang et al., 2009). Difficulties when considering previous studies include different definitions used for isthmocele and selection of the study population. Also, TVUS has mainly been used in diagnostics, which is not the gold standard nowadays.

All in all, uterine-wound healing is a complex cascade of biochemical events. The results of in vivo studies suggest that healing is both phenotype- and genotype-dependent. The expression of different growth-factor genes may vary between patients and affect the risk of Cesarean scar complications (Lofrumento, Nardo, Falco, & Lieto, 2016). This may have an influence on abnormal scar formation and partly explain the different and in some cases conflicting results.

6.3 Clinical outcome (Studies III & IV)

6.3.1 Bleeding disorders

Postmenstrual spotting and postcoital bleeding were associated with isthmocele when inquired about one year after the CD. Among the women with isthmocele the prevalence of postmenstrual bleeding was 20.0% and the prevalence of postcoital bleeding was 8.3%. The association between isthmocele and postmenstrual spotting remained significant when women with amenorrhea were excluded and also when women with hormonal contraception were excluded. Additionally, 25.9% of women who presented with a large isthmocele reported postmenstrual spotting. Data on menstrual bleeding patterns prior to the pregnancy were not collected because it would be susceptible to recall bias.

Our results are in line with those of previous prospective studies (Bij de Vaate et al., 2011; L F van der Voet, Bij de Vaate, et al., 2014). However, the prevalence of postmenstrual spotting in our study cohort was slightly lower, which may be explained by methodological differences between the current and previous studies. Van der Voet et al. reported a clearly higher prevalence of postmenstrual spotting related to isthmocele (28.9%). However, the response rate was low in their study, at 37.6% (L F van der Voet, Bij de Vaate, et al., 2014). Another Dutch study revealed an even higher prevalence of postmenstrual spotting (33.6%). Their study cohort was collected 3–9 months after CD (Bij de Vaate et al., 2011). In a retrospective study correlations between the width of isthmocele and both postmenstrual spotting and dysmenorrhea were found (Wang et al., 2009). In another retrospective study, an association between AUB and isthmocele was not found, but an association between AUB and the CD procedure itself was reported. This discrepancy may be explained by different methodology, as the investigators included only women with one delivery, and the time span between CD and US scanning was up to 10 years (Menada Valenzano, Lijoi, Mistrangelo, Costantini, & Ragni, 2006).

In addition to the unselected population and the prospective study design, we aimed to collect reliable data on symptoms and to minimize the risk of recall bias. Hence, we developed an electronic system, an e-mail inquiry, for reporting symptoms in three menstrual periods. In this electronic questionnaire, women were able to report their symptoms real-time instead of later recalling the bleeding days and other symptoms. At least partly due to this, we achieved a high response rate of 88.4%, which is likely to have increased the reliability of outcome assessment.

The relationship between the size of the isthmocele and postmenstrual spotting is in line with the hypothesis that spotting may be caused by the accumulated blood inside the isthmocele which functions as a reservoir for menstrual blood (Setubal et al., 2018; Thurmond, Harvey, & Smith, 1999). Surgical treatment of an isthmocele is a controversial issue (Setubal et al., 2018). However, the positive association between isthmocele and menstrual bleeding disorders allows us to consider invasive surgical interventions when encountering symptomatic patients. Nevertheless, other causes of AUB have to be ruled out, because, as we report, the majority of women with isthmocele (74.5% in our study cohort) are free from any bleeding disorders.

6.3.2 Subsequent pregnancies

Fortunately, isthmocele-related complications during subsequent pregnancy and delivery are rare. In the present cohort, only a few complications were diagnosed. There were no cases of uterine rupture, which is the most feared complication attributed to isthmocele. Two cases of placental abruption and two cases of uterine dehiscence were detected, both of which were not statistically significantly associated with the presence of isthmocele. Interestingly, the incidence of massive hemorrhage (≥1000 ml) at delivery was associated with isthmocele, with a prevalence rate of 37.5%. The incidence of massive hemorrhage was even greater in the subgroup of large isthmocele (41.7%) although the result was not significant as the number of cases of large isthmocele was only 12.

There appear to be no previous studies concerning the association between isthmocele and massive hemorrhage at subsequent delivery. A possible mechanism leading to excessive hemorrhage might be related to uterine contraction deficiency caused by a scar defect or scar tissue, although based on the present data this can only be speculated. On the other hand, there might be a shared mechanism behind both massive hemorrhage and previous incomplete healing of a CD scar leading to isthmocele development.

We found only two previous studies on the association between isthmocele and the outcome of subsequent delivery (Pomorski et al., 2014; Olga Vikhareva Osser & Valentin, 2011). In the Swedish study, 162 women with ≥1 previous CDs were recruited 5–9 months after CD and they were examined by means of either TVUS or SHG at 6–9 months after the CD. During the follow-up period, 99 pregnancies and 65 deliveries occurred. In the study cohort, there were two cases of uterine dehiscence and two cases of uterine rupture, which all occurred in women with

isthmocele. Moreover, both cases of dehiscence and one of the uterine ruptures occurred in the group of large isthmocele. Hence, the authors reported a trend for an association between a large isthmocele and uterine rupture or dehiscence. However, the association was not statistically significant, while the number of deliveries was low. They used a different definition for large isthmocele compared with ourselves. An isthmocele was defined as large according to RMT. In SHG the definition of large isthmocele was RMT ≤2.5 mm in women with one CD, and RMT ≤2.3 mm in women with ≥2 previous CDs. In TVUS, isthmocele was defined as large when RMT was ≤2.2 mm in women with one CD and ≤1.9 mm in women with ≥2 previous CDs.(Olga Vikhareva Osser & Valentin, 2011) In the other study, uterine dehiscence was found to correlate with the appearance of the CD scar in the non-pregnant uterus (Pomorski et al., 2014). The risk of uterine dehiscence rose when the ratio between the depth of isthmocele and RMT increased. However, the study included only women who delivered by repeat CD (n=41) and thus the results are not fully comparable with ours. Moreover, the presence of uterine dehiscence is clinically not the most important endpoint, as the patient is usually asymptomatic and the condition does not require special emergency attention. Also, typically, uterine dehiscence does not lead to problems in pregnancy, considering either the mother or the newborn (Levine, 2016).

The incidence of uterine rupture after ≥1 previous CDs has been reported to be 5/1,000 (Al-Zirqi, Stray-Pedersen, Forsén, & Vangen, 2010). Thus, a sufficiently powered study would require several thousand women with previous CD in order to discover if there is a true association between isthmocele and this serious adverse outcome in subsequent delivery. According to our results, no clinical recommendations on routine scanning of nonpregnant women with previous CD are necessary. However, it is justifiable to be aware that women in whom an isthmocele has been detected are at an elevated risk of massive hemorrhage in subsequent delivery. According to available data, limitations to possible subsequent pregnancy plans cannot be provided.

6.4 Strengths and weaknesses of the study

To the best of our knowledge, this is the largest prospective study carried out to investigate the prevalence, risk factors and clinical outcome of isthmocele. In all, 401 women were prospectively recruited at the time of CD. Non-selection of the study population can be regarded as a major strength of the study. Another strength concerns the commonly accepted method used in diagnostics. All participants were examined by means of both TVUS and SHG at the same visit and by the same sonographer, allowing us to compare these two methods of imaging. However, the actual diagnostics of isthmocele were based on SHG, which is the method of choice when assessing Cesarean scar defects. Moreover, the recommended definition of isthmocele was used (Jordans et al., 2018). The women were not informed about the possible presence of isthmocele, in order to prevent possible bias in later reports on their bleeding patterns.

In general, the recruited women were positively willing to participate. Up to 92.5% of them attended sonographic examination. Subsequently, we achieved a high response rate of 88.4% regarding the questionnaire concerning symptoms. This may be partly due to the facility to answer the electronic inquiry composed for this study. Moreover, we consider that the data collected electronically was reliable, because the women were able to answer the questionnaire right after menstruation instead of later recalling their bleeding days and symptoms.

It is a potential shortcoming that not all women who delivered by CD during the study period participated in the study. There were 742 CDs at our hospital during the study period out of which 401 women gave informed consent. The rate of CD during the study period was 14.7%. Some women may have dropped out of recruitment for very human reasons. Recruitment may have been deficient during certain time periods, for example holidays and rush-hour times. Also, we left many immigrants out of the recruitment because of lack of a common language. Basically, we cannot rule out the possibility that some kind of selection of the study population may have occurred. However, women participating in the study did not differ from non-participating women with respect to baseline characteristics such as elective or emergency CD rate, parity and age. Moreover, women who responded to the symptom questionnaire did not differ from non-responders regarding age, parity, BMI, previous vaginal delivery, previous CD, induction of labor or type of CD (elective versus emergency).

In Study I, it can be regarded as a limitation that a single sonographer performed the scans. Theoretically, TVUS performed first could have had an influence on

subsequent SHG. We chose this design for practical reasons, because organizing the examination of 400 women is laborious. Moreover, it may have been inconvenient for participants to attend the examination twice if TVUS and SHG were to have been performed in separate sessions. However, because the prevalence of isthmocele in first-performed TVUS was remarkably lower than in SHG, we think that the possible bias is probably not significant.

A possible limitation in Study III is a lack of a validated tool to assess postmenstrual spotting. Validated patient-reported outcome measures to assess AUB have been developed for heavy menstrual bleeding. These questionnaires give a measure of the volume of blood loss and were not suitable for the purpose of the current study (Matteson, Scott, Raker, & Clark, 2015; Traylor, Chaudhari, Tsai, & Milad, 2019). Another limitation is the significant difference in the method of contraception between the isthmocele and non-isthmocele groups. In particular, hormone-releasing IUDs were more commonly used in women with isthmocele compared with the non-isthmocele group (22.1% versus 8.9%). It is possible that such IUDs could partly explain the higher incidence of spotting associated with isthmocele. On the other hand, it is possible that these IUDs were originally inserted in order to treat existing spotting, and thus the prevalence of postmenstrual spotting could have been even higher without hormone-releasing IUDs. However, the association between isthmocele and postmenstrual spotting remained when women with hormonal contraception were excluded.

In Study IV, the number of subsequent deliveries was relatively small during the follow-up period. Therefore, we were not able to draw definitive conclusions as to the true prevalence of delivery complications related to isthmocele. However, the available data on this subject was scarce prior to our study and the numbers of deliveries in two previous prospective studies (Pomorski et al., 2014; Olga Vikhareva Osser & Valentin, 2011) were even lower than in the present study. Thus, our research data makes a valuable contribution to the topic even if a sufficiently powered study would require several thousand women with previous CD to be followed for years.

6.5 Clinical implications and future aspects

Isthmocele is a common phenomenon after CD and is often diagnosed by chance when transvaginal sonography is performed for a woman who has previously delivered by CD. According to the results of the current study, the majority of

women with isthmocele are symptomless. Moreover, subsequent pregnancy and delivery may be regarded as safe. Hence, no clinical recommendations on routine US scanning of non-pregnant or pregnant women with previous CD can be provided. Similarly, a randomly diagnosed isthmocele could remain ignored by a clinician.

However, when encountering a woman who suffers from AUB and in whom an isthmocele is diagnosed, it is possible that a bleeding disorder could result. Even if the current work does not handle the management of isthmocele, a treatment aimed at amenorrhea might be a first-line treatment option. This suggestion is based on the theory in which menstrual blood is thought to accumulate inside the isthmocele, thus causing a spotting problem.

On the other hand, considering a woman in whom an isthmocele has been diagnosed and who has future pregnancy plans, no recommendations or limitations regarding subsequent pregnancy can be provided. Similarly, the pregnancy and delivery deserve to be managed with similar caution as in any woman delivering after previous CD.

In the future, more research on the long-term effects of isthmocele is warranted. Longer follow-up of the participants would possibly give us more information on the magnitude of the clinical disorders. In this study, as in previous prospective studies, we have reported isthmocele-related symptoms up to one year after CD. Furthermore, a sufficiently powered study to reveal the impact of isthmocele on uterine rupture in subsequent delivery would require several thousand women with previous CD to be followed for years.

Considering the treatment of isthmocele in symptomatic patients, there is only one RCT presently available which addresses the impact of hysteroscopic resection of isthmocele on postmenstrual bleeding (Vervoort et al., 2018). More prospective studies and RCTs with long-term follow-up should be carried out before establishing guidelines on the clinical management of symptomatic isthmocele. Concerning treatment, it would be interesting to investigate the effects of hormone therapy. In particular, the impact of hormone-releasing IUDs on postmenstrual spotting in women with isthmocele could be a subject for future trials. Additionally, as far as we know, there are no prospective studies on the effect of isthmocele on fertility.

7 SUMMARY AND CONCLUSIONS

The main findings and conclusions in the study were:

1 The prevalence of isthmocele in transvaginal ultrasonography was 22.4%, and in sonohysterography, 45.6%. The use of transvaginal ultrasonography alone may lead to underestimation of the prevalence of isthmocele. Sonohysterography should be considered as the method of choice in the diagnostics of isthmocele (Study I).

2 Advanced maternal body mass index, gestational diabetes and previous Cesarean delivery are independent risk factors of isthmocele development. In the subgroup of emergency Cesarean delivery, a prolonged duration of active labor increases the risk of isthmocele (Study II).

3 Postmenstrual spotting and postcoital bleeding were significantly associated with the presence of isthmocele when inquired about one year after Cesarean delivery (Study III).

4 Women in whom an isthmocele is diagnosed are at a higher risk of massive hemorrhage in subsequent delivery. Otherwise, delivery can be regarded as safe, also considering the newborn, and the risk of uterine rupture does not seem to be increased. However, this study was underpowered to make conclusions about the risk of uterine rupture (Study IV).

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APPENDIX

Electronic questionnaire at one year after Cesarean delivery

1. Height and weight		
2. Current medication		

3. Current contraceptive use:	Yes	No
Combined oral contraceptive pills		
Progestin-only pills		
Hormone-releasing IUD		
Copper IUD		
Contraceptive implant		
No hormonal contraception		

4. Are you breastfeeding?		
5. Do you smoke?		
6. Are you pregnant?		
7. Have you had miscarriage or extrauterine pregnancy in the past 2 months?		
8. Did you suffer from dysmenorrhea/dyspareunia/postcoital bleeding last month?		

9. Because of pain or bleeding	Yes	No
Did you take painkillers?		
Did you skip work?		
Did you miss other activities?		

10. Did you have a period last month? If yes, indicate the dates

M	T	W	T	F	S	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

11. Did you have brownish discharge last month? If yes, indicate the dates

M	T	W	T	F	S	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

PUBLICATIONS

PUBLICATION I

Comparison of transvaginal ultrasound and saline contrast sonohysterography in evaluation of cesarean scar defect: a prospective cohort study

Antila-Långsjö, R., Mäenpää, J., Huhtala, H., Tomás, E., Staff, S.

Acta Obsterica et Gynecologica Scandinavica. 2018 Sep;97(9):1130-1136

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Comparison of transvaginal ultrasound and saline contrast sonohysterography in evaluation of cesarean scar defect: a prospective cohort study

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Key words
Cesarean scar defect, cesarean section, isthmocele, niche, sonohysterography

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Antila-Långsjö R, Mäenpää JU, Huhtala H, Tomás E, Staff S. Comparison of transvaginal ultrasound and saline contrast sonohysterography in evaluation of cesarean scar defect: a prospective cohort study. Acta Obstet Gynecol Scand 2018; 97:1130–1136.

Received: 27 February 2018
Accepted: 28 April 2018

DOI: 10.1111/aogs.13367

Abstract

Introduction. The aim of this study was to investigate the prevalence of post-cesarean isthmocele and to measure agreement between transvaginal ultrasonography and saline contrast sonohysterography in assessment of isthmocele. *Material and methods.* A prospective observational cohort study was carried out at Tampere University Hospital, Finland. Non-pregnant women delivered by cesarean section ($n = 371$) were examined with transvaginal ultrasonography (TVUS) and sonohysterography (SHG) six months after cesarean section. The main outcome measure was the prevalence of isthmocele using TVUS and SHG. Secondary outcome measures were characteristics of isthmocele. *Results.* In all, 371 women were included. The prevalence of isthmocele was 22.4% based on TVUS and 45.6% based on SHG. Sensitivity and specificity for TVUS was 49.1 and 100%, respectively, when compared with SHG. Therefore, half of the defects (50.9%) diagnosed with SHG remained undiagnosed with TVUS. Bland–Altman analysis showed an underestimation of 1.1 mm (range 0.00–7.90) for TVUS compared with SHG, with 95% limits of agreement from −1.9 to 4.1 mm. *Conclusions.* This methodological study provides confirmatory data that TVUS and SHG are not in good agreement in the isthmocele diagnostics and the use of only TVUS may lead to an underestimation of the prevalence of isthmocele. Thus, SHG should be considered as a method of choice in diagnostics of isthmocele.

Abbreviations: CS, cesarean section; OR, odds ratio; RMT, residual myometrial thickness; SHG, sonohysterography; TVUS, transvaginal ultrasonography; US, ultrasonography.

Introduction

In the last few decades, the cesarean section (CS) rate has increased worldwide. In 2014, over 1.2 million CS deliveries were performed in the USA, which was 32.2% of all deliveries (1). In China, the annual number of CS has been over 5 million for many years and between 2008 and 2014 the CS rate increased from 28.8% to 34.9%,

Key message

According to this large prospective study, sonohysterography is the method of choice in assessing cesarean scar defect in non-pregnant women.

which corresponds to a mean increase of 1.0 percentage point per year (2). According to the World Health Organization there are countries in which the CS rate has increased up to 56% (3).

Together with the growing CS rate, the complications related to CS have also increased. One of the known complications is a defect of the uterine wall at the site of the CS scar called isthmocele or niche. It has been associated with adverse pregnancy outcome, higher risk of complications during gynecologic procedures as well as clinical symptoms such as postmenstrual bleeding (4–7).

In previous studies the prevalence of isthmocele has ranged from 6.9 to 69% (8,9). The great variability may be caused by different definitions of isthmocele, various study designs and different diagnostic methods (5,10). Moreover, in most of the studies the patient material has been selected, i.e. only symptomatic patients have been enrolled (8,11–15). Only a few prospective studies addressed the prevalence of isthmocele. However, in those studies, participants have been asked to participate several months after CS, resulting in a possibility of selection bias (9,16). Various imaging methods have been utilized to assess an isthmocele, which is often visualized in the uterine isthmus. Nowadays, ultrasonography (US) has replaced other methods such as radiology-based hysterography. Transvaginal ultrasonography (TVUS) has been considered an accurate method for detecting isthmocele (9). However, contrast-enhanced sonohysterography (SHG) seems to facilitate its detection and measurement in non-pregnant woman (17). For this reason Vaate et al. (5) proposed that SHG should be the method of choice in the evaluation of isthmocele. Thus, the role and reliability of TVUS has remained controversial.

Using an unselected population of women who delivered by CS, we have performed a large prospective study to compare two different, widely accepted methods of imaging an isthmocele. Women were recruited at the time of CS, and US examinations were performed six months later.

The aim of this study was to determine the prevalence of isthmocele and, more specifically, to compare TVUS with SHG in the detection of isthmocele.

Material and methods

This prospective observational study was initially designed to assess the prevalence, risk factors and clinical outcome of cesarean scar defect. Here we report the results of comparison of TVUS and SHG in evaluation of CS scar; the risk factors and clinical outcome will be reported after follow up of the participants. The study was carried out at Tampere University Hospital, Tampere, Finland. The study was registered in ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02717312). All women who delivered by CS at Tampere University Hospital consecutively between January 2016 and February 2017 were asked to participate. Women were recruited either before the CS in the case of elective surgery or within three days of the operation in the case of emergency CS. Written informed consent was obtained from all participants. Exclusion criteria were a known anomaly of uterus, a lack of common language and age under 18. Participants were evaluated by TVUS, followed by SHG six months after the CS. This time point was chosen based on a previously reported healing time of six months of cesarean scar (18,19). US evaluations were performed at Tampere University Hospital. All US examinations were performed by the first author, who was blinded to the number of CS and obstetric history of the women.

Transvaginal sonography

Women were examined in lithotomy position with an empty bladder using a Samsung WS80 Elite (Samsung Healthcare). The examination was performed in a random phase of the menstruation cycle and in the case of no contraception it was performed only in follicular phase to avoid an early pregnancy. The uterus was examined in a standardized way (10). Isthmocele was defined as an anechoic defect communicating with the endometrial cavity at the anterior wall of lower uterine segment. In longitudinal plane, the scar was identified, and the depth and width of a possible isthmocele was measured. The length of the isthmocele was measured in transverse plane. If there was a visible isthmocele, the residual myometrial thickness (RMT) overlying the isthmocele and the adjacent myometrial thickness fundal to the isthmocele were measured. If there was more than one defect, the largest one was measured. As described in previous studies, the definition of isthmocele was a depth of the defect at least 2.0 mm in longitudinal plane (4,20). The US measurements are described in detail in Figure 1.

Sonohysterography

Immediately after the TVUS, sonohysterography was performed. A small catheter (Insemination cannula standard, Laboratoire CCD, Paris, France) was inserted into the uterus and sterile saline was flushed until the site of the cesarean scar was visualized. The volume of saline solution used was measured. In SHG analyses, equal measurements of the uterus were performed as described for TVUS examinations (Figure 1) and the same definition of isthmocele was used.

Statistical analyses

This study is a part of our DICE-trial (Defect in Cesarean Scar), which was designed to investigate the prevalence,

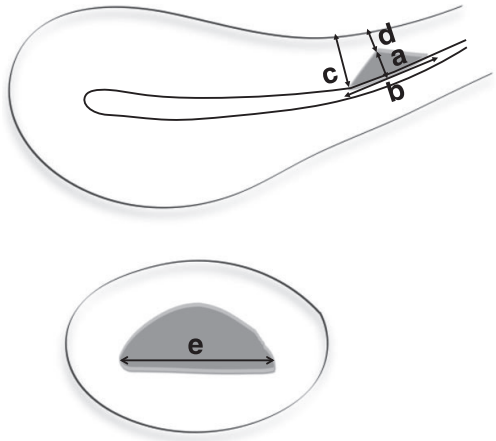

Figure 1. The following measurements were performed: (a) depth of isthmocele, (b) width of isthmocele, (c) thickness of adjacent myometrium, (d) thickness of residual myometrium, in the longitudinal plane; (e) length of isthmocele, in the transverse plane.

risk factors and clinical outcome of isthmocele. Here we report the results of US evaluation of CS scar by two different methods. The sample size of the whole study was calculated to investigate the clinical outcome (i.e. incidence of bleeding disorder) related to isthmocele. We wanted to detect a twofold increase of bleeding disorder in women diagnosed with isthmocele. Based on previous studies we assumed that the prevalence of bleeding disorder among patients without an isthmocele is approximately 15% (16). The prevalence of isthmocele in previous studies has been on average 50% (16). To achieve 80% power with an alpha of 0.05 and an anticipated dropout rate of 30%, we needed to include 400 women. Risk factor analysis and clinical outcome of isthmocele will be reported in subsequent publications. Data were analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA). Chi-squared test was used to compare the prevalence of isthmocele by TVUS and SHG in subgroups of elective and emergency CS. Cases of previous CS were categorized (no previous CS, one previous CS and two or more previous CS) and the prevalence of isthmocele by TVUS and SHG in each category of previous CS was also assessed. Bland–Altman plot was used to compare the two different methods of imaging to see whether they agree sufficiently (21,22).

Ethical approval

The study was approved by the Regional Ethical Committee of Tampere University Hospital, Tampere, Finland. Approval was granted on 2 September 2015 (ref. no. R15104).

Results

Altogether, 401 women gave an informed consent. Three women were excluded because of pregnancy at the time of scheduled US examination and one was excluded because of severe vulvodynia, which made it impossible to perform SHG. Twenty-six women refused to continue the study. A total of 371 women were examined successfully by both TVUS and SHG. There were no complications during SHG, which was well tolerated by all women. Patient characteristics and sonographic results are shown in Table 1. Median age of participants was 32.4 years (range 19–46). In all, 364 (98.1%) participants received a low transverse uterine incision. There were four (1.1%) J-shaped incisions, one vertical incision, one ruptured CS scar and one T-shaped incision in the study cohort. The uterine incision was sutured in double-layer in 370 of 371 women.

The prevalence of isthmocele was 22.4% by TVUS and 45.6% by SHG. Sensitivity and specificity for TVUS was 49.1 and 100%, respectively, compared with SHG. Therefore, half of the isthmoceles (50.9%) diagnosed with SHG remained undiagnosed with TVUS. The prevalence of isthmocele in the subgroups of elective vs. emergency CS diagnosed either with TVUS or SHG did not differ significantly ($p = 0.237$ and $p = 0.898$, respectively). The prevalence increased with the increasing number of previous CS diagnosed by either TVUS or SHG [odds ratio (OR) 1.83 and 2.64, respectively], but the difference in the detection rate between TVUS and SHG remained. The prevalence of isthmocele diagnosed by TVUS and SHG was respectively 18.9 and 35.4% in the subgroup of no previous CS; 22.6 and 63.1% in the subgroup of one previous CS; and 48.5 and 78.8% in the subgroup of two or more previous CS, respectively.

The median depth of isthmocele was 3.0 mm (± SD 1.1 mm) with TVUS compared with 3.3 mm (± SD 1.8 mm) with SHG. Most of the isthmoceles were triangular in shape (92%), and the rest were round or oval. Median volume of flushed saline was 7 mL (range 1–20). There was no difference in the saline volume between isthmocele and non-isthmocele groups ($p = 0.290$).

Figure 2 shows an image of a small isthmocele with concordant results with both TVUS and SHG. In contrast, in Figure 3 there is an isthmocele that seems to be unimportant based on TVUS but appears more obvious with saline contrast SHG.

We used a Bland–Altman plot to measure the agreement between TVUS and SHG. Figure 4 demonstrates the difference between the depth of an isthmocele measured

Table 1. Patient characteristics and ultrasonographic results.

Patient characteristics	*n* = 371
Maternal age, years, mean (SD)	32.5 (5.3)
Gestational age, weeks, mean (SD)	39^{+2} (2)
Parity, *n* (%)	
1	313 (84.4)
2	39 (10.5)
3	11 (3.0)
≥4	8 (2.1)
Number of previous CS, *n* (%)	
0	254 (68.5)
1	84 (22.6)
2	25 (6.7)
3	8 (2.2)
Type of CS, *n* (%)	
Elective	155 (41.8)
Emergency	216 (58.2)
Ultrasonographic results	
Time from CS to US, months, mean (SD)	6.7 (0.8)
Detected isthmocele, *n* (%)	
TVUS	83 (22.4)
SHG	169 (45.6)
Depth of isthmocele, mm, median (range)	
TVUS[a]	3.0 (2.0–7.3)
SHG[b]	3.3 (2.0–11.0)
Width of isthmocele, mm, median (range)	
TVUS[a]	3.5 (0.9–11.4)
SHG[b]	4.9 (1.0–14.3)
Length of isthmocele, mm, median (range)	
TVUS[a]	7.7 (2.3–16.4)
SHG[b]	8.2 (2.7–19.0)
RMT, mm, median (range)	
TVUS[a]	3.3 (0–9.9)
SHG[b]	3.7 (0–10.3)
RMT/AMT, mm, median (range)	
TVUS[a]	0.49 (0–0.99)
SHG[b]	0.60 (0–1.00)
Volume of flushed saline, mL, median (range)	7 (1–20)
Position of uterus	
Anteversion	257 (69.5)
Retroversion	113 (30.5)
Shape of an isthmocele, *n* (%)	
Triangular	257 (91.8)
Round	11 (3.9)
Oval	7 (2.5)
Total defect	5 (1.8)

AMT, adjacent myometrial thickness; CS, cesarean section; RMT, residual myometrial thickness; SHG, sonohysterography; TVUS, transvaginal ultrasonography; US, ultrasonography.
[a]*n* = 83; [b]*n* = 169.

by TVUS and SHG. It shows an underestimation of 1.1 mm (range 0.0–7.9) for TVUS compared with SHG, with 95% limits of agreement from −1.9 to 4.1 mm.

Residual myometrial thickness overlying the isthmocele was measured only when there was any visible indentation at the site of the cesarean scar. There was an

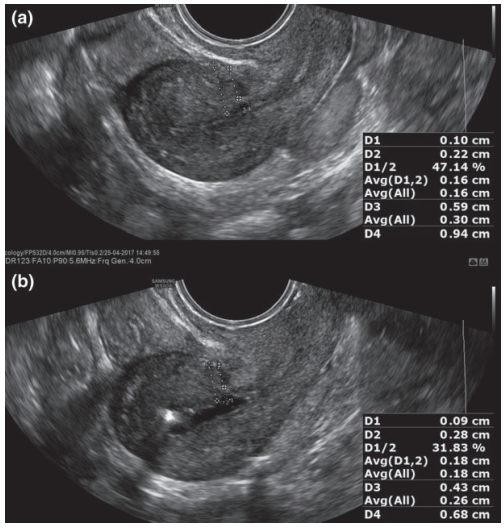

Figure 2. Both transvaginal ultrasonography (a) and sonohysterography (b) showing concordant results for a small isthmocele. D1, depth of isthmocele; D2, width of isthmocele; D3, thickness of residual myometrium; D4, thickness of adjacent myometrium. [Color figure can be viewed at wileyonlinelibrary.com]

underestimation of RMT was 0.3 mm with TVUS compared with SHG (range 0.00–15.55) with 95% limits of agreement from −3.8 to 3.2 mm. To determine a low RMT, we used a cut-off point of 3.0 mm. Thus, 59 (15.9%) and 73 (19.7%) of participants had RMT<3.0 mm with TVUS and SHG, respectively. If SHG was considered a reference method, sensitivity and specificity for TVUS were 50.7 and 92.6%, respectively.

Discussion

In this study, two different methods were compared in the diagnosis of cesarean scar defect. According to our results, TVUS leaves approximately half of the isthmoceles undiagnosed. These include even large isthmocele defects, which may be clinically relevant. Indeed, our results suggest that SHG is needed if the exclusion of isthmocele is truly warranted, because TVUS and SHG do not measure exactly the same phenomenon suggested by Bland–Altman analyses. Similarly, when measuring residual myometrium, almost half (49.3%) of the cases in which the RMT is <3.0 mm remain undiagnosed with TVUS compared with SHG. We used a cut-off level of 3.0 mm for RMT because it has been used in clinical practice to identify patients eligible for hysteroscopic resection of isthmocele (23). The type of CS (elective vs. emergency) or a history of previous CS did not

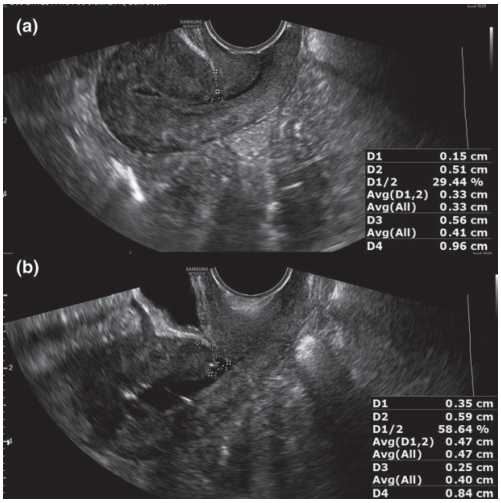

Figure 3. An isthmocele which seems to be unimportant with transvaginal ultrasonography (a) but which reveals a more obvious defect with sonohysterography (b). D1, depth of isthmocele; D2, width of isthmocele; D3, thickness of residual myometrium; D4, thickness of adjacent myometrium. [Color figure can be viewed at wileyonlinelibrary.com]

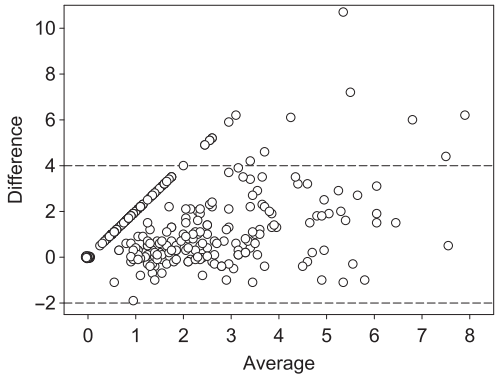

Figure 4. Bland–Altman plot for differences in depth of isthmocele measured by transvaginal ultrasonography and sonohysterography. Dashed lines represent the 95% limits of agreement for a depth of isthmocele.

influence the prevalence of isthmocele detected either with TVUS or SHG.

In the present study, women were prospectively recruited within three days of unplanned emergency CS or prior to elective CS, which can be regarded as strength of the present study. The vast majority of the previous studies assessing the prevalence of isthmocele have recruited the participants retrospectively. We think that this may have caused selection bias, at least partly explaining the large variation of previously reported prevalence numbers. Delayed recruitment can lead to enrichment of study population, for example by symptomatic patients. Thus, our study can be regarded as a valuable amendment to the scarce previous data.

In this comparative study of two different methods, it can also be regarded as a strength that all participants were examined by both TVUS and SHG at the same time point. Thus, the circumstances and the menstrual cycle point were constant. Additionally, as far as we know, this is the largest prospective study, altogether 371 women, carried out assessing cesarean scar prevalence using TVUS and SHG.

It is a limitation of the study that the same investigator performed both examinations. It can be argued that the SHG findings might have been affected by the previous TVUS findings, leading to possible subjectivity of the data and ruling out the possibility to make interobserver comparisons. This design was chosen due to practical reasons considering that performing US examinations of 371 women is quite laborious. However, the study design corresponds to the situation in everyday clinical practice where both examinations are performed one after the other. Therefore we do not think this could have caused a significant bias, particularly since the prevalence of isthmocele was smaller using TVUS, which was performed first.

Another limitation of the study is the lack of an objective reference when comparing these two methods of imaging. In an ideal situation, hysteroscopy could have provided a reference method to reveal the presence of isthmocele. However, hysteroscopy is also dependent on the surgeon who performs the procedure and is not totally objective. Here, our aim was to measure the agreement between two easily accessible and widely used noninvasive methods to diagnose the isthmocele. In order to evaluate the agreement between these two methods of clinical measurements, we used Bland–Altman analysis allowing analyses without a reference or golden standard.

The prevalence of isthmocele in our population was 22.4% with TVUS and 44.6% with SHG, which is comparable to a previous prospective study (16). Vaate et al. (16) reported the prevalence of 24.0% with TVUS and 56.0% with SHG when assessing a possible isthmocele 6–12 months after the CS. In their study, participants were recruited up to nine months after the operation.

Van der Voet et al. (4) found a clearly higher prevalence in their population (49.6 and 64.5% with TVUS and SHG, respectively) but they performed ultrasound examination as early as 6–12 weeks after CS, which may

have influenced the obtained result, since the wound-healing process may still have been ongoing. We decided to perform the examinations six months after CS because it has been suggested that the cesarean wound-healing process will take up to at least six months (18,19).

TVUS has been considered a reliable method to detect an isthmocele by Osser et al. (9). However, the same group stated later that the prevalence was nevertheless higher with SHG than with TVUS and isthmoceles appeared to be bigger with SHG (17). In that particular study only in 43% of cases were TVUS and SHG performed at the same visit and the participants were recruited several months after the CS. Our results show that the agreement between TVUS and SHG is not good. Half of the isthmoceles diagnosed with SHG remained undiagnosed with TVUS. When evaluating RMT, which is crucial when surgical treatment is considered, half of women (49.3%) with low RMT (<3.0 mm) remained undiagnosed with TVUS. On the other hand, not even SHG is perfect; in some instances, low RMT values were detected with TVUS while SHG appeared normal. However, the use of contrast-enhancement in transvaginal sonography seems to enable a better demarcation of isthmocele and both the defect and the RMT can be more exactly measured.

Conclusion

Several previous studies have attempted to evaluate isthmocele using TVUS or SHG in non-pregnant women. To the best of our knowledge, our study is the first study that compares the agreement of these two methods in a large prospectively collected unselected population examined at one visit. Our results suggest that the use of only TVUS may lead to an underestimation of the prevalence of isthmocele and that SHG should be considered the method of choice in diagnostics of isthmocele. We also acknowledge that the clinical outcome and significance of isthmocele detected by SHG will be ascertained only in the course of follow up of our prospective study cohort.

Funding

RAL was supported by The Scientific Foundation of the City of Tampere. This study was financially partly supported by the Competitive State Research Financing of the Greater Responsibility area of Tampere University Hospital (Grant Number 9U036/Mäenpää). Funding sources had no involvement in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

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PUBLICATION II

Cesarean scar defect: a prospective study on risk factors

Antila-Långsjö, R., Mäenpää, J., Huhtala, H., Tomás, E., Staff, S.

American Journal of Obstetrics and Gynecology. 2018 Nov;219:458.e1-8

GYNECOLOGY

Cesarean scar defect: a prospective study on risk factors

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BACKGROUND: Cesarean scar defect (isthmocele) is a known complication after cesarean delivery. It has become more common due to a rising cesarean delivery rate. Isthmocele has been associated with various gynecological and obstetric problems such as uterine rupture, cesarean scar pregnancy, and bleeding disorders.

OBJECTIVE: We sought to prospectively investigate factors associated with the risk for isthmocele assessed by sonohysterography.

STUDY DESIGN: A prospective observational cohort study was conducted in 401 nonpregnant women who were recruited within 3 days of cesarean delivery. Women were evaluated with sonohysterography 6 months after cesarean delivery to detect a possible isthmocele. The ultrasonographer was blinded to any clinical information. The main outcome measure was the presence of isthmocele. Type of surgery (elective vs emergency), maternal background variables, and factors related to pregnancy, labor, and postoperative recovery were analyzed in relation to isthmocele. A logistic regression model was used to assess independent risk factors from univariate analysis.

RESULTS: In all, 371 women were examined with sonohysterography resulting in a follow-up rate of 92.5%. The prevalence of isthmocele was 45.6%. Independent risk factors for isthmocele development were a history of gestational diabetes (odds ratio, 1.73; 95% confidence interval, 1.02−2.92; $P = .042$), previous cesarean delivery (odds ratio, 3.14; 95% confidence interval, 1.90−5.17; $P < .001$), and advanced maternal body mass index (odds ratio, 1.06; 95% confidence interval, 1.01−1.11; $P = .012$). Every additional unit of body mass index increased the risk of isthmocele by 6%. In the subgroup of emergency cesarean delivery, longer duration of active labor increased the risk for isthmocele (odds ratio, 1.06; 95% confidence interval, 1.01−1.11; $P = .032$). There was no statistically significant difference in prevalence between the groups of elective and emergency cesarean delivery ($P = .898$).

CONCLUSION: Based on sonohysterographic examination, maternal body mass index, gestational diabetes, and previous cesarean deliveries are associated with an increased risk for incomplete healing of the uterine incision.

Key words: cesarean delivery, cesarean scar defect, isthmocele, sonohysterography, ultrasonography

Introduction

Cesarean delivery (CD) is potentially a life-saving procedure if performed for the right indications.[1] The World Health Organization has stated that CD rates at up to 10−15% at the population level are associated with decreases in maternal, neonatal, and infant mortality. Above this level, the increasing rate of CD is no longer associated with reduced mortality.[2] However, rates up to 50% have been reported, which consequently can lead to a growing number of complications.[3,4] One of these complications, cesarean scar defect, has been shown to be associated with various gynecological and obstetric problems. Uterine rupture and ectopic cesarean scar pregnancy are fairly rare complications of cesarean scar defect yet with potentially catastrophic consequences.[5,6] However, postmenstrual spotting, dysmenorrhea, dyspareunia, or chronic pelvic pain are frequently described in relation to cesarean scar defect.[7−11] Additionally, cesarean scar defect may increase the risk for complications in gynecological procedures such as intrauterine device placement, evacuation, and embryo transfer.[11,12]

Therefore, in the past several years, numerous studies have been published concerning the scar defect (also called "isthmocele" or "niche"). The isthmocele represents an inadequate healing of the myometrium at the site of cesarean incision. Its prevalence varies substantially, between 6.9−69%, depending on the study population and the methodology used.[7,13] Appropriate diagnosis of isthmocele is made with contrast-enhanced ultrasonography.[14] A history of multiple CDs is generally considered to be a major potential risk factor for isthmocele. Additionally, advanced stage of labor and uterine retroflexion have been associated with isthmocele.[13,15] However, prospective studies on this subject are scarce and quite heterogeneous. Most of them include a small sample size or are performed in selected populations of symptomatic women. To develop preventive strategies for reducing the risk for isthmocele and thus overcoming possible adverse outcomes, it is essential to identify related risk factors. The aim of this study was to investigate factors that increase the risk of isthmocele in a large prospectively collected and unselected population.

Materials and Methods

This prospective observational cohort study was designed to assess the prevalence, risk factors, and clinical outcome of cesarean scar defect. The results of risk factor analysis are reported here, while the clinical outcome will be published after a sufficient follow-up of the

Cite this article as: Antila-Långsjö RM, Mäenpää JU, Huhtala HS, et al. Cesarean scar defect: a prospective study on risk factors. Am J Obstet Gynecol 2018;219:458.e1-8.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.09.004

AJOG at a Glance

Why was this study conducted?
The rate of cesarean deliveries is increasing. We evaluated the risk factors related to isthmocele in a large prospective cohort study.

Key findings
Gestational diabetes, obesity, and multiple cesarean deliveries increase the risk of isthmocele.

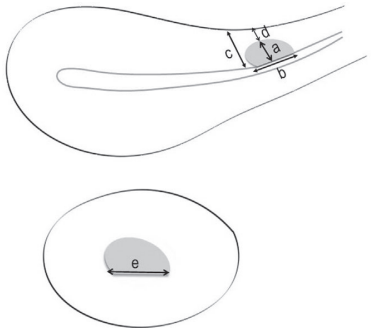
What does this add to what is known?
The identification of obesity and gestational diabetes as risk factors for isthmocele is a novel finding. Thus, the results reported here are significant because there has been a dramatic increase worldwide in the prevalence of obesity and diabetes in women of childbearing age.

participants. The study was carried out at Tampere University Hospital, Tampere, Finland. The date of the trial registration (ClincalTrials.gov identifier: NCT02717312, ID: R15104) of this study was March 9, 2016. The study protocol was approved by the institutional review board of Tampere University Hospital, Finland (ETL code R15104).

Women who delivered by CD at Tampere University Hospital from January 2016 through January 2017 were asked to participate. They were recruited either before the CD in the case of elective surgery or within 3 days after the operation in the case of emergency CD. All participants provided written informed consent before enrollment. Exclusion criteria included a known uterine anomaly, lack of common language, and age <18 years. Clinical information concerning pregnancy, operation technique, and recovery time were obtained from the electronic medical database. Six months after the CD, participants were invited to the gynecologic outpatient clinic for ultrasound (US) examination. Transvaginal ultrasonography (TVUS) and sonohysterography (SHG) were performed using the WS80 Elite (Samsung Medison Co Ltd, Gangwon-do, Republic of Korea).

Women without contraception were examined during the follicular phase of the menstrual cycle to avoid an eventual early pregnancy. Otherwise, a random phase of the menstrual cycle was accepted. Women who were pregnant at the time of US were excluded. All TVUS and SHG procedures were performed by the first author, who was blinded to the clinical information. Women were examined in the lithotomy position with an empty bladder. The uterus was examined in a standardized way, with TVUS performed first.[16] Isthmocele was defined as an anechoic defect in the anterior wall of the lower uterine segment, communicating with the endometrial cavity. If an isthmocele was detected, the depth and width of the isthmocele, the residual myometrial thickness (RMT) overlying the isthmocele, and the adjacent myometrial thickness fundal to the isthmocele were measured in the midsagittal plane. The length of the isthmocele was measured in the transverse plane (Figure 1).[8] The uterine position was classified as anteverted or retroverted. For the diagnosis of isthmocele, we used a predetermined definition of a defect at least 2.0 mm deep.[10] In case >1 defect was found, the largest one was measured. To assess a low RMT, we used the cut-off point of 3.0 mm because it is regarded as the minimum RMT for hysteroscopic treatment for symptomatic patients.[17] Women without isthmocele were included in the group of RMT of ≥3.0 mm because it is presumable that without isthmocele, the myometrium thickness remains unchanged. Moreover, isthmocele was considered large if the ratio between the depth of the isthmocele and the adjacent myometrial thickness was ≥0.50. Immediately after the TVUS, SHG was performed. A small catheter (insemination cannula standard; Laboratoire CCD, Paris, France) was inserted into the uterus, and sterile saline was flushed until the site of cesarean scar was visualized. The same measurements as mentioned above were performed. The volume of flushed saline was measured.

FIGURE 1
Schematic presentation of isthmocele measurements



In longitudinal plane: **a**, depth and **b**, width of isthmocele; thickness of **c**, adjacent and **d**, residual myometrium. In transverse plane: **e**, length of isthmocele.

Antila-Långsjö et al. Risk factors for postcesarean isthmocele. Am J Obstet Gynecol 2018.

Statistical analyses

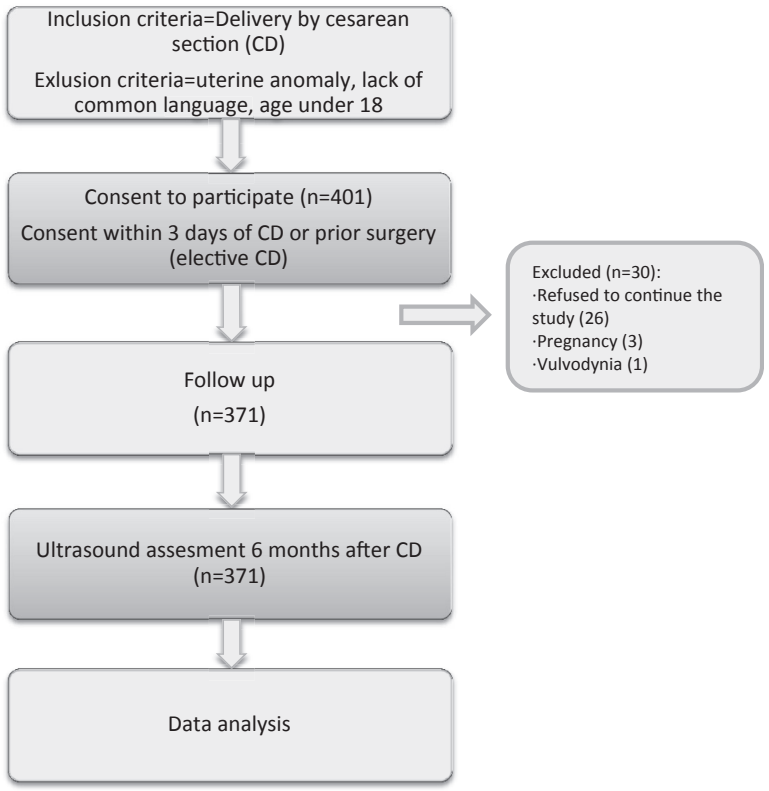
This prospective study was designed to investigate the prevalence, risk factors, and clinical outcome of isthmocele. The primary outcome measure of the entire study was the prevalence of isthmocele. The study was designed to assess the effect of isthmocele on the incidence of bleeding disorders (ie, postmenstrual spotting defined as ≥2 days of brownish discharge at the end of menstruation with total bleeding days of ≥7 or noncyclic bleeding not related to menstruation). The detection of a 2-fold difference in the prevalence of bleeding disorder between the isthmocele and nonisthmocele groups was the aim of the analyses. The sample size calculations were based on the following assumptions: the prevalence of bleeding disorders among women with isthmocele is 30%, and the prevalence of isthmocele was estimated to be approximately 50% according to previous data.[9] To achieve 80% power with a 2-sided alpha of 0.05, we needed to enroll 266 women in the study. Considering the

dropout rate, which we anticipated to be up to 30%, we planned to recruit 400 women. This number was supposed to be sufficient also for the present study on risk factors, where the primary objective was the association of elective vs emergency CD with the risk of isthmocele when the prevalence of elective CD corresponded to 44% of the total number of CDs at our hospital.

Data were analyzed using software (SPSS, Version 22.0; IBM Corp, Armonk, NY). Associations between categorical variables and the formation of isthmocele were compared with χ^2 tests and between continuous variables and isthmocele with binary logistic regression. A logistic regression model was used for the multivariate analysis assessing the effect of statistically significant risk factors from univariate analysis. Two-tailed P values of $<.05$ were considered statistically significant.

The isthmocele detected by SHG was defined as the outcome of interest in the statistical analyses because SHG is considered as a method of choice when evaluating isthmocele.[8,18]

FIGURE 2
Flow chart of study



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Results

In all, 401 women gave their informed consent. Later, 26 women refused to continue the study. Three women were excluded because of detected pregnancy at the time of examination, and 1 was excluded because of severe vulvodynia, which made it impossible to perform SHG. Finally, we examined 371 women successfully by both TVUS and SHG resulting in a follow-up rate of 92.5% (Figure 2). The examinations were performed, on average, 6.7 months after the CDs (range 4.5−10.0 months). Demographic background variables testing for their predictive ability are shown in Table 1. The mean age of all participants was 32.5 years. The gestational age at CD varied from 24−42 weeks, with a mean value of 39+2 weeks. A total of 215 (58%) participants had no previous deliveries. In all, 58 (16%) women had at least 1 previous vaginal delivery (range 1−6 deliveries), while 117 (32%) had a history of CD (range 1−3 CDs). In all, 155 women (41.8%) underwent elective CD, and 216 women (58.2%) underwent an emergency CD. This distribution corresponds to the rate upon which the statistical power calculations were based. Of the emergency CDs, 12 (3.2%) were emergent-crash (ie, requiring immediate intervention). The most common reasons for elective CD were fear of childbirth (32.9%), breech presentation (22.6%), and previous CD (20.0%). For emergency CD the most common reasons were prolonged labor (44.0%) and fetal asphyxia (32.4%). Intrapartum or postoperative infection was diagnosed in 59 of 371 women (15.9%). Diagnosed infections included chorioamnionitis, postpartum wound infections, and endometritis. The diagnostic criteria for chorioamnionitis included intrapartum fever and elevated infection parameters (C-reactive protein, leucocyte count) with maternal or fetal tachycardia. There were no differences regarding the rate of primary or emergency CD, age, gestational diabetes (GDM), body mass index (BMI), or parity between women who participated in the present study and those who also delivered by CD during the study period but did not participate in the study.

In all, 83 isthmocele cases were detected by TVUS and 169 by SHG. Thus, 86 women had a normal TVUS in spite of an isthmocele diagnosed by SHG. The prevalence of isthmocele was 22.4% with TVUS and 45.6% with SHG. Most of the isthmoceles were triangular in shape (91.8%), while the rest were round (3.9%), oval (2.5%), and total defect (1.8%). The prevalence of isthmocele detected by SHG was defined as the outcome of interest in the statistical analyses (Figure 3). There was no significant

TABLE 1
Demographic background data and results of univariate logistic regression analysis

	Without isthmocele, n = 202 (54.4%)	With isthmocele, n = 169 (45.6%)	OR	95% CI	*P* value
Maternal age, mean (SD), y	32.1 (5.6)	33.1 (4.9)	1.04	1.00–1.08	.074
Gestational age, mean (SD), wk+d	39+2 (2.5)	39+2 (2.2)	1	0.92–1.09	.947
Parity, mean (range)	0 (0–6)	1 (0–5)	1.54	1.22–1.93	.001
Prior vaginal delivery, n (%)	35 (17.3)	23 (13.6)	0.75	0.43–1.33	.327
Prior CD, n (%)	38 (18.8)	79 (46.7)	3.69	2.38–6.03	<.001
Indication for CD, n (%)					
Elective	85 (42.1)	70 (41.4)			.898
Emergency	117 (57.9)	99 (58.6)	1.03	0.68–1.56	
Birthweight, mean (SD), g[a]	3532 (705)	3595 (610)	1.02	0.98–1.05	.375
Smoking during pregnancy, n (%)	9 (4.5)	6 (3.6)	0.79	0.28–2.26	.660
Gestational diabetes, n (%)	49 (24.3)	66 (39.1)	2.00	1.28–3.12	.002
Diabetes mellitus, n (%)	6 (3.0)	6 (3.6)	1.20	0.38–3.80	.753
BMI before pregnancy, mean (SD), kg/m^2	25.1 (5.3)	27.1 (6.1)	1.07	1.03–1.11	.001
BMI at CD, mean (SD), kg/m^2	30.4 (5.3)	32.3 (5.9)	1.06	1.02–1.10	.002
Change in maternal weight, mean (SD), kg	14.3 (6.2)	13.4 (6.0)	0.98	0.94–1.01	.159
Uterine position at ultrasound, n (%)					
Anteversion	149 (73.8)	108 (64.3)			.049
Retroversion	53 (26.2)	60 (35.7)	1.56	1.00–2.44	
Cervical dilatation at CD, n (%), cm					
0	95 (47.0)	82 (48.5)			.071
1–4	62 (30.7)	36 (21.3)	0.67	0.41–1.12	.125
≥5	45 (22.3)	51 (30.2)	1.31	0.80–2.16	.284
Intrapartum or postoperative infection, n (%)	26 (12.9)	33 (19.5)	1.64	0.94–2.88	.083
Experience of operator, n (%)					
Resident	133 (65.8)	110 (65.1)			.879
Specialist	69 (34.2)	59 (34.9)	1.03	0.67–1.59	
Induction of labor, n (%)[b]	59 (29.2)	38 (22.5)	0.63	0.37–1.10	.103
Multiple pregnancy, n (%)	12 (5.9)	8 (4.7)	0.79	0.31–1.97	.609
Preeclampsia, n (%)	15 (7.4)	8 (4.7)	0.62	0.26–1.50	.288
Antenatal corticosteroid, n (%)	16 (7.9)	10 (5.9)	0.73	0.32–1.66	.453
Duration of labor, mean (SD), h[b]	13.9 (6.7)	16.2 (7.6)	1.05	1.00–1.10	.039
Oxytocin augmentation during labor, n (%)[b]	70 (59.8)	68 (68.7)	1.00	0.99–1.01	.530
Unsuccessful vacuum delivery prior to CD, n (%)[b]	8 (6.8)	5 (5.1)	0.73	0.23–2.29	.584
Station of presenting part, n (%)[b]					
At or above pelvic inlet	105 (48.8)	85 (39.5)			.494
Below pelvic inlet	12 (5.6)	13 (6.0)	1.34	0.58–3.09	

BMI, body mass index; *CD*, cesarean delivery; *CI*, confidence interval; *OR*, odds ratio.

[a] Twin pregnancies excluded; [b] in subgroup of emergency CD.

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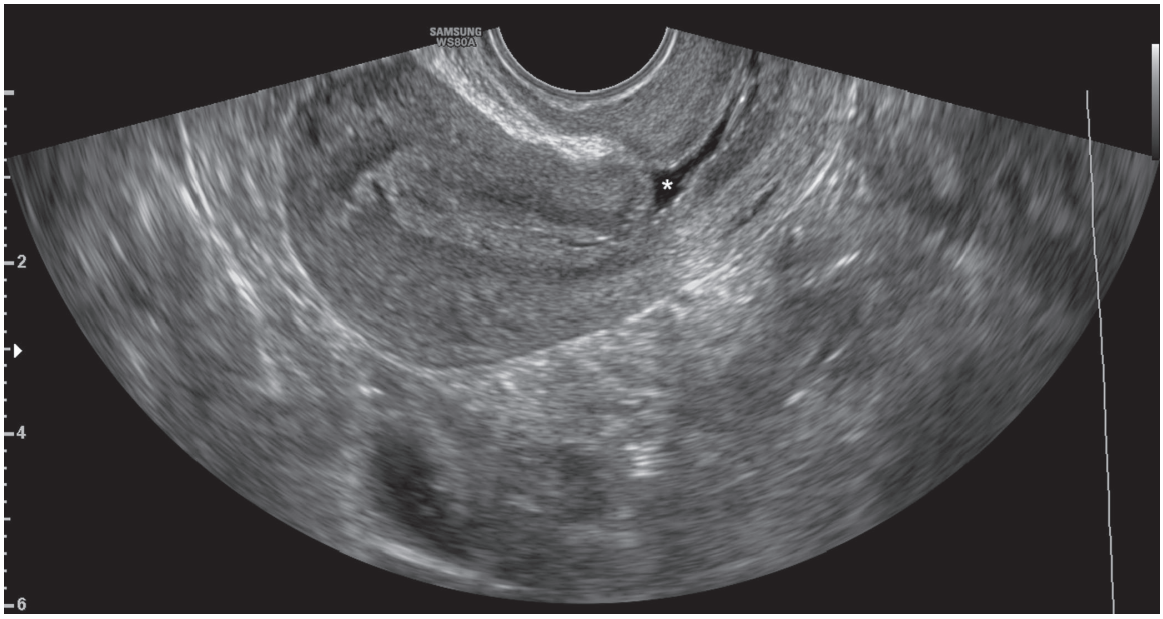
FIGURE 3
Sonohysterographic image of isthmocele (*)



The asterisk points to the triangular-shaped isthmocele.

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difference in the presence of isthmocele between the groups of elective and emergency CD ($P = .898$). Prior vaginal deliveries did not influence on the risk of isthmocele ($P = .327$), but a history of CD increased significantly the risk for isthmocele formation ($P < .001$). Women without previous CD had a 35% chance of having isthmocele, while after 1, 2, or 3 CDs the risk was 63%, 76%, and 88%, respectively. Similarly, parity increased the risk of isthmocele ($P < .001$).

Women with isthmocele had higher BMIs both before pregnancy and at the time of CD than women without isthmocele ($P = .001$ and $P = .002$, respectively). Every additional unit of BMI raised the risk by 6%. However, the absolute change in maternal weight during pregnancy was not associated with the risk of isthmocele. Women with GDM were more likely to have isthmocele ($P = .002$). However, type 1 diabetes did not increase the risk. A retroverted position of the uterus at US examination was associated with an increased risk for isthmocele ($P = .049$). The method of wound closure (single- vs double-layer sutures) could not be analyzed because in all but 1 woman, the uterine incision was closed in double layer with continuous unlocked sutures using polyglactin (Vicryl, Ethicon, Johnson and Johnson Ltd., India), which represents the standard way of uterine wound closure at our hospital. The remaining 1 woman had single-layer, continuous unlocked sutures. In a subgroup of women with emergency CD, the duration of active labor (ie, number of hours with regular contractions) was longer in women who developed isthmocele, with a mean duration of 16.3 vs 13.9 hours ($P = .039$). Previous CD ($P = .001$), maternal age ($P = .032$), peripartal infections ($P = .035$), and GDM ($P = .046$) were also associated with the development of isthmocele. Cervical dilatation or station of the presenting fetal part, induction of labor, multiple pregnancy, and unsuccessful vacuum delivery prior to CD did not influence the risk of developing isthmocele.

We entered the significant risk factors from the univariate analysis into the multivariate analysis. Additionally, maternal age was included in the multivariate analysis. Because BMI at CD is dependent on BMI before pregnancy, we decided to enter BMI at the time of CD in the multivariate analysis. The results of the multivariate logistic regression analysis are shown in Table 2. Independent risk factors for isthmocele were previous CDs, maternal BMI, and GDM (odds ratio [OR], 3.14; 95% confidence interval [CI], 1.90−5.17; $P < .001$; OR, 1.06; 95% CI, 1.01−1.11; $P = .012$; and OR, 1.73; 95% CI, 1.02−2.92; $P = .042$, respectively).

We also performed the multivariate analysis of the subcohort of patients undergoing an emergency CD (n = 216). Factors showing statistically significant associations with isthmocele in the univariate analysis were entered into the multivariate analysis (ie, previous CD, parity, maternal age, peripartal infections, duration of labor, and GDM). The independent risk factor for isthmocele in this subgroup was the duration of labor (OR, 1.06; 95% CI,

TABLE 2
Results of multivariate logistic regression analysis in study cohort (N = 371)

Parameter	Odds ratio	95% CI	*P* value
Maternal age, y	1.00	0.95–1.04	.846
Parity	0.90	0.64–1.27	.558
Previous CD	3.14	1.90–5.17	<.001
Gestational diabetes	1.73	1.02–2.92	.042
BMI at CD	1.06	1.01–1.11	.012
Uterine position at ultrasound	1.60	0.98–2.60	.058

BMI, body mass index; *CD*, cesarean delivery; *CI*, confidence interval.
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1.01–1.11; $P = .032$). The results of the multivariate logistic regression in this subcohort are shown in Table 3.

RMT was measured in 282 women. A total of 73 (19.7%) of participants had RMT <3.0 mm. Risk factors for reduced RMT (<3.0 mm) were peripartal infection ($P = .008$) and advanced cervical dilatation ($P = .045$). Parity and the number of previous CDs were associated with large isthmocele defects ($P = .033$ and $P = .002$, respectively).

Comment

In this prospective observational cohort study, we show that advanced maternal BMI, a history of GDM, and CD are independent risk factors for isthmocele development, regardless of the type of CD. In the subgroup of emergency CD, longer duration of active labor appears to increase the risk for isthmocele. We also report here that peripartal infections and advanced cervical opening raise the risk for low RMT values.

The strength of our study is that it represents, to our knowledge, the largest study performed to date in which isthmocele was evaluated with contrast-enhanced sonography in relation to the defined risk factors. As far as we know, only 1 previous study included a larger sample size in the assessment of isthmocele risk factors.[19] However, they used only unenhanced TVUS to diagnose isthmocele. Currently, contrast-enhanced ultrasonography is considered to be the gold standard in isthmocele diagnostics.[8]

Another strength of our study is the prospective observational cohort study design, in which participants were recruited as early as within 3 days of CD, thus avoiding possible selection bias. Only few previous prospective studies have been published, mainly recruiting participants a few months after CD, which may cause selection bias since symptomatic women may be more willing to participate. We found 2 previous studies that recruited participants close to CD.[10,20] However, in those studies, the US examination was performed as early as 6–12 weeks after CD. We decided to perform the examinations 6 months after CD because it has been suggested that the cesarean wound-healing process will take at least 6 months. On the other hand, we wanted to minimize the risk of a new pregnancy at the time of US, which would have prevented the performance of SHG. However, it is possible that the healing process will continue >6 months. Thus, doing the measurements at a later time point might have revealed different results, which has to be taken into account when interpreting the results.

It is a limitation of our study that 370 out of 371 women received a double-layer closure of the uterine incision. Therefore, we could not study the influence of closure technique on the risk of isthmocele. Another limitation of our study is that RMT was measured only if there was any visible indentation at the site of the CD scar. Therefore, in 89 (24.0%) women, RMT remained unmeasured. However, in that group, almost all women had no history of CD (n = 78/89; 88%). Low RMT values have been associated with the number of previous CDs, and a strong association between low RMT values and the presence of isthmocele has been shown.[19] Therefore, we found it reasonable to include women without isthmocele in the group with RMT ≥3.0 when we assessed the risk factors for low RMT.

Our results concerning the impact of obesity and GDM are novel. Maternal BMI and diabetes have not been regarded as risk factors for isthmocele in previous trials.[13,21,22] This may be due to a relatively small sample size in these studies; thus, the number of women was too small for significant associations. Additionally, the diagnostics and treatment of GDM may vary in different countries. In Finland, there is a population-wide maternity health care system and clear indications for glucose tolerance testing during pregnancy,

TABLE 3
Results of multivariate analysis in subcohort of emergency cesarean delivery (N = 216)

Parameter	Odds ratio	95% CI	*P* value
Maternal age, y	1.02	0.95–1.09	.670
Parity	1.28	0.65–2.51	.472
Previous CD	2.64	0.90–7.73	.076
Gestational diabetes	1.81	0.86–3.79	.118
Intrapartum or postoperative infection	2.05	0.95–4.42	.068
Duration of labor, h	1.06	1.01–1.11	.032

CD, cesarean delivery; *CI*, confidence interval.
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ensuring that almost all cases of GDM become diagnosed. Obesity has been associated with impaired cutaneous wound healing in general and total wound failure after surgical procedures.[23] Consistently, diabetes mellitus has a negative effect on wound healing by various mechanisms.[23,24] We think that it is reasonable to presume that obesity and diabetes affect also the healing of uterine incision and the negative effect may be true for GDM as well. Both obesity and diabetes have various systemic consequences. Chronic, low-grade inflammation, insulin resistance, and hyperglycemia are some of the factors associated with impaired wound healing related to these conditions.[24,25]

A relationship between multiple CDs and isthmocele has been reported previously.[7,15,26,27] A preexisting CD scar has been shown to negatively influence the healing of a new cesarean uterine incision. The results from our study support these data. The risk for isthmocele increased considerably with the number of previously performed CDs. The proposed pathophysiology is that repeated trauma to the isthmic wall disrupts the normal healing process. Additionally, vascular perfusion may be reduced in the scar tissue.[7,15]

In the subcohort of women who attempted a trial of labor, the duration of active labor increased the risk for isthmocele. As far as we know, there are no previous studies in which a subgroup of emergency CD is evaluated for the risk factors. In univariate analysis, the results obtained from the subgroup analysis were similar compared to the whole cohort with respect to parity, GDM, and obesity. In multivariate analysis, only the duration of labor remained as a significant risk factor for isthmocele. This may be attributable to smaller sample size in the subgroup analysis. It is possible that in active labor the healing circumstances are unique because the lower uterine segment is more stretched, which may specifically affect the healing properties of myometrium.

We found that advanced cervical dilatation raises the risk for low RMT values. This finding is in agreement with previous data.[13] Osser et al[14] found that cervical dilatation raises the risk for large isthmocele, which was defined by RMT $\leq$2.5 mm. In contrast to our results, they also found that the station of the presenting fetal part at CD was associated with the risk for large isthmocele. This difference may have arisen because our study included only a few women with presenting fetal part below the pelvic inlet. Moreover, the estimate of the height of the presenting part is quite subjective and thus sensitive to mistakes and hardly repeatable.

The development of isthmocele seems to depend on various patient-related and pregnancy-related, as well as operative, factors. We have shown here for the first time that both maternal obesity and GDM raise the risk for isthmocele. These findings are important since obesity and GDM are conditions that could be affected by early management and interventions. In the future, this association may become even more important because there has been a dramatic increase worldwide in the prevalence of obesity and GDM in women of childbearing age.[28] We want to emphasize that our results reflect the quantitative healing of the uterine scar. The clinical outcome of isthmocele will be ascertained only in the course of follow-up of our prospective study cohort. Nevertheless, more prospective high-quality studies are needed to ascertain the clinical significance of isthmocele to facilitate the definition of clinical guidelines for the possible prevention and management of isthmocele. ■

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Received May 25, 2018; revised Aug. 15, 2018; accepted Sept. 10, 2018.

This study was supported by competitive research funding of Pirkanmaa Hospital District, grant number 9U036 (J.U.M.) and University of Tampere (R.M.A-L.). The funding sources had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

The authors report no conflict of interest.

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PUBLICATION III

Association of caesarean scar defect with abnormal uterine bleeding; the results of a prospective study.

Antila, R., Mäenpää, J., Huhtala, H., Tomás, E., Staff, S.

European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020 Jan;244:134-140

European Journal of Obstetrics & Gynecology and Reproductive Biology 244 (2020) 134–140

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Full length article

Association of cesarean scar defect with abnormal uterine bleeding: The results of a prospective study

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ARTICLE INFO

Article history:
Received 29 August 2019
Received in revised form 18 November 2019
Accepted 20 November 2019
Available online xxx

Keywords:
Cesarean section
Cesarean scar defect
Isthmocele
Postmenstrual spotting
Abnormal uterine bleeding

ABSTRACT

Objective: To evaluate the relationship between cesarean scar defect and abnormal uterine bleeding at one year after cesarean section (CS).
Study design: A prospective observational cohort study was conducted in 401 women who delivered by CS between January 2016 and January 2017. Women were screened for isthmocele with sonohysterography six months after CS and followed by electronic questionnaires at 12, 13 and 14 months after CS. The main outcome measure was the prevalence of postmenstrual spotting. Secondary outcome measures were the duration of menstrual bleeding, prevalence of postcoital bleeding, dyspareunia or dysmenorrhea, usage of painkillers, and absence from work or other activities.
Results: The response rate was 88 %. In the isthmocele group, the prevalence of postmenstrual spotting was 20.0 % compared to 8.3 % in women without isthmocele (OR 2.75 [95 % CI 1.39–5.44]; P = 0.004). Additionally, women with isthmocele reported more frequently postcoital bleeding (8.3 % vs. 2.4 %; OR 3.73 [95 % CI 1.18–11.83]; P = 0.026). The prevalence of postmenstrual spotting was even higher in the subgroup of large isthmoceles, (25.9 % vs. 9.5 %; (OR 3.34 [95 % CI 1.72–6.49]; P < 0.001).
Conclusion: The prevalence of postmenstrual spotting among isthmocele patients was 20.0 %. Additionally, postmenstrual spotting was associated with the presence of isthmocele inquired at 1 year after CS.

Introduction

Cesarean section (CS) is the most frequently performed obstetric procedure [1]. Millions of women undergo this operation annually. Recently, multiple studies have been published concerning cesarean scar defect, also known as isthmocele. It represents inadequate healing of myometrium at the site of uterine incision. Isthmocele is frequently identified by ultrasonography [2]. The reported prevalence of isthmocele has varied considerably, between 6.9–69 % depending on the study population and the method used for evaluation [2,3]. Patients are not always symptomatic, but an association between isthmocele and various gynecological symptoms like abnormal uterine bleeding (AUB) has been suggested [4–6]. In particular, postmenstrual spotting has been associated with isthmocele and it has been found to correlate with the size of the defect [3,5,6]. Other reported symptoms are chronic pelvic pain, dysmenorrhea and prolonged periods [3–5,7]. However, in most studies evaluating the isthmocele-associated symptoms, selection bias is likely to play a role, as these studies have mainly included symptomatic women. This may have resulted in a falsely accentuated prevalence of postmenstrual spotting. In fact, a retrospective study showed no correlation between isthmocele and AUB but AUB was related to CS itself when compared to women with a history of only vaginal delivery [8]. We found only two previous prospective studies investigating the isthmocele-related symptoms in randomly selected populations [5,6]. Vaate et al. reported a two-fold increase in the prevalence of postmenstrual spotting among women with isthmocele compared to women without isthmocele [5]. In the study by Van der Voet et al. the prevalence of postmenstrual spotting was 28.9 % among women with isthmocele compared to 6.9 % among women without the defect [6]. Symptomatic women with isthmocele are

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https://doi.org/10.1016/j.ejogrb.2019.11.021
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frequently treated with invasive surgical techniques, although large prospective trials concerning the clinical outcome of isthmocele are lacking [9–11]. Hence, we found it justifiable to investigate the association between isthmocele and postmenstrual spotting in a prospective setting and in large, unselected population.

Materials and methods

This prospective observational cohort study was designed to assess the clinical outcome of isthmocele with respect to bleeding patterns. This study is a continuation of our previous studies, in which the prevalence and risk factors for isthmocele were investigated [12,13]. The study was carried out at Tampere University Hospital, which is a tertiary referral center for high-risk pregnancies, with annual rates of approximately 5000 deliveries and 700 CSs. The study was registered in ClinicalTrials.gov (Identifier: NCT02717312; "Prevalence, Risk Factors and Consequences Related to Cesarean Scar Defect (Defect in Cesarean Scar; DICE)"), and the study protocol was approved by the Ethics Committee of Tampere University Hospital, Finland (Identification code R15104). Women who had a CS performed in our hospital between January 2016 and January 2017 were asked to participate within 3 days of CS or prior to an elective CS. Exclusion criteria were a known uterine anomaly, a lack of common language, a known hematologic disorder and an age under 18. All participants provided a written informed consent before enrollment. Six months after the CS, participants were evaluated by saline-contrast sonohysterography (SHG) using Samsung WS80 Elite (Samsung Medison CO., Ltd, Gangwon-do, Republic of Korea). The uterus, uterine scar, and an isthmocele, if present, were examined in a standardized way as previously described in detail (Fig. 1) [14]. Isthmocele was defined as an anechoic defect at least 2.0 mm deep at the site of the CS scar (Fig. 2) [15]. Isthmocele was defined as a large defect if the ratio between the thickness of residual myometrium (RMT) and the thickness of the myometrium adjacent to the defect (AMT) was <0.50 as previously described (Fig. 2) [6].

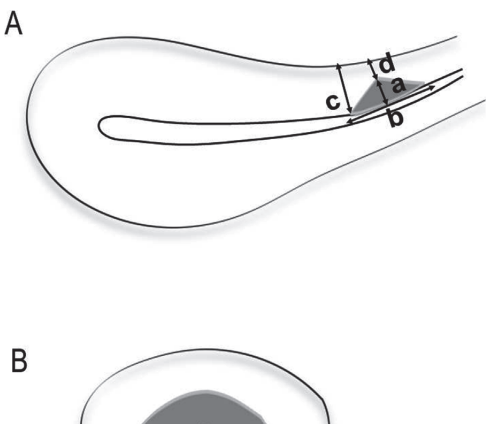

Fig. 1. Schematic presentation of isthmocele measurements. Isthmocele dimensions in longitudinal (A) and transverse (B) planes. a. Depth of isthmocele, b. Width of isthmocele, c. Thickness of adjacent myometrium, d. Thickness of residual myometrium, e. Length of isthmocele.

All examinations were performed by the first author, who was blinded to any clinical information. Women were not informed about the ultrasound findings. At 12, 13 and 14 months after the CS, women received an electronic questionnaire by e-mail (three separate questionnaires) in which menstrual bleeding pattern and other gynecological symptoms were inquired (Fig. 3). Additionally, age, current medication, breastfeeding, the use of contraception, smoking habits and body mass index (BMI) were asked as confounding factors. Details of menstrual bleeding pattern prior to the pregnancy were not collected because it would be susceptible to recall bias. Participants had been screened for sexually transmitted anogenital infections in early pregnancy at maternity health care as well as during the isthmocele assessment. The presence of pre-existing medical conditions possibly affecting the bleeding patterns (e.g. hypothyreosis, celiac disease, inflammatory bowel disease) was assessed from hospital medical records.

Women who completed the questionnaire at least once, were included in the statistical analyses. Those who were pregnant at the time of questionnaire or had undergone miscarriage or ectopic pregnancy during the past two months were excluded, because it would not have been possible to reliably analyze the menstrual pattern.

The primary outcome measure was the prevalence of post-menstrual spotting which was defined as ≥2 days of brownish discharge after the end of the menstrual period. For statistical analysis it was combined with intermenstrual bleeding, according to a previous prospective study [5]. Postmenstrual spotting was chosen as the primary outcome measure due to two previous prospective studies indicating an association between isthmocele and postmenstrual spotting [5,6]. Secondary outcome measures included prolonged menstruation (>7 days), presence of dysmenorrhea/dyspareunia/post-coital bleeding, a need for painkillers because of dysmenorrhea, and absence from work or other activities because of bleeding/dysmenorrhea.

Statistical analyses

The DICE study was primarily designed to assess the relation of isthmocele to AUB. Specifically, here the primary outcome measure was the prevalence of postmenstrual spotting. A detection of a two-fold difference in the prevalence of postmenstrual spotting between the isthmocele and non-isthmocele groups was aimed at in the statistical analyses. The sample size calculations were based on the following assumptions: the prevalence of postmenstrual spotting among women with isthmocele corresponds to 30 % and the prevalence of isthmocele was estimated to be approximately 50 % according to previous data [5]. To achieve an 80 % power with a two-sided alpha of 0.05, we needed to enroll 266 women in the study. Considering the dropout rate, which we anticipated to be up to 30 %, we aimed to recruit 400 women.

Data was analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY). The independent student's *t*-test was used for the comparison of continuous variables in case of normal distribution. Otherwise, non-parametric tests were used. Associations between categorical variables and isthmocele were compared with Chi-square or Fisher's exact test when appropriate. Two-tailed p values of <0.05 were considered as statistically significant. A binary logistic regression model was used to evaluate the effect of isthmocele on various symptoms. Results are shown as ORs (odds ratio) with 95 % confidence intervals (CI).

Potential confounding factors were predefined, and included age, breastfeeding, smoking, BMI, oral contraceptive use (combined oral contraceptive pill or progestin-only pill), and use of levonorgestrel-releasing (LNG) or copper (Cu) IUD. These potential confounding factors were analyzed using logistic regression in multivariate analysis.

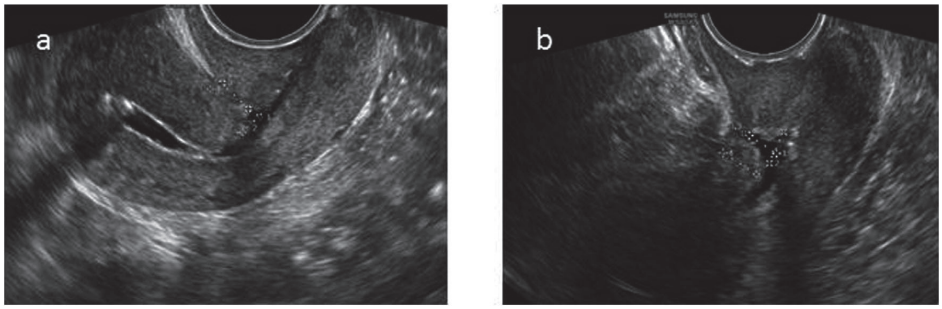

Fig. 2. Sonohysterographic image showing a small (a) and a large isthmocele (b).

Results

Between January 2016 and January 2017, four hundred and one women who delivered by CS gave an informed consent. Three hundred and seventy-one participants were successfully examined with SHG on average 6.7 months after the CS. The prevalence of isthmocele was 46.3 %. The prevalence and risk factors of isthmocele from the present data set have been reported previously [13]. In total, 88.4 % (328/371) of participants completed the symptom questionnaire at least once (Fig. 4). Forty-three women were lost to follow-up (non-responder or incorrect e-mail address). Later, 15 women were excluded (14 because of pregnancy and 1 because of miscarriage). The background variables among all participants and isthmocele/non-isthmocele groups are shown in Table 1.

There were no differences between the study participants who completed the questionnaire and those who were lost to follow-up regarding age, parity, previous CS, previous vaginal delivery, induction of labor, type of CS (elective versus emergency) or BMI (data not shown). At CS, a low transverse uterine incision and uterine closure with double layer continuous unlocked sutures were used for all participants. At the time of questionnaire, 29.7 % were breastfeeding and 19.2 % were in amenorrhea. Following methods of contraceptive use were reported: no hormonal contraception, 66.8 %; progestin-only pills, 9.9 %; combined oral contraceptive pills, 4.5 %; contraceptive implant, 1.0 %; LNG-IUD 15.0 % and Cu-IUD 2.9 %.

No other uterine pathologies (such as polyps or fibroids) were found at SHG. The prevalence of postmenstrual spotting in the whole study cohort was 13.7 %. According to hospital medical records, there were no differences in pre-existing medical conditions possibly affecting the bleeding patterns between women who suffered from AUB and those who did not (data not shown). In the isthmocele group, 20.0 % of women reported postmenstrual spotting, compared to 8.3 % without an isthmocele (OR 2.75 [95 % CI 1.39–5.44]; P = 0.004; Table 2). Moreover, the prevalence of postcoital bleeding was associated with isthmocele (8.3 % vs. 2.4 %; OR 3.73 [95 % CI 1.18–11.83]; P = 0.026; Table 2). In a subgroup analysis excluding the women with amenorrhea (n = 252), the association between postmenstrual spotting and isthmocele remained statistically significant (21.9 % vs. 10.1 %; P = 0.012). Using logistic regression analysis none of the predefined confounding factors or baseline characteristics were related to postmenstrual spotting (method of contraception, breastfeeding, smoking, age, BMI; data not shown).

There was no difference between the isthmocele and non-isthmocele groups concerning the prevalence of prolonged periods, dysmenorrhea, dyspareunia, use of painkillers and absence from work or activities (Table 2). All in all, 80.2 % of study participants were totally free from AUB and 74.5 % of women with isthmocele did not suffer from AUB at all.

In the subgroup analyses of large defects, women with large isthmocele reported even more often postmenstrual spotting compared to women with small isthmocele or no isthmocele at all (OR 3.34 [95 % CI 1.72–6.49]; P < 0.001; Table 3). Nearly half of the women with postmenstrual spotting (48.8 %) had a large isthmocele (data not shown).

Comment

In this prospective observational cohort study, we showed that postmenstrual spotting and post-coital bleeding were associated with isthmoceles, surveyed at 1 year after CS. The prevalence of postmenstrual bleeding among isthmocele patients was slightly lower than expected (20.0 %).

To the best of our knowledge, this study represents the largest study performed to date in which isthmocele was evaluated prospectively with contrast-enhanced SHG in relation to symptoms. We recruited participants within 3 days of CS aiming at avoiding possible selection bias. We decided to perform SHG six months after the CS because it has been suggested that the wound healing process will take at least six months [16]. Earlier assessment would have probably led to over diagnosis, and delayed assessment to higher dropout rate due to subsequent pregnancies. Here, the prevalence rate of isthmocele was 46.3 %, which is in line with a previous prospective study using SHG [5]. Women were not informed about the possible presence of isthmocele in order to prevent possible bias in later reports on the bleeding pattern. Additionally, other reasons for AUB were taken into account.

The use of electronic questionnaire in reporting the symptoms can also be considered as strength of the present study. Our aim was to minimize the risk for recall bias. We consider that the collected data was reliable because women were able to answer the questionnaire right after the menstruation instead of later recalling the bleeding days and symptoms. The inquiry time point at one year after CS was chosen in order to minimize the rate of lactation amenorrhea and subsequent pregnancies. The response rate was as high as 88.4 %, which is prone to increase the reliability of the outcome assessment.

A possible limitation of our study is a lack of any validated tool to assess postmenstrual spotting. The validated patient-reported outcome measures assessing AUB have been developed only for heavy menstrual bleeding. These questionnaires measure the volume of blood loss and are not suitable for the purpose of the current study [17,18].

Another limitation is the fact that not all women who delivered by CS during the study period participated in the study. There were 742 CSs at our hospital during the study period out of which 401

1. Height and weight		
2. Current medication		

3. Current contraceptive use:	Yes	No
Combined oral contraceptive pills		
Progestin-only pills		
Hormonal IUD		
Copper IUD		
Contraceptive implant		
No hormonal contraception		

4. Are you breastfeeding		
5. Do you smoke		
6. Are you pregnant		
7. Did you have miscarriage or extrauterine pregnancy in the past 2 months		
8. Did you suffer from dysmenorrhea/dyspareunia/post-coital bleeding last month		

9. Because of pain or bleeding		
Did you take painkiller		
Did you skip your work		
Did you miss other activities		

10. Did you have periods last month? If yes, write down the dates.*

M	T	W	T	F	S	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

11. Did you have brownish discharge last month? If yes, write down the dates.**

M	T	W	T	F	S	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

Fig. 3. Electronic questionnaire.
* Prolonged menstruation was defined as >7 bleeding days.
** Postmenstrual spotting was defined ≥2 days of brownish discharge after the end of the menstrual period or intermenstrual bleeding which starts within 5 days after the end of menstruation.

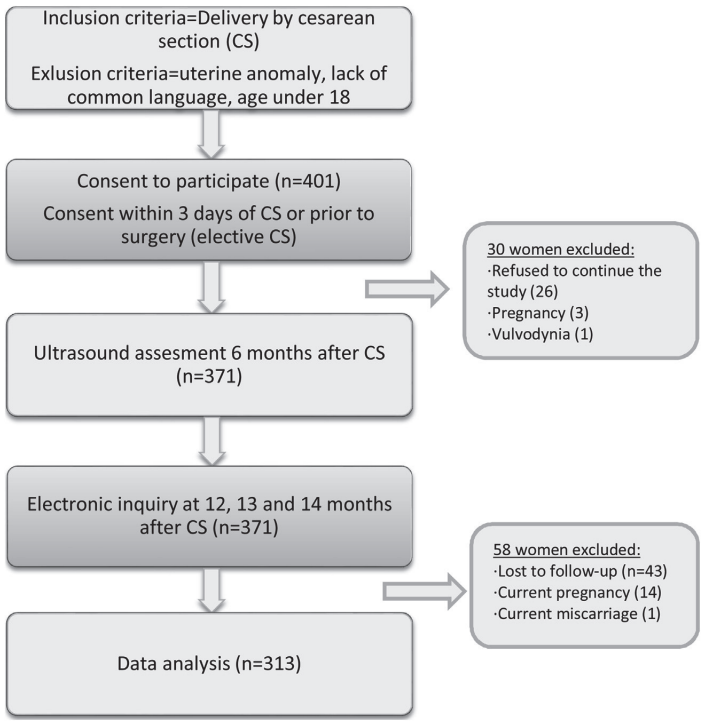

Fig. 4. Flow chart of study participants.

Table 1
Background characteristics at the time of electronic questionnaire.

Parameter	All	(n = 313)	Isthmocele (n = 145)		No isthmocele (n = 168)		p-value
Age, years; mean (SD)	32.7	(5.2)	33.4	(4.7)	32.0	(5.5)	0.018
Parity; median (range)	1	(1–7)	2	(1–6)	1	(1–7)	<0.001
Number of previous CS; median(range)	0	(0–3)	0	(0–3)	0	(0–2)	<0.001
Body mass index, kg/m^2; mean (SD)	26.6	(6.0)	27.9	(6.42)	25.5	(5.3)	0.001
Smoking; n (%)	19	(6.1)	8	(5.5)	11	(6.5)	0.703
Contraception							0.002
No hormonal contraception n (%)	209	(66.8)	85	(58.6)	124	(73.8)	
Oral contraceptive pills n (%)	14	(4.5)	10	(6.9)	4	(2.4)	
Progestin-only pills n (%)	31	(9.9)	13	(9.0)	18	(10.7)	
Hormonal IUD n (%)	47	(15.0)	32	(22.1)	15	(8.9)	
Copper IUD n (%)	9	(2.9)	5	(3.4)	4	(2.4)	
Contraceptive implant n (%)	3	(1.0)	0	(0.0)	3	(1.8)	
Women in amenorrhoea n (%)	60	(19.2)	31	(21.4)	29	(17.4)	0.370
Breastfeeding n (%)	93	(29.7)	45	(31.0)	48	(28.6)	0.634

CS = caesarean section, IUD = intrauterine devise.

women gave an informed consent. However, women participating in the study did not differ from non-participating women with respect to baseline characteristics such as elective or emergency cesarean section rate, age and parity.

The main outcome measure was the relation of postmenstrual spotting to the presence of isthmocele. Postmenstrual spotting inquired at 1 year after CS was associated with the presence of isthmocele detected with SHG at 6 months after CS. One out of five women with isthmocele reported postmenstrual spotting, compared with one out of twelve women without isthmocele. Additionally, postmenstrual spotting was reported even more often by women who presented with a large isthmocele. On the whole, the prevalence of postmenstrual spotting in our study cohort was slightly lower compared to previous prospective trials. Van der Voet et al. reported a prevalence of 28.9 % in the isthmocele group compared to 6.9 % in women without isthmocele [6] in a study population of 137 women. Also Bij de Vaate et al. reported that one third of women with isthmocele suffer from postmenstrual spotting compared to one in seven in women without isthmocele [5]. However, participants were recruited several months after the CS, which may have resulted in the selection of symptomatic patients. We suggest that selection bias may have less pronounced effect on the present study, which may explain the lower rate of postmenstrual spotting reported here.

According to our results, the isthmocele-related postmenstrual spotting is reported by 20.0 % of women with isthmocele and by

Table 2
Uterine bleeding pattern and gynecological symptoms at 12 months after cesarean section among 145 women with isthmocele and 168 women without isthmocele.

	Isthmocele (n = 145)		No isthmocele (n = 168)		p-value	OR	95 % CI
Postmenstrual spotting; n (%)[a]	29	(20.0)	14	(8.3)	0.004	2.75	1.39-5.44
Prolonged periods (> 7 days); n (%)	10	(7.2)	12	(7.2)	0.998	1.00	0.42-2.39
Postcoital bleeding; n (%)	12	(8.3)	4	(2.4)	0.026	3.73	1.18-11.83
Dysmenorrhea; n (%)	80	(55.2)	93	(55.4)	0.974	0.99	0.64-1.55
Dyspareunia; n (%)	24	(16.6)	18	(10.7)	0.133	1.65	0.86-3.19
Absence from activities; n (%)	2	(1.4)	7	(4.2)	0.172	0.33	0.07-1.62
Need for painkiller; n (%)	49	(34.0)	54	(32.1)	0.724	1.09	0.68-1.75
Absence from work; n (%)	0	(0.0)	1	(0.6)	0.996	0.99	0.98-1.01

[a] Primary outcome measure. Others are secondary outcome measures.

Table 3
Uterine bleeding pattern and gynecological symptoms at 12 months after cesarean section in the groups of large isthmocele (n = 81) and small/no isthmocele (n = 232).

	Large isthmocele (n = 81)		Small/no isthmocele (n = 232)		p-value	OR	95 % CI
Postmenstrual spotting; n(%)	21	25.9	22	9.5	<0.001	3.34	1.72-6.49
Prolonged periods (>7 days); n(%)	5	6.5	17	7.4	0.785	0.87	0.31-2.43
Postcoital bleeding; n(%)	7	8.8	9	3.9	0.097	2.38	0.86-6.61
Dysmenorrhea; n(%)	43	53.1	130	56.0	0.646	0.89	0.53-1.48
Dyspareunia; n(%)	11	13.6	31	13.4	0.960	1.02	0.49-2.14
Absence from activities; n(%)	2	2.6	7	3.0	0.833	0.84	0.17-4.14
Need for painkiller; n(%)	23	28.8	80	34.5	0.348	0.77	0.44-1.34
Absence from work; n(%)	0	0.0	1	0.4	0.997	1.00	0.99-1.00

25.9 % of women with large isthmocele, at least when inquired at one year after the CS. The association remained significant when women with amenorrhea were excluded. This is in line with the previous prospective studies [5,6]. The relationship between the size of isthmocele and postmenstrual spotting is in line with the hypothesis that spotting is induced by the accumulated blood inside the isthmocele pouch [19]. The positive association of isthmocele defects with menstrual bleeding disorders allows us to consider invasive surgical interventions when encountering symptomatic patients. However, only one randomized controlled trial (RCT) addressing the impact of hysteroscopic resection of isthmocele on postmenstrual bleeding is presently available [20]. More prospective studies and RCTs with long-term follow-up should be carried out before establishing guidelines on the clinical management of symptomatic isthmocele.

A longer follow-up of the participants would possibly have given us more information on the magnitude of the clinical disorders. Available studies, such as ours presented here, have followed the patients up to one year after the CS, and more data on long-term effects of isthmocele is warranted.

Conclusion

The presence of isthmocele was significantly associated with postmenstrual and postcoital bleeding.

Funding

Competitive Research Funding of Pirkanmaa Hospital District, Grant Number 9U036 (JM); Ph.D. School of University of Tampere (RA). The funding sources had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Authors' contributions

RA, HH, ET, JM, and SS contributed to all aspects of the study design. RA performed the ultrasound examinations and collected the data. Analysis of the data was performed by RA, HH and SS. The first draft was written by RA and SS, and JM contributed significantly to it. HH performed the statistical calculations, and ET helped to revise the article up to the final draft.

Declarations

This study was approved by the Regional Ethical Committee of Tampere University Hospital, Tampere, Finland. Approval was granted on 2 September 2015 (ref. no. R15104).

Availability of data and materials

Not applicable.

Declaration of Competing Interest

None of the authors have any relevant financial, personal, political, or religious interest linked to the subject of this article.

Acknowledgements

There was no acknowledgement.

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PUBLICATION IV

Association of post-cesarean isthmocele in non-pregnant woman with subsequent pregnancy outcome

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Submitted