Caesarean Section

Short- and long-term maternal complications

SUSANNE HESSELMAN
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Abstract

Caesarean section is a common major surgical procedure and long-term complications have not been fully investigated. By longitudinal population based register studies, based on National health registers and medical data records, maternal complications after caesarean delivery at subsequent labour (N=7,683), among extremely preterm births (N=406), and at remote gynaecologic surgery (N=25,354) were explored.

In Paper I, uterine closure was investigated in respect to uterine rupture in a subsequent delivery after caesarean section. Uterine rupture occurred in 1.3 % of women with a previous caesarean section. There was no increased risk of uterine rupture with single compared with double layers for closure of the uterus (adjusted Odds Ratio 1.17, 95 % CI 0.78-1.70). Modifiable risk factors of uterine rupture in a trial of labour after caesarean section included induction of labour and use of epidural analgesia.

In Paper II, maternal outcomes and surgical aspects of caesarean section in the extremely preterm period were assessed. Maternal complications were more frequently reported in extremely preterm- compared with term caesarean delivery. No increase in short-term morbidity was observed at 22-24 compared with 25-27 gestational weeks, but uterine corporal incisions were performed more frequently (18.1 % vs. 9.6 %, p=0.02).

Furthermore, risk factors for abdominal adhesions after caesarean section and organ injury in remote gynaecologic surgery were analysed (Paper III and IV). Numbers of prior caesarean sections were the most important factor for formation of adhesions. Advanced maternal age, obesity, infection and delivery year 1997-2013 were factors associated with adhesions in conjunction with caesarean section. Organ injury occurred in 2.2 % of women undergoing benign hysterectomy. A history of caesarean section increased the risk (adjusted Odds Ratio 1.74, 95 % CI 1.41-2.15), but was only partly explained by the presence of adhesions. The organ affected depended on medical history; prior caesarean predisposed for bladder injury, prior bowel/pelvic surgery for bowel injury and endometriosis was associated with ureter injury at time of hysterectomy. In conclusion; data from National health registers indicates that caesarean delivery is associated with long-term complications, although the absolute risk of severe complications for the woman is low.

Keywords: adhesion, caesarean section, extremely preterm birth, gynaecologic surgery, organ injury, uterine rupture, trial of labour

Susanne Hesselman, Department of Women's and Children's Health, Obstetrics and Gynaecology, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

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Den mätta dagen, den är aldrig störst. Den bästa dagen är en dag av törst.

Karin Boye. I rörelse, Härdarna.
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Abbreviations

AIP Abnormally Invasive Placentation
AOR Adjusted Odds Ratio
BMI Body Mass Index
CI Confidence Interval
CS Caesarean section
CTG Cardiotocography
GSEM Generalised Structural Equation Modelling
ICD International Classification of Disease
ICU Intensive Care Unit
IUGR Intrauterine Growth Restriction
MBR Swedish Medical Birth Register
OR Odds Ratio
PAR Swedish Patient Register
RCT Randomised Controlled Trial
TOL Trial Of Labour
VBAC Vaginal Birth After Caesarean
WHO World Health Organization
Preface

The word Caesarean section reflects more than a surgical procedure. For the resident on call, it is the first major intervention performed independently, but a caesarean section could also be a challenging surgical procedure for the experienced clinician. For the pregnant woman, caesarean delivery may be associated with relief or with sense of failure. It can be a life saving procedure, but at the same time it is associated with short- and long-term maternal morbidity. As a result, conflicting information about risks and benefits of caesarean delivery may be given in antenatal care, during labour and after labour. The risks and benefits are appreciated differentially between caregivers and mothers but also between caregivers. The increased rate of abdominal deliveries worldwide during the last few decades have resulted in programmes aiming to reduce the rate of caesarean section. A particular situation is women in labour after caesarean. These are high risks deliveries, and most clinicians agree that efforts to avoid a first caesarean section are beneficial for future reproductive health. However, knowledge of adverse effects of caesarean delivery occurring remote years after childbirth is limited. The following papers aim to investigate maternal complications after caesarean section, with emphasis on long-term.
Introduction

Caesarean Section

Historical notes, techniques and rates

Caesarean section (CS) is the most common abdominal surgery performed in women at present. The rate of caesarean deliveries varies substantially between nations and healthcare facilities but continues to rise worldwide [1, 2].

Historically, CS was performed post-mortem, according to lex regia, a Roman law forbidding burial of an undelivered woman. Caesarean delivery as a surgical procedure is described in the 15-16th century, but some scepticism might be appropriate when successful stories of women undergoing multiple caesarean deliveries are mentioned. In the 19th century, the mortality rate after abdominal delivery was around 75%. The introduction of closing the uterus, advocated by Max Sanger in 1882, and the use of aseptic technique around 1870, were both important factors to reduce maternal mortality [3]. Different CS techniques have been used and described over the years. In a classical CS, midline vertical incisions of the skin and the corporal part of the uterus are performed. In 1926, Munro Kerr proposed a transverse incision of the lower uterine segment, which proved to be superior to a corporal incision, with reduced maternal mortality and lower risk of uterine rupture in a subsequent pregnancy [4]. The transverse incision of the uterus did not gain acceptance until 1949 and was either combined with a midline incision of the skin or a low transverse incision - the Pfannenstiel-Kerr method. In these techniques, both visceral and parietal peritoneum layers were closed, but later clinical studies suggested that closure was not mandatory for peritoneal healing [5, 6]. In 1995, Stark and colleagues at the hospital Misgav-Ladach introduced a new CS technique, described in the paper by Holmgren et al. [7]. A transverse skin incision 5 cm above the symphysis, proposed by Joel-Cohen, was combined with blunt division of tissues, single layer closure of the uterus and non-closure of the peritoneal layers. The new CS technique, concomitantly referred to as Stark, Misgav-Ladach or Joel-Cohen technique, was further modified with a lower skin incision level and was introduced in Sweden from 1996-1999 [7-9].

The optimal surgical technique and the optimal rate of CS are still debated. The previously advocated optimal rate of CS of 10-15% [10] was replaced
in 2015 by the WHO stating: *Every effort should be made to provide caesarean sections to women in need, rather than striving to achieve a specific rate* [11]. Globally, around one-fifth of births are reported to be by CS. In 2014, more than 40% of births in South America and 30% of deliveries in North America, Oceania, Eastern Asia and Southern Europe were by CS. Sweden among the other Nordic countries has a lower CS rate [1, 12], although the rate has tripled during the last 40 years (Figure 1).

![Figure 1. Rate (%) of caesarean section in Sweden for years 1973-2015 in nulliparous and parous women (Source: MBR, National Board of Health and Welfare, Sweden)](image)

This increase could be related to demographic changes of women giving birth (age, weight, parity), or changed obstetric practice (induction, fetal monitoring, decreased operative vaginal delivery), as well as wider indications for CS (breech, preterm, previous CS and CS on request). The wide variation in CS rate is not only attributed to differences in demographic factors, but could also arise from different conceptions of maternal and neonatal risks and benefits of CS, among healthcare providers and women. The rate of CS based on maternal request is unknown due to imprecise definitions and conceptions of medical indications [13]; however, 38% of the CS performed in 2011 in China was considered non-medical indicated [14]. Non-medical indicated CS rates may be driven by economic reasons and convenience of scheduled birth, and for profit hospitals usually report higher rates of CS compared with non-profit [15].

Implications of CS for the mother in subsequent pregnancy, labour and surgery are not completely understood and are of major interest and concern.
Short-term complications of Caesarean Section

The reported incidence of complications after CS varies by method of collecting data: time to follow-up, population studied and definitions of complications used. A limited number of randomised controlled trials (RCT) have been performed for breech presentation and report a small increased risk of short-term maternal morbidity with planned CS compared with planned vaginal birth [16]. However, evidence of maternal complications related to CS is mostly based on observational studies, investigating the effect of the actual mode of delivery and not the intended mode. The overall complication rate after CS has been estimated to occur in one-third of patients and suggests that emergency CS carries the highest risk [17, 18]. In a population based register study, risk of severe obstetric haemorrhage, defined as blood loss >1000 ml, was two-fold after elective CS and three-fold following emergency CS compared with vaginal delivery [19]. In a prospective cohort of 106,546 deliveries, severe maternal morbidity was assessed to be two-fold with CS compared with vaginal delivery and with four-fold increased risk of hysterectomy. In this publication, emergency CS compared with elective CS was not associated with higher maternal morbidity [20]. Post-operative infection following CS, including febrile morbidity requiring antibiotic treatment, has been reported in 7-17 % in retrospective and prospective studies [17, 21-23], but is reduced by 60 % with prophylactic antibiotics [24]. Post-partum thromboembolism is a major complication with five-fold increased risk after CS compared with vaginal delivery and affects at least 0.23 % [23, 25].

The interpretation of observational studies of complications is confounded by the indication for CS. Complications recorded after CS may result from underlying maternal conditions resulting in a CS, and not from the procedure per se. Preeclampsia increases the risk of haemorrhage and thromboembolism [17, 25]. Chronic hypertension, diabetes and multiple births are all risk factors for severe sepsis [26]. Dystocia and high birth weight are related to uterine atony and blood loss [27]. According to a prospective observational study of 2,751 caesarean deliveries, intra-operative complications including lacerations of cervix, vagina and bladder increased with advanced cervical dilatation [27, 28], and a second stage CS has been associated with higher risk of intensive care unit (ICU) admission, blood transfusion and infectious morbidity [29-31]. Increased maternal morbidity is seen with repeated CS [32] and preterm CS [17, 33], which could be related to the indication of CS or the technical difficulties encountered in these cases.

CS performed before labour is usually regarded as elective but includes both CS with emergent obstetric indications such as placental abruption and severe preeclampsia. CS after onset of labour includes emergent procedures, with different indications and maternal conditions, which make risk esti-
mates between different categories of CS imprecise [13]. Moreover, the lack of strict definitions of maternal outcomes limits interpretations and comparisons between studies.

Surgical techniques and complications

Observational studies of the Joel-Cohen based technique demonstrate reduced risk of per- and post-operative complications, with less post-operative pain and infection and faster maternal recovery [34, 35]. Decreased blood loss, shorter duration of surgery and time to deliver the baby has been reported in randomised controlled trials, whereas the effect on infectious morbidity diverges [8, 9, 36, 37]. A Cochrane report from 2014 concluded that single layer closure of the uterus compared with double layer closure decreases blood loss but not febrile morbidity [38]. Another Cochrane review, investigating the effect of peritoneal closure, concluded that non-peritoneal closure compared with closure of both peritoneal layers reduces duration of surgery and hospital stay but does not affect the rate of post-operative infection [39]. The CORONIS trial (N=15,935) found no difference in comparing sharp vs. blunt division of tissues, single or double-layer closure of the uterus, suture material or peritoneal closure and non-closure in respect to maternal infection, re-operation or blood transfusion [40]. The Caesar trial (N=3,033) investigated maternal infection in respect to uterine closure, peritoneal closure and use of subrectus drain and found no technique to be superior to the other, but duration of surgery was shorter with non-peritoneal closure (mean 2.4 minutes, 95 % CI 1.3-3.6 minutes) [21].

Preterm caesarean section

The rate of preterm births, defined as birth before 37 completed gestational weeks, is estimated to 5 % in northern Europe and to 12 % in North America and constitutes of both spontaneous and iatrogenic births [41]. Extreme preterm birth (gestational age 22-27 weeks) constitutes around 5 % of all preterm births and is associated with risk of adverse maternal complications, independent of the mode of delivery [42].

Preterm, compared to term, CS has been associated with higher proportion of maternal complications, such as increased blood loss, hysterectomy, sepsis, thrombosis and post-operative hematoma [17, 27, 33], but low rates of serious maternal complications have also been reported in selected populations [42, 43]. In a retrospective cohort of 540 extremely preterm deliveries, adverse maternal outcome defined as maternal death, admission to ICU, sepsis, hysterectomy, transfusion, postpartum haemorrhage, surgical injury, reoperation, endometritis or re-admission to hospital, occurred in one-fifth of delivered women, but CS did not increase the risk (aOR 0.67, 95 % CI 0.40-
An underdeveloped lower segment of the uterus or malpresentation of the fetus may lead to a corporal uterine incision, which is performed in 20-56% of the extremely preterm CS, and has been associated with increased blood loss and infection [33, 42-45]. In subsequent pregnancy, incisions extending into the corpus increase the risk of uterine rupture [46], and data also suggest an increased risk of rupture after a low transverse CS performed at 20-26 weeks of gestation [47, 48].

Sweden, with about 400 extremely preterm births annually, has a high rate of perinatal interventions, including delivery by CS at gestational age 22-26 [49]. According to a guideline proposed by an expert group from the Swedish Neonatal Society and Swedish Society of Obstetrics and Gynaecology 2015, caesarean delivery on fetal indication is recommended at 24 weeks of gestation and should be considered at 23 gestational weeks [50]. The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine recommend CS on fetal indication from 25 gestational weeks and that decision of CS on fetal indication should be individualised at lower gestational weeks [51].

The restricted number of prospective trials comparing planned CS and planned vaginal delivery for preterm births limits conclusions about maternal and neonatal risks and benefits of CS to observational studies [52]. Results are conflicting and prone to selection bias, but CS may be beneficial for the growth restricted infant and breech presentations [53-55].

Increased survival rates among infants who are delivered extremely preterm [49, 53, 56], and a potential benefit of CS for the neonate raise the question about maternal complications of abdominal deliveries performed extremely preterm.

Long-term complications of Caesarean Section

In a subsequent pregnancy and delivery, abnormal placentation [32, 57], uterine rupture [46, 58] and adhesions associated with intra-operative difficulties [59] are all feared complications of previous CS, with major impact on maternal health.

Abnormal location and invasion of placenta

Placenta previa and abnormally invasive placentation (AIP) are strongly associated with prior CS and increase risks of haemorrhage, peripartum hysterectomy and maternal mortality [32, 57]. Placenta previa, when the placenta is at the margin or covers the cervix inlet, occurs in 10% of women with a history of four or more CS compared with 0.23% of women without prior CS. AIP results from deficient decidua formation, when the placenta villi morbidly attach or invade the myometrium. In a Nordic population based
study, the prevalence of AIP was estimated to 1 out of 720 women with prior CS, and the seven-fold risk after one prior CS rose dramatically to a 56-fold increased risk of AIP after three or more CS [57]. The risk of placenta accreta and peripartum hysterectomy have been thoroughly investigated by Silver et al., and rates increases with each repeat CS [32]. Corporal incision and pre-labour CS have been associated with increased risk of AIP [60, 61], whereas single compared with double layer closure of the uterus, according to a case-control study, did not influence the risk [62].

Myometrium disruption after CS may also result in implantation of the conceptus in the scar, resulting in a scar pregnancy.

Uterine rupture
Uterine rupture, which is full disruption of the uterine wall in labour, is an obstetric emergency associated with high maternal and neonatal morbidity, and the main risk factor in developed countries is a previous caesarean delivery [46, 58].

Incidence of uterine rupture
The incidence of uterine rupture depends on definition, population and study method used, and there is great variation of reported rates [63]. The rate is influenced by the validity of diagnosis in national registers, and both over- and underreporting is observed [64, 65].

In the Nordic countries, uterine rupture has been reported to occur in 0.06 % of all deliveries [66, 67]. Rupture of an unscarred uterus is a rare event, affecting 0.005 % [67]. The main risk factor for uterine rupture is a previous CS, and uterine rupture occurs mainly after onset of labour [63]. The rate of uterine rupture in women attempting a trial of labour (TOL) after previous low transverse CS has been estimated from 0.21-1.5 %; the variation may reflect that selection of patients and management of TOL differ between settings [46, 63, 68-72]. Apart from population studied, different definitions of uterine rupture will have an effect on reported rates [63]. Usually, uterine rupture refers to a full thickness disruption of the uterine wall [73], but cases with any separation of the uterine wall associated with clinical symptoms could also be included [74]. Associated symptoms help to distinguish rupture from asymptomatic dehiscence of the uterine scar, which has little impact on maternal and neonatal outcome [46, 75].

Risk factors of uterine rupture
Risk of rupture of the uterine scar might depend on the integrity and strength of the scar and the strain on the scar during labour. The risk of uterine rupture in TOL is closely associated with previous modes of births. In a trial of labour, the risk is three-fold in women with ≥ 2 prior CS compared with one prior CS, whereas a prior vaginal delivery lowers the risk of uterine rupture
substantially [71, 76, 77]. Induction of labour, especially with the use of oxytocin and prostaglandins, has been identified as a risk factor for uterine rupture in women with a uterine scar [46, 71]. Prostaglandins have been associated with a two- to six-fold increased risk of rupture compared with spontaneous onset of labour [46, 69, 72, 75, 78], but these findings have been suggested to be confounded by its indication with an unripe cervix and thus longer duration of labour [79]. Advanced maternal age both at index CS and subsequent labour, high birth weight, postpartum fever and short delivery interval are also reported risk factors for uterine rupture in a subsequent TOL [70, 71, 75, 80-83].

**Surgical techniques and risk of uterine rupture**

The strength of the scar may be result of the surgical technique used for uterine closure, and single and double layer have been studied in respect to uterine rupture. Results from retrospective observational studies are conflicting. Bujold et al. have reported a four-fold increased risk of rupture after single layer closure compared to double layer closure, but a meta-analysis from 2011 including nine studies (one RCT, six cohort and two case control studies) found no increased risk [73, 84]. The largest RCT, investigating effects of CS technique is the CORONIS trial [40]. In the recently published 3-year follow-up, the risk of uterine rupture according to single or double layer closure of the hysterotomy did not differ. However, there was a lack of power to detect differences due to the low incidence of subsequent pregnancies (n=4,992). Further, two-thirds were delivered with a pre labour CS; consequently, the risk of rupture was low [85].

In attempt to overcome the methodological problems, measurement with ultrasonography of lower uterine thickness after CS has been investigated. Disruption of the anterior wall and a visible scar defect increases with number of caesarean deliveries, but the incidence proportion is high, ranging from 61 % after one CS to 100 % after > 3 CS [86], which limits the clinical utility. Myometrium thickness has been used in follow-up studies of uterine closure with conflicting results [87] [88]. To set cut-off values of antenatal myometrium thickness for predicting uterine rupture has proved to be hard [89]. The lower uterine segment thickness decreases with gestational length and has been measured to 2.3 mm at term, in women without a prior CS [90]. A meta-analysis, including 21 studies, concluded that there was a strong negative predictive value of myometrium thickness 2.1-4.0 mm and a strong positive predictive value of 0.6-2.0 mm for diagnosing defects of the uterine wall in CS.

Due to the rare outcome and presumably multifactorial cause of uterine rupture, long-term follow-up studies of uterine closure and risk of uterine rupture has posed methodological problems, and the optimal surgical technique is still debated.
Clinical signs and symptoms of uterine rupture

Efforts to improve safety of vaginal delivery after CS have focused on the identification of risk factors for uterine rupture, and few studies have examined the actual course of labour or aspects of intrapartum management in cases of rupture [91, 92]. Recognition of clinical signs of uterine rupture is challenging due to the lack of specific symptoms; moreover, most signs do not precede but follow uterine rupture. Clinical signs include fetal heart rate abnormalities, abdominal pain, vaginal bleeding, haematuria, loss of engagement of the presenting fetal part and maternal cardiovascular collapse [93-96]. In a case control study, pathological CTG occurred in 77 % of cases with uterine rupture but was also present in 53 % of labours without rupture [95]. The most common CTG patterns in uterine rupture were severe variable decelerations and terminal fetal bradycardia indicating overt rupture. Arrest of labour is commonly reported in cases with uterine rupture [92], and augmentation with oxytocin poses a risk [72, 78, 91, 97], but these features can also be present in labours without rupture. Despite the high-risk procedure, there are no specific protocols of augmentation of labour or surveillance of women undergoing TOL after caesarean in Sweden.

Adhesions

Incidence and clinical burden of adhesions

Intra-abdominal adhesions are fibrous structures formed between abdominal organs, peritoneum and the abdominal wall after inflammation caused by surgery, infection or chemical irritation and may develop in more than 90 % after laparotomy [98, 99]. In epidemiologic studies, burden of adhesions after different types of surgery has been evaluated by rates of re-admissions, diagnosis or surgical procedures that could be attributed to adhesions [100, 101]. Abdominal adhesions are associated with small bowel obstruction and accounts for 65-75 % of cases requiring surgery [99, 102]. Morbidity from post-surgical adhesions is closely related to type of index surgery; small bowel obstruction has been reported in only 0.5/1000 after CS compared with 15.6/1000 after abdominal hysterectomy [103]. In a Swedish register and populations based study, Andolf et al. reported a higher incidence of bowel obstruction and symptomatic adhesions, affecting 2.2/1000 women with previous CS [101]. Adhesions have also been related to subfertility and pelvic pain and were formerly an indication of gynaecologic adhesiolysis [59, 104]. Following CS, subfertility has been reported in 3 % and chronic pain in 6 % of women [85].

Even if severe morbidity after CS occurs infrequently, adhesions may increase intra-operative complications in subsequent surgery. Pelvic adhesions are estimated to develop in one- to two-thirds of women who delivered by CS, and may contribute to bladder- bowel and ureter injuries, longer operat-
ing times, blood loss and delayed delivery in repeat CS [105-107]. At time of subsequent gynaecologic surgery, prior caesarean delivery has been associated with increased risk of surgical complications [108-110] such as bladder injury, haemorrhage and conversion from minimal invasive routes to laparotomy, but studies are restricted in number and participants.

**Risk factors for adhesions**

Number of previous surgeries influences the adhesion formation. Repeat CS is associated with more and dense pelvic adhesions and requires adhesiolysis more often [106, 111, 112]. In a prospective study of 1,000 laparoscopic procedures, a low rate of adhesions following laparoscopy was observed, but intestinal adhesions increased for each number of surgery.

Closure of the peritoneum after CS has been studied with respect to adhesion formation, and results are conflicting. In a systematic review of observational studies, Shi et al. concluded that a modified Joel Cohen CS with peritoneum closure was associated with fewer adhesions than non-closure [113]. However, in a RCT with 97 women followed up with second look at a repeat CS, no difference in adhesion rate according to peritoneal closure was observed [114]. The large CORONIS study found no evidence of an effect of peritoneal closure on adhesion related symptoms [85].

In a secondary analysis from a prospective cohort, Blumenfeld et al. observed that bladder adhesions occurred more frequently after single compared with double layer closure of the uterus [115].

Apart from surgical history and technique, predisposing factors for post-operative adhesions may be related to medical history and individual susceptibility [116-119]. Pelvic inflammatory disease caused by infections and/or endometriosis is strongly associated with the occurrence of adhesions [118]. The gold standard for diagnosis of endometriosis is laparoscopy with direct visualisation of abdominal lesions followed by histopathology examination. [120]. Endometriosis has been reported in one-fifth of women undergoing hysterectomy because of chronic pelvic pain [120].

Knowledge of obstetric factors for post-operative adhesions after CS is limited. In a retrospective study of 160 patients, gestational weeks, pregnancy complications, emergency vs. elective CS or infection at first CS did not differ between women with and without adhesions at repeat CS [116]. Moro et al. investigated 308 women with a history of CS, prospectively with abdominal and transvaginal ultrasonography and after exclusion of women with prior pelvic surgery other than CS, 40 % of women had adhesions. Post-operative infection after CS posed over ten-fold risk of abdominal wall adhesions [121].

As a repeat surgical procedure is required, there are methodological difficulties to assess the rate of adhesions resulting from different types of surgeries
and techniques. As a result, study populations are often restricted to small number or to symptomatic women.
Rationale

Randomised controlled trials that investigate surgical techniques and rare outcomes requiring long-term follow-up are hard to perform, and observational studies must contribute to evidence. The Swedish National registers, kept by the National Board of Health and Welfare, are valuable resources for large-scale register-based studies [122], and by combining registers a variety of research questions could be addressed.

Uterine rupture is a rare but severe complication, and the main risk factor is a previous CS. The high number of CS surgeries performed worldwide puts many women at risk, and identification of potential modifiable risk factors, such as surgical technique, is of importance. Long-term follow-up studies of uterine closure and risk of uterine rupture have posed methodological problems due to both limited number of participants and outcome, and the question remains unanswered.

The optimal mode of delivery at extreme preterm birth is complex, and the risk and benefit for the mother and the infant might diverge. The restricted number of participants and recruitment failure of prospective trials comparing planned CS and planned vaginal delivery for preterm birth limits drawing conclusions about maternal and neonatal risks to observational trials. Increased survival rates among neonates delivered extremely preterm and a potential benefit of CS for the infant raise the question about complications for the mother.

Another knowledge gap that requires long time to follow up is formation of abdominal adhesions after CS, and studies are limited in number and participants. National health registers combined with National quality registers, which contain detailed data of gynaecologic surgery, give an opportunity to investigate the association between obstetric risk factors and adhesions as well as complications in gynaecologic surgery on large scale.
Aims

The overall aim with this thesis is to explore maternal complications following caesarean section, with focus on long-term complications.

The specific objectives of the studies are:

• To compare single with double layer closure of the uterus at caesarean section, for the risk of uterine rupture in a subsequent trial of labour (Paper I)

• To describe the maternal short-term outcomes after CS in the extremely preterm period (Paper II)

• To assess the incidence of abdominal adhesions at gynaecological surgery, according to previous mode of delivery and to investigate obstetric factors associated with development of adhesions (Paper III)

• To investigate associations between history of caesarean delivery and complications at time of hysterectomy (Paper IV)
Methods

Table 1. Study populations and designs

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<tr>
<td>I</td>
<td>Cohort</td>
<td>7,683 in a trial of labour after a previous caesarean section</td>
<td>2001-2009</td>
<td>National health registers and medical records</td>
</tr>
<tr>
<td>II</td>
<td>Case-Referent</td>
<td>647 deliveries in 22-27 weeks of gestation</td>
<td>2001-2012</td>
<td>Medical records</td>
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Data sources

National Registers

The Swedish Medical Birth Register (MBR) was founded in 1973 and provides information about pregnancy, labour and perinatal outcome. The register is validated and covers more than 98% of all deliveries in Sweden [123, 124]. Information is prospectively collected from standardised prenatal, obstetrical and neonatal medical records. It includes demographic data of the mother, previous pregnancies and modes of delivery, medical conditions and medication before and during pregnancy, onset and mode of delivery, fetal presentation, blood loss, analgesia and anaesthesia used and maternal diagnosis according to the International Classification of Diseases (ICD) [125]. Information provided from the neonatal care includes birth weight, body length and head circumference of the infant, single or multiple birth, gestational week, Apgar score and diagnoses of the neonate by ICD codes.

The Swedish Patient Register (PAR) [126] was launched in 1964, but complete coverage did not begin until 1987. The register includes nearly all inpatient diagnoses and surgical procedures by codes from ICD and Classification of Surgical Procedures. The proportion of valid diagnoses in the PAR is considered high in patients with severe disease and among patients with iatrogenic complications [127].
The *Quality register of gynaecologic surgery* has collected information of indication, surgical technique, results and complication rates in gynaecological surgery since 1997. Information in this register is retrieved from two different sources (Gynop and GKR register) and covers 75% of all clinics offering gynaecologic surgery in Sweden.

Data are collected by patient questionnaires (pre operatively, at eight weeks and one year after the surgery) [128]. Information of the surgical procedure and per- and post-operative complications is retrieved from standardised tick boxes filled in by the surgeon and the attending physician.

**Medical records**

*Obstetrix*® (Siemens AB, Healthcare) is a medical data record system for antepartum care, labour and postpartum period, used in more than 90% of maternity wards in Sweden today. A standardised surgical template of CS was introduced in 2001, and a detailed surgical report is constructed from check-boxes, with information about station of fetal presenting part, extraction of fetus and placenta, suture material and techniques of uterine-, peritoneal and fascia closure.

*Cosmic*® (Cambio Healthcare Systems) is the medical data record system at Uppsala University Hospital, which provided information for part of the study population in Paper II. Data were retrieved with a predefined protocol including information about the woman’s medical and obstetric history and the actual pregnancy.

**Study populations and designs**

**Paper I**

A cohort study including 19,604 nulliparous women who delivered by CS at 23 maternity units in Sweden was conducted. Centres of recruitment were all units that were users of the data record system *Obstetrix*® during the time period (23 out of 46). In the second pregnancy, 7,683 women attempted a trial of labour at 42 different maternity units in Sweden and defined the study population.

Data in the *Obstetrix*® database were linked to the MBR and PAR by each woman’s unique personal identity number. The research database contained information about the women’s first delivery during the years 2001 to 2007 and second delivery between 2001 and 2009.

The MBR provided maternal, pregnancy, labour and neonatal data from first and second delivery based on standardised check boxes and diagnosis.
according to ICD-10. The Obstetrix® database provided information about uterine closure dichotomized into single or double layers.

Paper II

In this observational study, data were collected from medical charts of extremely preterm deliveries at Uppsala University Hospital and Umeå University Hospital (n=647) for the years 2001-2012. The hospitals support a proactive management of extremely preterm births in Sweden, including obstetric and neonatal interventions from 22 weeks of gestation. CS procedures < 24 weeks of gestation were restricted to maternal indications at Uppsala during the study period. Detailed information about the CS was collected, and indication of CS was regarded as fetal (breech or transverse presentation, fetal distress and IUGR) or maternal (preeclampsia, abnormal placentation and abruption). If coexisting maternal and fetal conditions prevailed, indication was regarded maternal. Gestational length was divided into two strata, 22-24 (n=105) and 25-27 (n=301) completed gestational weeks for extremely preterm CS. A referent group was retrieved from the cohort of nulliparous women from study I with CS performed at term (n=16,907).

Papers III-IV

A cohort of 44,455 women undergoing benign hysterectomy and/or adnexal surgery at 46 different units in Sweden during the years 2000-2014, with a previous delivery during 1973-2013, was identified in the Gynop register. Data retrieved from the register were aggregated with MBR and PAR through the woman’s personal identification number.

In Paper III, women with any history of other abdominal surgeries than CS, bowel or pelvic inflammatory disease and endometriosis were excluded. Twelve units reporting in GKR did not provide information about adhesions (n= 5,584). The study population consisted of 15,479 women undergoing hysterectomy and/or adnexal surgery. Data from Gynop included demographic variables at surgery and details of the surgical procedure. From MBR, information regarding prior mode of delivery, number of CS, maternal pregnancy and labour characteristics were retrieved. Year of first CS was divided into before and after 1997 to reflect the introduction of the modified Joel-Cohen technique and transition in Sweden [7-9]. Indications of caesarean section and information about post partum complications, retrieved from diagnosis according to the ICD codes, were restricted to deliveries from 1987. A composite variable “postpartum infection” included intra partum fever, puerperal sepsis or post-operative uterine or wound infection, diagnosed in the MBR or PAR until six weeks after delivery.
The study population in Paper IV included all women, regardless of prior medical and surgical history, undergoing hysterectomy (N=25,354). A personal history of: CS (n=5,152), other bowel/pelvic surgery (n=11,376) and/or endometriosis (n=2,116) visualised or diagnosed at time of the gynaecologic surgery were considered as main conditions predisposing for adhesions. Route of hysterectomy was divided into abdominal or minimally invasive which included laparoscopic and vaginal approaches.

Main outcome measures

Paper I

Cases with uterine rupture in the second delivery were identified in the MBR by the diagnosis codes: O71.0 or O71.1, according to ICD 10.

For identified cases with uterine rupture, full surgical reports were obtained from the maternity departments. Uterine rupture during labour was defined as a full thickness separation of the uterine wall or when a separation covered by the visceral or bladder peritoneum presented with clinical symptoms such as excessive vaginal bleeding, fetal heart rate abnormalities, abdominal pain or palpable fetal part through the abdominal wall. The diagnosis was confirmed during caesarean section or during laparotomy performed immediately after delivery and, in one case, by abdominal ultrasound that revealed an abdominal haemorrhage and a scar defect of the uterus.

Paper II

Multiple maternal outcomes were assessed: the composite ‘post-operative’ infection included sepsis, wound-, uterine- and urinary tract infection. A major maternal complication was defined as blood loss ≥2000 ml, sepsis, deep hematoma, re-operation or thromboembolism. Type of uterine incision was divided into low transverse and other types (classic-, T or J shaped- or low vertical incision).

Paper III

The main outcome was adhesions in the surgical field. Presence of adhesions was assessed and filled in by the surgeon as yes, no, mild, moderate or extensive by standardised check boxes at time of the gynaecologic procedure. Occurrence of adhesions was dichotomised into yes or no.
Paper IV

The main outcome was organ injury at hysterectomy. Organ injuries included mild and severe bladder-, vascular-, bowel- and ureter injuries identified per-operatively or during the hospital stay and detected ureter injuries within eight weeks post-operatively. Information was retrieved from Gynop, by standardised check boxes, which information of blood loss, duration of surgery and post-operative infection and hematoma reported by the caregiver either at discharge or at eight weeks follow-up.

Statistical methods

Measures of disease occurrence

The average risk for a group of people of a diseases or health event to occur could be referred to as an incidence proportion.

Descriptive measures in the studies included absolute and relative frequencies (Papers I-IV). Continuous data were checked for normal distribution by normality plots and presented as means ± standard deviation (SD) and medians with 10th-90th percentiles when appropriate. In Paper III, differences were tested with Welch’s t-test because of unequal sample sizes and variances and by non-parametric test in Paper IV.

Continuous variables were further categorised, and differences in proportions between groups were investigated with Pearson’s Chi2 test (Papers I-IV). A p-value <0.05 was considered statistically significant.

Logistic regression and point estimates

In the following papers, the term risk and risk factor refers to an increased incidence of the outcome after exposure. To control for potential confounders, associations were investigated using logistic regression and presented as crude and adjusted risk estimates, Odds Ratios (OR) with 95 % Confidence Intervals (CI). In Paper I, factors from the first and second deliveries and uterine rupture were analysed, and significant factors retrieved from bivariate analysis and logistic regression were included in the models. In Paper III, factors from the time point of caesarean delivery and presence of adhesions at subsequent gynaecologic surgery were adjusted for number of CS. Paper IV investigated associations of prior CS, other abdominal surgery and endometriosis with complications at hysterectomy. In the multiple logistic regression model, factors with plausible biologic associations with the outcome were included.
Heterogeneity and clustering
As more than one individual was recruited from the same unit (hospital), observations for different variables might cluster. The independence assumption of observations in regression analysis is then violated, hence necessitating multilevel regression to be conducted. Multi-level logistic regression with mixed-effect models were performed in order to rule out heterogeneity in Paper I and control for observed heterogeneity between hospitals in Papers III-IV.

Generalised structural equation modelling (GSEM) and mediation effects
In Paper III, a GSEM was performed to explore the causal pathways leading to formation of adhesions and to estimate size effects of mediation between explanatory variables. Factors, selected with the means of logistic regression and with plausible biologic associations with adhesions, were used in the model.

In Paper IV, the direct effect of prior CS, other abdominal surgery and endometriosis on occurrence of organ injury in subsequent hysterectomy and the proportion mediated by presence of adhesions was investigated by GSEM.

Ethical considerations
Risk and benefit of the importance of the research question and the integrity of individuals in the research databases were assessed and regarded as being balanced.

The Regional Ethical Board at Umeå University approved study I. The Regional Ethical Board at Uppsala University approved studies II-IV.

Data for studies I, III and IV were aggregated and delivered from the Swedish National Board of Health and Welfare without personal identification numbers. The Swedish National Board of Health and Welfare keep the key of personal identification number for three years. Patients included in the quality register of gynaecologic surgery Gynop are informed about the register and have the right to decline participation.

Paper II required access to medical records by personal identification numbers. Data from the medical records were kept in a database without personal identification, and the key of personal identification number was kept separately in a key-locked computer.
Personal identification was not possible, neither during data analysis or following publication of data.
Summary of results

Uterine closure and risk of uterine rupture (Paper I)

Uterine rupture during labour occurred in 103 (1.3%) of the women with a previous CS. There were 70 anatomically complete ruptures and 33 incomplete ruptures. There was no significant difference in the rate of uterine ruptures when single layer closure was compared with double layer closure of the uterus. Non-modifiable risk factors from the first delivery for uterine rupture in a subsequent labour included maternal age $\geq 35$ years and maternal height $\leq 160$ cm. No effect was seen of BMI, short delivery interval or type or indication of first CS. Delivery of an infant large for gestational age and infectious morbidity from the first CS increased the risk of uterine rupture about two-fold in a subsequent labour.

In the trial of labour after caesarean, vaginal delivery succeeded in 71% of cases. The majority had a spontaneous onset of labour, and 1,242 (16%) women were induced. Modifiable risk factors for uterine rupture in the second delivery included induction of labour and use of epidural analgesia. Gestational diabetes and birth weight $\geq 4500$ g increased the risk.

Table 2. Factors from first and second delivery associated with uterine rupture.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N=7,683</th>
<th>n=103</th>
<th>aOR*</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single layer closure</td>
<td>2,589</td>
<td>38</td>
<td>1.17</td>
<td>0.78-1.76</td>
</tr>
<tr>
<td>Age $\geq 35$ (years)</td>
<td>672</td>
<td>15</td>
<td>2.08</td>
<td>1.19-3.63</td>
</tr>
<tr>
<td>Maternal height $\leq 160$ (cm)</td>
<td>1,595</td>
<td>32</td>
<td>1.69</td>
<td>1.11-2.58</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>214</td>
<td>7</td>
<td>2.46</td>
<td>1.12-5.40</td>
</tr>
<tr>
<td>Infection</td>
<td>326</td>
<td>9</td>
<td>2.03</td>
<td>1.01-4.08</td>
</tr>
<tr>
<td><strong>Second delivery (TOL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>1,242</td>
<td>27</td>
<td>1.71</td>
<td>1.09-2.68</td>
</tr>
<tr>
<td>Epidural analgesia</td>
<td>3,698</td>
<td>68</td>
<td>1.99</td>
<td>1.31-3.02</td>
</tr>
<tr>
<td>Birth weight $\geq 4500$ g</td>
<td>314</td>
<td>9</td>
<td>2.11</td>
<td>1.05-4.26</td>
</tr>
</tbody>
</table>

* adjusted for explanatory variables at first or second delivery
A secondary analysis with review of labour records including partograms and CTG tracings for cases with uterine rupture (N=103) identified in study I was performed [129]. The aim was to describe clinical signs preceding uterine rupture, and maternal as well as neonatal outcomes in relation to the stage of labour at which rupture was diagnosed.

The most frequent clinical signs anticipating uterine rupture were fetal distress (65 %), abdominal pain (56 %) and protracted labour (54 %). Vaginal bleeding, palpable scar defect or contraction ring were less frequently reported. When uterine rupture was diagnosed at the second stage of labour, loss of station of the fetal head and cessation of contractions were more common, indicating overt rupture. CTG tracings were available in half of the cases. The most common pathological CTG pattern before diagnosis was prolonged decelerations and bradycardia. All women with uterine rupture had operative deliveries. Operative vaginal delivery failed in 10 out of 16 cases. There were no maternal deaths. Eight women had blood loss > 2000 ml and two underwent peripartum hysterectomy. Bladder injury occurred in 7 out of 103 women with uterine rupture. Diagnosis at later stages of labour increased the risk of maternal complications.

Maternal complications after CS in the extremely preterm period (Paper II)

Two-thirds of women with extremely preterm births had a CS, and the proportion increased with gestational length (Figure 2). Breech, cord prolapse, abnormal placentation and preeclampsia were more common among deliveries by CS, whereas premature rupture of membranes and spontaneous preterm contractions were associated with vaginal delivery. The majority of CS was performed due to fetal indication. Maternal indications of CS were associated with increased risk of complications.

The most common complication recorded after an extremely preterm CS was infection (19 %). Major maternal complications occurred in 7 % of the extremely preterm compared with 2 % of term births (p < 0.01). No increased blood loss was found among extremely preterm compared with term CS. Uterine incisions extending into corpus were required more often at 22-24 (18 %) than at 25-27 gestational weeks (10 %). Surgery and fetal extraction were assessed as being more difficult at gestational week 22-24, but there was no increased blood loss, infections or other complication rates compared with gestational week 25-27.
Abdominal adhesions at gynaecological surgery following CS (Paper III)

Of 15,479 women, 2,646 (17 %) had a personal history of one or more caesarean deliveries. In women with previous CS, the incidence of adhesions was 37 % compared with 10 % in women with only vaginal deliveries. Figure 3 shows how the rate of adhesions increased with number of CS, from 32 % after one CS (n=1,756) to 42 % after two (n=683) and to 59 % after three or more CS (n=207) (p < 0.001). Simultaneously the rate of adhesiolysis and surgery assessed complicated increased with number of prior CS.
Factors from the time point of any CS associated with adhesions in subsequent gynaecologic surgery are presented in Table 3. Age $\geq$ 35 years, BMI $\geq$ 30 kg/m$^2$, first CS 1997 to 2013 compared with the time period 1973-1996 and postpartum infection were obstetric factors associated with adhesions, regardless of number of previous CS. Diabetes mellitus, preterm CS, emergent CS, placenta previa and uterine rupture did not increase the risk of adhesions in subsequent gynaecologic surgery.
Table 3. Factors from the caesarean section (CS) associated with adhesions in subsequent surgery (N=2,646)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>n=</th>
<th>n (%)=</th>
<th>aOR</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,756</td>
<td>568 (32)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>683</td>
<td>286 (42)</td>
<td>1.51</td>
<td>1.26-1.82</td>
</tr>
<tr>
<td>≥3</td>
<td>207</td>
<td>123 (59)</td>
<td>3.16</td>
<td>2.34-4.26</td>
</tr>
<tr>
<td>Maternal age ≥35 (years)</td>
<td>577</td>
<td>246 (43)</td>
<td>1.28</td>
<td>1.05-1.55</td>
</tr>
<tr>
<td>BMI ≥30 (kg/m2)</td>
<td>264</td>
<td>143 (54)</td>
<td>1.91</td>
<td>1.49-2.45</td>
</tr>
<tr>
<td>Extremely preterm</td>
<td>34</td>
<td>15 (44)</td>
<td>1.43</td>
<td>0.71-2.87</td>
</tr>
<tr>
<td>Preterm</td>
<td>533</td>
<td>197 (37)</td>
<td>0.93</td>
<td>0.76-1.15</td>
</tr>
<tr>
<td>Year of CS 1997-2013</td>
<td>901</td>
<td>379 (42)</td>
<td>1.47</td>
<td>1.24-1.75</td>
</tr>
<tr>
<td>CS with labour</td>
<td>1,840</td>
<td>704 (38)</td>
<td>1.10</td>
<td>0.92-1.32</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td>113</td>
<td>56 (50)</td>
<td>1.55</td>
<td>1.05-2.30</td>
</tr>
</tbody>
</table>

* Number of CS presented as crude OR. All other explanatory variables adjusted for number of CS and hospital unit at second level.

CS and risk of complications at subsequent hysterectomy (Paper IV)

Adhesions were recorded in 5,713 (23 %) women undergoing hysterectomy. The main indication for hysterectomy was bleeding disorder, and two-thirds were performed as open abdominal. Overall, organ injury occurred in 2.2 %, most commonly affecting the bladder (1.1 %). Previous caesarean delivery increased the risk of per-operative organ injuries and was the strongest predictor of bladder injury (aOR 1.86, 95 % CI 1.40-2.47). Bowel/pelvic surgery was associated with bowel injury (aOR 2.27, 95 % CI 1.37-3.78), and endometriosis increased the risk of ureter injury (aOR 2.15, 95 % CI 1.34-3.44).

In the conceptual model underlying the GSEM analysis, factors found in the logistic regression with plausible biologic associations were considered to estimate sizes of causal pathways leading to organ injury at time of hysterectomy (Figure 4).
Adhesions were a strong predictor of organ injury (logit coefficient 0.53, 95% CI 0.28-0.77, p<0.001). However, the direct effect of prior CS on organ injury was estimated to 73%, and only 27% was mediated by adhesions. In the model, route of hysterectomy, uterine weight and patient characteristics (BMI and age) were of minor importance predicting organ injury compared with adhesions.
Discussion

The rate of CS is increasing, resulting in increasing number of women who are exposed to potential complications at short- and long-term. In labour and surgery following CS, factors that can be modified such as surgical technique, management of labour and postpartum care are important to investigate in relation to complications to prevent future maternal morbidity.

General conclusions

The risk of uterine rupture in a subsequent trial of labour did not differ between single and double layer closure of the uterus. Major maternal complications occurred more frequently in extremely preterm compared with term CS, but there was no increased blood loss. In the extremely preterm period, maternal complications could not be attributed to the gestational week and the surgical procedure per se but were more related to the indication of the CS.

Number of CS was the most important obstetric factor for formation of adhesions after caesarean delivery. A history of CS was associated with increased risk of per- and post-operative complications in hysterectomy. The risk of bladder injury during hysterectomy after previous CS was almost doubled, regardless of route of hysterectomy, maternal characteristics and uterine weight but was not always attributed to presence of adhesions.

Incidence of maternal complications

Uterine rupture occurred in 1.3 % of women attempting a TOL, which is a higher rate compared with 0.6 % in a retrospective cohort by Lydon-Rochelle but similar to the 1.5 % reported in a prospective study from the Netherlands [72]. The rate of uterine rupture is influenced by selection of patients for TOL and obstetric management. In the study by Kwee et al., TOL was attempted in 72 % compared to 62 % in this Swedish setting.

Major maternal complications were assessed in 7 % of extremely preterm CS. Interestingly, blood loss was not increased in extremely preterm compared to term, and there was a low rate of corporal incisions (12 %) compared with other settings [33, 42].
The incidence proportion of adhesions after CS in gynaecologic surgery depended on exclusion criteria. In a non-selected group of women undergoing hysterectomy, adhesions were recorded in 23% (45% of women with prior CS and 17% in women with no prior CS). In women with no other prior surgery in the abdomen except CS, adhesions were reported in 32-59%, depending on prior numbers of caesarean deliveries. A similar increase in rates of adhesions according to numbers of CS has been reported at time of repeat caesarean delivery [105, 106].

Risk factors for maternal complications

Surgical techniques

**Caesarean Section**

The conclusion from study I that single, as opposed to double, layer closure of the uterus does not increase the risk of uterine rupture in subsequent labour is in concordance with results from the largest RCT (CORONIS) that has investigated short- and long-term effects of different CS techniques. In the trial, risk of uterine rupture did not differ between single and double closure, although it was underpowered to detect modest differences [85]. This reflects the methodological difficulties encountered when studying rare outcomes. In both the CORONIS trial and the Caesar trial, none of the different parts of the Joel-Cohen technique was proven superior to the other, in respect to short-term complications [21, 40].

The role of peritoneal closure for development of adhesion-related complications was also investigated in CORONIS. They found no difference in rates of pelvic pain, bowel obstruction, infertility or ectopic pregnancy following a CS with peritoneal closure or non-closure. A clear advantage in Papers III and IV is that assessment of adhesions was by direct visualisation and not restricted to symptoms associated with adhesions. In Paper III, women with a first CS during 1997-2013 had 47% increased odds of adhesions present at gynaecologic surgery compared with women with prior CS 1973-1996. This finding might be interpreted as indication of an association with the introduction of the new surgical technique of CS and adhesions. This is in accordance with results from two systematic reviews from 2009 and 2011, suggesting a benefit of peritoneal closure at CS in respect to formation of adhesions [113, 130]. Presence of adhesions after preterm CS was investigated in Paper III. As extremely preterm CS could be technically difficult and requires a corporal incision more often, we anticipated the incidence of adhesions to be increased compared with CS at term. This could not be confirmed, probably due to the small number (n=34) of extremely preterm CS in the material.
**Hysterectomy**

A personal history of CS increased the risk of organ injury, independent if hysterectomy was abdominal or by minimally invasive route. In a case control study, rates of incidental cystotomy according to type of hysterectomy were 0.76 % in abdominal, 1.3 % with vaginal and 1.8 % with laparoscopic assisted vaginal hysterectomy; a previous CS doubled the risk [108]. Increased risk of bladder injury at surgery is well documented in women with prior CS [107-110], but results have been inconclusive and sparse regarding ureter and bowel injuries. In a review of 307 women with prior laparotomy undergoing laparoscopic surgery, there was no increased risk of organ injury or conversion to laparotomy after CS, but prior myomectomy posed an almost five-fold risk [131]. During vaginal hysterectomy (n=741), bowel injury was reported in 1.4 % of women with prior CS compared with 0.14 % of women with no history of CS [109]. However, the risk of organ injury in minimally invasive techniques is closely related to volume of surgical procedures and experience of the surgeon [132]. In the survey from Finland, the proportion of vaginal hysterectomy increased from 18 % to 44 % from 1996-2006; simultaneously, there was a significant decrease of bowel injury from 0.5 % to 0.1 % in vaginal approaches. In the same time period, ureter complications decreased from 1.1 % to 0.3 % following laparoscopic hysterectomy [132].

**Maternal characteristics**

Advanced maternal age in conjunction with CS was associated with both uterine ruptures in subsequent labour and development of adhesions. Advanced maternal age increases the risk of complications during pregnancy and labour such as hypertensive disorders, diabetes, dystocia and high birth weight, but the effect of age remained after adjusting for these factors in Paper I. The results are in agreement with a Norwegian population based register study where maternal age ≥40 years doubled the risk of rupture [75]. This could be attributed to increased risk of advanced maternal age of impaired healing at first CS, or more augmented labours at subsequent deliveries with age. The impact of age at time of surgery on adhesion formation remains unclear. There are no previous studies investigating the effect of age on development of adhesions after CS, but appendectomy at 20-39 years has been associated with lower risk of subsequent small bowel obstruction compared with appendectomy at all other age categories [133].

Obesity is associated with increased risk of surgical morbidity including infection and suboptimal wound healing [134], and obesity could also decrease fibrinolysis, leading to more adhesions [119]. In concordance, we found that BMI ≥30 at CS, regardless of number of CS, almost doubled the rate of adhesions at subsequent gynaecologic surgery. Age and obesity are
factors to consider when counselling women, and the risks of a trial of labour must be balanced against risk of repeat CS and the development of adhesions.

In Paper IV, age and BMI were not associated with increased risk of organ injury at time of hysterectomy. Obesity at hysterectomy and caesarean section is a known risk factor of post-operative complications such as thrombosis, wound dehiscence and infection [135], whereas the risk for organ injury in fact might be decreased [136, 137]. In a study by Lee et al., neither age nor BMI were predictors of re-admission to hospital after hysterectomy.

Pregnancy and labour characteristics

Modifiable risk factors for uterine rupture included induction of labour and epidural analgesia. Results from a population based study concluded that an increasing trend of uterine rupture in Norway from 1967 to 2008 could be attributed to induction with prostaglandins and more labours augmented with oxytocin in women with a scarred uterus [67]. In protracted labour, epidural analgesia is more frequently used [138], and repeated epidural dosing has been suggested as a warning sign for uterine rupture [139].

In Paper III, number of CS was the main obstetric risk factor for adhesions in subsequent gynaecological surgery. Number of CS can to some extent be modified by avoiding CS in the first delivery and by encouraging a trial of labour after CS.

The high maternal morbidity observed after an extremely preterm CS could be result of the indication for delivery that often is related to maternal complications such as hypertensive disorders, abruption and sepsis. In Paper II, maternal complication rates did not differ between gestational weeks 22-24 and 25-27, but a maternal indication of delivery carried a higher risk of complications compared with fetal indication of an extremely preterm CS. Reddy et al. analysed women with placental conditions (previa, accreta and abruption) separately, and a serious maternal complication was recorded in 26 % (GW 23-27), 31 % (GW 28-31) and 35 % (GW 32-33) [33]. The overall rate of incisions extending into the corpus of 12 % was low compared to 25-56 % reported in prior studies [33, 42], but rates might be influenced by different definitions of incisions and populations studied. A previous preterm CS was not associated with increased rate of abdominal adhesions at gynaecological surgery.

Post-operative infection

The incidence of a post-operative infection reported in MBR and PAR after CS was 4 % (Paper I, refersnts Paper II and Paper III). Infectious morbidity was much higher after extremely preterm CS (18 %) (Paper II). Complica-
tion rates vary by method of collecting data and post-operative infection following CS, including all febrile morbidity requiring antibiotic treatment, was estimated to 17% in the Caesar trial with prospectively collected data [21]. As a milder postpartum infection is likely to be treated in an outpatient clinic, diagnosis will not be provided by PAR; hence, register based rates will be underestimated and comparison between study groups biased. However, results indicate that extremely preterm CS is a high-risk procedure in terms of infectious morbidity, which may result from the fact that infection is an important cause of preterm birth. Post-operative infection was a risk factor for both uterine rupture and adhesions, making measures to prevent the occurrence of post-operative infections important also for complications occurring in the long-term. The majority of women had received prophylactic antibiotics in the cohort of study I (67%) and among extremely preterm (84%). According to a review of Smaill et al. 2014, prophylactic antibiotics halves rates of wound-uterine infections following both elective and emergent CS [24].

Adhesions and complications

Results from Paper IV suggest that history of CS poses risk for complications at remote hysterectomy, but the risk is only partly attributable to presence of adhesions. Previous caesarean delivery and endometriosis were major predisposing factors for organ injury at time of hysterectomy, whereas patient and operation characteristics were of minor importance. Results from Paper IV demonstrate that prior CS poses a higher risk of organ injuries at hysterectomy (aOR 1.74, 95% CI 1.41-2.15) compared with history of other bowel/pelvic surgery or endometriosis. The organ affected depended on medical history; prior CS predisposed for bladder injury, prior bowel/pelvic surgery for bowel injury, and endometriosis was associated with ureter injury at time of hysterectomy. Endometriosis is a well-recognised strong predictor of intra-operative complications and ureter injury at pelvic surgery [131, 140].

Methodological considerations

Observational studies are subject of two types of errors: random error and systematic error. With sufficiently large data the impact of random errors decreases but systematic errors remain, causing bias.
Systematic errors

Selection Bias
The population-based designs in Papers I, III and IV decrease the likelihood of selection bias. Adhesions after CS have been associated with pelvic pain, infertility and dyspareunia [59]; as a result, these indications of surgery might influence the reported rates of adhesions of the study group in Papers III and IV. Pelvic pain was reported as the main indication of hysterectomy in only 5% in Paper IV; consequently, this selection bias is of minor concern.

In Paper III, the study population consisted of women who delivered extremely preterm at two University clinics with proactive management, and results may not be attributable to other settings.

Type of surgery depends on a woman’s medical history; even if prior CS is not a contraindication for vaginal approach, a lower proportion of women with prior CS planned for this route (Papers III-IV). Type of surgery influences the rate of adhesions reported by the surgeon; adhesions are less reported in vaginal hysterectomy compared with the abdominal route, which might reflect restricted inspection of the abdomen or reflect the true status of adhesions present in this group.

Information Bias
Misclassification of information can be differential and non differential. Non-differential misclassification occurs at random of either exposed/non exposed and independently of the outcome. In contrast, differential misclassification occurs if information of exposure differs between cases and controls, for example caused by recall bias.

It is plausible that misclassification occurred in the reporting of diagnosis and checking of boxes by different physicians. In Paper I, closure of the uterus may have been reported as single when double layers were sutured, or the opposite (exposure). We believe that misclassification did not differ between women with uterine rupture or no uterine rupture (outcome), and it was considered non-differential. Non-differential misclassification can bias an effect towards the null effect.

Differential misclassification may have occurred in Papers III and IV, as encountered difficulties in surgery might affect reporting of adhesions, giving an overestimated association between adhesions and obesity, as well as overestimation of adhesions and risk of complications.

In Paper II, various methods of collecting data potentially overestimated the risks of extremely preterm CS compared with term CS.
**Confounding and mediation**

A confounder is a cause for both the exposure and the outcome resulting in a confusion of effect. In contrast, a mediator is on the causal pathway from exposure to outcome. In Paper III, potential confounding between CS and adhesions, depending on prior medical history, was addressed by excluding patients with diagnosis of pelvic/bowel surgery and or inflammatory disease of the abdomen preceding the gynaecological surgery. In Papers I and IV, covariates included in the models were based on the framework of associations found in prior studies and by the results of bivariate analysis. Multi-level logistic regression analysis was performed to adjust for potential confounding at the individual and contextual level (hospitals). However, unmeasured and unknown confounders may still be a problem. The results of the GSEM analysis of Paper IV suggest presence of an unrecognised mediator associated with both CS and organ injury. The effect of organ injury at surgery following a CS could only be attributed to adhesions in less than one-third.

**Random errors**

**Question of power and erroneous statistical inference**

In observational studies, power calculation could be considered as being irrelevant, but reflections about size of study population and statistical inference are appropriate.

Power calculation of Paper I was designed to detect a two-fold increased risk of uterine rupture with respect to uterine closure. The study was underpowered to detect smaller differences and potentially subject to a type 2 error (false negative). However a small risk difference would have no clinical significance since the baseline risk of uterine rupture is low. Statistical power in between group comparisons in Paper II was restricted by stratification of the extremely preterm and could contribute to non-detected differences between the gestational age strata. One should remember, ‘Absence of evidence is not evidence of absence’ (Altman).

Table 4. Types of statistical errors

<table>
<thead>
<tr>
<th>Null hypothesis</th>
<th>Null hypothesis rejected</th>
<th>Null hypothesis not rejected</th>
</tr>
</thead>
<tbody>
<tr>
<td>True</td>
<td>Type 1 error</td>
<td>Correct inference</td>
</tr>
<tr>
<td>False</td>
<td>Correct inference</td>
<td>Type 2 error</td>
</tr>
</tbody>
</table>

In all studies, multiple testing increased the risk of a type 1 error (false positive), and some of the associations may be by chance. To reduce this error, all testing was based on a conceptual framework of plausible biological ac-
tions. The confidence intervals around the estimates reported in Papers III and IV were all narrow, indicating a high precision.

Another problem resulting from large study populations (Paper I, III and IV) may be the interpretation of statistical significance at group level to clinical significance at the individual level. In Paper IV, the absolute risk of organ injury was 2.2%. Although statistically significant, a small risk increase may not have a strong impact for the individual, and the development and use of predictive models may be limited.

Strengths
The aggregation of National health registers and medical records have permitted for conclusions to be drawn for long-term complications of CS. Randomised controlled trials investigating long-term effects of surgical techniques, as well as optimal mode of delivery of the extremely preterm, have been hard to perform, due to the time span required and recruitment problems.

Strengths of Studies I, III and IV include population-based settings, large study samples and reliable data for exposure and outcome. Standardised operation template with check boxes provided information for suture layers in 99% (Paper I), was complete for presence of adhesions (Paper III) and included information about organ injury in 89% of patients (Paper IV). Recall bias was not a concern since all exposure and outcome information was recorded prospectively and independently. Selection bias was minimised since the cohorts were well defined. In the cohort studies, potential heterogeneity and clustering between hospitals were controlled for by multi-level logistic regression.

The observational study II provided detailed information of the rare condition of extremely preterm CS.

Clinical implications
The results are in agreement with evidence from well designed RCT and meta analysis concluding that one compared with two layer closure of the hysterotomy at CS, neither improves short-term morbidity or increases the risk of uterine rupture in subsequent labour [21, 40, 73]. As a result, either technique can be used. Locked sutures of the hysterotomy have been associated with defect healing and increased risk of uterine rupture [73, 88]. Babu has proposed a technique with a continuous modified mattress suture, which stresses the importance of correct approximation of cut margins, i.e. decidua to decidua and myometrium to myometrium [141].
Figure 5. Suture technique for closing the hysterotomy proposed by Babu.

In pre labour counselling after CS, adverse effects of repeat CS should be balanced against risk of uterine rupture. Predictive models of uterine rupture have proved to be difficult to develop [76, 142], but a validated model to predict failed vaginal birth after caesarean has been proposed by Smiths et al. [143]. Prior indication of CS influences the chance of vaginal birth in a trial of labour. Index indication of multiple births, breech and placenta previa are associated with CS rate of 17-18 %, whereas prior indication of macrosomia or complications during labour increases CS rates in TOL to 40 % [144]. Maternal characteristics such as age and height as well as diabetes are important factors to consider in pre labour counselling for a trial of labour after CS. Induction of labour after CS increases the risk of uterine rupture, and should be used cautiously in women with a scarred uterus. These factors are closely related to an emergency CS during a trial of labour [143], which, in turn, carries the highest risk of adverse maternal outcome [46].

On the other hand, encouragement of VBAC will decrease complications caused by multiple caesarean deliveries; number of CS is the most important factor for development of adhesions, and adhesions are closely related to organ injury in subsequent surgery.

There was a high rate of postpartum infection after an extremely preterm CS, and type and dose of prophylactic antibiotics needs to be explored further in this group. The low rate of corporal incisions, with reproductive consequences for the mother in the long-term, indicates that centralisation of extremely preterm deliveries may also benefit the mothers.

Clinicians acknowledge that surgery in women with endometriosis is high-risk procedure, but a personal history of CS carried higher risks for organ injury and post-operative complications at time of hysterectomy compared with previous bowel/pelvic surgery or endometriosis. As medical history and prior CS indicates which organ is most affected, preventive measures including operation techniques [145], patient information and follow-up is essential and should be individualised. As route of hysterectomy was of minor importance for organ injury, prior CS should not be regarded as a contraindication for the vaginal approach. Vaginal hysterectomy is associated with faster recovery and less haemorrhage, whereas laparoscopic sur-
gery requires longer operating times and might increase the risk of urinary tract injuries compared with abdominal route [146].

Future research

Large studies are needed to evaluate important but rare outcomes, and RCTs are often proved to be underpowered.

The main drawback with observational studies is the risk of uncontrolled confounding, which can result in false associations and confusion of effects. Epidemiologic studies restrict interpretation of causality and biological actions between exposures and outcomes. The recently established network in Sweden called SNAKS (Svenskt nätverk för Nationella Kliniska Studier inom OB/Gyn) gives an excellent opportunity to conduct well-designed prospective multicentre studies with the possibility of randomisation. By combining National quality registers, allocation to certain interventions and treatments and follow-up is feasible in respect to recruitment and costs. Short- and long-term morbidity can be assessed by evaluating a bundle of peri-operative processes of CS, including choice of surgical technique.

The low rate of adhesions following a CS compared with other gynaecological procedures such as myomectomy is puzzling and contradicts the fact that fibrinolysis is decreased during pregnancy. Basic biochemical research and animal models might be beneficial to investigate effects of pregnancy, for example, the role of amniotic fluid on adhesion formation.

The lack of standardised outcome measures concerning adverse outcomes restricts interpretation and comparison between studies and often leads to contradictory results. The initiated work of core outcomes for evaluations of interventions preventing preterm birth [147], should inspire to elaborate standardised maternal outcomes in obstetric clinical trials.

An important issue that requires follow-up is the implementation of team-led hospital based care, which has been associated with reduced rates of CS in nulliparous women without increased risk of neonatal complications [148]. The pregnancy register, with detailed information regarding labour management and maternal and neonatal outcomes, could be a valuable resource to investigate and evaluate specific procedures of these programmes.

I arbete I studerades om risken för uterusruptur efter ett kejsarsnitt påverkades av suturering av livmoderväggen i ett jämfört med två suturlager. Genom länkning av datajournalsystem, med data om operationsteknik, och Medicinska födelseregistret identifierades en kohort av 19 604 förstföderskor som förlöstes med kejsarsnitt 2001-2007. Under andra graviditeten gjorde 7 683 ett vaginalt förlossningsförsök, varav 103 kvinnor (1,3 %) fick en livmoderbristning. Ingen skillnad för livmoderbristning, avseende ett och två lager suturering av livmodern kunde påvisas, däremot medförde högre ålder hos modern, kortvuxenhet, infektion efter första kejsarsnitt, igångsättning av den andra förlossningen samt barn med större födelsevikt en ökad risk.


I arbete III och IV används en kohort av kvinnor som genomgått gynekologisk buk kirurgi, 2000-2014, och som var registrerade i ett nationellt kvalitetsregister (Gynop). Data från kvinnans tidigare graviditeter, förlossningar, bukoperationer och diagnoser från Nationella hälsoregister sammanlänkades med Gynop. I samband med den gynekologiska operationen registrerade operatören förekomst av sammanväxningar. I studie III exkluderas kvinnor med tidigare bukoperationer från sett kejsarsnitt och 15 479
kvinnor undersöktes med avseende på sammanväxningar. Andel med sammanväxningar ökade med antal kejsarsnitt från 32 % efter ett kejsarsnitt till 42 % efter två och 59 % efter tre eller fler kejsarsnitt. Faktorer i samband med kejsarsnitt kopplade till sammanväxningar var ålder ≥35 år, BMI ≥30 och infektion. I arbete IV studerades komplikationsrisk vid bortopererande av livmodern utifrån tidigare kejsarsnitt, övrig bukoperation och endometrios, och hur stor andel av organskada som drifs av sammanväxningar i buken. Tidigare kejsarsnitt var en stark riskfaktor för komplikationer vid och efter bortopererande av livmodern och var kopplat till skada på inre organ, men endast en del av dessa komplikationer förklarades av sammanväxningar.

Sammanfattningsvis har länkning av data av Svenska Nationella kvalitetsregister möjliggjort studier av långsiktiga komplikationer för modern av kejsarsnitt. Även om de absoluta riskerna för allvarliga komplikationer såsom uterusruptur och organskada kan tyckas små, så är den relativa riskökningen av kejsarsnitt av stor betydelse. Med kartläggning av riskfaktorer kan vård för förlossning och operationer av kvinnor med tidigare kejsarsnitt optimeras.
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