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FACTORS OF IMPORTANCE FOR LABOR INDUCTION

Tove
Wallström

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Factors of importance for labor induction

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By

Tove Wallström

Principal Supervisor:
Associate professor Eva Wiberg-Itzel
Karolinska Institutet
Department of Clinical Science and
Education
Division of Obstetrics and Gynecology

Co-supervisor(s):
Professor Helena Åkerud
Uppsala University
Department of Immunology, Genetics and
Pathology
Division of Obstetrics and Gynecology

Professor Elisabeth Darj
Uppsala University
Department of Immunology, Genetics and
Pathology
Division of Obstetrics and Gynecology

Professor Kristina Gemzell-Danielsson
Karolinska Institutet
Department of Women´s and Children´s
health
Division of Obstetrics and Gynecology

Opponent:
Thora Steingrimsdottir
University Hospital of Iceland
Department of Obstetrics and Gynecology
Division of Obstetrics and Gynecology

Examination Board:
Docent Karin Pettersson
Karolinska Institutet
Department of Clinical Science,
Intervention and Technology (CLINTEC)
Division of Obstetrics and Gynecology

Professor emeritus Per Olofsson
Lund University
Department of Medical Faculty
Division of Obstetrics and Gynecology

Docent Josefine Nasiell
Karolinska Institutet
Department of Clinical Science,
Intervention and Technology (CLINTEC)
Division of Obstetrics and Gynecology

"Women are not dying of diseases we can't treat...they are dying because societies have yet to make the decision that their lives are worth saving."

Mahmoud Fathalla, past president of FIGO.

To my Grandmothers ♥

ABSTRACT

Background

What initiates the onset of labor is still not clarified, and it is debated whether expectant or active management is the best for the woman and the fetus. Active management means induction of labor (IOL) which is a very common obstetric intervention and is used in several situations. During the last five years, 17 % of all singleton pregnancies in Sweden were induced. There are large variations worldwide from less than five percent in some African countries such as Kenya, to extreme cases like for example Iran where IOL is performed in up to 80% of the labors. Both maternal and fetal complications are related to IOL, for instance prolonged labor, postpartum haemorrhage (PPH) and instrumental interventions as vacuum extraction/forceps or Cesarean section (CS).

The increasing rate of CS continues to cause global concerns. The ideal management of the subsequent labor for women who have undergone one previous CS has been intensely debated. The two available options are Trial of Labor after Cesarean section (TOLAC) or an elective CS. Previous CS is the most important risk factor for Uterine rupture (UR). UR is a wellknown but unusual complication in vaginal deliveries with a previous CS in the history. The risk of UR is at least two-fold when labor is induced. In Sweden, women are allowed to deliver vaginally after one previous CS, regardless if labor starts spontaneously or is induced.

Aim

The overall aim of the thesis is to identify factors of importance for the decision of IOL, and to find out which method for IOL is the most effective and safe for women with or without a previous CS.

Study I, a prospective observational study of 52 healthy women with mixed parity examined at their post-term control in gestational week 41+3. CTG, ultrasound assessment of amniotic fluid, a vaginal examination for cervical status and a five-minute skin conductance measurement, including a 'cold pressor test' was performed. The aim of the study was to evaluate if altered skin conductance activity could predict spontaneous onset of labor in post-term pregnancies. The probability of having a spontaneous onset of labor increased 4.0 times if the skin conductance score was negative and increased 6,8 times to start within 48 h if the cervix was open ≥2 cm.

Study II, a retrospective cohort study of 4002 women induced to labor with mixed parity. Inclusion criteria were viable singleton fetus in cephalic presentation, gestational age of ≥34 weeks. The women were divided into six groups according to method of IOL; Cytotec®, Minprostin®, Propess®, balloon catheter, amniotomy, or oxytocin. Methods of induction, baseline data, and delivery outcomes were compared. The primary endpoint of the study was the frequency of CS in each method of IOL. The lowest rate of CS overall, for both primi- and multiparous women with an unfavorable cervix Bishop Score (BS) ≤5, was found in the group where Cytotec® was administrated as an oral solution.

Study III, a retrospective cohort study for evaluating the proportion of UR in 208 women with IOL after one previous CS. The women were divided into two subgroups regarding the method of IOL. Group 1 (n=121) was the unexposed group, meaning that the women did not receive Cytotec® as the method of IOL. Group 2 (n=87) serves as the exposed group meaning that most of the women (89%) received Cytotec® as an oral solution. Method of induction, baseline data, and delivery outcomes were recorded. The primary outcome of the study was the frequency of UR in each group. There was no significant difference in the incidence of UR between group 1 and 2 (4.1 vs 4.6%, p=0.9) despite a more favorable cervix in group 1.

Study IV, a retrospective cohort study of 910 women with one previous CS, unfavorable cervix, and IOL. The study was performed at the four largest hospitals in Stockholm, the women were divided into three subgroups according method of IOL (Cytotec®, balloon catheter and Minprostin). The aim of the study was to compare the difference in the proportion of UR between the three methods There was no significant difference in the proportion of UR between Cytotec® and balloon catheter (p=0.64) for IOL after one previous CS. Orally administrated Cytotec® and balloon catheter resulted in a high success rate of vaginal deliveries of almost 70% compared to Minprostin® with the proportion of vaginal deliveries of 57% and which also had more than doubled rate of UR (5%).

Study V, an open label randomized controlled trial of 196 women induced to labor, BS ≤4 and no previous CS divided into two subgroups. Participating women were randomized to receive an oral solution of misoprostol (Cytotec®) or vaginal slow release misoprostol (Misodel®) for IOL. The primary outcome was the induction-to-vaginal-delivery time. Vaginal delivery after IOL with slow release misoprostol resulted in a shorter induction-to-vaginal-delivery time compared with oral misoprostol solution but was associated with a higher risk of hyperstimulation, and fetal distress. There were no differences in mode of delivery or neonatal outcome.

Conclusion

Spontaneous onset of labor is usually preferred, because it generally means lower risk of complications compared to IOL. An oral solution of misoprostol for IOL in women with an unfavourable cervix is safe, cheap, easy to control and can be used in all settings as it gives a high success rate of vaginal deliveries without hyperstimulation. It is also a good method for IOL among women with one previous CS and is as safe as balloon catheter. Both methods give a high success rate of Vaginal Birth after Cesarean Section almost 70% despite an unfavorable cervix. These studies give further support to the feasibility of an oral solution of misoprostol for IOL which is in line with the recommendations from International Federation of Gynecology and Obstetrics.

LIST OF SCIENTIFIC PAPERS

Skin conductance activity in post-term pregnancies
Wallstrom T, Hellgren C, Akerud H, Wiberg-Itzel E. J
Maternal Fetal Neonatal Med. 2014, 1912–1916

Labor Induction with Orally Administrated Misoprostol: A Retrospective Cohort Study
Wallstrom T, Jarnbert-Pettersson H, Stenson D, Helena Akerud, Elisabeth Darj, Kristina Gemzell-Danielsson, Eva Wiberg-Itzel
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Stenson D, Wallstrom T, Sjostrand M, Akerud H, Gemzell-Danielsson K, Wiberg-Itzel E.
Maternal Fetal Neonatal Med. 2015, 3286-3291

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Tove Wallstrom, Jenny Bjorklund, Joanna Frykman, Hans Jarnbert-Pettersson, Helena Akerud, Elisabeth Darj, Kristina Gemzell-Danielsson, Eva Wiberg-Itzel
PLOS one July 2, 2018, doi.org/10.1371/journal.pone.0200024

Slow release vaginal insert of misoprostol versus orally administrated solution of misoprostol for induction of labor: a randomized controlled trial
Tove Wallstrom, Moa Strandberg, Kristina Gemzell-Danielsson, Christina Pilo, Hans Jarnbert-Pettersson, Matilda Friman-Mathiasson, Eva Wiberg-Itzel
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CONTENTS

LIST OF ABBREVIATIONS

AUC	Area Under the Curve
aOR	Adjusted Odds Ratio
BS	Bishop Score
BMI	Body Mass Index
CS	Cesarean Section
CTG	Cardiotocography
EM	Expectant Management
FIGO	International Federation of Gynecology and Obstetrics
IOL	Induction Of Labor
IUFD	Intrauterine Fetal Death
LGA	Large for Gestational Age
LMP	Last Menstrual Period
OR	Odds Ratio
PPH	PostPartum Hemorrhage
PROM	Prelabor rupture of membranes
RCT	Randomized Controlled Trial
SD	Standard Deviation
TOLAC	Trial of Labor After Cesarean section
UR	Uterine Rupture
VBAC	Vaginal Delivery After one previous Cesarean section
WHO	World Health Organization

1. INTRODUCTION AND RATIONALE

What initiates the onset of labor is still not clarified, and it is debated whether expectant or active management is the best for the woman and the fetus [1]. Active management means induction of labor (IOL), which is a very common obstetric intervention.

"*The decision to induce labor is made if ending the pregnancy is considered more beneficial for the mother or the baby than awaiting spontaneous onset of labor, to obtain a safe vaginal delivery for mother and the baby with minimum interventions, complications and maximum satisfaction*" citation from Dr. Michael Robson, at the National Maternity Hospital, Dublin, Ireland.

During the last five years IOL was performed in 17% of all deliveries in Sweden [2]. Figures as high as up to 30% is described internationally [3-5]. IOL is associated with several risks such as prolonged labor, postpartum hemorrhage (PPH) and instrumental deliveries such as vacuum extraction/forceps or Cesarean section (CS) [4, 6-9]. According to these numbers, it means that more than 20.000 women only in Sweden go through an IOL every year. Therefore, it is very important to have a safe and effective method, clear indications and evidence based guidelines for IOL. To find out which method for IOL that is the most effective and safe, is the purpose with this thesis.

When this research project started in 2013, not so much was known about the use of misoprostol (Cytotec®) as an oral solution. Most studies described vaginal use of misoprostol which like other prostaglandins has a higher presence of hyperstimulation than the oral route of administration [10]. The prostaglandin Minprostin® and balloon catheter were the primary used methods in women with an unfavorable cervix with or without a previous CS in Sweden. During this project, we tried to evaluate the effect of misoprostol administrated as an oral solution compared to the previous primary methods used in women with an unfavorable cervix with or without a previous CS. Misoprostol has advantages in being cheap and stable at room temperature, and is widely available also in most resource-poor settings. Misoprostol is included in the World Health Organization´s (WHO) essential medicine list on several indications including labor induction [11].

My first contact with misoprostol administrated as an oral solution was in Kenya 2011, when I was working in a rural hospital in the village Mutomo at the countryside with about 1500 deliveries a year. At the hospital misoprostol was mixed with water used as a solution for IOL to all patient (according to WHO´s recommendations). The dose was 25ug up to three times, and if the patient did not feel any contractions the dose was increased to 50ug, which

was given at a maximum of three times. If there still was no effect, the women rested over the night and the IOL was restarted the next day. Although my observation period was not long (only six weeks) and the patients few, to me it seemed effective. At the department of obstetrics and gynecology at Sodersjukhuset we had discussed to start to use misoprostol, and after my experience in Kenya we started to use misoprostol in the same way as they did, but without the increased dose and the pause over the night. There was a clinical follow up of the method by the chief physician of the delivery ward at Sodersjukhuset that compared the first 100 women that received misoprostol with the other used methods for IOL at the clinic (Minprostin®, balloon catheter, Propess® and amniotomy). The frequency of CS decreased from almost 40 to 23-24% in primiparous women with IOL without increasing complications for the woman and child the following years. Later the administration of misoprostol in this dose has been tested by the Swedish Institute of Pharmacology [12] and was validated to give the correct dosage to the woman. In 2017 the rate of CS in primiparous women with IOL was below 20% at our clinic.

2. BACKGROUND

2.1. SPONTANEOUS ONSET OF LABOR

''When the fetus has grown and the mother can no longer provide it with sufficient nourishment, it becomes agitated, breaks through the membranes and incontinently passes out into the external world free from any bonds'' (Hippocrates, 460–370 BC). This was one of the first ideas about the mechanism for spontaneous onset of labor. The length of the pregnancy is remarkable constant in each species. Despite that, the mechanism for the onset of labor is still not clarified. Physiological processes and adaptive changes take place in the woman's body in the preparation for onset of labor. Close to the delivery the pain threshold is increased in women and other mammals. Women can tolerate more strain and are less sensitive to stress than otherwise [13-15]. These phenomena are believed to be due to changes in opioid signaling in the spinal cord, resulting from the increased amount of steroid hormones.

The changes in pain threshold and the reactivity of the autonomic nervous system and the response of the hypothalamic-pituitary-adrenal axis of stress have been shown to be down-regulated during late pregnancy [16, 17]. One explanation could be that this is a way to protect both the mother and fetus from damaging stress during the latter part of pregnancy and labor [18, 19].

In a study performed by Hellgren et al. [20], the main finding was that the skin conductance response to the ''cold pressor test'' (used in experiments as a stressor and also for pain threshold evaluation) was lower in women with fewer days left to spontaneous onset of labor. If women were divided according to the median of days remaining, women with fewer than two weeks had a significantly lower skin conductance activity compared with women with 2–4 weeks remaining.

Adaptive changes in the woman's body take place, including interactions with different physiological mechanisms in preparation for the onset of labor. A study by Slattery et al [19] reveals profound physiological adaptations of neuroendocrine and behavioral stress responses in various parts of the brain and peripheral nervous system during the final weeks of pregnancy. It is believed that these adjustments are intended to ensure the healthy development of the offspring by preventing that the child is exposed to stress.

The WHO definition of a normal vaginal delivery (Partus normalis) represents a gestational age of 37+0-41+6 weeks and lack of medical risk factors that are expected to influence the process in a negative way [21]. It also requires that the onset of labor was spontaneous, a cephalic presentation and no complications for mother and child from the onset of labor until third stage of labor [21].

2.1.1. Post-term pregnancy

Post-term pregnancy is defined by WHO as gestational age ≥42+0 weeks [21]. Post-term pregnancy increases the risk of morbidity and mortality for both mother and fetus [1, 22]. How to identify women with an increased risk of delivering post-term is still not known. Being post-term is more common among primiparous, older women, smokers and women with previous post-term pregnancies. The recurrence risk is 30% after one and 40% after two previous post-term pregnancies. A familial predisposition is presumed, and there is an ethnic difference as post-term pregnancy is more common among Caucasians [23].

The incidence of post-term pregnancy varies between 2-14% in Sweden [21]. The difference could be explained partly depending on how gestational age is estimated. Last menstrual period (LMP) is an uncertain method to approximate the gestational age, because women with uncertain menstrual data are included. If ultrasound is used for calculating the gestational age in the first or early in the second trimester, the incidence of post-term pregnancies is 5% compare to 10% if using LMP. In Sweden 98% of all pregnant women have their gestational age estimated by ultrasound.

The increased maternal risk in post-term pregnancy comprises primarily of the risk of complications during delivery, such as an increased risk of labor dystocia, which results in a greater risk of instrumental delivery, PPH and infections [1].
At 42 or more weeks of gestation, the perinatal mortality rate (defined as stillbirth plus early neonatal deaths) is twice the rate at term (4–7 deaths versus 2–3 deaths per 1000 deliveries) [24-27]. Except from the increased risk of perinatal mortality for the post-term fetus there are other risks such as hypoxemia during labor, shoulder dystocia and secondary trauma due to complicated delivery [28, 29]. The increased incidence of infants large of gestational age (LGA) and the deteriorating placental function after 40 gestational weeks are the main reasons for increased morbidity and mortality for fetuses in the post-term group [22]. This is

one of the reasons why a good prediction for the onset of labor should be considered important both for the fetus and the woman. There is a considerable controversy regarding recommendations for managing an otherwise uncomplicated post-term pregnancy, particularly when the woman has an unfavorable cervical status (low Bishop Score (BS) at vaginal examination).

Two main approaches have been used when handling post-term pregnancies: either planned IOL at 41 weeks of gestation, recommended by WHO [5] or expectant management until 42 weeks or more, as used in Sweden. If expectant management is planned, intermittent fetal monitoring with Cardiotocography (CTG) and biophysical profile and elective IOL is recommended. The clinical management of post-term pregnancies differs between countries and even in Sweden there are regional differences.

In the Stockholm County, there is a recommendation of intensified surveillance from gestational age of 41+0 weeks to detect fetal complications. The clinical management changes if there is an increased risk of complications such as diabetes, hypertension, preeclampsia or other risk factors during pregnancy [21].

An important question in clinical obstetrical practice is whether a woman with a post-term pregnancy will have a spontaneous onset of labor, and when this will occur [30-32]. In a previous publication by Hellgren et al [20], where the sympathetic stress response in normal pregnant women at term was measured by skin conductance activity, the activity was shown to have a negative association with the number of days remaining before delivery. The sympathetic activity during pain provocation was shown to be significantly lower in women with less than two weeks to spontaneous delivery, in comparison with women with two weeks or more left until labor [20].
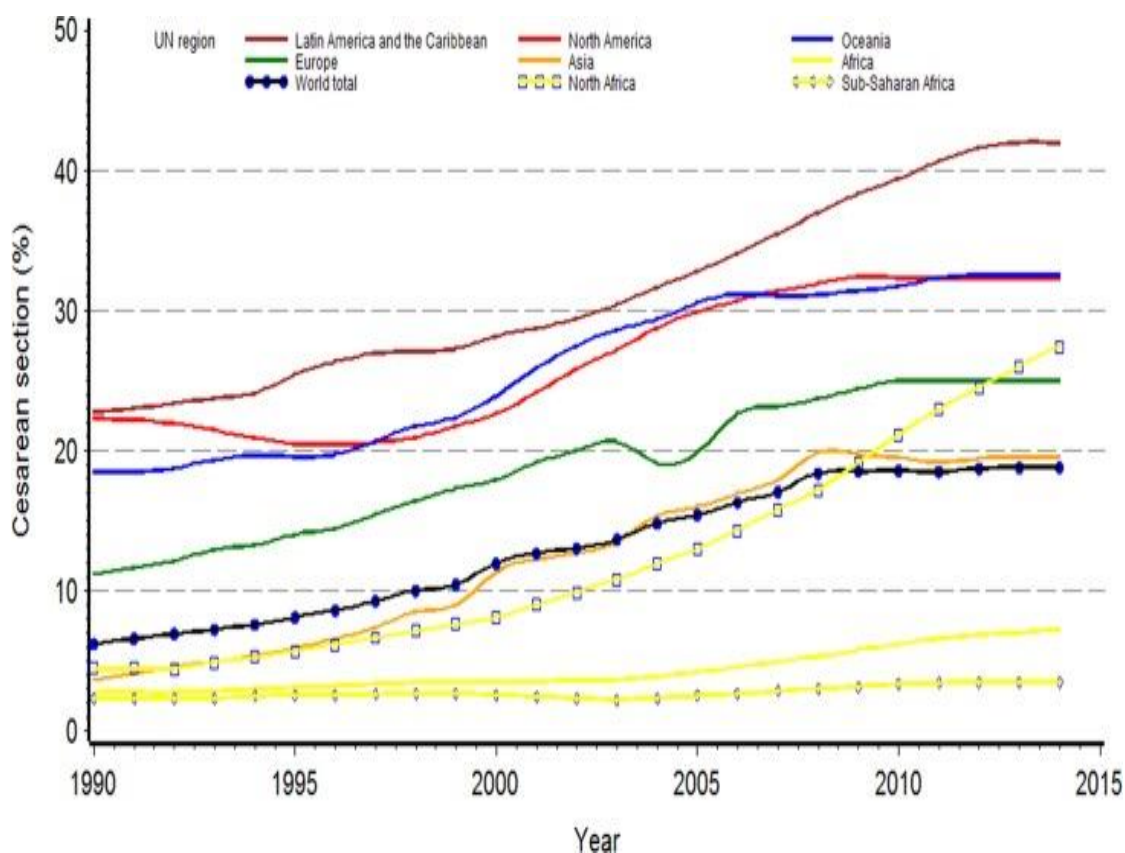
It is debated whether it is an advantage with active rather than conservative management of uncomplicated post-term pregnancies. It is well known that delayed parturition involves several risks to the fetus and to the pregnant woman [1, 22, 30]. However, the spontaneous onset of labor is usually preferred, since it in generally means lower risks of complications compared to IOL.

The use of skin conductance activity might be a more objective method in the future for determining the imminence of onset of labor. Evidence indicating what starts human parturition is still lacking. If there would be a possible method to find a way to predict the spontaneous onset of labor, it would be an advantage in the clinical management of the post-term woman.

2.2. CESAREAN SECTION

The increasing rate of CS continues to cause global concerns. There is a lack of consistency regarding the appropriate CS rate and associated additional risks, both long and short term [33]. WHO suggested in 1985 that an appropriate CS rate is 10-15% of all deliveries, however this statement has been widely debated over the years [34, 35]. Latin America and the Caribbean region have the highest rate of CS (40.5%), and Africa the lowest (7.3%), especially in sub-Saharan Africa (3.5%, Figure 1).

Figure 1. **Latest available data on Cesarean section rates by country (not earlier than 2005).**

There is a huge gap between high- and low-resource settings regarding rates of CS (Figure 2). An unjustified increase of CS in high-resource countries and a decrease of CS in low-resource countries are present [33] due to limited resources. Inadequate access to CS may result in complications such as perinatal asphyxia, stillbirth, UR or obstetric fistula, which are all markers for exceptionally prolonged, obstructed labor [36]. On the other hand, risks after a CS could not be ignored.

Figure 2. **Global and regional trends in cesarean section, 1990–2014.**

Permission to publish from PLOS One; from the article:

Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. PLOS One. 2016; 11(2): e0148343. Epub 2016/02/06. doi: 10.1371/journal.pone.0148343. PubMed PMID: 26849801; PubMed Central PMCID: PMCPMC4743929

2.2.1. Complications after Cesarean section

There are increased risks for short term complications such as infections and PPH (3-5 times increased compared to vaginal deliveries), thrombosis (approximately eight times raised), hysterectomy, impaired breastfeeding, delayed mobilization and pain. Surgical complications from the procedure include risk of injury to other organs such as the intestines and bladder and PPH etc. Long term complications include future risk of abdominal adhesions, UR,

abnormally invasive placenta, placenta previa and placental abruption, infertility are all raised as well [37-40].

2.2.2. Higher risk for Cesarean section after induction of labor

Nowadays in Sweden, there is a major focus on obstetric care from the municipality. In Stockholm, the goal is to reduce the incidence of major vaginal tears and sphincter damage, but also to reduce the rate of CS. Most hospitals in Stockholm focus on reducing the rate of emergency CS. Sodersjukhuset has focused on reducing the proportion of elective CS without medical indication as the rate of emergency CS is quite low. In Sweden and in Scandinavia, IOL means a higher risk of emergency CS than spontaneous onset of labor. The risk of CS is at least three-fold compared to spontaneous onset of labor [2]. When the risks for woman and/or fetus increase by continuing the pregnancy, IOL should always be performed. When a woman opts for an IOL without medical indication the risks should be carefully considered. There is also an ongoing debate in the United States and parts of Europe whether to induce women in gestational week 39 despite a complete normal pregnancy. In some contexts, in clinics with high rates of CS, the risk to induce labor does not increase the risk for CS compared to expectant management (EM).

2.3. INDUCTION OF LABOR

2.3.1. History of Induction of labor

IOL was first described by Hippocrates (in 400 BC). The first methods he recommended were mammary stimulation and mechanical dilatation of the cervical canal [41, 42]. During the 16th centuries, manual dilatation of the cervix and several instruments for the dilatation of cervix were used and even strong enemas and mixtures of several traditional folk medicines [42-45]. From the 17th century it became more common to induce labor and there were discussions about ethics and efficacy of IOL. Mechanical methods were most widely used until 1900 [41, 45, 46].

In 1913 extract from pituitary gland was used for the first time but adverse effects such as UR was noted. In 1943 oxytocin (as an extract) was made possible to use for intramuscular or subcutaneous administration and synthetic oxytocin was introduced for IOL in 1955 [41, 47-50]. Karim et al were the first to report the use of prostaglandins for IOL in 1968 [50]. Since then, different administrations forms of prostaglandins have mainly been used for an unfavorable cervix for IOL [51]. Recently, the synthetic prostaglandin E1 analogue (PGE1) misoprostol has been accepted as an effective and safe method for induction of labor [52].

2.3.2. Indication for induction of labor

IOL is performed for many reasons. In this thesis, we separate the indications into five groups: postdate indication, prelabor rupture of membranes (PROM), maternal indication, fetal indication and non-medical indication/woman request. The purpose of IOL is to obtain a safe vaginal delivery for both mother and child and to avoid compilations during pregnancy.

WHO recommends IOL after 41 weeks of gestation even though this is associated with higher risk of emergency CS, due to complications such as maternal and perinatal morbidity, PPH, UR, meconium aspiration, low Apgar score at five minutes, admission to neonatal intensive care unit (NICU), stillbirth and early neonatal death [53].

There are several randomized controlled trials (RCT) comparing the risks and benefits of IOL to EM at and beyond 41 weeks of gestation. These reviews consistently report that IOL at 41 completed weeks of gestation reduces complications of post-term pregnancies compared to EM [53]. On the other hand, EM was associated with a lower risk of emergency CS compared to IOL [53].

There are increased risks of both maternal as well as fetal complications with IOL such as prolonged time of labor, PPH and the risk of instrumental deliveries and emergency CS compared to spontaneous onset of labor [10, 54, 55].

IOL, a determined time for the start of labor before spontaneous onset, is a common obstetric intervention. Citation from Dr. Michael Robson: "*The decision to induce labor is made if ending the pregnancy is considered more beneficial for the mother or the baby than awaiting spontaneous onset of labor, to obtain a safe vaginal delivery for mother and the baby with minimum interventions, complications and maximum satisfaction*" Quite contrary to citation above, IOL is commonly performed due to women´s request without medical indication. During the last five years 17% of all singleton pregnancies, were induced in Sweden [2]. International the figures are even higher; between 20 and 3% are reported [4, 5, 10, 54, 55]. There are different methods for IOL in an unfavorable cervix, including mechanical dilatation with a balloon catheter, pharmacological inductions with prostaglandin E1 (misoprostol), prostaglandin E2 (dinoproston or Propess®). When cervix is favorable the use of amniotomy or oxytocin is preferred [56].

The most common reasons for IOL are post-dated pregnancies, PROM, and maternal/fetal indication. A significant number of inductions are also performed for humanitarian reasons at women´s request without any medical indication [21, 57].

2.3.3. Induction of labor in gestational week 39?

IOL is a very hot topic for discussions. International trends, especially in USA and parts of Europe advocates IOL after 39 gestational weeks. Those who promote IOL after 39 weeks believes that IOL will not increase the risk for emergency CS compared to EM [58-60]. A RCT of primiparous women with an unfavorable cervix (BS ≤5) [59] showed that the risks of emergency CS was not doubled, but still the frequency of CS was 30.5% in the IOL

group compared to 17.7% in the expectant group. A retrospective study of women with a favorable cervix (BS ≥5) [58] concluded that the risk for CS was equal in the IOL group and the EM group (20.8 vs 20.1%). A new RCT of IOL vs EM in low-risk nulliparous women at 39 weeks of gestation, published in The American College of Obstetricians and Gynecologists (ACOG) August 2018, showed a significantly lower rate of CS, 18.6% in the IOL group vs 22.2% in the EM group [61].

The results and the benefits may differ depending on context. If the clinic/country has a general high rate of CS, the difference in CS rate after spontaneous onset of labor and IOL would probably be small, even if women were to be induced at 39 weeks of gestation. On the other hand, there would be no benefit of IOL at this week if the rate of CS is low in spontaneous labor and the difference between spontaneous labor and IOL CS rates are high like in Sweden and the rest of Scandinavia [2]. In this context, the risks for CS would increase if the clinics changed to induce labor in gestational week 39.

An example of this is Sodersjukhuset in Stockholm, with a large delivery ward with almost 8000 deliveries a year. During the two years 2016-2017, 6328 primiparous women delivered at the hospital between 39+0-42+5 gestational weeks (Table 1). There were 5199 women that had a spontaneous onset and 1129 women were induced to labor. The rate of emergency CS in the spontaneous onset group were 7.0 vs 20.5% in the IOL group. Thus, the rate of CS after IOL is three times higher in this group of women compared to them with a spontaneous onset of labor.

Table 1. Primiparous with spontaneous onset and induction of labor (IOL) and rate of emergency Cesarean section (CS) divided in gestational week and separated in spontaneous labor vs IOL during 2016-2017 at Sodersjukhuset Stockholm, Sweden (n=6328).

	39+0-39+6 (n=1763)	40+0-40+6 (n=2301)	41+0-41+6 (n=1694)	42+0-42+5 (n=570)
Spontaneous onset	1636 (92.8%)	2076 (90.2%)	1356 (80.0)	131 (23.0%)
CS after Spontaneous onset	89 (5.4%)	125 (6.0%)	140 (10.3%)	11 (8.4%)
IOL	127 (7.2%)	225 (9.8%)	338 (20.0%)	439 (77.0%)
CS after IOL	25 (19.7%)	38 (16.9%)	80 (23.7%)	88 (20.0%)

Table 2 describes the proportion of IOL, the proportion of CS in IOL and after spontaneous onset of labor among primi and multiparous women in Sweden, Stockholm and Sodersjukhuset [2]. There is a two-fold risk of an emergency CS for primiparous after IOL compared to spontaneous onset of labor in this context.

Table 2. A comparison of IOL and spontaneous onset in primi and multiparous women in Sweden, Stockholm and Sodersjukhuset. Data are presented in percent (%).

	Sweden	Stockholm	Sodersjukhuset
Proportion of IOL (%)	21.2	23.2	24.3
Elective CS (%)	5.7	8.2	9.3
Rate of CS after spontaneous onset in primiparous women (%)	10.9	11.4	10.2
Rate of CS after IOL in primiparous women (%)	23.1	24.3	20.0
Rate of CS after spontaneous onset in multiparous women (%)	9.9	10.4	8.5
Rate of CS after IOL in multiparous women (%)	6.1	6.0	4.5

In Sweden, there is a large ongoing study (SWEPIS, Swedish Post-term Induction Study), that randomize women to IOL either after 41+0 or 42+0 gestational weeks. The aim of the study is to investigate the optimal choice of time for IOL for women and their unborn child among pregnancies that last more than 41+0 gestational weeks. This study differs quite much from other studies internationally that mainly focus on IOL in gestational week 39.

2.3.4 Misoprostol

Misoprostol is a prostaglandin E1 analogue, developed for the treatment and prevention of gastric ulcers. It´s proven effect on uterine contractility and cervical ripening has resulted in the drug currently being used for termination of unwanted pregnancy, treatment of

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incomplete and spontaneous abortions, IOL, augmentation of labor and treatment of PPH as well as for cervical ripening in pregnant and non-pregnant women [11, 62, 63]. Misoprostol is cheap and stable at room temperature, and has high availability even in the most resource-poor settings. It is better tolerated by women than many other methods of IOL [64]. Misoprostol is also included in the WHO essential medicine list on several indications including IOL [11, 62]. Orally administered misoprostol is an effective method for IOL, comparable with PGE2, balloon catheter and oxytocin [11, 54, 65, 66]. Oral misoprostol is associated with lower rate of CS, less uterine hyperstimulation with fetal heart rate changes, lower rates of low Apgar score and PPH and is as effective as the vaginal route of administration [4].

2.4 INDUCTION OF LABOR AFTER ONE PREVIOUS CESAREAN SECTION

2.4.1 Options after a previous Cesarean section

The ideal management of the subsequent labor for women who have undergone one previous CS has been debated for more than 100 years [67, 68]. The two options are trial of labor after a CS (TOLAC) and elective CS, which can lead to three possible outcomes: elective CS, a successful VBAC or a failed one, meaning a repeated CS with higher risks than with the elective CS. In the TOLAC group labor could start spontaneously or by IOL. As the proportion of women with TOLAC has increased so did the frequency of UR with increased complications like maternal and perinatal morbidity [69, 70]. Despite this, a successful uncomplicated TOLAC resulting in a VBAC has many short and long term benefits compared to repeated CS. It has the lowest morbidity of the three options. On the other hand, a failed TOLAC has higher morbidity than a successful TOLAC and elective CS because is it associated with UR [71]. The incidence of UR is low in high resource settings, but when it occurs it is mostly associated with TOLAC and can be life-threatening because the increased risk of peripartum hysterectomy, septicemia, maternal and neonatal deaths and fetal severe neurologic morbidity [72-76]. There is no consensus concerning the best method of planned delivery after one previous CS, TOLAC or elective CS in subsequent pregnancies [77, 78].

No large RCT has been performed to provide comparative data on outcomes of TOLAC vs elective CS.

Previous CS is the most important risk factor for UR [73]. Other risk factors are IOL, fetus large for gestational age ((LGA), >4000g), labor dystocia, maternal length ≤160 cm and age >35years [73, 79-81]. The incidence of UR is increased in women with a previous CS with TOLAC during their second pregnancy, it is 0.45-0.9 % [69, 74, 79], compared to the incidence of UR in women with a previous vaginal delivery after or before the CS, 0.18‰ [73].

2.4.2 Methods for Induction of labor after one previous Cesarean section

So far there are no randomized studies with strength enough to provide guidance on the efficiency and safety regarding method of IOL in women with previous CS. The current literature is mainly based on observational studies [82]. Whether prostaglandins increase the risk of UR compared to other methods for IOL is still an unanswered question [74, 83]. There are various arguments advocating the most beneficial method for IOL in women who have undergone one previous CS. IOL after a previous CS is a controversial intervention [69, 74, 75, 77, 84, 85], the risk of UR is increased and frequencies from 1.4% are reported. The highest risk is associated with the use of prostaglandins [69, 86].

In the TOLAC group, a former vaginal delivery in addition to the previous CS reduces the risk of UR significantly (40-80%) [74, 87]. In women with one previous CS without former vaginal birth, the risk for UR increased 2.5 times compared to women with a previous vaginal delivery [88]. Women with a prior vaginal delivery are often included in studies which intend to study the risk for UR among women with a previous CS. That complicates the interpretation of the results and makes it difficult to compare studies.

In a study of Bujold et al. [76], the rates of UR were 1.2% in spontaneous onset of labor compared with 1.9% during IOL with balloon catheter and there was no significant difference in labor outcome. The studies are small in numbers and the results should therefore be interpreted with caution. Prostaglandins were used in patients with unfavorable cervix, because of that it is difficult to separate the independent effect of cervical status and the effect of prostaglandins on the rate of UR, unless information about cervical status of the patients had been obtained. In two other studies including 5047 and 158 patients respectively, who

underwent TOLAC, there was not an association between the use of prostaglandins and UR [4, 89]. It is notable that unfavorable cervical status has been associated with prolonged labor and high intrauterine pressure [76].

Chauhan et al [85] showed that the risk of UR with mechanical methods (Foley catheter) for cervical ripening had a non-significant lower frequency than prostaglandins in their study of 142,075 patients who attempted VBAC.

Landon et al [74] examined the risk of UR during IOL with oxytocin compared to spontaneous onset of labor in 17,989 women with one previous CS (TOLAC). The study showed that IOL regardless of method and augmentation of labor with oxytocin were significantly associated with a higher risk of UR than spontaneous labor without oxytocin use (p<0.001). Half of the women had a former vaginal delivery (0.4 vs 1.1%, OR 3.01; 1.66). Furthermore, they could not confirm the increased risk of UR after using prostaglandins in IOL compared with the use of oxytocin solely as was demonstrated by Lydon-Rochelle el al [69]. The dosage of oxytocin and duration of treatment is probably of importance for the risk of UR and a dose-response relationship described in two studies from USA in which a recommended maximum dose is 20 mU / min [74, 90, 91].

Previous studies have indicated a high risk of UR in labor induced with misoprostol vaginally among women with a previous CS. In a study by Wing et al [92] that was terminated prematurely because of safety reasons, 25 µg of misoprostol was administered vaginally every six hours. Vaginal administration of misoprostol was compared with intravenous oxytocin for IOL in women with a previous CS. The study showed that 2/17 (11.8%) women that had undergone IOL with vaginal administrated misoprostol had an increased frequency of poor outcome in terms of UR. There was no UR in the group of women (n=21) receiving oxytocin.

Aslan et al [93] performed a study, in which 47 women with one previous CS and 50 without a previous CS received 50 µg of misoprostol vaginally for IOL due to IUFD and an unfavorable cervix BS<6. The dose was repeated after four hours if the BS was still <6. The risk of UR in that study was 10% in the group with a previous CS compared to 0% in the group without a uterine scar. The study by Plaut et al [94] presented retrospective data on patients receiving misoprostol vaginally for IOL after one or two previous CS. 25 ug of misoprostol was administrated vaginally every three hours until frequent contractions occurred. 5/89 (6%) of the women had a UR, including two cases of dehiscence.

The use of misoprostol is believed to increase the risk of UR compared to other methods of induction [92-94]. IOL with misoprostol in women with a previous CS has therefore been discouraged in many guidelines [11, 24, 95]. However, the evidence is based on small studies and vaginal administration solely.

Gemzell Danielsson et al [96], Aronsson et al [65] and Alfirevic et al in the Cochrane review from 2014 [4] showed that orally administrated misoprostol caused less uterine hyperstimulation than vaginal or sublingual administration. This is consistent with the pharmacokinetics and effect on cervical ripening and uterine contractility observed after various mode of administration of misoprostol [11, 65, 97].

In Sweden, IOL is recommended for the same indications after one previous CS as for women without no former CS. Since 2016 Swedish guidelines have discouraged the use of misoprostol administered as an oral solution for IOL after one previous CS. The decision was made despite that only vaginal and not oral administrated solution of misoprostol was used in the studies. Thus, the scientific knowledge was limited [11, 95, 98, 99]. According to these studies, prostaglandins were considered to increase the risk of UR compared to the balloon catheter, why no prostaglandins at all were recommended. To advise against vaginal prostaglandins had been warranted, but not for the oral route of misoprostol.

2.4.3 Types of Uterine ruptures

There is no clearly established definition of UR. In some studies, a rupture of the muscular wall of the uterus, verified during laparotomy, was considered as a rupture of the uterus. Hence, cases where the defect was covered by peritoneum (elsewhere sometimes defined as uterine scar dehiscence) has been loosely defined as a clinically occult and incomplete disruption that does not lead to any serious maternal or neonatal consequences in comparison to a complete UR. It is often incidentally discovered at the time of CS. The inclusion of cases with only uterine scar dehiscence might explain the high incidence of UR in the study groups as well as in the groups with spontaneous onset of labor.

2.4.4 Risk factors for uterine rupture

Harper et al [100] retrospectively studied 111 cases of UR in TOLAC. They did not show an increased risk of UR following IOL. However, initial unfavorable condition of the cervix (dilatation <4cm) was associated with an increased frequency of UR in their study. Prolonged labor was also associated with UR even in the group with spontaneous onset. A possible suggestion is that the primary concern is not the method if induction used, but rather the status of the cervix at the time of induction and the time and progress of labor. The lack of studies of misoprostol in an oral solution with water is still a problem. Even one of the latest studies on the topic contains only vaginally distributed misoprostol [98].

According to Bujold et al. a history of a previous CS should not be a contraindication to IOL [76]. Among patients with an unfavorable BS<6, the rate of successful VBAC is lower, especially in patients with no previous vaginal delivery (approximately 50%), while women with a BS ≥6 had a rate of successful VBAC greater than 80% and a frequency of UR lower than 1.0% [76].

The question is raised, should we continue to induce women after a previous CS at all? If the answer is yes, the challenge might be to identify women suitable for this intervention.

3 AIMS OF THE THESIS

The overall aim of the thesis is to identify factors of importance for the decision of IOL, and to find out which method for IOL is the most effective and safe for women with or without a previous CS.

The first part of the thesis includes studying and acquiring more knowledge about the factors that control and initiate spontaneous onset of labor. If further comprises studying the possibility to anticipate a spontaneous start and to investigate whether the sympathetic nervous system response, measured as skin conductance activity, is different in post-term pregnancies with spontaneous onset of labor, compared to those without spontaneous onset within 42+0 gestational weeks.

The second part of the thesis focus on different ways of IOL used in clinical practice. The aim is to study if there are differences in defined outcomes of delivery, efficacy and safety for different methods of IOL, including women with an unfavorable cervix and one previous CS.

The specific objectives of each study were as follows:

Study I

➤ To investigate whether monitoring of the sympathetic nervous system response to stimuli by skin conductance activity might be a useful predictor of spontaneous onset of labor in post-term pregnancies.

Study II

➤ To compare existing standard methods for IOL with an orally administered solution of misoprostol and defined outcomes.

Study III

➤ To evaluate the safety and efficiency of oral misoprostol compared to standard methods of IOL in women with a previous CS.

Study IV

> To compare the proportion of UR between balloon catheter, Minprostin® and Cytotec® as methods for IOL in women with an unfavorable cervix and one previous CS.

Study V

> To compare orally administered solution of misoprostol (Cytotec®) with vaginal slow release misoprostol (Misodel®-MVI, 7ug/h) regarding time of labor (the time interval from drug administration to delivery), and safety.

4. MATERIALS AND METHODS

Different designs and methods have been used, depending on the research question of the individual study. All studies were performed at the department of obstetrics at Sodersjukhuset, Stockholm, Sweden except study IV. Data from study IV were collected from all large delivery wards in Stockholm. Data from all included women were collected from the Obstetrix database (the mainly used obstetric medical record system in Sweden). All personal data were anonymized. More detailed description of the materials and methods is provided in the original articles (Study I-IV) and manuscript (Study V). An overview of the studies is presented in Table 3.

4.1 STUDY DESIGN

Table 3. Overview of study designs and methods for the sub-studies.

Study	Design	Population	Statistics
I. Skin conductance activity in post-term pregnancies	Prospective observational study	52 healthy women, with a mixed parity at their post-term pregnancy control.	Mann–Whitney U-test, Fisher exact test, Logistic regression
II. Labor Induction with Orally Administrated Misoprostol: A Retrospective Cohort Study	Retrospective cohort study	4002 women with IOL, viable fetus in cephalic presentation, singleton, at gestational age of ≥34 weeks divided into six subgroups.	one-way ANOVA (Analysis of Variance), Chi square-test, logistic regression
III. Induction of labor in women with a uterine scar	Retrospective cohort study	208 women with IOL after one previous CS divided into two subgroups.	one-way ANOVA (Analysis of Variance), Chi square-test, logistic regression.
IV. Induction of labor after one previous Cesarean section in an unfavorable cervix: a retrospective cohort study	Retrospective cohort study	910 Women with one previous CS and IOL, viable fetus in cephalic presentation, singleton, at gestational age of ≥34 weeks and an unfavorable cervix, divided into three subgroups.	one-way ANOVA (Analysis of Variance), Chi square-test, logistic regression.

V. Slow release vaginal insert of misoprostol versus orally administrated solution of misoprostol for induction of labor: a randomized controlled trial	RCT Open label randomized controlled trial	196 women with IOL, no previous CS viable fetus in cephalic presentation, singleton, at gestational age of ≥37 weeks, BS ≤4 divided into two subgroups.	Independent t-test, Chi square, Kaplan-Meyer, log-rank test.

4.2. STUDY POPULATION

4.2.1 Study I

A total of 52 healthy primi-and multiparous women were included in the study at their post-term pregnancy examination at gestational week 41+3 in the outpatient clinic at Sodersjukhuset, Stockholm Sweden in 2011. All women received oral and written information. 54 women were consecutively invited to participate and only two of the women declined. Exclusion criteria included not being able to understand the questionnaire written in Swedish, or any signs of complications found at the examination.

4.2.2 Study II

In study II, all induced deliveries taking place at Sodersjukhuset, Stockholm, during the years of 2009-2010 and 2012- 2013 were included. Data were collected retrospectively from the database of Obstetrix and all personal data were anonymized. The year of 2011 was excluded, due to the changing of method of IOL during that year from Minprostin® and balloon catheter to Cytotec®. Inclusion criteria were: women with a viable fetus in cephalic presentation, singleton gestation, IOL and gestational age ≥34 weeks, remaining 4002 women for the study. The women were divided into six groups according to the chosen method of induction, Cytotec®, Minprostin®, Propess®, balloon catheter, amniotomy, or oxytocin administrated primarily for augmentation.

4.2.3 Study III

This retrospective study included 208 women with one previous CS, a viable fetus in cephalic presentation at a gestational age of 240–300 days, during 2009-2010 (Group 1, n=121) and 2012-2013 (Group 2, n=87) at Sodersjukhuset, Stockholm Sweden. In Group 2, consisting of "the exposed group", the women were primarily induced with Cytotec® (89%). The remaining 11% in group 1, received balloon catheter (n=6), Minprostin® (n=1) and oxytocin (n=3). Group 1 was considered as "the unexposed group", meaning that no woman in this group received Cytotec®. In Group 1 the distribution of methods used for IOL was Minprostin® (50.4%, n=61), amniotomy (21.5%, n=26), balloon catheter (16.5%, n=20), oxytocin (6.6%, n=8) and Propess® (5.0%, n=6). Data were collected from the Obstetrix database. All personal data were anonymised.

4.2.4 Study IV

All women with one previous CS, unfavorable cervix, and IOL at the four largest hospitals in Stockholm: Danderyd's hospital, Karolinska University Hospital in Huddinge and Solna, and Sodersjukhuset during the four years from 2012 to 2015 (n=910) were included in the study. Inclusion criteria for participation in the study were women with one previous CS and IOL. All women included had a viable fetus in cephalic presentation, singleton, at gestational age of ≥34 weeks. Data from all induced deliveries at these four delivery wards during the actual study period were retrospectively collected from the Obstetrix database. All personal data were anonymized so that individuals could not be identified in the analysis.

4.2.5 Study V

196 women with IOL at the Department of Obstetrics and Gynecology at Sodersjukhuset, Stockholm, Sweden during 1st of October 2016 to 21st of February 2018 were included in this RCT. Inclusion criteria: were primiparous women with singleton gestations and cephalic presentation ≥37 week, BS ≤4. Exclusion criteria: inability to understand the information written in Swedish, suspected scar in the uterine myometrium because of previous surgery

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and prenatal fetal complications as IUGR or non-reassuring fetal heart rhythm on the Cardiotocography (CTG) assessed on admission (the "door-test", first 20 minutes of registration at CTG).

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4.3 ETHICAL PERMITS AND CONSIDERATIONS

All studies were approved by the Regional Ethical Review Board, Karolinska Institutet, in Stockholm, Sweden. **Study 1**: Dnr 2010/144432, **Study II and III**: Dnr 2014/757-31/2, **Study IV**: Dnr 2016/1494 and **Study V**: Dnr 2016/047, clinical trial registration no NCT02918110 and by the National Medical Product Agency (EuduraCT-2016-000949-31). All studies were conducted according to the World Medical Association Helsinki Declaration regarding ethical conduct of research involving human subjects. All participating women in **Study I** and **V** were provided with oral and written information and signed informed consent prior to participation. A participant could at any time withdraw from the studies, which they also were informed of from the start. There are no economic interests in the study for the authors. The results from the studies are published/to be published in peer-reviewed journals. In all five studies data were collected from the Obstetrix database and personal data were encoded, so that individuals could not be identified in the analysis. In **Study II-IV** the projects cause no pain or discomfort for the individual participating woman since these studies are retrospectives. For that reason, no informed consent is necessary. The benefits of the studies are an increased knowledge of the different methods of IOL, and in extension better and safer future obstetric care.

4.4 METHODS

4.4.1 Methods Study I

This was a prospective observational study performed in the outpatient clinic during the post-term control at gestational week 41+3 at Sodersjukhuset, Stockholm, Sweden 2011. 52 healthy primi-and multiparous women were included in the study. CTG was recorded for at least 20 minutes (door test) at admission, followed by a five-minute skin conductance measurement, including a 'cold pressor test'. Finally, an ultrasound to measure the amount of amniotic fluid and a digital examination to assess the status of the cervix was performed. One person (TW) examined all the women and made the interviews. According to the local clinical guidelines, IOL should be performed at gestational week 42+0 if labor did not start spontaneously before that date. Data from all included women were collected from the Obstetrix database and all personal data were anonymized.

The main outcome of the study was to evaluate if altered skin conductance activity could predict spontaneous onset of labor in post-term pregnancies.

4.4.1.1   Cold pressor test

The cold pressor test is used in experiments as a stressor and also for pain threshold evaluation [17, 101, 102]. Most commonly the patient submerges her/his hand or foot into cold water or crushed ice until the pain becomes intolerable or for one minute. The response could be measured as a physiological response, reflecting the sympathetic nervous system or as a subjective experience measured by a visual analogue scale (VAS) 0-10. Previous studies have used the cold pressor test in pregnant and postpartum women as a measurement of pain tolerance. It is suggested that the pain tolerance during late pregnancy is increased [102].

4.4.1.2   Skin conductance

By using the Med-Storm Skin Conductance Algesimeter and the SCMS software (Med-Storm Innovation AS, Oslo, Norway), skin conductance activity was measured, reflecting the response on the sympathetic nervous system reactivity. The test is a simple and non-invasive measurement of the sympathetic activity [103].To perform the test, three self-adhesive, single-use electrodes (Med-Storm Pain Monitor™ Electrodes, Med-Storm Innovation AS, Oslo, Norway) were attached to the palmar skin of the woman's non-dominant hand according to the manufacturer´s instructions.

To ensure that a baseline skin conductance activity was obtained, three minutes of measurement were performed before the cold pressor test started. The last of these minutes was used in this calculation as a reference measurement to the provocation. The woman was told to relax and to be as still as possible during the measurement, and to sit down and let her dominant hand rest on a pillow. Then the woman was instructed to place her non-dominant hand in a +3°C water and to keep it there for 1 minute, if she experienced an intolerable pain, remove her hand. Another minute was recorded after the cold pressor test. To perform the measurement, three self-adhesive, single-use electrodes were used in the palm of the hand. The reactions in the nervous system were noted and then presented graphically (figure 3). The measured data of the analysis of skin conductance measurement resulted in an area under the curve (AUC) measured in μSs and were stored directly in the associated computer and later analyzed using the software analysis package (Med-Storm Pain Monitor ™). The woman´s subjective experience was also recorded on a VAS scale where number 0 means no pain at all and 10 corresponds to ''worst imaginable pain'. The points in time for immersion in cold water, reporting of pain sensation (cold-induced pain threshold), and the withdrawal of the woman's hand (cold endurance) were recorded.

Figure 3. A clinical example from the study

Scatterplot of skin conductance against time (min)
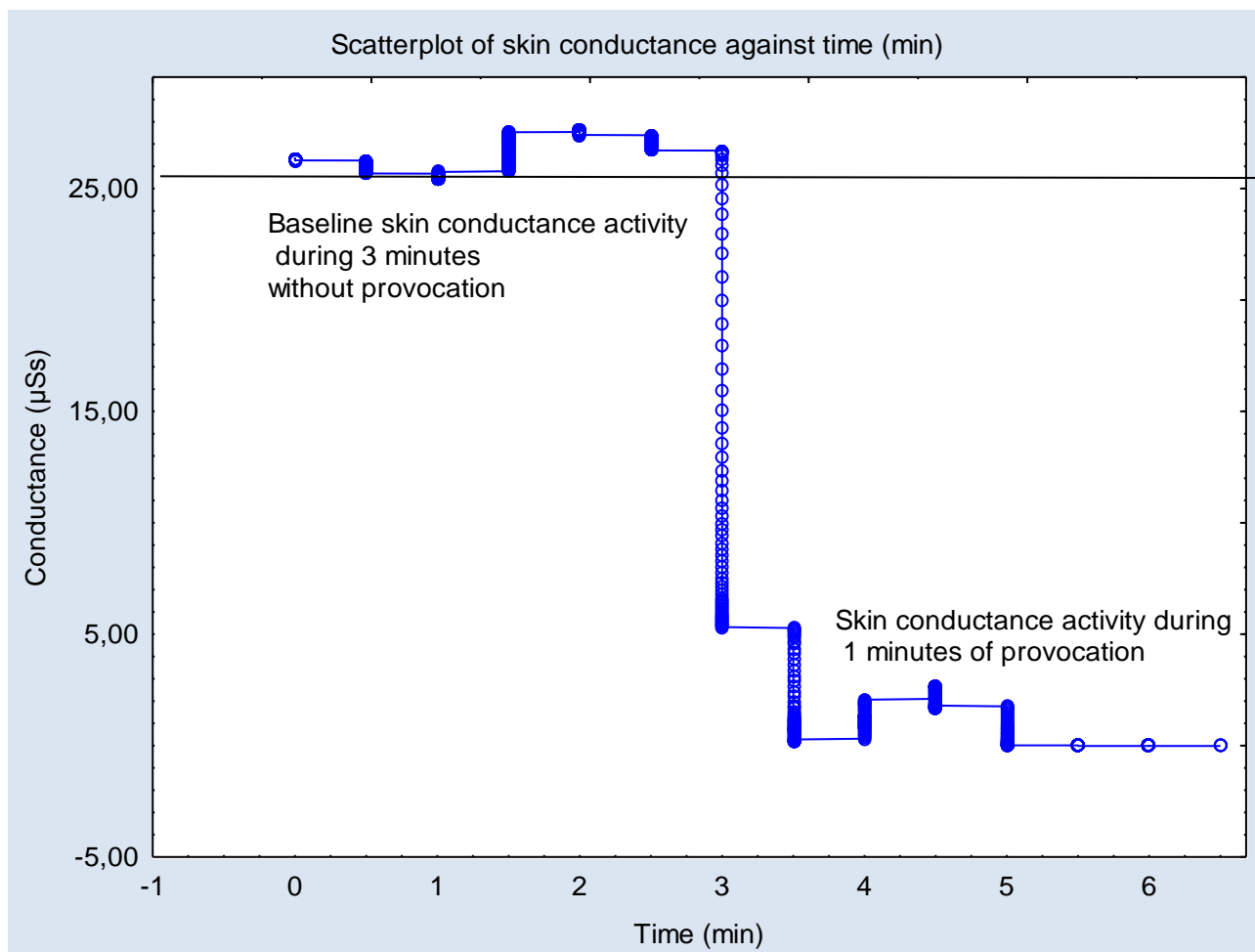
4.4.2 **Methods study II**

The 4002 women were divided into six groups according to the method of induction chosen for IOL, Cytotec®, Minprostin®, Propess®, balloon catheter, amniotomy, or oxytocin administrated as a primarily method for augmentation of labor. Methods of induction, baseline data, and delivery outcomes were compared. The data were collected from the Obstetrix database. All personal data were anonymized.

The primary endpoint of the study was the frequency of CS among the six methods of IOL. Secondary endpoints were acid-base status in cord blood at delivery, Apgar score <7 after five minutes, active time of labor, and PPH (blood loss >1500 ml).

4.4.2.1   Methods of induction of labor

In the Cytotec® group one tablet of $200\,\mu g$ Cytotec® was dissolved in 20 ml of water to prepare a solution containing $10\,\mu g$ of misoprostol/ml. This method of oral administration of Cytotec® has been tested by the Swedish Institute of Pharmacology [12] and was approved to give the correct dosage to the woman. An oral dose of $2.5\,\text{ml}/25\,\mu g$ of Cytotec® was administered to the women every two hours until regular painful contractions were obtained. If the woman experienced painful contractions at the time for the next dose, induction was paused for one hour waiting for the contractions to continue spontaneously. If contractions disappeared the woman received another dose, but if contractions continued spontaneously, a vaginal digital examination was performed to evaluate cervical ripening. The oral dose of Cytotec® could be repeated up to eight times as a maximum. When cervix was favorable before or after the eight doses (BS ≥6), amniotomy and oxytocin were used to support uterine contractions if necessary.

In the Minprostin ® group, 1 or 2 mg of dinoproston was given vaginally. Depending on the frequency and magnitude of contractions, cervical progress was evaluated digitally every six hours or less. If the cervix was still unfavorable, additional doses were administered, up to a maximum of 6 mg of Minprostin®. When the cervix was favorable before or after 6 mg of Minprostin® (BS ≥5), amniotomy and oxytocin were used to support uterine contractions if necessary.

In the Propess® group, dinoproston was given as a vaginal 10 mg slow-release insert with continuous output. It was inserted high into the posterior vaginal fornix. If the woman did not experience painful contractions the insert could remain in place for up to 24 hours. The maturation of the cervix was evaluated by a vaginal examination after 24 hours or less, depending on the frequency and intensity of the contractions. When cervix was favorable before or after the 24 hours (BS ≥5), amniotomy and oxytocin were used to support uterine contractions if necessary.

In the balloon group, mechanical IOL was performed with a balloon catheter (Bard®). The balloon was inserted into the cervix above the internal os and the bulb was inflated with 50 ml of sterile water. The midwife stretched the catheter every 30 minutes. The balloon could

be used for a maximum of 10h. When the cervix was dilated at least 3 cm, the balloon slipped out and the IOL was followed by an immediate amniotomy and oxytocin if necessary.

Amniotomy as a primary method of IOL was only used when the cervix was favorable (BS ≥5), mostly in multiparous women. If there were no regular contractions or any progress of the cervix in one to two hours, induction was continued by stimulation with oxytocin.

Oxytocin as a primary method was only used in women with ruptured membranes and a favorable cervical status (BS ≥5) of the cervix.

4.4.3   Methods study III

The 208 women were divided into two groups depending on the method of IOL and the different years studied. Group 1 (n=121) during 2009-2010 was the unexposed group, meaning that the women did not receive Cytotec® as the method of IOL. Group 2 (n=87) during 2012 and 2013 serves as the exposed group in that the women in this group were primarily induced with an oral solution of Cytotec® (89% of the women received Cytotec®). Inclusion criteria in the study were: viable singleton fetus in cephalic presentation at a gestational age of 240–300 days with one previous CS and a planned IOL. The methods of induction, baseline data, and delivery outcomes were recorded among all the included deliveries during the actual study period from the Obstetrix database. All personal data were anonymized.

The primary outcome of the study was the frequency of UR in each group, defined as a separation of the muscular wall of the uterus, verified during laparotomy. Thus, a defect covered by peritoneum a dehiscence, was also defined as a rupture. Secondary outcomes were the frequency of pH <7.05 in cord blood (artery) of the newborn at delivery and/or Apgar score <7 at five minutes.

4.4.3.1   Methods of induction of labor

The same six methods used for IOL, as described in Study II were used.

4.4.4 Methods study IV

A retrospective cohort study where 910 women with one previous CS, IOL and an unfavorable cervix, were included at the four largest delivery wards in Stockholm, Sweden: Danderyd's hospital (no 1), Karolinska University Hospital in Huddinge (no 2), Karolinska University Hospital in Solna (no 3), and Sodersjukhuset (no 4) during 2012 to 2015. Data from all included women during the study period were collected from the Obstetrix database. All personal data were encoded, so that individuals could not be identified in the analysis.

A total UR was defined as a complete separation of all layers of the uterine wall, including the myometrium and the serosa. A dehiscence was defined as a separation of the muscular layers, with an intact serosa [88].

Arterial and venous umbilical cord blood sample were analyzed, directly after birth before the new-born's first cry, with a point-of-care device (ABL 800 Bayer®), which is available in all delivery wards as it is a routine clinical procedure in all delivery wards in Stockholm. Arterial and venous pH and base deficit (BD) were analyzed, but at least 15-20% of the test is not performed at the clinics in general.

Inclusion criteria for the study were: women with one previous CS and IOL. All women included had a viable fetus in cephalic presentation, singleton pregnancy, and gestational age of ≥34 weeks.

4.4.4.1   Methods of induction of labor

Minprostin®, Cytotec® as an oral solution, and balloon catheter were used as methods for IOL in this study, with the same clinical procedure as described in Study II.

To reach amniotomy is the first step in the progress of IOL in an unfavorable cervix. For that reason, amniotomy is not considered as an additional method of IOL in this study.
In 84.1% (248/295) of the deliveries where Cytotec® had been used, no additional method was used after the primary method of IOL. The same was for 80.4% (226/281) in the Minprostin® group and in 97.1% (326/335) of the women in the balloon catheter group. Since the majority of the women (minimum 80 %) received only one method of induction, we consider it appropriate to use the first method for IOL as the main method for calculation. In the Minprostin® group 37.5% (105/280) of the women received two doses and 9.3% (26/280) received a third dose of Minprostin®. Amniotomy followed by oxytocin stimulation were used in deliveries with a favorable cervix (BS ≥6). Oxytocin only was primarily used in women with ruptured membranes and a favorable cervix.

4.4.5 Methods study V

An open label randomized controlled trial of 196 women undergoing IOL, conducted in accordance with the CONSORT guidelines for clinical trials in the Department of Obstetrics and Gynecology at Sodersjukhuset, Stockholm, Sweden during 1st of October 2016 to 21st of February 2018. Women were included if they were primiparous with a singleton fetus in cephalic presentation, ≥37 weeks of gestation, BS ≤4 without prior uterine surgery. Exclusion criteria included not being able to understand the information written in Swedish, prior uterine surgery and prenatal fetal complications such as IUGR or pathological CTG at the "door-test. If the woman fulfilled the inclusion criteria she was given oral and written information about the trial and about the methods. Information was given by a physician or a midwife at the delivery ward. After written consent the woman was randomized to receive either MVI or an oral solution of misoprostol for IOL. Sealed Envelope Ltd. 2016 generated the randomization sequence available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 1 Oct 2016]. Number: **Seed:** 100953215495341. The allocation of treatment was generated using a

computer random schedule in blocks at the start of the study. Assignment was concealed by placement in consecutively numbered, opaque, sealed envelopes drawn in consecutive order by an administrator, who was unaware which agent was allocated until the envelope was opened. The investigators were blinded to allocation, but blinding of the participant and the midwife administering the treatment was not possible due to the differences in preparations used.

Differences between the two groups' oral solution of misoprostol and MVI were assessed according to:

Primary outcome

- Induction-to-vaginal-delivery time (the time interval from drug administration to vaginal delivery)

Secondary outcomes
- Mode of delivery (vaginal delivery, Vacuum or CS)
- Proportion of children born with Apgar <7 at 5 minutes and arterial cord blood with pH <7.10
- Proportion of deliveries with hyperstimulation > 6 contractions / 10 minutes
- Frequency of PPH > 1000ml
- Women's birth experience (VAS 0-10, where 0 means not satisfied at all with the delivery and 10 very satisfied with the delivery)

4.4.5.1   Methods of induction of labor

The two methods used were oral solution of misoprostol (Cytotec®) as described in study II and MVI. In the MVI group, MVI was given as a removable vaginal reservoir of 200 ug of continuous output disruption of misoprostol (7ug / hour; 158 ug / day) over a period of maximum 24 hours. A CTG was performed every 4–6 h; or once regular contractions were established. The MVI was removed when the midwife considered that labor was established or if the 24-h dosage period was completed.

4.5 STATISTICS

All Statistical analyses in the five studies were performed using SPSS 20.0 (SPSS Inc. Chicago, IL) and the statistical package Statistica for Windows, version 10.0 (Stat Soft, Tulsa, OK) was also used in study I and III.

4.5.1 Study I

Baseline characteristics and delivery outcome data were presented as frequencies with percentages and medians with ranges. The Mann–Whitney U-test, Fisher´s exact test and the chi-square test were used. The AUC during the minute of provocation (A2) was compared with the AUC of the baseline minute (A1), measured 1 minute before the cold pressor test. The differences between these measurements were calculated as a skin conductance score (A1–A2). When the skin conductance score was negative, the sympaticus reaction during provocation was equal to or lower than baseline. When the sympaticus reaction was higher than baseline reaction, the skin conductance score was positive. A p-value <0.05 was considered statistically significant. A logistic regression was performed to estimate the association between spontaneous onset of labor before 42 weeks of gestation and the following independent variables; negative skin conductance score after provocation cervical length <2 cm at inclusion, cervical dilation ≥2 cm at inclusion, VAS value <4 after provocation.

4.5.2 Study II and IV

To compare mean values and proportions between the different groups of methods of IOL in study II and IV, one-way ANOVA (Analysis of Variance) and the Chi-square test were used. The association between the frequency of CS (primary outcome) and method of induction was analyzed in study II. In study IV, the association between the proportion of UR (primary outcome) and method of induction was analyzed. Logistic regression was used to adjust the association regarding potential explanatory variables for CS in study II and for UR in study IV. Primarily the crude (unadjusted) associations of each potential explanatory variable and CS in study II and for UR in study IV were calculated. Secondarily, we used multivariable models to study the adjusted associations regarding the potential explanatory variables and

CS in study II and for UR in study IV. Finally, to assess whether the method of induction differed in any subgroup regarding the levels of variables, we added an interaction to the adjusted model between the method of induction and each of the potential explanatory variable, one at a time. Model fit was judged based on the Hosmer and Lemeshow Goodness-of-fit test, if p>0.05 the model fit was acceptable. The associations are presented as odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

4.5.3 Study III

Baseline characteristics and delivery outcome data were presented as frequencies with percentages and medians with ranges. The Mann–Whitney U-test, Fisher exact test and the chi-square test were used. A p value of <0.05 was considered statistically significant.

4.5.4 Study V

To compare means and proportions in the two groups of interventions for IOL, independent t-test and the Chi-square-test were used. In addition, to describe time of labor (the time interval from drug administration to vaginal delivery) and compare intervention times between oral solution of misoprostol and MVI the Kaplan-Meyer and log-rank test was used.

The study was planned as a two-center trial. Two separate main outcomes were identified (time to delivery and proportion of CS) and two separate power calculations were performed one including the two main outcomes and one including only time to delivery. It was estimated that 160 participants were needed in each arm to detect a statistical difference in time of labor and proportion of CS (alfa=0.05, two-sided) with 80% power. Based on patient load it was decided that our site should include 200 patients and the other site 120 patients, Because of slow recruitment and problems with conduct of the study the other site was terminated.

The power calculation showed that 52 participants was needed in each arm to detect a mean difference in time of 5.0 hours between the two groups of IOL (corresponding to means of 12.0 vs 7.0) with 80% power (alfa=0.05, two-sided). This effect was selected as the smallest

effect that would be important to detect, in the sense that any smaller effect would not be of clinical significance. The calculation assumed that the common within-group standard deviation is 9h and the study will have a power of 80%. In addition, we assumed that 5h is of clinical relevance since it means 5h less in the delivery ward.

5. RESULTS

5.1 STUDY I

5.1.2 Summary of main findings

Out of the 30 participating women with a spontaneous onset of labor, 63% (19/30) had a negative score at the cold pressor provocation, compared to 30% (6/20) of the women in the induced group. There was a statistically significant lower pain reaction (increased pain tolerance) during the cold pressor test in women close to spontaneous onset of labor compared to women that were induced to labor before 294 days (p=0.02). The possibility of having a spontaneous onset of labor was increased 4.0 times if the skin conductance score was negative (OR 4.0, 95% CI;1.2–13.5) and increased 6.8 times for labor to start within 48h if the cervix was open ≥2 cm (OR 6.8, 95% CI; 1.9–24.7). Nine of the participating women had a negative skin conductance score in combination with a cervical dilatation >2 cm. All of them had a spontaneous onset of labor within 48h.

5.2 STUDY II

5.2.1 Summary of main findings

4002 women with mixed parity and IOL were included at Sodersjukhuset, Stockholm, Sweden during 2009-2010 and 2012-2013. The lowest rate of CS overall, for both primi- and multiparous women with an unfavorable cervix BS ≤5, was found in the group where Cytotec® was administered as an oral solution; 23% among primi and 11% in the group of multiparous women. In women induced with Minprostin® the rate of CS was 36 vs 24% and with balloon catheter 29 vs 17% respectively among primi/multiparous women. The delivery time was shorter in the balloon group (in average 12h). Women in the balloon group had a more favorable cervix (in average BS=5) compared to the Cytotec® and Minprostin® groups who had a longer delivery time (in average 20h) and a more

unfavorable cervix (in average BS=3). The proportion of emergency CS decreased from 26 to 17% when an oral solution of Cytotec® was introduced at the clinic (p<0.01). There was no significant difference between the different methods of induction between the frequency of low Apgar score (p=0.3), low arterial pH in cord blood (p=0.1), or PPH (p=0.4).

5.3 STUDY III

5.3.1 Summary of main findings

During the study time 2009-2010 and 2012-2013, 1525 (6.8%) of the women had one previous CS in the history, 1193 (78.2%) had a spontaneous onset of labor and 208 (13.6%) were induced. The remaining women were planned for an ES. The IOL group was divided into two groups, 1 and 2. There were no differences in maternal or fetal baseline data between the two groups. The proportion of BS < 4 was not significantly different (41 vs 52%) between the groups 1 and 2, nor was time to delivery > 10h (74 vs 76%) The proportion of emergency CS was significantly lower in group 1 compared to group 2 (43 vs 56%, p=0.04), there were more inductions with amniotomy in group 1 compared to group 2 (21.5 vs 0%, p<0.01). In a subgroup analysis, no significant difference in mode of delivery between IOL with Minprostin® and Cytotec® was seen. There was a significant difference between the groups in the incidence of labor dystocia 24 vs 9% respectively. The proportion of UR in the group with spontaneous onset was 1.2% compared to 4.3% in the IOL group. There was no significant difference in the incidence of UR between group 1 and 2 (4.1 vs 4.6%, p=0.9) despite a high rate of IOL with amniotomy in group 1 indicating a more favorable cervix compared to group 2 (21.5 vs 0%). Cytotec® was used for IOL in 89% of the women in group 2.

5.4 STUDY IV

5.4.1 Summary of main findings

There were 87,774 deliveries in the four largest hospitals in Stockholm County during 2012-2015 and in 9,941 of these (11.3%) the women had a previous CS. After the exclusion of pregnancies planned for a CS, prematurity <34 gestational weeks, multiples and IUFD, 4,997 (5.7%) deliveries remained, defines as the TOLAC group. The TOLAC group consisted of women with spontaneous onset of labor and women with IOL. In the whole TOLAC group there were 78 UR (1.6%). In the group of women with spontaneous onset there was 49/3847 (1.3%) UR and 29/1150 (2.5%) in the IOL group (Table 4). The risk of having an UR was significantly higher in women with IOL compared to women with spontaneous onset of labor (p<0.01). These figures are in accordance with previous studies. One interesting finding that is not statistically significant is that the type of UR differs between the two groups (p=0.49). In the spontaneous onset group, there was more manifest UR 41/49 (83.7%) than in the IOL group 20/29 (69.0%), hence there were more dehiscence in the IOL group. Time to delivery was almost equal in the two groups (19.8 vs 20.0h) and the frequency of women with no vaginal delivery before or after the CS was almost the same (91.8 vs 93.1%).

Only two variables reached statistical significance. One was the duration of oxytocin infusion that was doubled in the IOL group, 8.9 vs 4.3h (p<0.01) in the spontaneous onset group, the other was gestational age at birth. In the IOL group the fetuses were 5 days older (285 vs 280 days, p=0.01) than in the spontaneous onset group. There was one fetal death due to UR in the spontaneous onset group.

Table 4. Maternal and fetal background and outcome data in the group uterine ruptures (UR, n=78), presented for spontaneous onset and induction of labor. Data are presented as numbers (%) or mean (SD). P -Values <0.05 were considered as statistically significant *.

	Spontaneous onset (n=49)	Induction of labor (n=29)	p-value*
Hospital			0.70
Danderyd no 1 (n=29)	17 (34.7 %)	12 (41.4 %)	
Huddinge no 2 (n=16)	9 (18.4 %)	7 (24.1 %)	
Karolinska no 3 (n=11)	7 (14.3 %)	4 (13.8 %)	
Sodersjukhuset no 4 (n=22)	16 (32.7 %)	6 (20.7 %)	
No previous vag. delivery (%)	45 (91.8 %)	27 (93.1 %)	0.47
Previous AS (n=58, 74.4 %))	39 (79.6 %)	19 (65.5 %)	0.17
Gestational age (days)	280 (8.1)	285 (8.1)	0.01*
Delivery time (h)	19.8 (14.1)	20.0 (8.8)	0.16
Frequency of oxytocin infusion (n=51, 65.4 %)	29 (59.2 %)	22 (75.9%)	0.14
Time of Oxytocin infusion (h)	4.3 (3.1)	8.9 (6.4)	< 0.01*
Type of UR			0.49
Dehiscence (n=17, 21.8 %)	8 (16.3 %)	9 (31.0 %)	
<5cm (n=26, 33.3 %)	18 (36.7 %)	8 (27.6 %)	
>5cm (n= 18, 23.1 %)	12 (24.5 %)	6 (20.7 %	
Total rupture (n=17, 21.8 %)	11 (22.4 %)	6 (20.7 %)	

			0.06
Mode of delivery			
Vaginal (n=8, 10.3 %)	2 (4.1 %)	6 (20.7 %)	
VE (n=8, 10.3 %)	5 (10.2 %)	3 (10.3 %)	
CS (n=62, 79.5 %)	42 (85.7 %)	20 (69.0 %)	
PPH >1000ml (n= 24, 30.8%)	15 (30.6 %)	9 (31.0 %)	0.97
Fetal death (n)	1 (2 %)	0	0.44

In the IOL group with an unfavorable cervix, baseline data were the same except for maternal age and BS. Maternal age ranged from 32.5-34.1(p< 0.01) with the youngest women in the balloon group and the oldest in the Cytotec® group. BS were highest in the balloon group (4), followed by Cytotec® (2.9) and the lowest in the Minprostin® group (2.4, p<0.01). The time interval from IOL to delivery was shortest in the balloon group in which women had the most favorable cervix, 14.3h (1.2-43.1h). The longest time were found in the Minprostin® group, 21.7h (2.1-62.1h). The highest proportion and longest time of stimulation with oxytocin infusion was found in the balloon group (88.4% and 8.5 h), and the lowest proportion and shortest time of stimulation was found in the Cytotec® group, (56.9% and 6.9h, p<0.01, Table 2.). 27/910 (3.0%) UR were found in the group of IOL with an unfavorable cervix, 91% of them had no previous vaginal delivery. Most of the UR in this study occurred with Minprostin® (5.0%). The risk was more than two-fold compared to balloon catheter (2.1%) and oral solution of Cytotec® (2.0%). There was no significant difference in the proportion of UR between Cytotec® and balloon catheter (p=0.64) for IOL after one previous CS. Orally administered Cytotec® and balloon catheter resulted in a high success rate of vaginal deliveries (69.2 vs 69.0%) compared to Minprostin® with the proportion of vaginal deliveries of 57.0%.

There were no statistical differences between the four hospitals in Stockholm according mode of delivery, frequency and type of UR, low Apgar or pH and methods of induction (Table 5.). Age, BMI, previous vaginal delivery, gestational age and type of method for IOL are all significant different among the four hospitals (Table 5). In hospital no 2, women had the highest BMI, the lowest gestational age and highest rate of previous vaginal delivery. The

most common method of IOL was Minprostin® at hospital no 1 and no 2, balloon catheter at hospital no 3 and Cytotec® at hospital no 4. The lowest BMI, highest gestational age and lowest rate of previous vaginal delivery was found at hospital no 1, the most common method of IOL was Minprostin® and that hospital also had the highest rate of UR (4.9%, not statistically significantly higher).

Table 5. **Maternal baselines, labor and fetal outcome among women with IOL after one previous CS and unfavourable cervix distributed in the four large hospitals in Stockholm, Sweden (n=910). Data are presented as numbers (%) or mean (SD). P -Values<0.05 were considered as statistically significant ***

	Hospital No 1 (n=206)	Hospital No 2 (n=211)	Hospital No 3 (n=222)	Hospital No 4 (n=271)	p-value*
Age (years)	33.9 (4.8)	32.7 (4.9)	32.7 (4.9)	34.0 (4.9)	< 0.02*
BMI (kg/m2)	25.3 (4.6)	27.3 (5.2)	26.4 (5.4)	25.5 (5.0)	< 0.01*
No previous vag. delivery (n=691)	166 (80.6)	137 (64.9)	175 (78.8)	213 (78.6)	< 0.01*
Gestational age (days)	283.3 (10.9)	279.0 (13.7)	281.7 (11.0)	281.4 (12.8)	< 0.01*
Method of induction: Balloon (n=335)	78 (37.8)	91 (43.1)	160 (72.1)	6 (2.2)	< 0.01*
Minprostin® (n=280)	125 (60.7	106 (50.2)	48 (21.6)	1 (0.4)	
Cytotec® (n=295)	3 (1.5)	14 (6.6)	14 (6.3)	264 (97.4)	
Mode of delivery: vag. delivery (n=595)	126 (61.2)	145 (68.7)	144 (64.9)	180 (66.4)	0.42
CS (n=315)	80 (38.8)	66 (31.3)	78 (35.1)	91 (33.6)	
Frequency of UR (n=27)	10 (4.9)	7 (3.3)	4 (1.8)	6 (2.2)	0.24
Type of UR (n=27) -Dehiscence (n=9)	3 (30.0)	1 (14.7)	1(25)	4 (66.7)	0.60
<5cm (n =6).	2 (20.0)	2 (28.6)	2 (50)	0	
>5cm	2 (20.0)	2 (28.6)	1(25)	1 (16.7)	

(n=6) Total rupture (n=6)	3 (30.0)	2 (28.6)	0	1 (16.7)	
Apgar <7, 5' (n=13) missing	3 (1.5) 0	4 (1.9) 0	3 (1.4) 0	3 (1.1) 0	0.91
pH < 7.10 (n=51) missing (n=222)	10 (4.9) 66 (32.0)	10 (4.7) 51 (24.2)	8 (3.6) 54 (24.3)	13 (4.8) 51 (18.8)	0.07
Fetal death	0	0	0	0	1.0

5.5. STUDY V

5.5.1 Summary of main findings

There were 912 women eligible (primiparous for IOL) for the study. 32 of the women were excluded because they didn't meet the inclusion criteria (twins, IUGR, non-reassuring CTG at admittance). 348 of the women were not asked, 267 had BS >4 and 65 declined to participate. One of the envelopes was lost and not replaced. Thus, 199 women remained to be allocated to one of the two treatment groups; 99 women were allocated to and received oral misoprostol and 100 women were allocated to MVI but only 96 received MVI (four of the women in the MVI group received oral misoprostol instead). Three women in the MVI group discontinued the intervention (1 multipara, 1 received both MVI and Cytotec®, 1 had a BS=6) resulting in 196 women remaining for the analysis (Figure 4).

Figure 4. CONSORT Flowchart from study V.

Assessed for eligibility (n=912)

Excluded (n=32)
Not meeting inclusion criteria (n=267)
Declined to participate (n=65)
Not asked (n=348)
Other reasons (n=1, lost from the box)

Randomized (n=199)

Allocation

Allocated to Cytotec® (n=99)
Received allocated intervention (n=99)
Not receive allocated intervention (n=0)

Allocated to Misodel® (n=100)
Received allocated intervention (n= 96)
Not receive allocated intervention *(n=4)*

Follow-up

Lost to follow up-reason (n=0)
Discontinued intervention (n=0)

Lost to follow up-reason (n=0)
Discontinued intervention (n=3)
(1 multipara, 1 received both Misodel and Cytotec®,1 BS=6)

Analysis

Analyzed according to ITT (n=99)
Analyzed according to PP (n=99)
Analyzed according to as treated (n=103)
Excluded from analysis (n=0)

Analyzed according to ITT (n=97)
Analyzed according to PP (n=93)
Analyzed according to as treated (n=93)
Excluded from analysis (n=0)
Excluded from analysis (n=0)

The main finding in study V was that the induction-to-vaginal-delivery time (the time interval from drug administration to vaginal delivery) was significantly shorter in the MVI group, 21.6h compared to 24.8h in the Cytotec® group (p=0.04). In the MVI group, there were significantly more women with hyperstimulation during labor with non-reassuring CTG (n=14 vs 3, p<0.01) and women who received Terbutaline (Bricanyl®) during labor (n=22 vs 4, p<0.01).

Despite this there were no more admissions to NICU in the MVI group. Except from these findings there were no significant differences in baseline data, delivery outcome or fetal outcome. The rate of CS was low and did not differ between the groups; 14.1% in the Cytotec® group and 19.6% in the MVI group (p=0.59).

6. METHODOLOGICAL CONSIDERATIONS

6.1. INTERNAL VALIDITY

6.1.1 Systematic error

When measures tend to deviate from the true values, it is called systematic errors. They are predictable and typically constant or proportional to the true value. In a study, systematic errors occur due to incorrect selection of a study group, misclassification of the variables or because there are no adjustments for possible confounders. If the validity is high, there is absence of systemic error. Systematic errors can be addressed through the design of the study and in the statistical analysis.

6.1.1.1 Selection bias

In study, I and V patients were recruited voluntary when they came to the outpatient clinic (study I) or the delivery ward (study V) for their IOL. The woman was given oral and written information about the study by a physician or a midwife (only in study V). Participation was given through written consent. Because women were excluded if they could not understand the information written in Swedish, there was a risk that the population studied was to homogenous and that would affect the generalizability. In study I, all eligible women according the inclusion criteria, were asked to participate during the study period, only two refused due to stress and active labor. This minimizes the risk of selection bias. In study V all eligible women were not asked, some due to a stressful situation at the delivery ward and some due to oblivion. Analysis of the non-included women showed that this group did not differ from the included women regarding age, gestation, BS or BMI.

Prospective cohort studies have a risk of selection bias due to loss to follow up. Since study II, III and IV are all retrospective studies, there are no drop outs and thus this is not a problem. We included all consecutive women that were induced to labor at Sodersjukhuset during the four years of the study period in study II. In study III we did the same to all

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women with a previous CS and IOL at the same hospital. In study IV all consecutive women that were meeting the criteria were included in the study, which included all women with one previous CS and IOL in Stockholm at the four large delivery wards during the study period of four years.

6.1.1.2   Information bias

Study II, III and IV are all retrospective registry studies. These kinds of studies have inherent problems, because the available information is restricted to the register´s content. A register is not better than the information presented in the medical records. The exposure, outcomes and confounders are all dependent on the quality of the register. In all five studies outcome and exposure were clearly defined. The strength with these three studies, even though they are retrospective, is that the researcher read every single medical record of the included women. That makes the results more reliable and minimize information bias and even misclassifications. In study, I and V, databases were prepared by the researcher. This means that the risk is low for misclassification and information bias in these studies too.

6.1.1.3   Confounding

Confounders could be controlled for in the design of the study or in the statistical analyzes. We tried to adjust for possible confounders by using multivariable regression in the statistical analysis in study I-IV.

In study I, we controlled for possible confounders in the multivariable regression analyzes, such as negative skin conductance score after provocation, cervical length <2 and ≥2 cm at inclusion, VAS value <4 after provocation because they all were considered to affect the result.

In study II, we adjusted for possible risk factors for CS in the multivariable regression, maternal age, parity, gestational age, years of induction, indication for induction and method of induction.

In study III, we adjusted for BS and duration of delivery since they are possible confounders for UR.

In study IV we adjusted for possible risk factors for UR in the multivariable regression, such as maternal age, previous vaginal delivery, gestational age, delivery unit/hospital, indication for induction, BS, method of induction, time of augmentation with oxytocin and type of previous CS as these variables could affect the result of the study.

A successful randomization adjusts for confounders, both known and unknown. Study V is a RCT, which will take care of possible confounders if the randomization is successful. The randomization in this study was successful as baseline characteristics are similar in both groups.

6.1.2 Random error

Random error is always present and stands for variability in measurement that we cannot explain. It could affect the precision of the estimates, presented by the width of the confidential interval. The confidence intervals indicate the amount of random error in the estimate. Random errors are depending and could be controlled by the size of the analysis sample. Random error will decrease if the sample size increases. Lack of random error gives a high precision

6.1.2.1 Precision

In all five studies the confidence interval is set at 95% and p-value is considered statistical significant if <0.05.
Study I, has a small study population with only 50 women. Because of the small population the confidence interval (CI) is wide which gives a lower precision, on the other hand all deliveries included had a complete examination with a good reproducibility of the measurements. The precision would increase with a larger study population size, which may be of importance since the result seems to be of obstetrical clinical interest.

Study II; III and IV are large retrospective cohort studies which will decrease the risk of systematic errors by the large size of the population. However, in study III and IV the outcome is very rare so the studies would have benefited from larger sample sizes even though the precision of the results is good, with generally quite small confidence intervals.

In study V sample size was decided in a power calculation which showed that 52 participants were needed in each arm to detect a mean difference in time of 5.0h between the two groups of IOL with 80% power. The study is well-powered to give a good precision (200 participants) and therefore makes it possible to detect if there is a difference in time between the two methods of induction.

6.2. EXTERNAL VALITDY OR GENERALIZABILITY

External validity reflects if the results of the study can be extrapolated in settings outside the source population, national, regional or global.

Study I-III represent the obstetric population in an urban setting, in a large hospital with almost 8000 deliveries a year. Demographic and obstetric interventions vary to some extent over the country in Sweden, but the result in these studies are probably applicable to similar settings in Sweden and at least even in the western part of Europe.
In study IV the study population is expanded to the four large delivery units in Stockholm County. Although results thus would be even more applicable to other similar settings, a limitation of the study could be if there is a difference between hospitals in how the different methods of IOL are used, affecting the results. In study I and V, women were excluded if they were not literate in Swedish, thus excluding many immigrants, and this makes it difficult to generalize to all ethnic groups. In study V women from a large hospital in an urban area are included which might make it applicable to similar obstetric settings.

7. DISCUSSION

7.1 SPONTANEOUS ONSET OF LABOR

Skin conductance activity in post term pregnancies (study I)

Study I showed a statistically significant lower pain reaction during the cold pressor test in women close to spontaneous onset of labor compared to women that were induced to labor before 294 days of gestation (p=0.02). 63% (19/30) of the participating women with a spontaneous onset of labor had a negative value at the cold pressor provocation, compared to 30% (6/20) of the women with IOL. The possibility of having a spontaneous onset of labor increased 4.0 times if the skin conductance score was negative and increased 6,8 times for labor to start within 48h if the cervix was open ≥2 cm. Nine of the participating women had a negative skin conductance score in combination with a cervical dilatation >2 cm. All of them had a spontaneous onset of labor within 48h. Our findings indicate that a decreased response to pain stimuli, as a sign of the sympathetic nervous system decreased sensitivity, has a strong correlation to spontaneous onset of labor in post term pregnancy.

According to the WHO, pregnancies with gestational age longer than 293 days (first day of the LMP) are considered prolonged, resulting in post term labor [104]. Perinatal morbidity increases with gestational age, especially after 39 weeks of gestation. [105]. Compared with pregnancies at term (37+0-41+0 weeks of gestation), post term pregnancies result in greater risk of complications for both the child (meconium aspiration, fetal distress, traumatic injury) and the mother (PPH, dystocia, CS) [30].

Grunewald et al. showed that there are no advantages to continue pregnancy after 42+0 gestational weeks, and that the risk of morbidity for mother and fetus was increased in post term pregnancies. Since a decrease in the perinatal morbidity was seen with active management in post term pregnancies, this was recommended [1]. Other studies show similar results, and an important aspect is also that the woman in several studies prefer an active instead of expectant management [106].

Due to increased risk of complications as mentioned above, a good prediction of spontaneous onset of labor has to be considered as very important for both fetus and the woman. There is a major controversy about the recommendations for handling uncomplicated post term pregnancies especially when the status of the cervix is

unfavorable. It is suggested that post term pregnancies should be handled in two ways: IOL at 41 weeks of gestation, or IOL at 42 gestational weeks or more if labor does not start spontaneously. However, the spontaneous onset of labor is usually preferred, since it generally means lower risks of complications compared to IOL (explained in next section).

As we concluded in study I, the use of skin conductance activity might be a more objective method in the future for determining the imminence of onset of labor. Evidence indicating what starts human parturition is still lacking. A method that could predict spontaneous onset of labor would be a valuable contribution to the clinical management of the post term woman.

7.2 INDUCTION OF LABOR

Labor induction with orally administered misoprostol: a retrospective cohort study (study II)
Slow release vaginal insert of misoprostol versus orally administered solution of misoprostol for induction of labor: a randomized controlled trial (study V)

In this retrospective cohort study of 4002 women (study II) with mixed parity we found that an orally administered solution of misoprostol is an effective and safe method for IOL. The lowest rate of CS overall, for both primi- and multiparous women with an unfavorable cervix BS ≤5, was found in the group where oral solution of misoprostol was administered, compared to balloon catheter and Minprostin®.
Our main findings are consistent with earlier studies, such as the study published by Agideh et al. [107], and in the Cochrane review recently published by Alfirevic et al. [4].

The delivery time was shorter in the balloon group (12h), and the women in the balloon group had a more favorable cervix (BS=5) compared to the Cytotec® and Minprostin® groups who had a longer delivery time (20h) and a more unfavorable cervix (BS=3).

This is probably the explanation why the time is shorter when balloon catheter was used. A common criticism when oral solution of misoprostol is used, is that it takes a long time to induce labor, but it is not taken into account that the women who usually receive Cytotec® have a more unfavorable cervix. The proportion of emergency CS decreased from 26% to

17% when an oral solution of Cytotec® was introduced at the delivery ward in Sodersjukhuset (p<0.01) without increased complication for the women and children, which is of major importance.

In study V our main finding was that the induction-to-vaginal-delivery time (the time interval from drug administration to vaginal delivery) was significantly shorter in the MVI group, 3.2h compared to the Cytotec® group (p=0.04). But the MVI group had significantly more women with hyperstimulation during labor with non-reassuring CTG (p <0.01) and women who received Terbutaline (Bricanyl®) during labor (p<0.01). There was no difference in the proportion of women with VD24, (p=0.40) between the two groups, despite of the shorter time of labor in average in the MVI group.

For primiparous with intact membranes a benefit of vaginal administration was suggested, with a higher chance of VD24. This was not seen in the present study (study V), and the rates of CS in both groups were similar and low; 14.1% with oral solution of misoprostol and 19.6% with MVI (p=0.56), compared to other studies [108, 109], where the rate of CS was higher even with mixed parity.

Shorter time of labor has several benefits, such as lower frequency of infection and less use of oxytocin and it will also decrease the demand on hospital resources as staff etc. [109]. When using MVI as we did in study V, the delivery time was shorter but there was no decrease in oxytocin use, infection rate or better delivery outcome like decreasing rate of CS. Using MVI caused an increased risk of hyperstimulation with non-reassuring CTG, which could lead to an increased risk of fetal asphyxia, why IOL with MVI cannot be used in other settings except the delivery ward that had a high standard of fetal surveillance during labor due to safety reasons.
The time was 3.2h shorter in average with MVI compared to oral solution of misoprostol, which is of importance for the busy delivery wards. But a disadvantage is that IOL with MVI had to take place in the delivery ward because of safety reason. The average time that the women had the MVI inserted was 9.5h, which means almost 10h at the delivery ward without active labor, while oral solution of misoprostol could be administered at the antenatal care or in a ward for IOL.

The health care given to women in different settings is largely unequal as well as disparate. In poor-resource settings the problem is "too little, too late care" [110], while risk for over-

medicalization and interventions like unnecessary CS, routine IOL, augmented labor with oxytocin, continuous CTG and episiotomy of healthy and normal pregnancies is the problem in high and middle income countries. "Too much, too soon care" without supported evidence may rather harm women and raise the health costs for society. In countries like Sweden with lower rates of obstetric interventions, midwifes taking care of women with normal pregnancies while the obstetricians focus on high-risk pregnancies and complications during labor [111]. This system decreases the risk for over-medicalization in healthy women.

The growing problem of over-medicalization is a large problem in middle-income countries, like Dominican Republic, Brazil and Egypt that have the world's highest rate of CS between 51.8-58.9%. CS seems to be more common in private settings and in wealthy women. Another risk with all these clinics performing too many CS, is the lack of skills attending normal births, and knowledge on the normal process of labor.

In addition to CS, interventions like IOL, augmentation of labor with oxytocin, epiostomy can be both live-saving and harmful depending on the different situations and settings.

The rate of IOL differs a lot between countries too, from less than 5% in some low-resource settings like Kenya and Paraguay to 71% in Iran. This overuse of obstetric interventions and over-medicalizations like CS and IOL may be life-threatening due to complications such as UR, infections and PPH [111].

7.3 INDUCTION OF LABOR AFTER ONE PREVIOUS CESAREAN SECTION

Induction of labor in women with a uterine scar (study III)
Induction of labor after one previous Cesarean section in an unfavorable cervix: a retrospective cohort study (study IV)

The increasing numbers of CS worldwide, is a cause for concern and deserves serious attention. The procedure is not benign and should only be practiced when conditions clearly demand it [112]. It is of high importance to avoid the very first CS, for the woman and the fetus and for the future, unless it is necessary. The increasing proportions of CS in many countries, in healthy women with normal pregnancies and expected normal births also causes

a loss of knowledge of the normal delivery process, which is of major concern in addition to the increasing complications that may occur after a CS.

UR could be a life-threatening complication for both mother and fetus, other adverse outcomes such as severe hemorrhage, bladder laceration, hysterectomy, and neonatal morbidity are more common [113]. A dehiscence does not lead to any serious maternal or neonatal consequences and it is often incidentally discovered at the time of CS.
In high income countries, most UR are associated with TOLAC, but in poor resource settings, UR are mainly associated to obstructed labor and lack of access to operative delivery [114].
In study III the high incidence of UR was explained by the inclusion of cases of dehiscence, where only two out of nine recorded UR were total ruptures with fetal parts in the abdominal cavity. Notably, was that none of the total UR had received oral solution of misoprostol.

In a conference on VBAC, The National Institutes of Health Consensus Development confirmed that the incidence of UR in women with a prior CS was about 325 per 100,000 women experiencing a TOLAC [115].
Despite a low risk of UR, management of VBAC is controversial. The first study of IOL in women with a previous CS demonstrated that prostaglandin administration is a safe procedure to achieve vaginal delivery and that the risk of UR is low [116].

Prolonged labor and high intrauterine pressure have been associated with unfavorable cervix, and since labor dystocia is a risk factor for UR, an unfavorable cervical status at IOL may be a confounding factor of importance for UR [76].

In study IV we showed that despite an unfavorable cervical status at the start of IOL, almost 70% of the women deliver vaginally in 24h when IOL with oral solution of misoprostol or balloon catheter were used.

Women with unfavorable cervical status at IOL are more likely to have higher frequency of oxytocin infusion, longer duration of labor and are often induced with prostaglandins. Due to this fact it is not surprising that observational and non- RCT studies showed an increased risk of UR when prostaglandins are used for IOL [117].

The method of IOL with the highest success rate and lowest risk of UR has not been confirmed in this high risk population [118].

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If prostaglandins, administered in various forms compared to other methods of IOL really is associated with an increased risk of UR, is still not known and debated [74, 83]. Vaginal administration of misoprostol was associated with an increased risk of UR according to Wing, Aslan, and Plaut et al [92-94]. Despite the limited scientific knowledge, all various forms of administrations of misoprostol have been discouraged in different guidelines for IOL among women with a former CS [11, 95, 106]. However, the evidence is based on small studies where only vaginal misoprostol had been used, why there is an uncertainty in scientific knowledge.

There is no evidence that methods for IOL should be less effective among women with a former CS, and therefore it is logical to use the same methods for IOL as in women with no previous CS [117].

When prostaglandins were used for IOL after a previous CS, there was no statistically significant difference in the rate of UR compared to other methods of IOL [74]. There are some studies that describe outcomes for IOL with oxytocin alone, but only a few describe outcomes for use of prostaglandins alone. In one of these studies Macone et al. showed there were no associations between UR and prostaglandins used solely however prostaglandin in combination with oxytocin was associated with UR (OR 3.07, 95% CI 0.98-9.88) [119]. In summary IOL with oxytocin alone resulted in 11 UR per 1000 VBAC and IOL without prostaglandins (mechanical dilation with or without oxytocin) resulted in 9 UR compared to IOL with prostaglandins with or without oxytocin that resulted in 14 UR per 1000 VBAC.

Study IV shows that IOL with oral solution of Cytotec® after one previous CS is a safe and effective method well comparable with the use of a balloon catheter, despite a more unfavorable status of the cervix. Oral solution of Cytotec® gives a significantly increased rate of VBAC compared to Minprostin® (69.2 vs 57.2%, p=0.02) and the same successful rate as balloon catheter (69.2 vs 69.0%) even though the primary BS was different in the two groups (lower in the Cytotec® group).

Whether UR is dependent on frequency and duration of contractions during labor is difficult to prove. To avoid hyperstimulation of the uteri must be preferable to reduce the stress of the uterine wall. When using oral solution of misoprostol, the occurrence of hyper-stimulation was low (1%) compared to the Minprostin® group where at least 15% experienced hyper-stimulation at the clinic (no published data available). Our current results are in accordance with Gemzell-Danielsson et al. [65, 96], How et al [120] and

Aronsson et al [65] who concluded that orally administered misoprostol actually caused less uterine hyper-stimulation than vaginal or sublingual administration. Furthermore, the proportion of CS decreased significantly in the group of women with a previous CS after IOL when an oral solution of Cytotec® was introduced at the delivery ward in Sodersjukhuset, without increasing complications.

There are no other previous studies to this date that have investigated the safety and effectiveness of oral solution of misoprostol for IOL in women with a previous CS, only the vaginal route has been investigated. According to the results in study IV we suggest that it is time to update the guidelines for IOL in women with a previous CS and to include oral solution of misoprostol as an option when labor needs to be induced. In our opinion, an oral solution of misoprostol is a good alternative when IOL is needed in women with one previous CS and an unfavorable status of the cervix.

However, safety and not effectiveness is the most important in the decision for the obstetrician in these women with high-risk pregnancies. The indication for IOL must be considered together with other potential risk factors before IOL in women with a previous CS should take place.

8. CONCLUSIONS

➢ Spontaneous onset of labor is usually preferred, since it in general means lower risks of complications compared to IOL. Knowledge of what actually initiates spontaneous onset is still lacking. Our findings indicate that a decreased response to pain stimuli, as a sign of the sympathetic nervous system decreased sensitivity, has a strong correlation to spontaneous onset of labor in post-term pregnancy. This objective information is a new knowledge that hopefully can be used together with a vaginal assessment when handling post-term pregnancies in the future.

➢ Oral solution of misoprostol for IOL in women with an unfavourable cervix is safe, cheap, easy to control and can be used in all settings as oral solution of misoprostol gives a high success rate of vaginal deliveries without hyperstimulation. If the time of labor can be shortened, the frequency of CS decreased, and the proportion of healthy mothers and children increased, this will lead to safer and better obstetrical care. In the long run, probably even to a shorter length of stay in hospital, which is interesting also from a socioeconomic perspective. These studies give further support to the feasibility of an oral solution of misoprostol for IOL which is in line with the updated recommendations from FIGO.

➢ UR is an unusual and serious complication, and increase with the numbers of increasing TOLAC. However, a successful VBAC represents the lowest risk for the woman after one previous CS, why it is of great importance to choose the women suitable for IOL after one previous CS. Oral solution of misoprostol is a good method for IOL even among women with one previous CS and is as safe as balloon catheter. Most UR occurred when Minprostin® was used (5.0%), the risk is more than two-fold compared to oral solution of misoprostol and balloon catheter. Both methods give a high success rate of VBAC (almost 70%) despite an unfavorable cervix.

9. CLINICAL AND SCIENTIFIC IMPLICATIONS

9.1 IMPLICATIONS IN CLINICAL PRACTICE

Awareness of risks with IOL can help to identify women suitable for IOL with or without a previous CS. It is important to have a strict indication before IOL is performed as the procedure is associated with higher risk of complications during labor and instrumental deliveries like vacuum extraction and CS.

To have a good experience and knowledge of different methods for IOL is of major importance to provide a safe and effective obstetric care.

It is further of importance to have safe and effective methods for IOL to reduce the risk of - and possibly avoid - a first CS in healthy low-risk women.

To increase awareness among the general population and to inform women of the risks with IOL and elective CS is a major and important challenge for the staff in obstetric care especially the obstetricians.

In case approved oral preparations for IOL is lacking oral solution of misoprostol should be used to provide a safe and effective method for IOL, with low proportion of CS without affecting maternal and neonatal outcome.

9.2 IMPLICATIONS FOR THE RESEARCH FIELD

Research is still lacking of what actually initiates onset of labor. A larger study similar to study I as well as development of a simpler skin conductance test that would make it more applicable in daily obstetric care would be welcome contributions to this field of research.

There is a gap of knowledge regarding which factors that actually make women respond to misoprostol; BMI, receptors, gestational age, BS, other factors?

Another important study on oral administration of misoprostol is if women would benefit from a step-wise increased dose of misoprostol to 50 ug, after for example tree doses of 25 ug

misoprostol with no response. A possible future study would be to perform a RCT and randomized women to either raised doses of misoprostol after three doses or the regular administration of 25 ug every second hour up to a maximum of eight times.

It is of major importance to perform a RCT of IOL with balloon catheter and oral solution of misoprostol in women with a previous CS, since retrospective studies do not give the same conditions. The group in study IV that received balloon catheter had a more favorable cervix than the other groups which makes it difficult to compare the groups.

Recently an oral preparation of misoprostol has been approved for IOL; Angusta® 25 mch tablets. However, in settings where the dedicated product is not available oral solution of misoprostol is a good off label alternative. A package of Angusta® contains eight tablets of misoprostol in the doses of 25 ug, the tablet has to be swallowed and not mixed in water. Before the preparation was approved it was not compared with the off-label use of oral solution of misoprostol, only with dinoproston, vaginal administration of misoprostol and oxytocin. Therefore, it is of high importance to detect if there are any differences between the two different administration forms of misoprostol; oral solution or as a tablet. A RCT of these two different preparations is needed.

Another possible approach to develop method of inductions would be to use mifepristone for IOL. Based on the mechanism of action and physiology of labor this would be a logic approach. So far there are only very few studies available with unclear rational for the dose chosen.

10.   POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Vad som initierar starten av en förlossning är fortfarande inte känt och det diskuteras huruvida exspektant eller aktiv handläggning är bäst för kvinnan och hennes ofödda barn. Aktiv handläggning betyder i det här sammanhanget förlossningsinduktion, vilket är en mycket vanlig obstetrisk intervention och innebär att man försöker starta förlossningen artificiellt. Under de senaste fem åren inducerades 17% av alla enkelbördsgraviditeter i Sverige. Internationellt är siffrorna mycket högre, i medel kring 30%. Variationerna är mycket stora, från mindre än fem procent i vissa afrikanska länder som t.ex. Kenya, till extrema fall som i t.ex. Iran där man inducerar upp mot 80% av förlossningarna. Förlossningsinduktion är associerad med komplikationer både för kvinnan och barnet, såsom långdragen förlossning, stor blödning efter förlossningen, infektioner och instrumentell förlossning med sugklocka/tång eller kejsarsnitt. Eftersom förlossningsinduktion är en vanlig obstetrisk intervention innebär det att många kvinnor kommer att induceras, därför är det av största vikt att hitta en säker och effektiv metod.

Den ökande andelen kejsarsnitt i stora delar av världen på friska kvinnor med normala graviditeter och förväntade normala förlossningar medför också att kompetensen för att handlägga det normala förlossningsförloppet går förlorad. Bristen på upprätthållen kompetens är ett stort problem utöver den ökade frekvensen komplikationer som förekommer efter ett kejsarsnitt. Ett annat problem är att det i vissa delar av världen görs det för få kejsarsnitt pga. bristande resurser. De ojämlikt fördelade resurserna och den på många håll övermedikaliserade vården förorsakar stor oro globalt.

Vilken handläggning som är den ideala vid den efterföljande förlossningen för kvinnor som har genomgått ett tidigare kejsarsnitt har länge diskuterats.
Det finns två alternativ: försök till vaginal förlossning eller ett planerat kejsarsnitt. Ett eller flera genomgångna kejsarsnitt är den viktigaste riskfaktorn för ruptur av livmodern (vilket innebär att livmoderns vägg inte håller för värkar=uterusruptur). Uterusruptur är en välkänd och fruktad men trots allt ovanlig komplikation vid vaginala förlossningar hos kvinnor med ett tidigare genomgånget kejsarsnitt. Uterusruptur förekommer i princip inte om man inte har gjort en operation i livmodern, där kejsarsnitt är den vanligaste typen av operation. Risken för uterusruptur är minst dubblerad när förlossningen induceras. I Sverige får

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kvinnor föda vaginalt efter ett tidigare kejsarsnitt oavsett om förlossningen startar spontant eller induceras, vilket inte är självklart i andra länder pga. bristande resurser och möjligheten till övervakning. Således bör resurser läggas på en god förlossningsvård för att försöka att undvika det första kejsarsnittet som kan innebära stora risker för kvinnan och hennes ofödda barn i framtiden.

Syfte

Det övergripande syftet med avhandlingen är att identifiera faktorer som är viktiga för beslutet av förlossningsinduktionen och att ta reda på vilken metod som är den mest effektiva och säkra för kvinnor med eller utan tidigare genomgånget kejsarsnitt.

Studie I var en prospektiv observationsstudie av 52 friska först-och omföderskor vid deras överburenhetskontroll i graviditetsvecka 41+3 på Södersjukhusets specialistmödravård i Stockholm. CTG, ultraljudsbedömning av mängden fostervatten, vaginal undersökning för att fastställa mognaden av livmoderhalsen (cervix) och en fem-minuters hudkonduktansmätning (sympaticusaktiviteten i nervsystemet mättes via tre klisterlapps-elektroder i handflatan, som vid en lögndetektor) inklusive ett "Cold pressor test" (innebar att kvinnan fick sänka ned tre av sina fingrar i ett isbad under en minut och sedan skatta smärtan) utfördes. Den primära frågeställningen i studien var att utvärdera om förändrad hudkonduktivitetsaktivitet skulle kunna förutsäga spontan start av förlossningen vid överburenhet. Resultatet visade att chansen till en spontan förlossningsstart ökade 4.0 gånger om hudkonduktansmätningens värde var negativt (jämfört med en baslinje) och ökade 6.8 gånger om en start av förlossningen skulle ske inom 48 timmar om cervix var öppen ≥ 2 cm.

Studie II var en retrospektiv kohortstudie av 4002 först och omföderskor med enkelbörd som inducerades med ett levande foster i huvudbjudning, vid graviditetslängden≥ 34 veckor på Södersjukhuset i Stockholm. Kvinnorna delades in i sex grupper utifrån vilken metod som användes vid förlossningsinduktionen, medicinsk igångsättning med Cytotec®, Minprostin®, Propess®, eller mekanisk vidgning, ballongkateter, amniotomi (innebär att man tar hål på fosterhinnorna så att vattnet går) eller värkstimulerande dropp, oxytocin. Metoderna för förlossningsinduktionen, bakgrundsdata och förlossningsutfall jämfördes. Den primära frågeställningen för studien var frekvensen av kejsarsnitt för varje induktionsmetod. Den lägsta andelen av kejsarsnitt för både först-och omföderskor med en omogen cervix (Bishop score≤ 5), återfanns i gruppen där Cytotec® administrerades som en oral lösning.

Studie III var en retrospektiv kohortstudie med 208 kvinnor som genomgick förlossningsinduktion efter ett tidigare genomgånget kejsarsnitt. Kvinnorna var uppdelade i två undergrupper utifrån vald induktionsmetod. Grupp 1 (n=121) var den icke exponerade gruppen, vilket innebar att ingen av kvinnorna erhöll Cytotec® vid induktionen. Grupp 2 (n=87) var den exponerade gruppen vilket innebar att de flesta kvinnorna (89%) fick en oral lösning av Cytotec®. Induktionsmetod, bakgrundsdata och förlossningsutfall jämfördes mellan de två grupperna. Den primära frågeställningen i studien var frekvensen av uterusrupturer i respektive grupp. Det fanns ingen signifikant skillnad i incidensen av uterusrupturer mellan grupp 1 och 2 (4.1 respektive 4.6 %, p=0.9) trots en mer mogen cervix i grupp 1.

Studie IV var en retrospektiv kohortstudie av 910 inducerade kvinnor som alla hade ett tidigare genomgånget kejsarsnitt och en omogen cervix. Studien utfördes på de fyra största sjukhusen i Stockholm. Kvinnorna delades in i tre undergrupper utifrån induktionsmetod, Cytotec®, ballongkateter och Minprostin®. Den primära frågeställningen i studien var att undersöka om det förelåg någon skillnad i andelen uterusrupturer mellan de tre metoderna. Resultatet visade att förlossningsinduktion med Cytotec® och ballongkateter hos kvinnor med ett tidigare genomgånget kejsarsnitt inte innebar någon signifikant skillnad i andelen uterusrupturer mellan grupperna (2.0 respektive 2.1 %, p=0,64). Minprostin® hade mer än dubbel så stor andel uterusrupturer (5.0%) jämfört med Cytotec® och ballongkateter. Cytotec® administrerad som en oral lösning och ballongkateter resulterade i en hög lyckandefrekvens av vaginala förlossningar nästan 70% jämfört med Minprostin® som endast hade 57% vaginala förlossningar.

Studie V var en randomiserad kontrollerad studie av 196 inducerade förstföderskor som hade en omogen cervix (Bishop score ≤4). Ingen av kvinnorna hade tidigare opererats i livmodern. De deltagande kvinnorna randomiserades till antingen en oral lösning av misoprostol (Cytotec®) eller vaginalt misoprostol (Misodel®) med långsam kontinuerlig frisättning) vid förlossningsinduktionen. Den primära frågeställningen var om induktion till vaginal förlossningstid skiljde sig mellan de två grupperna. Den vaginala administrationen av misoprostol med långsam kontinuerlig frisättning resulterade i en kortare induktion till vaginal förlossningstid jämfört med den orala lösningen av misoprostol, men innebar en högre risk för överstimulering av värkarbetet med CTG påverkan. Det fanns inga signifikanta skillnader i övrigt förlossnings eller neonatalutfall.

Konklusion

Vanligtvis är spontan start av förlossningen att föredra, eftersom det i allmänhet betyder lägre risk för komplikationer jämfört med förlossningsinduktion. Om förlossningen behöver induceras hos kvinnor med ett ogynnsamt cervixstatus är en oral lösning av misoprostol en säker och billig metod som är lätt att kontrollera och kan användas i alla kontexter eftersom det ger en hög lyckandefrekvens av vaginala förlossningar utan överstimulering.

Oralt administrerat misoprostol är också en bra metod för förlossningsinduktion bland kvinnor med ett tidigare genomgånget kejsarsnitt och är lika säker som när man använder ballongkateter. Båda metoderna ger en hög lyckandefrekvens av vaginal förlossning efter tidigare genomgånget kejsarsnitt (nästan 70%) trots en omogen cervix. Dessa studier ger ytterligare stöd för användandet av en oral lösning av misoprostol för förlossningsinduktion som överensstämmer med rekommendationerna från FIGO.

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