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INDUCTION OF LABOR BY FOLEY CATHETER

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ACADEMIC DISSERTATION

To be presented by the permission of the Medical Faculty of the University of Helsinki for public discussion in the Seth Wichmann Auditorium of the Department of Obstetrics and Gynecology, Helsinki University Hospital, on March 31st 2017 at 12 o'clock noon.

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To my family

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following publications:

I. Kruit H, Heikinheimo O, Ulander V-M, Aitokallio-Tallberg A, Nupponen I, Paavonen J, Rahkonen L. Management of prolonged pregnancy by induction with a Foley catheter. Acta Obstet Gynecol Scand 2015; 94 (6): 608-614.

II. Kruit H, Heikinheimo O, Ulander V-M, Aitokallio-Tallberg A, Nupponen I, Paavonen J, Rahkonen L. Management of Foley catheter induction among nulliparous women: a retrospective study. BMC Pregnancy and Childbirth 2015; 15:276.

III. Kruit H, Tihtonen K, Raudaskoski T, Ulander V-M, Aitokallio-Tallberg A, Heikinheimo O, Paavonen J, Rahkonen L. Foley catheter or oral misoprostol for induction of labor in women with term premature rupture of membranes: a randomized multicenter trial. American Journal of Perinatology 2016; 33 (9): 866-872.

IV. Kruit H, Heikinheimo O, Ulander V-M, Aitokallio-Tallberg A, Nupponen I, Paavonen J, Rahkonen L. Foley catheter induction of labor as an outpatient procedure. Journal of Perinatology 2016; 36 (8):618-622.

V. Kruit H, Heikinheimo O, Sorsa T, Juhila J, Paavonen J, Rahkonen L. Manuscript: Cervical Biomarkers as Predictors of Successful Induction of Labor by Foley Catheter. Submitted, December 2016.

 The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AFI	Amniotic fluid index
BE	Base excess
BMI	Body mass index
Bpm	Beats per minute
CI	Confidence interval
CS	Cesarean section
ELISA	Enzyme-linked immunosorbent assay
FC	Foley catheter
FGR	Fetal growth restriction
GBS	Group B streptococcus (Streptococcus agalactiae)
GDM	Gestational diabetes mellitus
IEMA	Immunoenzymometric assay
IGFBP-1	Insulin-like growth factor binding protein-1
IOL	Induction of labor
IVF	In vitro fertilization
MMP	Matrix metalloproteinase
NICE	National Institute for Health and Care Excellence UK
NICU	Neonatal intensive care unit
OR	Odds ratio
PG	Prostaglandin
PGE1	Prostaglandin E1
PGE2	Prostaglandin E2
PhIGFBP-1	Phosphorylated insulin-like growth factor binding protein-1
PROM	Premature rupture of membranes
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
RR	Relative risk
SD	Standard deviation
SOGC	Society of Obstetricians and Gynaecologists of Canada
SPSS	Statistical Package for Social Sciences
TIMP	Tissue inhibitor of metalloproteinase
WHO	World Health Organization

ABSTRACT

The rates of induction of labor (IOL) are rising worldwide; in 2015 approximately every fourth labor (24.8%) in Finland was induced. The role of cervical ripening in success of IOL is well established. Pharmacological and mechanical methods, including Foley catheter (FC), are available for cervical ripening. The methods have comparable vaginal delivery rates, but FC is associated with lower risk of uterine hyperstimulation and adverse events. The mechanism of FC use consists of direct mechanical dilation of the cervix and lower uterine segment, and local secretion of endogenous prostaglandins. Little is known of the effect of FC on cervical biochemical mediators, such as insulin-like growth factor binding protein-1 (IGFBP-1) and its phosphorylated isoform (phIGFBP-1), matrix metalloproteinases (MMPs), and their tissue inhibitors (tissue inhibitors of metalloproteinase, TIMPs). Although risk factors for induction failure, such as unfavorable cervix, post-term pregnancy, and nulliparity, are recognized, prediction of successful IOL is difficult. The aim of this study was to evaluate FC for labor induction in prolonged and post-term pregnancy, in nulliparous women, in women with premature rupture of membranes (PROM) at term, and in outpatient use. The secondary aim was to investigate the effect of FC on cervical biomarkers, and their predictive value in indicating the success of IOL by FC.

Our studies were conducted in the Department of Obstetrics and Gynecology of Helsinki University Hospital between 2011 and 2015. The randomized controlled trial (RCT) on labor induction after term PROM (III) was carried out in collaboration with Helsinki, Tampere, and Oulu University Hospitals. The participants were randomly allocated to IOL by FC or oral misoprostol in 1:1 ratio. In all studies, the data on study population characteristics, pregnancy, and delivery outcomes were collected from the hospital records. The main outcome measures of studies I–IV were the rates of cesarean section (CS) and maternal and neonatal infections. In study V, the main outcome measures were the concentrations of cervical biomarkers IGFBP-1, phIGFBP-1, MMP-2, MMP-8, MMP-9, TIMP-1, and TIMP 2. Univariate and multivariate logistic regressions were used to estimate relative risks (RRs) by odds ratios (ORs) with 95% confidence intervals (CIs). In the study on cervical biomarkers, serial cervical swab samples were collected at FC insertion and expulsion. The concentrations of IGFBP-1, phIGFBP-1, MMP-2, MMP-8, MMP-9, TIMP-1, and TIMP-2 were analyzed by immunoenzymometric assays and by commercial enzyme-linked immunosorbent assay (ELISA) kits.

The total study population consisted of 1693 women, of which 1344 (79%) underwent IOL by FC. The lowest rate of CS (24%) occurred in women undergoing IOL after term PROM, and the highest rate (44%) was observed in nulliparous post-term women (V). In post-term pregnancy, a sixfold risk (OR 6.2, 95% CI 3.2–12.1) of CS occurred in nulliparous women undergoing IOL compared to those with spontaneous onset of labor (37% vs. 9%; p<0.001). In multiparous women, the corresponding rates of CS were not significantly different (3% vs. 1%, p=0.2). The CS rates were significantly different neither between FC and misoprostol groups (24% vs. 18%; p=0.36), nor between outpatients and inpatients (32% vs. 32%; p=0.82). In our univariate analysis, the factors associated with an increased risk of CS in nulliparous women following IOL by FC were maternal age ≥ 37 years (OR 1.9, 95% CI 1.0–3.6; p=0.04), obesity (OR 1.8, 95% CI 1.1–3.1; p=0.03), gestational diabetes (OR 1.9, 95% CI 1.2–3.1; p=0.01), and Bishop score ≤ 3 (OR 1.6, 95% CI 1.1–2.4; p=0.02). By our multivariate analysis, need for oxytocin induction (OR 2.9, 95% CI 1.8–4.5), and request of early epidural analgesia (OR 9.9, 95% CI 2.1 – 47.5) were associated with increased risk of CS.

The median (range) rate of maternal intrapartum infections following IOL by FC was 5 (2–6) % in our study, and the rate of postpartum infections was 3 (1–4) %. The maternal intrapartum infection rates were not significantly different between induced and spontaneous labor (6% vs. 2%; p=0.13 in nulliparas, and 2% vs. 1%; p=0.54 in multiparas), between the methods of FC and misoprostol (2% vs. 2%; p=0.47), or between outpatients and inpatients (7% vs. 3%; p=0.51). Gestational diabetes was associated with an increased risk of intrapartum infection (OR 4.3, 95% CI 1.7–11.0; p=0.002). No significant risk factors were identified for postpartum infections. The median (range) rate of neonatal infections following FC induction was 6 (1–9) % (clinical sepsis 2 [1–3] % and suspected infections 4 [1–5] %). The neonatal infection rates were similar following FC and misoprostol (1% vs. 5%; p=0.22), and between outpatients and inpatients (5% vs. 5%; p=0.83).

The median cervical IGFBP-1 and phIGFBP-1 concentrations increased, while MMP-8, MMP-9, and TIMP-2 concentrations decreased during FC induced cervical ripening. However, there were no significant differences in the biomarker concentrations in successful and failed labor inductions.

In conclusion, labor induction by FC in prolonged and post-term pregnancy was as safe as spontaneous labor, but was associated with a high rate of CS in nulliparous women. Factors associated with the increased risk of CS in nulliparous women were advanced maternal age, obesity, gestational diabetes, unfavorable cervix, need for oxytocin induction, and request for early epidural analgesia. Since the first CS has a major impact on subsequent pregnancies, indications and management of labor induction in nulliparous

women should be carefully considered. FC and misoprostol can both be used for IOL in women with term PROM, with no difference in the rates of maternal or neonatal infections when prophylactic antibiotics are used. FC also appears safe and feasible for outpatient use. The concentrations of cervical biomarkers IGFBP-1 and phIGFBP-1 increase, whereas MMP-8, MMP-9, and TIMP-2 decrease during FC induced cervical ripening in nulliparous women. However, these cervical biomarkers appear unsuitable for predicting the success of labor induction.

INTRODUCTION

The incidence of induction of labor (IOL) is rising worldwide, with a rate of 20–30% in developed countries at present (1-3). In Finland, almost every fourth pregnancy is induced (4). The increasing rates of IOL may be explained by increasing maternal age, obesity, and medical conditions, as well as improved fetal monitoring. Several clinical guidelines and recommendations on indications and optimal timing for IOL exist (3, 5-7). The most common indications for IOL are post-term pregnancy and premature rupture of membranes (PROM) (1, 2, 8).

The exact mechanism of initiation of parturition is not completely understood. Cell-free fetal DNA has been suggested to trigger the biochemical process of cervical ripening, leading to onset of labor (9, 10). The role of cervical ripening in success of IOL is well established; an unripe cervix is associated with high risk of induction failure, failure to progress in labor, cesarean section (CS), infections, fetal distress, and postpartum hemorrhage (11-13).

The pharmacological and mechanical cervical ripening methods available in Finland include misoprostol and Foley catheter (FC). The use of FC has been widely adopted in clinical practice in Finland over the past few years. The mechanism of FC use consists of direct mechanical stretching of the cervix and lower uterine segment, and stimulation of endogenous prostaglandin (PG) release (14, 15). The rates of vaginal delivery and infectious morbidity are comparable following the use of FC and PG, as demonstrated by several studies (16-20). FC is associated with a lower risk of uterine hyperstimulation and adverse events, thus appearing suitable for use in outpatients and in women with a history of a previous CS (21-26). Little is known about the use of FC in women with PROM at term.

IOL has previously been considered to increase the rate of CS, but more recent research demonstrates that IOL is, in fact, associated with a decrease in CS rates compared to expectant management at or beyond term (27-31). Post-term pregnancy and nulliparity are significant risk factors for induction failure and perinatal complications (32, 33). When considering IOL, the indication, maternal and fetal well-being, gestational age, risk factors, and cervical ripeness need to be individually assessed, and the women informed of the risks and benefits related to IOL.

A quantity of maternal, neonatal, resource, and treatment related factors influence the total health care costs of labor induction. However, there is evidence that inducing labor in women with complications is associated with

lower health care costs than expectant management (34, 35). Moving the process of cervical ripening from inpatient to outpatient setting may also decrease use of health care resources and costs (26, 36). Maternal satisfaction is associated with several health, social, and care factors (37). Women may be less satisfied with their care if their labor is induced (38), which highlights the importance of information, support, and counseling in care of women undergoing IOL.

The present study was designed to investigate the safety and efficacy of the FC in labor induction. We specifically focused on IOL in late-term and post-term pregnancies, with an interest in nulliparous women, term pregnancies with PROM, and outpatient labor induction. Furthermore, we examined the effect of FC on cervical biomarkers, and their predictive value in the success of labor induction by FC.

FINNISH SUMMARY

Synnytyksen käynnistysten määrä on kasvanut kaikissa kehittyneissä maissa, nykyisin noin joka neljäs synnytys käynnistetään. Suomessa synnytyksistä käynnistettiin 13.9 % vuonna 1993, ja 24.8 % vuonna 2015. Synnytyksen käynnistys aloitetaan kohdunkaulan kypsyttämisellä mekaanisesti pallokatetrilla, eli ns. balonkimenetelmällä, tai lääkkeellisesti prostaglandiinilla. Kansainvälisten julkaisujen mukaan balonkimenetelmän ja prostaglandiinien tehossa, keisarileikkausten määrissä tai infektioiden esiintymisessä ei ole todettu eroja. Balonkimenetelmässä esiintyy kuitenkin vähemmän haittoja, kuten kohdun hyperstimulaatiota ja sikiön sykemuutoksia. Balonkimenetelmässä kohdunkaulan sisäsuun ja lapsivesikalvojen väliin viedään katetri, jonka päässä oleva balonki täytetään fysiologisella suolaliuoksella. Balonki laajentaa kohdunkaulaa mekaanisesti ja aiheuttaa myös endogeenisten prostaglandiinien vapautumista kudoksista. Balonkimenetelmän vaikutusta kohdunkaulakanavan biokemiallisiin välittäjäaineisiin, tai niiden vaikutusta balongilla käynnistetyn synnytyksen kulkuun ei tunneta.

Helsingin yliopistollisessa keskussairaalassa vuosien 2011 ja 2015 välillä toteutettu tutkimus selvittää balonkimenetelmän tehokkuutta ja turvallisuutta synnytyksen käynnistyksessä yliaikaisessa raskaudessa, ensisynnyttäjillä, lapsivedenmenon jälkeen, sekä polikliinisessa käynnistyksessä. Lisäksi halusimme tutkia kohdunkaulakanavassa tapahtuvia biokemiallisia muutoksia balonkikäynnistyksen aikana, sekä niiden vaikutusta synnytyksen käynnistymiseen.

Tulostemme mukaan balonkikäynnistys on yliaikaisessa raskaudessa (≥ 41+5 raskausviikolla) yhtä turvallista kuin synnytyksen spontaani käynnistyminen, mutta käynnistys kuitenkin lisää keisarileikkausten määrää ensisynnyttäjillä. Jopa yli kolmasosa ensisynnyttäjistä, joiden synnytys on käynnistetty, joutuu kiireelliseen keisarileikkaukseen, kun taas spontaanisti käynnistyneessä synnytyksessä vain joka yhdestoista synnytys päätyy keisarileikkaukseen. Tavallisin keisarileikkauksen syy on epäonnistunut synnytyksen käynnistys tai pitkittynyt synnytys. Synnyttäjän ikä ≥ 37 vuotta, ylipaino (BMI ≥ 30), raskausdiabetes, kohdunkaulan kypsymättömyys (Bishopin pisteet ≤ 3), oksitosiinin tarve supistusten aloittamiseksi ja aikainen epiduraalipuudutus (ennen säännöllisiä supistuksia tai kohdunsuun ollessa avautunut ≤ 3 cm) vaikuttivat käynnistyksen epäonnistumiseen. Äidin synnytyksenaikaisia infektioita esiintyi tutkimuksen aikana 5 (2–6) %, synnytyksenjälkeisiä infektioita 3 (1–4) % ja vastasyntyneiden infektioita 6 (1–9) % (kliinisiä infektioita 1.8 [1–3] % ja infektioepäilyjä 4 [1–5] %). Raskausdiabetes,

pitkittynyt synnytys ja aikainen epiduraalipuudutus liittyivät äidin ja syntyneen lapsen infektioihin.

Helsingin, Tampereen ja Oulun yliopistosairaaloiden yhteisessä satunnaistetussa monikeskustutkimuksessa vertasimme balonkia ja misoprostolia synnytyksen käynnistämisessä lapsivedenmenon jälkeen. Totesimme molempien olevan turvallisia vaihtoehtoja, eikä keisarileikkausten tai infektioiden määrissä ollut eroja käynnistysmenetelmien välillä. Tulostemme mukaan myös polikliininen balonkikäynnistys, jossa kohdunkaulan kypsytys tapahtuu kotona, on täysiaikaisissa normaaleissa raskauksissa yhtä turvallinen kuin osastopotilaana toteutettava balonkikäynnistys. Synnyttäjistä 85 % oli tyytyväisiä polikliiniseen menetelmään, ja yli 90 % koki saamansa ohjauksen riittävänä ja turvallisena.

Analysoimme balonkikäynnistyksen vaikutusta ensisynnyttäjien kohdunkaulan biokemiallisiin välittäjäaineisiin, kuten insuliininkaltaista kasvutekijää sitovaan proteiiniin-1 (IGFBP-1) ja sen fosfyryloituneeseen muotoon (phIGFBP-1), matriksin metalloproteinaaseihin (MMP) -2, -8, -9, sekä niitä säätteleviin estäjäproteiineihin (TIMP) -1 ja -2. Totesimme, että IGFBP-1- ja phIGFBP-1-pitoisuudet kohdunkaulassa lisääntyvät, ja MMP-8-, MMP-9- ja TIMP-2-pitoisuudet vähenivät balonkikäynnistyksen aikana. Näiden biomarkkereiden pitoisuuksien muutosten avulla ei kuitenkaan voitu ennustaa synnytyksen käynnistyksen kulkua tai synnytystapaa.

Yhteenvetona voidaan todeta, että balonki on tehokas ja turvallinen synnytyksen käynnistysmenetelmä, joka soveltuu myös polikliiniseen käyttöön ja synnytyksen käynnistykseen lapsivedenmenon jälkeen. Tutkimuksemme mukaan synnytyksen käynnistys ensisynnyttäjän yliaikaisessa raskaudessa kuitenkin lisää keisarileikkauksen todennäköisyyttä. Tutkimamme kohdunkaulan biomarkkerit IGFBP-1, MMP-2, MMP-8, MMP-9, TIMP-1 ja TIMP-2 eivät vaikuta soveltuvan kliiniseen käyttöön synnytyksen balonkikäynnistyksen onnistumisen ennustajina.

REVIEW OF THE LITERATURE

CERVICAL RIPENING AND ONSET OF LABOR

PHYSIOLOGY OF CERVICAL RIPENING

Cervical ripening consists of a series of biochemical processes involving various inflammatory mediators including PGs, interleukins, insulin-like growth factor binding protein-1 (IGFBP-1), matrix metalloproteinases (MMPs), and hormonal factors such as estrogen and progesterone (39-42). However, the exact mechanism is not completely understood. The cervix contains approximately 15% smooth muscle, mostly located in the upper segment of the cervix (43). The underlying stroma consists of collagen bundles, with glycosaminoglycan and proteoglycan molecules between the collagen fibers (43). During cervical ripening, an increase in hyaluronic acid concentration, and a decrease in dermatan and chondroitin sulfate concentrations, occur in the cervical stroma (44). The resulting reduction in collagen density, remodeling of collagen fibers, decreased collagen fiber strength, and diminished tensile strength of the extracellular matrix, contribute to cervical softening and swelling (44-47).

ASSESSMENT OF CERVICAL RIPENESS

The Bishop score

The degree of cervical ripeness is usually described by the Bishop score (48). The Bishop score, originally derived from multiparous women, utilizes cervical dilation, cervical effacement, cervical consistency, cervical position, and station relative to the ischial spines to estimate the degree of cervical ripeness (48). The initial scoring system by Bishop in 1964 used a maximum score of 13, with a score of 9 meaning that IOL and spontaneous labor were equally likely to result in vaginal delivery. In 1966, Burnett modified the Bishop score to the current form with each variable attributing 0–2 points to a maximum score of 10 (Table 1) (49). Friedman proposed a weighted score with cervical dilation having twice the influence of effacement, station, and consistency, and four times the influence of cervical position (50). Several later studies also emphasize cervical dilation as the most important contributor for success of labor induction, while consistency and position have the least predictive value (51-53). Later modifications of the Bishop

score, such as only using dilation, effacement, and station for determining cervical ripeness, have also been described (54).

Table 1. Determining the Bishop score (0−10) (49). Bishop score < 6 indicates unripe cervix, and score ≥ 6 is used as a marker for ripened cervix

Variable	Score		
	0	1	2
Dilation (cm)	0	1−2	3−4
Effacement (cm/%)	>3/0−30%	1−3/40−50%	<1/60−70%
Consistency	Firm	Medium	Soft
Position	Posterior	Mid	Anterior
Station	−3 or above	−2	−1−0

Transvaginal ultrasonography

Transvaginal ultrasonographic parameters, such as cervical length, cervical wedging, and the distance from fetal head to perineum (Figure 1), have been suggested useful in the assessment of cervical ripeness and predicting the outcome of IOL (55, 56). A recent study found ultrasonography better tolerated than vaginal exam (55). According to a recent review and meta-analysis of 735 pregnancies, a woman with ultrasonographic cervical length of ≤ 10 mm has an 85% chance of spontaneous delivery within a week (57). However, ultrasonographic assessment is not considered superior to vaginal examination or the Bishop score (58).

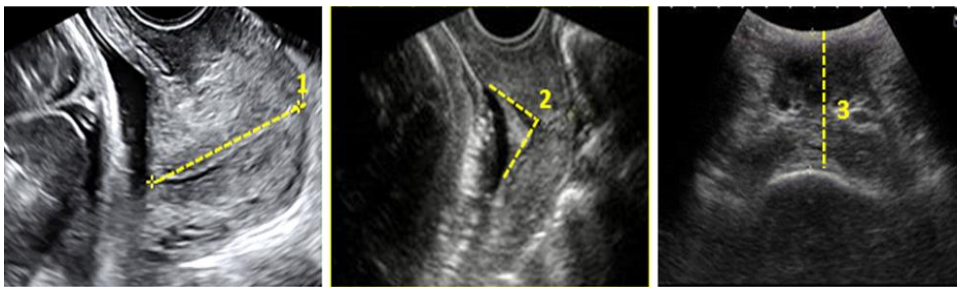


Figure 1. Ultrasonographic measurements (cm) of cervical length (1), cervical wedging (2), and distance from fetal head to perineum (3).

Cervical biomarkers

Some studies suggest that the presence of cervical fetal fibronectin, derived from the chorionic-decidual membranes, may be associated with initiation of labor at term (59, 60). However, many studies show no predictive value over the Bishop score or ultrasonographic determination of cervical length (58).
IGFBP-1 increases during pregnancy (61). Non-phosphorylated isoform of IGFBP-1 is the major protein in the amniotic fluid from the second trimester onwards, while decidual cells secrete phosphorylated isoforms (phIGFBP-1) (61, 62). Dogl et al. showed a correlation between an increased cervical IGFBP-1 concentration and spontaneous labor or successful IOL in post-term pregnancy (63). However, IGFBP-1 was not considered superior to cervical sonographic length or the Bishop score (63). PhIGFBP-1 reflects cervical ripeness, and the concentrations of cervical phIGFBP-1 increase during ripening induced with PG (64). Presence of cervical phIGFBP-1 was recently suggested to predict onset of spontaneous labor and vaginal delivery in term and post-term pregnancies (65).

MMPs contribute to cervical ripening and initiation of labor at term (66, 67). The proteolytic or non-proteolytic effects of MMPs and their tissue inhibitors (tissue inhibitors of metalloproteinase, TIMPs) in the cervical mucus may include degradation of local extracellular matrix components, thereby enhancing cervical softening and affecting the overlying cervical membranes (68). The concentrations of MMP-8 and MMP-9 are higher during labor compared to pregnant women not in labor (69, 70). TIMP-1 and TIMP-2 concentrations are also higher in the cervix during pregnancy compared to non-pregnant cervix (66), and increase in spontaneous labor (67). Also, an increase in TIMP-1 concentration has been observed during progressive cervical dilation in labor (45). The role of MMPs in assessing cervical ripeness is yet unknown.

ONSET OF LABOR AT TERM

An abundance of research regarding onset of parturition exists throughout the last century, yet the exact mechanism remains unclear. Multiple studies support the activation of inflammatory signaling pathways leading to increased secretion of cytokines and chemokines, uterine inflow of neutrophils and macrophages, production of uterotonins and uterine activation proteins including oxytocin receptors, and activation of MMPs (39-41). These biochemical processes may lead to cervical ripening, rupture of membranes, and myometrial contractions. Recently, cell-free fetal DNA, derived from placental trophoblasts and fetal membranes following apoptosis, has been suggested to trigger this inflammatory cascade and onset of labor (9, 10). The presence of cell-free fetal DNA in the maternal plasma,

as well as the presence of increasing placental and membrane apoptosis at term, supports the theory (71). Furthermore, recent studies provide evidence of increasing maternal serum concentrations of cell-free fetal DNA during the last weeks of gestation, with a peak just before parturition followed by a fall to undetectable levels by some hours postpartum (72).

HISTORY AND TRENDS OF LABOR INDUCTION

The concept of IOL has existed throughout recorded history, mechanical dilation of the cervix being the oldest induction method (73). Before the first century A.D., Hippocrates described the use of mammary stimulation and manual dilation of the cervical canal for labor induction (74). Methods of IOL have significantly evolved over the last century, improving safety and labor outcomes. Until 1931, IOL was carried out by surgical dilation of the cervix, including use of pressurized douches, laminaria tents, elastic cylinders (bougies), fluid-filled bags (de Ribes bags), early versions of balloon catheters, and even vaginal CS (74). The use of aggressive surgical procedures, associated with high rates of maternal mortality, rapidly decreased as medical options were developed (73). Also, amniotomy became the surgical method of choice by 1948 (73). Amniotomy was introduced in 1810 by James, but was first avoided due to the belief that amniotic fluid loss endangered the fetus (73). Until 1955, high amniotomy (rupturing the membranes with a catheter and a metallic wire as high above the fetal head as possible) was preferred over low rupturing of the membranes, as preserving the membranes was thought to accelerate cervical dilation (74).

The concept of cervical balloon catheter was first introduced by Gariel and Mattei in 1854 (75). The first balloons were made of rubber or sheep's bladder, and were applied for cervical dilation after onset of labor. Mattei first described the intrauterine placement and traction of the catheter, while Storer suggested the use of water for balloon distension (75). Several improved versions of balloon catheters were developed during the end of the 19th century (75). After pharmacological options were invented, the use of unhygienic and infection-prone balloon catheters decreased (75), until reintroduced by Embrey and Mollison in 1967 (76).

The first pharmacological methods included ergot alkaloids, castor oil, quinine, and teratogenic stilboestrol (73). Oxytocin, extracted from the pituitary gland by Dale, was first used for IOL in 1909 (74). However, the method was first discarded, since the impurities and erratic intramuscular and subcutaneous administration resulted in increased adverse perinatal outcomes (73). In 1953, the formula of oxytocin was discovered, and

synthetic intravenous oxytocin gradually became a common pharmacological method for IOL (74). PGs, first introduced by Karim et al. in 1968, became commercially available for labor induction in 1980 (77).

IOL is defined by the World Health Organization (WHO) as initiation of labor by artificial means prior to its spontaneous onset at a viable gestational age, with the aim of achieving vaginal delivery in a pregnant woman (3). An average of 20–30% of women undergo IOL in developed countries, and the incidence is rising worldwide (1-3). According to the European Perinatal Health Report, the rates of IOL vary between 7% and 32% in European countries (1). In the USA, the rates of IOL have more than doubled, from 9.5% to 23.4%, during the last two decades (2). In the UK, the IOL rate has been relatively high over the past 20 years, with a modest increase from 18.3% to 20.8% (78). A secondary analysis of the WHO Global Survey reported a 4.4% rate of IOL in African countries, while in Asia the IOL rate is 12.1% (79). In Latin America, the rate of IOL is 11.4%, but the rates of CS are some of the highest in the world (80).

In Finland, the rate of IOL has risen from 13.9% to 24.8% over the past 20 years (Figure 2) (4). The increase is observed at all gestational ages (Figure 3) (4).

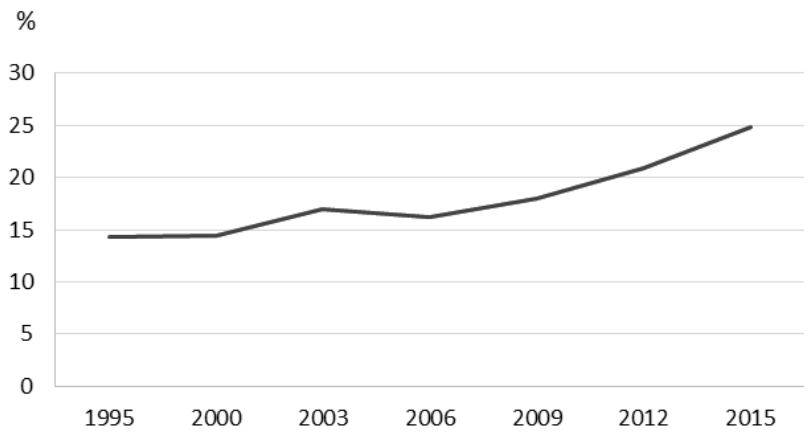


Figure 2. The rates of labor induction in Finland during 1995–2015 (4).

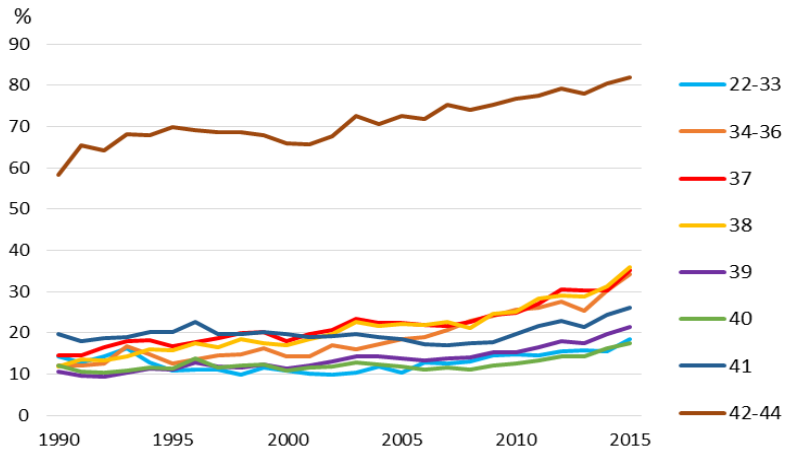


Figure 3. Labor inductions in Finland in 1990-2015 according to the gestational age in weeks (4).

The rates of IOL vary considerably between individual hospitals in Finland (10.5–38.6%, Figure 4) (4). In Helsinki University Hospital, the rate of IOL was 21.8% in 2015 (4). The differences between individual hospitals may be explained by differences in the proportions of maternal age, weight, and pregnancy complications, as well as different management practices and distances to the delivery unit.

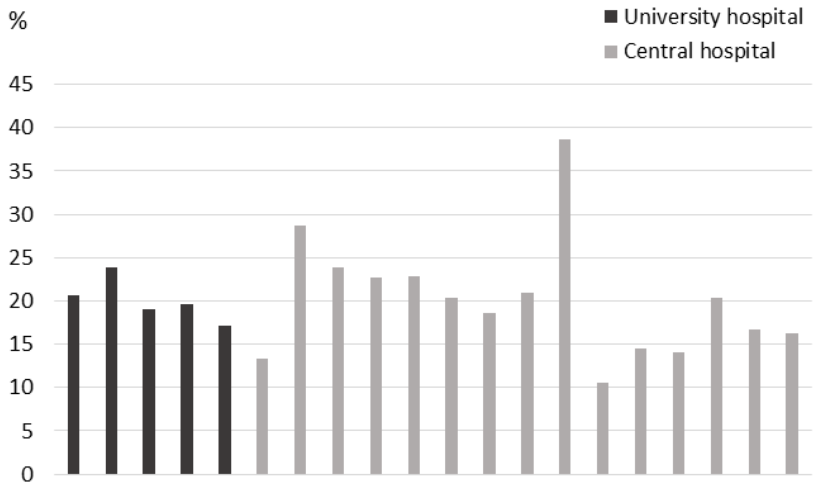


Figure 4. The average rates of labor induction in Finnish university hospitals (n=5, annual delivery rates 2441−14 476) and central hospitals (n=15, annual delivery rates 275−2955) during 2007−2015 (4).

INDICATIONS AND TIMING OF LABOR INDUCTION

The decision on labor induction should be carefully weighed against the potential risks and benefits of continuing the pregnancy. Several clinical guidelines and recommendations on indications for IOL have been published, such as the WHO recommendations, the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, the Clinical Practice Guidelines of the Society of Obstetricians and Gynaecologists of Canada (SOGC), and the National Institute for Health and Care Excellence (United Kingdom, NICE) guidelines (3, 5-7). Indications for IOL according to these guidelines are presented in Table 2 (3, 5-7). The most common indications for IOL are post-term pregnancy and term PROM, constituting 50–60% of all inductions (1, 2, 8). Although labor is mostly induced for maternal or fetal indications, elective inductions for non-medical indications have also increased (8, 81). IOL may, for example, be considered for psychosocial or logistic reasons, such as maternal exhaustion or distance to delivery unit. However, each pregnancy should be assessed individually, considering maternal and fetal well-being, gestational age, risk factors, and cervical ripeness.

Contraindications for IOL comprise vasa previa, complete placenta previa, transverse fetal lie, umbilical cord prolapse, pelvic structural deformity, invasive cervical carcinoma, previous uterine rupture, active primary genital herpes infection, previous classical CS, history of more than one previous CS, and uterine surgery entering the endometrial cavity (3, 5-7). According to the NICE guidelines, severe fetal growth restriction (FGR) with confirmed fetal compromise should also be considered a contraindication for IOL (7). Furthermore, the existing guidelines for IOL in breech presentation are controversial. The SOGC guidelines do not recommend IOL (6), while the NICE guidelines state that IOL in breech presentation should not be routinely offered but may be considered after discussing the potential risks with the woman (7). The ACOG and most European national guidelines have no recommendation on the topic, while IOL in breech presentation is in some hospitals practiced with careful clinical criteria (82). The few existing studies with sample sizes of 13–73 pregnancies have reported favorable maternal and neonatal outcomes following IOL in term breech presentation (82-84).

Table 2. Indications for labor induction according to the guidelines of WHO, ACOG, SOGC, and NICE (3, 5-7)

WHO recommendations	ACOG recommendations	SOGC recommendations	NICE recommendations
Post-term pregnancy	Post-term pregnancy	Post-term pregnancy	Post-term pregnancy
PROM	PROM	PROM	PROM
	Intrauterine fetal death	Intrauterine fetal death	Intrauterine fetal death
	Preeclampsia	Preeclampsia	Maternal request
	Chorionamnionitis	Chorionamnionitis	
	Gestational hypertension	Antepartum hemorrhage	
	Placental abruption	Diabetes mellitus	
	Maternal disease[1]	Maternal disease[1]	
	Fetal compromise[2]	Fetal compromise[2]	
	Logistic reasons[3]	Twin pregnancy ≥ 38 weeks	
		Logistic reasons[3]	

[1]Diabetes, hypertension, renal disease, chronic pulmonary disease. [2]Severe fetal growth restriction, isoimmunization, oligohydramnios. [3]Fear of rapid labor, psychosocial reasons, distance from hospital

POST-TERM PREGNANCY

Post-term pregnancy is defined as a pregnancy extending to ≥ 42^{+0} weeks (≥ 294 days) (85). Approximately 5% of pregnancies continue post-term (1, 85). The incidence of post-term pregnancy depends on pregnancy dating, fetal monitoring, management protocols, number of elective CSs, and population characteristics, such as genetic predisposition and pregnancy complications. Known risk factors for post-term pregnancy include nulliparity, age > 30 years, low socioeconomic status, prior post-term pregnancy, male fetus, and white ethnic origin (86-88). In Finland, 8–10% of pregnancies extend beyond 41 weeks of gestation, and the rate of post-term pregnancy has ranged between 4.1% and 5.4% during the last 20 years (Figure 5) (4).

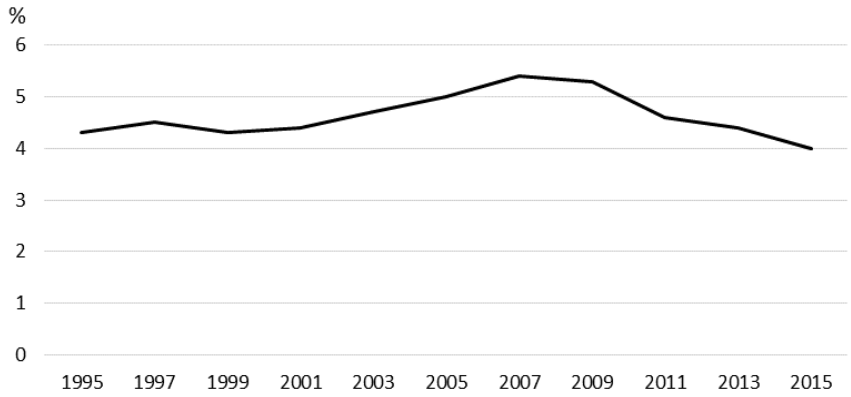


Figure 5. The rates of post-term pregnancies (≥ 42 weeks) in Finland during 1995−2015 (4).

In the Nordic countries, the rate of post-term pregnancy is the lowest (1.9%) in Denmark, and the highest (7.1%) in Sweden (Figure 6) (89). The rates of post-term pregnancy have decreased in Norway and Iceland, perhaps due to implementation of antenatal pregnancy dating, and a more active induction policy.

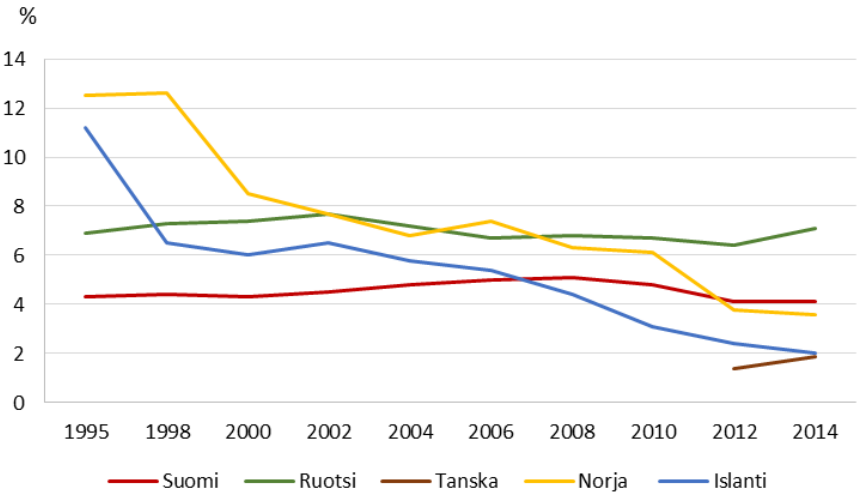


Figure 6. The rates of post-term pregnancies (≥ 42 weeks) in the Nordic countries 1994−2014 (89).

Post-term pregnancy is associated with increased risk of perinatal mortality and morbidity, including placental failure, meconium aspiration, shoulder dystocia, macrosomia, and fetal asphyxia (32, 33). The risk of stillbirth in post-term pregnancy is twice as high as at term, and more than sixfold at 43 gestational weeks (85). After term, the risk of stillbirth increases tenfold in fetuses with growth restriction or oligohydramnios as a consequence of placental failure, and in these cases IOL is recommended by term (90). For the neonate, post-term pregnancy is also a risk factor for death in the first year of life as well as for cardiovascular and metabolic diseases later in adulthood (91, 92). The rates of maternal adverse outcomes and operative deliveries also increase with increasing gestational age beyond 40 weeks (32, 33).

The Cochrane review (n=9383) concluded that IOL at 41 gestational weeks results in improved perinatal outcomes without increasing the rate of CS (31). A Danish national cohort study (n=832 935) reported a decrease in risk of stillbirth after introducing a more proactive induction policy in Demark (28). Women with increased risk of stillbirth, such as women with body mass index (BMI) > 30, women > 40 years of age, and women with a pregnancy complication, were induced by 41 gestational weeks (28). In a recent review of 157 randomized controlled trials (RCTs) (n=31 085), the rates of CS, stillbirth, and neonatal intensive care episodes decreased following IOL at 40 gestational weeks compared to expectant management (27). Furthermore, a retrospective cohort study comparing the outcomes of elective induction and expectant management in 1 271 549 women with gestational age of 37–41 weeks, suggests that IOL can reduce perinatal mortality without increasing maternal complications (93).

TERM PREMATURE RUPTURE OF MEMBRANES

Term PROM occurs in approximately 8% of pregnancies (94). PROM is defined as rupture of membranes at least one hour before the onset of contractions. Sixty percent of the women with PROM deliver spontaneously within 24 hours (95). Prolongation of the onset of labor for more than 24 hours is associated with an increased incidence of chorionamnionitis and neonatal sepsis (95, 96). The TERMPROM trial (n=1670) also reported less chorionamnionitis and neonatal infections following IOL by oxytocin compared to IOL with vaginal PGs (95). The management guidelines for PROM recommend immediate IOL as well as expectant management for 24-48 hours (94, 97, 98).

PROM is also a risk factor for Group B streptococcus (GBS) infection (95). GBS is the leading cause of early neonatal sepsis, and also associated with maternal peripartum infections (99). Approximately 10–30% of pregnant

women are GBS-positive (99). The TERMPROM trial reported a higher rate of neonatal infections in GBS-positive women managed expectantly after PROM compared to IOL (95). A recent cohort study of 542 women showed similar rates of infections in GBS-positive and GBS-negative women following membrane stripping (100). Studies on FC induction in GBS-positive women are non-existent. A small cohort study (n=45) reported an increase in GBS-colonization during FC retention, but the relation to maternal or neonatal infections was not assessed (101).

PREGESTATIONAL AND GESTATIONAL DIABETES

Approximately 1% of pregnancies are complicated by pregestational type 1 or type 2 diabetes mellitus, and the incidence is rising with increasing rates of maternal obesity (1, 2). In Finland, pregestational diabetes is present in approximately 350 (0.6% in 2015) pregnancies annually (4). Pregestational diabetes is accompanied by increased risk of pregnancy complications, such as preeclampsia, diabetic ketoacidosis, progression of diabetic nephropathy or retinopathy, macrosomia, shoulder dystocia, stillbirth, and perinatal morbidity (102). Timing of IOL is based on glycemic control and possible maternal or fetal complications. In case of suboptimal glycemic control or maternal cardiovascular disease, IOL is supported at 37–39 gestational weeks (103).

The incidence of gestational diabetes mellitus (GDM) is also steadily increasing (4). In Finland, 16% of pregnant women were diagnosed with GDM in 2015 (4). A 2-hour oral glucose tolerance test with diagnostic blood glucose values of 5.3 (fasted glucose) – 10.0 (1 h) – 8.6 (2 h) mmol/L has been used in Finland since 2008, but screening criteria, sampling technique, and diagnostic values vary around the world (104). If complicated by poor glycemic control and fetal macrosomia, GDM increases the risk of fetal asphyxia and perinatal complications (105, 106). Women with insulin dependent GDM have an almost fivefold risk of fetal macrosomia compared to women with dietary treatment (107).

In insulin dependent and drug therapy dependent GDM, the Cochrane review as well as the Finnish national Current Care Guidelines recommend IOL at 38–40 gestational weeks due to an increased risk of fetal asphyxia, macrosomia, and shoulder dystocia (104, 108). However, if the estimated fetal weight exceeds 4500 g, an elective CS is recommended (104).

In non-insulin dependent GDM, routine IOL is not supported unless poor glycemic control or complications, such as fetal macrosomia or placental failure, occur (104, 108, 109). On the other hand, a recent population-based study on 8392 women with non-insulin dependent GDM demonstrated a

decrease in CS rate following routine IOL at 38–39 gestational weeks compared to expectant management (110). However, IOL before 39 gestational weeks increased the risk of neonatal intensive care unit (NICU) admission (110). Similar results were reported by a secondary analysis comparing IOL between 37 and 40 gestational weeks and expectant management in women with non-insulin dependent GDM (111). This study also observed a threefold increase in CS rate following IOL beyond 41 gestational weeks compared to IOL at 39 weeks of gestation (111).

Fetal macrosomia, defined as birth weight greater than 4000–4500 g, is associated with maternal and neonatal complications including shoulder dystocia, operative delivery, and postpartum hemorrhage (112). In Finland, 13.7% of newborns were 4000–4500 g of weight and 2.3% were over 4500 g of weight in 2015 (4). In case of macrosomia and maternal GDM, IOL is recommended at 38–40 gestational weeks, and elective CS is recommended if fetal weight exceeds 4500 g (104, 108). An abundance of studies and current clinical guidelines do not support IOL in case of non-diabetic fetal macrosomia, but increased rates of CS have been reported (104, 112-114). However, contradicting results have also been reported. Cheng et al. found lower rates of CS in women undergoing IOL at 39 gestational weeks compared to women delivering at later gestational age, with infants of birth weight 4000 g or more (115). Moreover, a recent multicenter RCT of 822 women demonstrated a decreased risk of shoulder dystocia and perinatal morbidity without an increase in CS rate, when labor was induced at 37–39 weeks of gestation compared to expectant management (116).

HYPERTENSIVE DISORDERS

Chronic hypertension complicates approximately 1–5% of pregnancies, and the incidence is increasing with advancing maternal age and obesity. Chronic hypertension is associated with pregnancy complications including preeclampsia, maternal stroke, FGR, stillbirth, and CS (117). RCTs on optimal timing of IOL in these pregnancies are non-existent. A Canadian cohort study on 171 669 women recommended IOL at 38–39 weeks in non-medicated chronic hypertension, and at 37 weeks in case of medication (118). A Dutch birth register study supported IOL by 38–40 weeks in pregnancies complicated by maternal chronic hypertension (119).

The incidence of gestational hypertension varies between 2% and 17%. Pregnancy outcomes in women with mild gestational hypertension are similar to pregnancy outcomes of normotensive women (120, 121). Severe gestational hypertension is associated with an increased risk of FGR and placental abruption, and almost 50% of these women develop preeclampsia (121, 122). The existing literature supports IOL in gestational hypertension,

yet the optimal timing remains unclear. A retrospective cohort study found the lowest risk of maternal morbidity and mortality with IOL at 38 gestational weeks, and the lowest risk of neonatal morbidity at 39 gestational weeks (123). A Dutch RCT (the HYPITAT-II trial) comparing pregnancy outcomes between IOL and expectant management in 703 women with hypertensive disorder at 34–37 weeks of gestation, found no significant difference in maternal adverse outcomes, such as thromboembolic complication, pulmonary edema, eclampsia, HELLP syndrome, or placental abruption (124). The study concluded that IOL is recommended between 34 and 37 weeks of gestation, considering maternal and fetal well-being, and the risk of fetal respiratory distress syndrome (RDS) (124). On the other hand, Barton et al. reported increased rates of neonatal complications in women with gestational hypertension undergoing IOL at 34–36 gestational weeks (125). A recent retrospective cohort study on 114 651 low risk women reported an increased risk of CS and maternal morbidity in expectant management compared to elective IOL at term (126).

The incidence of preeclampsia, one of the leading causes of maternal mortality worldwide, is approximately 5% (127). Preeclampsia is associated with placental abruption, maternal kidney and liver failure, intracranial hemorrhage, pulmonary edema, FGR, and neonatal morbidity and mortality (128). The randomized HYPITAT trial (n=756) reported a 13% decrease (relative risk [RR] 0.71, 95% confidence interval [CI] 0.59–0.86; p<0.0001) in maternal morbidity when labor was induced by 37 gestational weeks compared to expectant management in cases of preeclampsia with no severe complications (129). Neonatal outcomes did not differ between the groups (129). In cases of eclampsia, immediate labor after stabilization of maternal condition is recommended regardless of the gestational age (130).

FETAL GROWTH RESTRICTION AND OLIGOHYDRAMNIOS

FGR is associated with an increased risk of stillbirth and perinatal mortality, particularly for fetuses with estimated weight less than the fifth percentile. ACOG management guidelines recommend delivery at 38–40 weeks, and earlier if additional fetal or maternal complications are present (131). In previous observational studies on FGR, IOL has been associated with demonstrable benefit in neonatal outcomes (132-134). In cases of isolated FGR or small for gestational age fetus, IOL before 37 gestational weeks has not been shown to improve neonatal outcomes but has been linked to increased rates of CS and neonatal complications (135-137). The randomized DIGITAT trial (n=650) on isolated FGR concluded that IOL after 38+0 weeks appears the option of choice for preventing neonatal morbidity and stillbirth, with no increase in CS rate (138). A follow-up analysis of the DIGITAT trial reported comparable neonatal morbidity rates, and concluded

that IOL after 38 weeks may prevent stillbirths (139). The 2-year follow-up study noted no differences in developmental outcomes in the DIGITAT children (140). A recent cost analysis of the DIGITAT study found no improvement or economic benefit in outcomes with expectant management beyond 38 weeks of gestation (35).

Oligohydramnios is defined as an amniotic fluid index (AFI) less than 5 cm or a single deepest amniotic fluid pocket smaller than 2 cm (141). Higher rates of IOL have been reported when AFI is used for diagnoses of oligohydramnios compared to the single deepest amniotic fluid pocket (142). Oligohydramnios may occur as an idiopathic finding, but it may also be associated with FGR, fetal congenital anomalies, and multiple gestations (143). In post-term pregnancy, oligohydramnios may be related to placental failure leading to increased risk of fetal distress and perinatal mortality, and IOL is recommended (144). In case of isolated oligohydramnios with no pregnancy complication, IOL prior to term is not considered beneficial (145, 146).

OTHER INDICATIONS

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy, a condition of unknown etiology with elevated serum bile acids and pruritus, occurs in approximately 1–1.5% of pregnancies in western countries (147-149). The risk of maternal complications is insignificant, while the risk of stillbirth increases 1–3% with increasing maternal serum bile acid concentration (especially > 100 μmol/L) and gestational age (150). Maternal elevated serum bile acids may cause placental vasoconstriction, fetal cardiac rhythm disorders, and increased myometrial sensitivity to oxytocin, thus possibly compromising the fetal well-being (151-153). Other risks associated with intrahepatic cholestasis include meconium-stained amniotic fluid, preterm delivery, and RDS. Literature supports IOL at 37–40 gestational weeks in pregnancies complicated by cholestasis, but RCTs and evidence-based management guidelines on optimal timing of IOL are unavailable. A case-control study comparing expectant management and IOL at 38 gestational weeks in 320 women with intrahepatic cholestasis, reported similar perinatal mortality rates (1.8% vs. 1.3%) in both groups (148). Another case study (n=206) reported lower rates of stillbirth (0% vs. 1.6%; p=0.05) when labor was induced by 37 gestational weeks in women with intrahepatic cholestasis compared to those induced later (154). A recent decision-analytic model applied to 18 studies with an average perinatal mortality rate of 1.7% found

36 gestational weeks was an optimal time for IOL, considering the risks of perinatal mortality and the risks of preterm birth (155).

Twin gestations

The rate of twin gestations in Finland was 1.3% in 2015 (4). A recent retrospective cohort study comparing outcomes between 100 twin and 100 singleton pregnancies found no difference in CS rates following IOL (156). A cohort study on planned vaginal deliveries ≥ 34 weeks reported a twofold risk of CS in women undergoing IOL compared to women with spontaneous onset of labor (21% vs. 12%; $p<0.001$) (157). However, vaginal delivery rate of 80% following IOL was reported (157). On the other hand, a multicenter RCT on 235 uncomplicated monochorionic or dichorionic twin pregnancies found a significant reduction in adverse outcomes without an increase in CS rate following IOL at 37 gestational weeks, compared to expectant management and IOL at 38 gestational weeks (158). The recent Cochrane review also supported IOL at 37 gestational weeks in dichorionic twin gestations (159). Furthermore, a recent systematic review and meta-analysis on 29 685 dichorionic twin and 5486 monochorionic twin pregnancies concluded that considering risk of perinatal mortality, IOL is recommended at 37 gestational weeks in uncomplicated dichorionic pregnancy, and at 36 weeks of gestation in monochorionic pregnancy. NICE guidelines recommend IOL at 35 weeks of gestation in monochorionic twin gestations (160).

TIMING OF LABOR INDUCTION

The optimal timing of IOL has been extensively studied in some cases, such as post-term pregnancy, while only limited data are available for other clinical situations. Table 3 summarizes the optimal timing of IOL according to the current recommendations by WHO, ACOG, SOGC, and NICE (3, 5-7), as well as the recent review on timing of IOL (103).

Table 3. Timing of labor induction summarized from the recommendations of WHO, ACOG, SOGC, and NICE (3, 5-7). The gestational weeks refer to completed weeks. Quality of evidence is determined by the recent review on timing of IOL in the following way: a = high, b = moderate, c = low, d = very low (103).

Indication for labor induction	Timing of induction	Quality of evidence
Post-term pregnancy	41−42 weeks	a
PROM	Immediate to 48 hours	a
Intrauterine growth restriction	38−39 weeks. Earlier if fetal or maternal complications	b
Oligohydramnios	39−40 weeks	c
Pregestational diabetes	37−39 weeks (depending on glycemic control, fetal complications, maternal cardiovascular disease)	c
Insulin-dependent gestational diabetes	38−39 weeks	c
Non-insulin dependent gestational diabetes	Not recommended[1] 38−40 weeks if poor glycemic control, macrosomia, or placental failure	b
Non-diabetic fetal macrosomia	Not recommended[2]	b
Chronic hypertension	38−40 weeks, 37 weeks if medication	c
Gestational hypertension	38−39 weeks	b
Mild preeclampsia without severe features	37 weeks	b
Severe preeclampsia with severe features	Latest 34 weeks	b
Eclampsia	Immediate after stabilization	c
Intrahepatic cholestasis of pregnancy	36−39 weeks	d
Dichorionic twins	37−38 weeks	b
Monochorionic-diamniotic twins	34−36 weeks	c

[1]Melamed et al. 2016 and Sutton et al. 2014 support routine IOL at 38−39 weeks (110,111)

[2]Boulvain et al. 2015 and Cheng et. al 2012 support IOL at (37−) 39 weeks (115,116)

METHODS OF LABOR INDUCTION

In women with unfavorable cervices (Bishop score < 6), IOL is started with mechanical or pharmacological cervical ripening, whereas with ripened cervix, typically marked by Bishop score ≥ 6, amniotomy and oxytocin will be considered for IOL. In Finland, balloon catheters and misoprostol are presently available for cervical ripening depending on maternal and fetal factors, such as IOL indication and history of previous CS.

MECHANICAL CERVICAL RIPENING BY BALLOON CATHETERS

Single balloon catheters, including FC, and double balloon catheters are available for cervical ripening. The mechanism of balloon catheter induced cervical ripening consists of direct mechanical stretching of the cervix and lower uterine segment, and stimulation of endogenous PG release following separation of the chorionic membrane and decidua (14, 15). Mechanical stretching of the cervix also augments production of hyaluronic acid, which may enhance cervical swelling and softening (161). In addition, myometrial stretching increases expression of cyclooxygenase-2 (COX-2) and production of PGs (162). Another potential mechanism enhancing cervical softening, is the stimulation of inflammatory cytokine secretion, such as interleukins and MMPs (163).

A balloon catheter is inserted through the cervical canal into the space between the amniotic membrane and lower uterine segment digitally or by direct visualization during a speculum examination. Digital insertion is performed by placing a finger on either side of the cervical opening during vaginal examination, then guiding the tip of the catheter into the cervix and pushing it through the cervical canal with a dominant hand. In instrumental insertion, a speculum is inserted into the vagina to gain access to the cervix, and the catheter is guided through the cervical canal. Double balloon catheters include a stylette for insertion, while single balloon catheters may be guided through the cervical canal by holding it with forceps. After ensuring the tip of the catheter lies above the internal cervical os, the balloon is inflated with 30–80 ml of saline, and retracted to rest on the internal cervical os (Figure 7). In addition to the uterine balloon, a double balloon catheter includes a cervicovaginal balloon, which is inflated with a maximum of 80 ml saline after uterine balloon inflation (Figure 8). With a single balloon catheter, traction is applied by using a 500 mg weight or taping onto the inner thigh, whereas the two balloons of the double balloon catheter create cervical compression and traction is not required. Following expulsion of the balloon, the cervix is typically dilated to 3–4 cm (164).

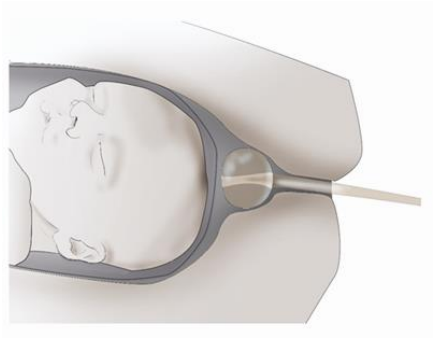


Figure 7. A single balloon catheter is inserted through the cervical canal into the space between the amniotic membrane and lower uterine segment, and the balloon is inflated with saline.

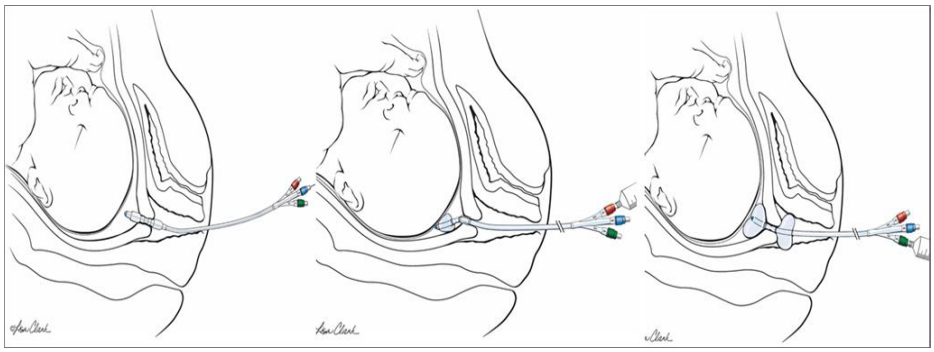


Figure 8. Application of a double balloon catheter. Reprinted on permission of Clark Illustrations.

Insertion of a balloon catheter may be challenging and cause discomfort in women who are nulliparous or have a low Bishop score (165), although a learning curve for catheter insertion has been demonstrated (166). Digital insertion is faster and causes less discomfort than instrumental insertion (167). A recent RCT showed that insertion with a stylette is comparable to insertion without a stylette in pain score, insertion time, and misplacement (168). During a balloon catheter insertion, cervical bleeding may occur in 2–6% of women (165, 169). Higher balloon volume (60–80 ml) results in greater cervical dilation, with no difference in the mode of delivery or induction to delivery interval compared to a lower 30 ml volume (164, 170). Application of traction on the catheter, particularly by using a weight (500 mg) compared to inner thigh taping, may speed up balloon expulsion by 1–2 hours (171, 172).

Use of balloon catheter for cervical ripening is supported by the WHO, ACOG, SOGC, and NICE guidelines (3, 5-7). No increase in maternal or neonatal infectious morbidity has been associated with FC cervical ripening (16, 18, 173), although contradicting results have also been presented by one older study (174).

Two RCTs reported similar efficacy in single and double balloon catheters for cervical ripening, but lower pain scores and shorter induction to delivery interval were reported when using a single balloon catheter (20, 175). Another RCT reported a higher rate of adverse labor outcomes associated with the use of double balloon catheter (176).

PHARMACOLOGICAL CERVICAL RIPENING BY PROSTAGLANDINS

PGs, cyclopentane derivatives of arachidonic acid, stimulate remodeling of cervical collagen, and act within the uterine myocytes, increasing contractility (177). Two synthetic forms of PG, prostaglandin E1 (PGE1) analogue misoprostol and prostaglandin E2 (PGE2) analogue dinoprostone, are available for cervical ripening. Dinoprostone is the only PG approved by the US Food and Drug Administration for labor induction. Misoprostol, originally developed for gastric protection, is unlicensed for labor induction in most countries. However, off-label use has become common practice with a large quantity of research and clinical experience supporting its safety and efficacy. Misoprostol is considered more effective than dinoprostone in achieving vaginal delivery (178-182). On the other hand, concerns about higher rate of hyperstimulation and fetal heart rate changes with the use of misoprostol have been raised. However, the risk of hyperstimulation is dependent on the dose and administration route of misoprostol, with high doses and vaginal administration being associated with higher risk of hyperstimulation, while with lower oral (20–25 μg) doses the risk is similar to that detected with the use of dinoprostone (182). The ACOG, SOGC, and WHO approve the use of misoprostol, and it is currently the only prostaglandin analogue in obstetric use in Finland (3, 5, 6). In contrast, the NICE guideline recommends dinoprostone as the method of choice, and use of misoprostol only in cases of intrauterine fetal death (7).

Misoprostol

Oral administration of misoprostol has a faster rate of metabolism, but the overall exposure to drug is greater in vaginal administration. When administered orally, maternal plasma concentration of misoprostol acid rises rapidly, reaching peak concentration in 30 minutes, and then declining until 120 minutes (Figure 9) (183). Therefore, repeated oral doses may be required

to induce regular uterine contractions. Vaginal application results in slower increase of plasma concentration, with a lower peak in 70–80 minutes, and a slow decline in 4–6 hours (Figure 9) (183). Vaginal absorption can be altered by the presence of blood or amniotic fluid (184). The most common maternal side effects of misoprostol are diarrhea, nausea, fever, and shivering (184).

Misoprostol is commercially available in 100 μg and 200 μg scored tablets, and vaginal inserts. Because oral doses are metabolized faster than vaginal doses, safe and efficacious doses of orally administered misoprostol have been documented as double the vaginal dose. Clinically acceptable doses of misoprostol are 25 μg vaginally or 50 μg orally every 4 hours (182, 185-187). The WHO recommends use of 25 μg of misoprostol either orally every 2 hours, or vaginally every 4 hours (188). Administration of misoprostol requires tablet cutting, which may lead to unstandardized doses and confusion.

Misoprostol 200 μg vaginal insert is a removable, controlled-release vaginal delivery system releasing 7 μg of misoprostol hourly for a maximum of 24 hours. The peak of plasma concentration of misoprostol acid is reached in 4 hours, with a quick elimination after 3 hours from removing the insert (Figure 9) (189). Use of misoprostol vaginal insert appears to lead to shorter induction to delivery interval, lower rate of oxytocin augmentation, and an increased rate of uterine hyperstimulation, compared to the use of dinoprostone insert (190). So far, no studies comparing the use of misoprostol tablet and insert are available.

Figure 9. Pharmacokinetics of misoprostol administered by oral or vaginal tablet or by vaginal insert (183, 189).

Various studies confirm that misoprostol is effective for IOL, but the optimal dose and route of administration remain controversial. According to a recent systematic review and network meta-analysis on 280 RCTs (n=48 068), low dose (< 50 μg) oral solution appears the safest in terms of risk of CS, while vaginal tablet (≥ 50 μg) seems the most effective in achieving vaginal delivery within 24 hours (186). The Cochrane review found that oral misoprostol was equally effective as vaginal misoprostol, but was associated with fewer cases of uterine hyperstimulation, 5-minute Apgar score < 7, and postpartum hemorrhage, and endorsed the use of oral misoprostol as the method of choice (182). Oral administration may also reduce the need for vaginal examinations, thereby reducing the risk of ascending infection in cases of PROM (191). According to the ACOG, SOGC, WHO, NICE, and the Cochrane review, misoprostol is not recommended for IOL in women with a history of previous CS or other uterine surgery due to an increased risk of uterine rupture (3, 5-7, 182).

SEQUENTIAL AND COMBINED USE OF FOLEY CATHETER AND MISOPROSTOL

A case-control study comparing 100 women with sequential use of 30 ml FC for 6 hours followed by 50 μg of misoprostol vaginally every 6 hours, and 50 μg of vaginal misoprostol alone every 6 hours, reported more vaginal deliveries, shorter duration of labor, and less need for oxytocin augmentation in the combination group (192). Similarly, of 1030 women who underwent subsequent cervical ripening by a 50 ml FC following 24 hours of misoprostol, more than 80% of the women delivered vaginally (193). However, a recent retrospective cohort study of 862 women concluded that need for subsequent cervical ripening after use of vaginal PG was associated with a high (51%) risk of CS, particularly in nulliparous women (194).

Three RCTs have reported that the combination of FC and oral (100 μg every 4–6 hours) or vaginal (25–50 μg every 4 hours) misoprostol results in a shorter induction to delivery interval than misoprostol induction alone, with no increase in labor complications or adverse maternal or neonatal outcomes (195-197). Another recent RCT (n=491) reported that the combination of FC (30 ml for maximum of 12 hours) and misoprostol (25 μg vaginally every 3 hours) resulted in twice the chance of vaginal delivery compared to either method alone, with no difference in delivery outcomes (hazard ratio 1.92, 95% CI 1.42–2.59) (198). The induction to delivery interval was also shortest following the use of a combination of FC and misoprostol compared to FC or misoprostol alone (13 h vs. 18 h vs. 18 h; p<0.001) (198). Additionally, the recent Cochrane review demonstrated that the addition of FC to PG increases the likelihood of vaginal delivery within 24 hours with comparable rates of CS (199). Furthermore, uterine hyperstimulation with fetal heart rate

changes was less frequent in the combination group (199). In contrast, a meta-analysis found increased rates of chorionamnionitis associated with the combination method compared to misoprostol induction alone (200).

COMPARISON OF FOLEY CATHETER AND MISOPROSTOL FOR CERVICAL RIPENING

Vaginal delivery rates following the use of FC and PG are comparable, as well established by several RCTs (17-20, 173). An abundance of studies also demonstrate that FC and PGs have comparable neonatal primary outcomes (20, 173, 201, 202). The RCTs comparing FC and misoprostol for cervical ripening over the last decade are summarized in Table 4.

Table 4. The RCTs from 2006–2016 comparing FC and misoprostol for cervical ripening (17-19, 203-205). No significant differences in adverse maternal or neonatal outcomes were found between treatment arms in any of these studies. Two trials including women with a previous CS (206), or pregnancies with fetal compromise (207) are not included.

Study (ref.)	N	FC	Misoprostol	Vaginal delivery % (*p*)	Hyper-stimulation % (*p*)	Intrapartum infection % (*p*)
Prager et al. 2008 (19)	397	50 ml, until spont. expulsion (n=198)	25 µg vaginally every 4 h (n=199)	78 *vs.* 72 *(NS)*	2 *vs.* 6 *(NS)*	13 *vs.* 17 *(NS)*
Moraes Filho et al. 2010 (204)[1]	240	30 ml, max. 24 h (n=121)	25 µg vaginally every 6 h (n=119)	64 *vs.* 73 *(NS)*	3 *vs.* 4 *(NS)*	–
Vahid et al. 2011 (203)	108	50 ml, max. 12 h (n=59)	25 µg vaginally every 4 h (n=49)	63 *vs.* 90 *(<0.01)*	0 *vs.* 2 *(NS)*	–
Kandil et al. 2012 (205)	100	30 ml, max. 12 h (n=50)	25 µg vaginally every 4 h (n=50)	76 *vs.* 80 *(NS)*	0 *vs.* 3 *(NS)*	6 *vs.* 6 *(NS)*
Jozwiak et al. 2014 (17)	109	30 ml, max. 24 h (n=56)	25 µg vaginally every 6 h (n=64)	75 *vs.* 83 *(NS)*	4 *vs.* 2 *(NS)*	–
Ten Eikelder et al. 2016 (18)	1859	30 ml, max. 48 h (n=927)	50 µg orally every 6 h, max. 3/24 h (n=932)	80 *vs.* 83 *(NS)*	4 *vs.* 4 *(NS)*	4 *vs.* 3 *(NS)*

[1]In the study by Moraes Filho et al. 2010 (204), oxytocin alone was used following expulsion of FC, while amniotomy and oxytocin were applied in the other studies. NS= not significant.

Only one Iranian study found a lower vaginal delivery rate with the use of FC (203), while the other studies reported similar rates (Table 4) (17-19, 204, 205). No significant differences in adverse maternal or neonatal outcomes were found between treatment arms in any of these studies (17-19, 203-205).

A recent review and meta-analysis comparing FC and misoprostol for IOL (n=4234) found no difference in the rates of CS, but concluded that FC was associated with better safety outcomes, such as less hyperstimulation, fewer vaginal instrumental deliveries, and fewer CSs for non-reassuring fetal heart rate (25). The recent Cochrane review (n=9722) also concludes that balloon catheters are associated with lower risk of hyperstimulation compared to PG (199). A review and network meta-analysis on 96 RCTs (n=17 387) comparing misoprostol, FC, and dinoprostone, concluded that no method showed overall superiority (181). Vaginal misoprostol was considered the most effective, but was associated with the highest rate of uterine hyperstimulation and fetal heart rate changes (181). FC was associated with the lowest rate of hyperstimulation, while oral misoprostol was associated with the lowest CS rate (181).

Compared to spontaneous labor, FC IOL in women with a history of previous CS is associated with lower risk of uterine rupture (odds ratio [OR] 0.47, 95% CI 0.06–3.59) (23) than use of dinoprostone (OR 14.1, 95% CI 3.4–309.6) (208). The reported incidence of uterine rupture following one previous CS ranges between 0.3% and 1.1% in spontaneous labor, between 0.4% and 1.6% in FC induced labor, and between 0.3% and 2.9% in IOL with PG (Table 5) (21-23, 208-212). In women with previous CS, vaginal delivery rates of 56–71% have been reported following IOL by FC (21-23, 209), and 61–71% following IOL by dinoprostone (209, 211) (Table 5).

Some older studies have investigated the use of misoprostol for IOL in women with a history of previous CS. In the RCT by Wing et al., comparing vaginal misoprostol and oxytocin for IOL in women with a history of previous CS, two uterine ruptures (12%) in the misoprostol group occurred after the enrollment of 17 women, and the trial was stopped (213). Five retrospective studies with small sample sizes (n=39–145) on a total of 378 women reported uterine rupture rates of 3.5–8.3% following the use of misoprostol in women with a history of previous CS (214-218). Due to the increased risk of uterine rupture or dehiscence, most clinical guidelines do not recommend IOL by misoprostol in women with a history of previous CS (3, 5-7).

Table 5. The rates of uterine rupture and vaginal delivery following spontaneous onset of labor, IOL by FC, and IOL by PGE2, in women with a history of one previous CS (n >100 per method group) (21-23, 208-212)

Study (ref)	Design	N	Spontaneous		FC		Dinoprostone	
			UR (%)	VD (%)	UR (%)	VD (%)	UR (%)	VD (%)
Ravasia et al. 2000 (209)	Retrospective	26 868	0.5	78	0.8	61	2.9	61
Lydon Rochelle et al. 2001[1] (208)	Retrospective	20 095	0.5	–	–	–	2.4	
Landon et al. 2004 (210)	Prospective	17 898	0.4	–	0.9	–	1.4	–
Bujold et al. 2004 (23)	Retrospective	2 479	1.1	78	1.6	56	–	–
Locatelli et al. 2004 (211)	Retrospective	310	0.3	82	–	–	0.3	71
Macones et al. 2005 (212)	Case control	25 005	–	–	–	–	2.2	–
Jozwiak et al. 2014 (22)	Retrospective	208	–	–	0.4	71	–	–
Zaki et al. 2014 (21)	Retrospective	149	–	–	0.0	68	–	–

[1]Misoprostol may have also been included during the last year of the study period 1987–1996, since it was introduced then; more detailed data not available. UR, Uterine rupture; VD, Vaginal delivery

Misoprostol is inexpensive, stable at room temperature, and may also be used in the treatment of postpartum hemorrhage, making it particularly useful in poor resource settings (219). The advantages of FC are low cost, easy reversibility, feasibility in outpatient use, less need for continuous fetal monitoring during cervical ripening, and safety in a scarred uterus (21-24, 220).

Women's experiences of duration of labor, pain during labor, general satisfaction with labor, and feelings of control and fear related to their expectations are comparable between women undergoing IOL by FC and women undergoing IOL by oral misoprostol (221). In the oral misoprostol group, 6% of the women would prefer the other method in future IOL, while in the FC group the corresponding rate was 12% (RR 0.70, 95% CI 0.55–0.90; p=0.02) (221).

AMNIOTOMY

Amniotomy, artificial rupturing of the membranes, is used for introducing internal monitoring devices and for IOL in women with a favorable cervix (Bishop score ≥ 6) (222, 223). After excluding the presence of umbilical cord and blood vessels across the membranes, and ensuring the fetal head is no higher than two stations above the ischial spines, amniotomy is performed by rupturing the membranes with a crochet-like hook or fetal scalp electrode. Potential risks of amniotomy include umbilical cord prolapse, cord compression, ascending infection, and bleeding from fetal or placental vessels (224).

Under normal conditions, amniotic membranes remain intact until full dilation in 70% of labors (225). Amniotomy is considered to result in a release of endogenous PG leading to cervical ripening and uterine contractions (226). In women who need oxytocin for adequate uterine contractions, the concentration of plasma PG metabolites is found to decline quickly to initial level (226). Amniotomy can be used for IOL as the sole method, or in combination with oxytocin (223).

Although amniotomy and intravenous oxytocin are widely used in IOL, surprisingly little literature on the efficacy or safety of the method exists. The Cochrane reviews on amniotomy alone, and amniotomy combined with oxytocin for IOL, concluded that due to lack of data to support these methods, no recommendations for clinical practice could be made (223, 227). Early amniotomy at cervical dilation less than 4 cm may shorten induced labor (228). An RCT, comparing early amniotomy concomitant with oxytocin infusion and late amniotomy at 4 hours after oxytocin administration, concluded that early amniotomy was associated with a shorter labor (229). Similarly, a recent matched case-control study found early amniotomy within one hour of FC expulsion, shortening the expulsion to delivery interval by 3 hours (10.6 h vs. 13.8 h; $p<0.001$) with no difference in the vaginal delivery rates (52% vs. 48%; $p=0.30$) (230).

OXYTOCIN

The uterine response to oxytocin gradually increases from 20 to 30 weeks of gestation, followed by a steady level until 37 gestational weeks, after which the uterine response rapidly rises again (231). Oxytocin stimulates uterine contractions by activation of receptor-operated calcium channels, and release of calcium from the sarcoplasmic reticulum (232). The myometrial sensitivity to oxytocin is determined by the concentration and binding kinetics of oxytocin receptors (232). The uterine response ensues after 3–5 minutes of intravenous oxytocin infusion, and a steady plasma concentration of oxytocin

is reached in 40 minutes (231). The half-life of oxytocin is short, 3–17 minutes (231). Maternal side effects of oxytocin include hypotension, tachycardia, arrhythmias, nausea, vomiting, headache, and flushing (233). The main risk of oxytocin use is excessive uterine activity, which may lead to fetal distress (234).

Oxytocin is typically used in women with a favorable cervix (Bishop score ≥ 6), since oxytocin induction in case of an unfavorable cervix is associated with high rates of induction failure (235). Cervical dilation, nulliparity, obesity, and gestational age < 37 gestational weeks may diminish the response to oxytocin induction (236). Rupturing the amniotic membranes may further provoke the response to oxytocin (227, 237). According to previous studies, oxytocin receptors undergo desensitization to exogenous and endogenous oxytocin after prolonged stimulation, such as during labor induction (238). Some studies suggest that discontinuing oxytocin during the active phase of induced labor may improve outcomes (239, 240). In the RCT by Daniel-Spiegel et al. (n=104), the median duration of labor was similar in continued oxytocin and discontinued oxytocin groups (3.8 h vs. 3.1 h; p=007), and there were fewer CSs (12% vs. 6%) when oxytocin induction was stopped at the beginning of the active phase of labor (239). The recent RCT by Bor et al. (n=200) found that the duration of the median active phase of labor was prolonged by 41 (95% CI 11-75) minutes when oxytocin was discontinued after 5 cm of cervical dilation (median 125 minutes vs. 88 minutes; p<0.001) (240). However, the incidence of fetal heart rate abnormalities (50% vs. 20%, RR 2.63; 95% CI 1.67–4.14; p<0.001) and hyperstimulation (12% vs. 2%, RR 5.62; 95% CI 1.28–24.65; p<0.008) was greater in the continued oxytocin group (240). The rates of CS and postpartum hemorrhage were similar between the groups (240). In the discontinued oxytocin group, oxytocin was administered in 36 women after a 2-hour labor arrest, and 78% of them delivered vaginally (240).

Various oxytocin protocols for IOL have been described in the literature. A recent cohort study demonstrated that significantly higher dose of oxytocin was needed for obese women than for lean women (241). The Cochrane review on oxytocin use in women with delay of labor compared a high starting dose (≥ 4 mU/min) of oxytocin to low dose oxytocin (< 4 mU/min), and concluded that high dose oxytocin may increase vaginal deliveries in women with delay of labor. However, the data were insufficient to draw conclusions on maternal and neonatal outcomes (242). An RCT comparing immediate and 4 hours delayed oxytocin following amniotomy in 206 parous women, found no difference in the rates of CS and maternal satisfaction (237).

ALTERNATIVE METHODS

Most complementary and alternative methods for IOL are recommended on the basis of traditional knowledge and empirical evidence. The scientific research and clinical evidence available are limited, except for membrane sweeping. Membrane sweeping, also called membrane stripping, may result in endogenous PG release following separation of the chorionic membrane and decidua. Several RCTs, as well as the Cochrane review, have shown that membrane sweeping reduces the rate of post-term pregnancy, and increases the rate of spontaneous labor in post-term pregnancy (243-246).

Laminaria tents, made from seaweed or synthetic hydrophilic materials, are inserted intracervically to induce cervical stretching. The use of laminaria is not shown to be beneficial, and they potentially increase infectious morbidity (199, 247).

Use of isosorbide mononitrate, relaxin, hyaluronidase, corticosteroids, and estrogens for IOL have been described in the literature. However, the existing data are scarce and inconclusive, with large pharmacological variation in different compounds and doses (179). The use of herbal remedies, such as raspberry leaf, blue cohosh, black cohosh, evening primrose oil, and castor oil, is not supported by scientific data (248). These remedies for IOL appear to not be beneficial, although no harm has been demonstrated in the use of raspberry leaf (248). On the other hand, castor oil and evening primrose oil may increase complications related to side effects of nausea, vomiting, and diarrhea (249, 250). Although no clinical trials exist, there is some evidence that blue and black cohosh should be avoided during pregnancy (251). Currently, the clinical evidence is insufficient for recommendations on the use of homeopathy as a method of labor induction (252).

A number of RCTs and the recent Cochrane review found no significant differences in the duration of labor or the number of spontaneous labors following acupuncture (246, 253-255). The recent Cochrane review concluded that evidence is insufficient for assessing the effect of hypnosis for IOL (256). Only preliminary research on the use of reflexology for IOL is presently available. One RCT on 288 women stated that use of the shiatsu technique, a massage involving the physical body and the points of acupuncture, may be a safe alternative method for reducing the need for IOL in post-term pregnancy (257). Stimulation of nipples may cause a release of endogenous oxytocin, and some evidence supports its use for IOL (258). However, the Cochrane review states that since the safety of nipple stimulation cannot be fully evaluated based on the existing studies, it should not be considered for use in high risk populations (258). Although sexual intercourse may stimulate the onset of labor via oxytocin secretion, and PG

stimulation by the semen upon the cervix, the data are insufficient for conclusions to be made (259, 260).

FACTORS ASSOCIATED WITH LABOR INDUCTION FAILURE

MATERNAL CHARACTERISTICS

An abundance of research demonstrates the role of parity in IOL. Nulliparity increases the risk of prolongation of pregnancy, but it is also an independent risk factor for induction failure and CS regardless of the induction method (86, 261-263).

The average age of pregnant women is steadily increasing in all western countries (264). In Finland, the proportion of nulliparous women ≥ 35 years of age was 20.4% in 2015 (4). The risk of perinatal death, hypertensive disease, gestational diabetes, placenta previa, placental abruption, and IOL are higher among women ≥ 35 years of age than among younger women (264, 265). A Canadian population-based study on 157 445 women demonstrated a CS rate of 38% in nulliparous women ≥ 35 years of age, and a 50% rate in women ≥ 40 years of age (265). An RCT showed no difference in the rate of CS and perinatal outcomes between IOL at 39 gestational weeks and expectant management in women ≥ 35 years of age (266).

In Finland, every third pregnant woman is overweight with a pre-pregnancy BMI of ≥ 25, and 13% of the women were obese (BMI ≥ 30) in 2015 (4). Obese women are at risk of multiple labor complications, such as failed IOL, prolonged labor, postpartum hemorrhage, and postpartum endometritis (267-270). A retrospective cohort study on 470 obese nulliparas reported an increased risk of CS (40% vs. 26%; p=0.02) and neonatal intensive care episodes (18 vs. 6%; p=0.01) in the women undergoing IOL compared to those with spontaneous onset of labor (268). Maternal height appears to be an independent predictor of success of IOL. Taller women are more likely to have a vaginal delivery (53), whereas shorter stature (< 155 cm, OR 1.1 per cm less in maternal height) is associated with induction failure and CS (263, 271).

A recent study suggests that women of black ethnic origin have a threefold risk of CS in induced labor compared to white and Asian women (272). In another study, black women showed a twofold increase in perinatal mortality rate at 40 and 41 gestational weeks compared to Caucasian women (273). Similar rates of induction failure across ethnicity were reported by the

secondary analysis of the misoprostol vaginal insert trial (274). However, white women (29%) and Hispanic women (24.5%) delivered less frequently by CS compared to black women (32.7%) (adjusted OR 0.87, 95% CI 0.44–0.97, p=0.03)(274). Postpartum hemorrhage occurred more frequently in Hispanic women compared to black women and white women (OR 2.27, 95% CI 0.23–0.82, p=0.02 vs. OR 3.69, 95%CI 0.14–0.51, p<0.001) (274).

PREGNANCY RELATED FACTORS

Cervical ripeness is considered the most important factor affecting the success of IOL. Low Bishop score < 5 is associated with high rates of induction failure and CS (11-13). Cervical dilation, effacement, and station are considered more important variables, while cervical consistency is less emphasized (51-53). Higher gestational age beyond 40 weeks is a significant risk factor for induction failure, CS, and perinatal complications (28, 31-33). A population-based cohort study described a CS rate of 49% in post-term nulliparous women (263). In line with these findings, several studies have demonstrated a lower risk of CS following IOL at 39–41 weeks compared to expectant management (27, 30, 31). Indication for IOL may impact the risk of CS. A recent retrospective cohort study on 796 women undergoing IOL reported that nulliparous women undergoing IOL for fetal indications, including oligohydramnios, post-term pregnancy, FGR, and macrosomia, were at increased risk of CS, with the total CS rate being 17% (275). Another factor associated with increased risk of CS was IOL after week 40+0 (275).

An increasing number of women have a history of a previous CS. The CS rate in Finland was 15.9% in 2015, with 9.6% of the CSs being unplanned (4). The greatest predictors of success of trial of labor in women with a previous CS are a prior vaginal delivery and a nonrecurring indication, such as breech presentation, for the previous CS (276, 277). With a history of previous CS, vaginal delivery rates of 87% have been reported in women with previous vaginal delivery compared to 61% in those with no previous vaginal delivery (OR 4.2;95% CI 3.8–4.5) (277). IOL increases the risk of repeat CS compared to spontaneous labor, and success rates of 56–75% for vaginal delivery following IOL with FC and dinoprostone have been reported (278, 279).

PROGRESS OF INDUCED LABOR

A cohort study on 5288 women concluded that women undergoing IOL have a significantly longer latent phase of labor than women with spontaneous onset of labor (median 5.5 h vs. 3.8 h; $p<0.001$ for nulliparous women, and 4.4 h vs. 2.4 h; $p<0.01$ for multiparous women, Figure 10) (280). However, during the active first stage of labor, at ≥ 6 cm cervical dilation, the median time to progress 1 cm cervical dilation was similar in induced and spontaneous labor (Figure 10) (280).

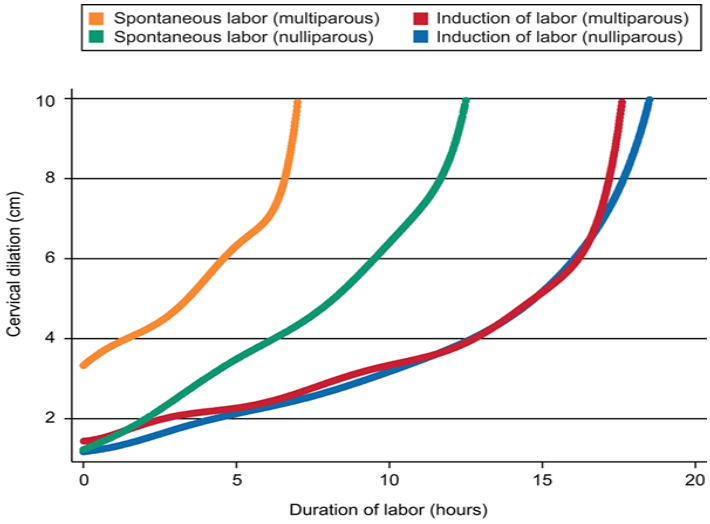


Figure 10. Average labor curves stratified by parity and type of labor onset. Reprinted from Harper et al. with permission of the publisher (280).

Recent guidelines for assessing progress of labor substantially differ from those initially described by Friedman in 1954 (281). Previous studies have concluded that for most nulliparous women undergoing IOL, the active phase of labor occurs only at 6 cm of cervical dilation, and between 6 and 18 hours of the latent phase (282-284). A retrospective cohort study demonstrated that the transition from latent to active labor occurred at 4 cm of cervical dilation with IOL by misoprostol, and at 6 cm of cervical dilation with IOL by FC (Figure 11) (285). The initial dilation from 1 to 4 cm was more rapid with use of FC (3.4 h vs. 5.6 h; $p<0.01$), but the dilation from 4 to 10 cm was faster with the use of misoprostol (6.3 h vs. 3.6 h; $p<0.01$). However, the total duration of labor was similar between women induced with FC and women induced with misoprostol (14.2 h vs. 12 h; $p=0.19$, Figure 11) (285).

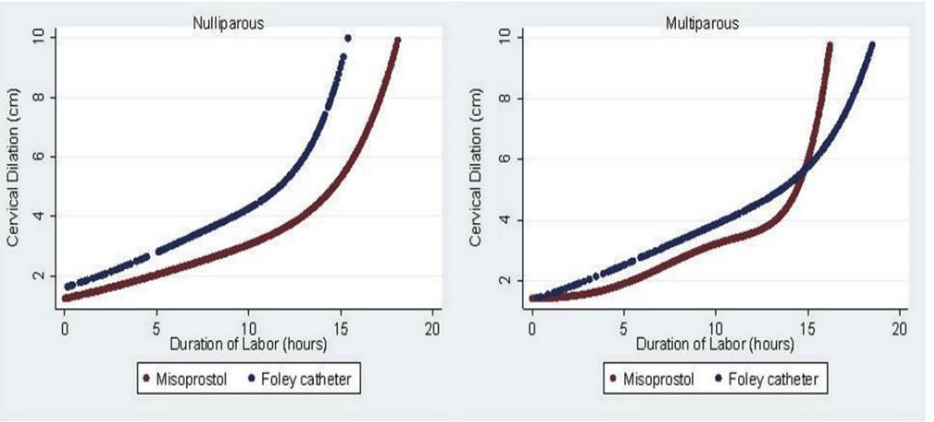


Figure 11. Average labor curves for women induced with misoprostol (red line) or FC (blue line). Reprinted from Tuuli et al. 2013 with permission of the publisher (285).

Several studies have demonstrated that a substantial proportion of women will transit into active labor and deliver vaginally if induction is continued in the setting of ruptured membranes and oxytocin administration for 12–18 hours (282, 286). A recent retrospective cohort study on 228 562 deliveries concluded that before considering an induction failed, at least 12 hours of oxytocin administration with ruptured membranes are reasonable in nulliparous women, and 15 hours in multiparous women (284). The study also demonstrated that the amount of nulliparous women entering active labor increased to over 60% between 6 and 18 hours of the latent phase (284). Nulliparous women remaining in the latent phase for ≥ 12 hours had increased rates of chorionamnionitis (12.1% vs. 4.1%; $p<0.001$), postpartum endometritis (3.6% vs. 1.3%; $p<0.01$), and NICU admission (8.7% vs. 6.3%: $p<0.05$) compared to nulliparous women who had transited into the active phase of labor earlier (284). Similar patterns were seen for multiparous women at 15 hours of the latent phase (284). Furthermore, postpartum hemorrhage was more common in women with a prolonged latent phase of ≥15 hours compared to those with a shorter latent phase of labor (14.8% vs. 3.1%; $p<0.001$ for nulliparous women, and 6.5% vs. 4%; $p<0.05$ for multiparous women) (284).

MATERNAL SATISFACTION WITH LABOR INDUCTION

Maternal satisfaction is associated with several health, social, and care factors, such as young age, no physical disability, positive reaction to pregnancy, no antenatal depression, fewer worries about pregnancy and labor, and access to information about choices of care (37). A secondary analysis of surveys regarding care during labor showed that women undergoing IOL were less likely to be satisfied with their care and labor (38). Women also reported feelings of neglect, insufficient pain relief, plans not being followed, wasted effort, and disappointment if their IOL was unsuccessful (38). A small interview study demonstrated that the feelings of women undergoing IOL vary considerably (287). Some women are concerned about the impact of IOL on the fetus, whereas some express anxiety over the effect on themselves and a loss of a natural birth (287). Women's experiences of IOL with oral misoprostol and FC are similar (221). Cervical ripening in an outpatient setting may increase maternal satisfaction (288, 289). The progress of IOL and labor is shown to be the most important factor affecting overall maternal satisfaction (290). Although most studies on maternal satisfaction are small and biased, the results highlight the aspects of care where patient experience may be improved by additional support and counseling.

ECONOMIC IMPLICATIONS OF LABOR INDUCTION

HEALTH CARE COSTS RELATED TO LABOR INDUCTION

Maternal, neonatal, and treatment related factors influence the total costs of IOL. Moving cervical ripening from inpatient to outpatient setting may decrease the use of health care resources and costs. An American cost-minimization analysis on 76 women undergoing either outpatient or inpatient cervical ripening by PGE2 preparation reported that outpatients incurred significantly less costs (mean $3835 vs. $5049) and time (74.4 h vs. 33.1 h) compared to inpatients (36). In an Australian study, the total health-care costs were not lower with outpatient IOL by FC compared to inpatient IOL by PG (291). However, outpatients experienced fewer inpatient hours and costs prior to delivery (291). According to a recent European cohort study, the mean total cost of IOL in a woman with unfavorable cervix is approximately 3600€, with maternal and neonatal outcomes, mode of delivery, professional fees, epidural analgesia, maternal stay, consumables, and drugs taken into account (292). The highest costs of labor induction were

associated with an unfavorable cervix and hypertension as the indication for IOL (292).

CS following IOL was significantly more expensive than vaginal delivery following IOL (292). However, there is evidence that inducing labor in women with complications is associated with lower health-care costs than expectant management (34, 35). In Finland, the rate of IOL has increased by over 50% during the past decade. During this period the rate of CS has remained stable, and the number of vaginal deliveries following IOL has increased (4) (Figure 12).

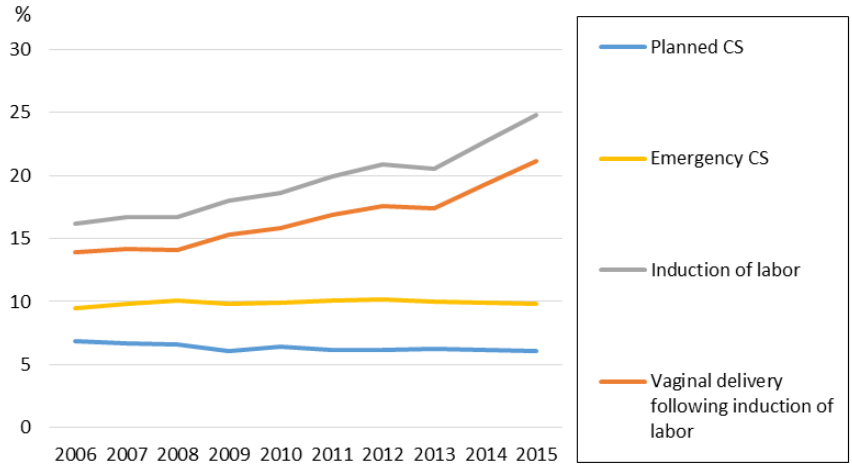


Figure 12. The rates of all planned and emergency cesarean deliveries, IOL, and vaginal deliveries following labor induction in Finland during 2006–2015 (4) (submitted).

Different induction methods have different direct and indirect costs, including retail price, frequency of fetal monitoring needed, risk of complications, CS, and admissions to NICU. Unfortunately, little evidence on the total costs related to specific methods of IOL is available. A recent meta-analysis and cost-effectiveness analysis found, with considerable uncertainty in estimates, that titrated low dose solution of misoprostol appeared the most cost-effective method (293). Misoprostol solution was used in early clinical studies due to unavailability of low dose tablets, and the pharmacokinetics compared to tablets is unclear. Also, buccal or sublingual misoprostol, intravenous oxytocin with amniotomy, and vaginal misoprostol were deemed cost-effective (293). When comparing the efficacy and cost-effectiveness of single and double balloon catheters, FC is the method of choice based on its significantly lower cost, association with lower rates of adverse outcomes,

and improved pain scores (20, 176). Two economic evaluation models have suggested that IOL with misoprostol vaginal insert may lead to a reduction in resource use and hospital stay, leading to lower total costs (294, 295).

OPTIMIZING DAYTIME DELIVERY

Several studies suggest that in addition to being more cost-effective, daytime deliveries have better outcomes compared to deliveries at night (296-298). A similar effect has been demonstrated between working days and weekends (298). Different starting times of IOL may be beneficial when optimizing daytime deliveries, depending on parity and the method of IOL. No strong evidence exists that timing of the first dose of misoprostol tablets or dinoprostone affects the risk of nighttime delivery (299, 300). According to a recent clinical trial, optimal starting time for achieving daytime delivery in use of vaginal misoprostol insert appears to be 19:00 for nulliparous women, and 23:00 for multiparous women (301). A retrospective study on 732 women suggests that the risk of nighttime delivery in nulliparous women is lower if FC is inserted in the evening after 18:00 (300). The recent Cochrane review concluded that no evidence on the superiority of morning versus evening IOL with intravenous oxytocin exists (302). However, a recent retrospective cohort study demonstrated that morning induction with oxytocin in multiparous women carries a lower risk of nighttime delivery (299).

AIMS OF THE STUDY

The present study was carried out to investigate the safety and efficacy of labor induction by FC. The specific aims were:

1. To evaluate delivery outcomes in prolonged and post-term pregnancies induced by FC compared to women with spontaneous onset of labor.

2. To study labor outcomes in nulliparous women undergoing IOL by FC, and to assess risk factors for cesarean delivery and maternal and neonatal infections.

3. To compare FC and oral misoprostol for IOL in women with term PROM.

4. To investigate outpatient IOL by FC, and to compare labor outcomes and preferences of inpatients and outpatients.

5. To examine cervical biomarkers including IGFBP-1, phIGFBP-1, MMPs -2, -8, -9, and their tissue inhibitors (TIMP) -1 and -2 during FC induced cervical ripening in nulliparous women, and to analyze their concentrations in relation to outcome of labor induction.

SUBJECTS AND METHODS

SUBJECTS

The study was conducted in the Department of Obstetrics and Gynecology of Helsinki University Hospital between 2011 and 2015. The Department of Obstetrics and Gynecology of Helsinki University Hospital includes three individual hospitals: the Women's Hospital, the Maternity Hospital, and Jorvi Hospital. Study III was carried out in collaboration with the Department of Obstetrics and Gynecology in both Oulu University Hospital and Tampere University Hospital. The study protocols were approved by the Helsinki and Uusimaa Hospital District Ethics Committee for Obstetrics and Gynecology, Pediatrics, And Psychiatry (No. 30/13/03/03/2012 and No. 268/13/03/03/2012). Approval to carry out the study was granted by the Hospital District of Helsinki and Uusimaa (§7, §14, §20, and §41).

The total study population consisted of 1693 women. The characteristics of studies I–V are summarized in Table 6. Written informed consent was obtained from all women participating in the prospective studies III–V.

Table 6. Summary of studies I–V (n=1693)

	Study I	Study II	Study III	Study IV	Study V
N	553	432	188	485	35
Design	Retrospective cohort	Retrospective cohort	RCT	Prospective cohort	Prospective cohort
Study period	Jan 2011–Jan 2012	Jan 2012–Jan 2013	Mar 2012–Sep 2014	Jan 2011–Jan 2012	Dec 2014–Jun 2015
Hospital	Helsinki University Hospital	Helsinki University Hospital: Women's Hospital	Helsinki, Tampere, and Oulu University Hospitals	Helsinki University Hospital: Maternity Hospital	Helsinki University Hospital: Maternity Hospital
Inclusion criteria	Uncomplicated singleton pregnancy ≥41^{+5} Cephalic presentation Intact amniotic membranes Bishop score <6 No previous CS	Nulliparous singleton pregnancy ≥37^{+0} Cephalic presentation Intact amniotic membranes Bishop score <6 Medical indication for IOL	Singleton pregnancy ≥37$^{+0'}$ PROM ≥18 h Cephalic presentation No prior CS Bishop score <6 No maternal infection	Uncomplicated singleton pregnancy ≥37^{+0} Cephalic presentation Intact amniotic membranes Bishop score <6 Medical indication for IOL Reassuring antenatal CTG Normal fetal biophysical profile	Nulliparous, singleton pregnancy ≥40^{+0} Cephalic presentation Intact amniotic membranes Bishop score <6 Medical indication for IOL
IOL method	FC 40–50 ml for max. 24 h Spontaneous labor	FC 40–50 ml for max. 24 h	FC 40–50 ml for max. 8 h Oral misoprostol 50 µg every 4 h	FC 40–50 ml for max. 24 h	FC 40–50 ml for max. 24 h
Main research question	Delivery outcomes in pregnancies ≥41^{+5} with FC IOL *vs.* spontaneous labor	Delivery outcomes in FC IOL. Risk factors for CS. Maternal or neonatal infectious morbidity	Safety and efficacy of FC IOL *vs.* misoprostol in term PROM	Safety and delivery outcomes of outpatient FC IOL *vs.* inpatient FC IOL	Prediction of IOL success with cervical biomarkers
Main outcome	CS rates Maternal and neonatal infections	CS rates Maternal and neonatal infections	CS rates Maternal and neonatal infections	CS rates Maternal and neonatal infections	Cervical IGFBP-1, phIGFBP-1, MMP-2, MMP-8, MMP-9, TIMP-1, TIMP-2

STUDY I

Table 6 and figure 13 describe the characteristics of study I. The data were collected from the medical records.

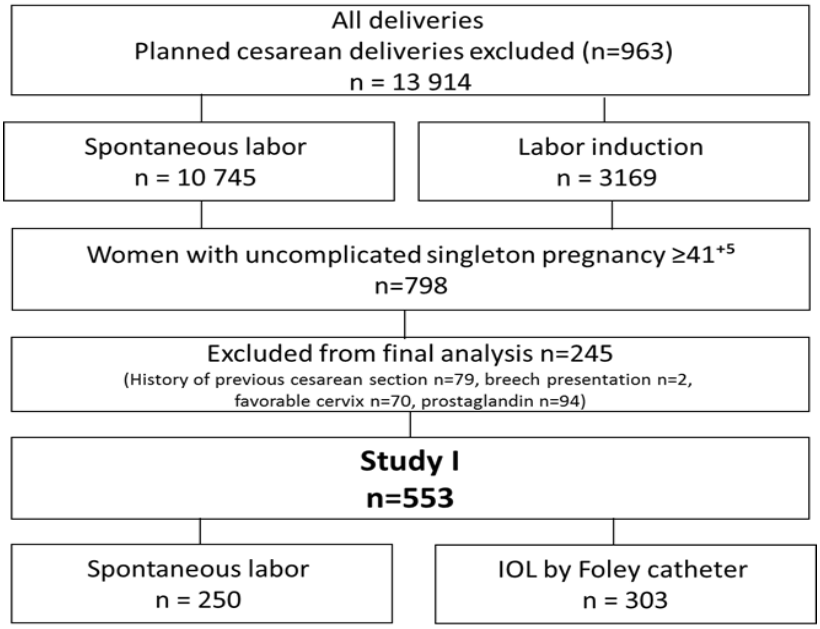


Figure 13. Flow chart of the women ≥ 41^{+5} weeks of gestation undergoing IOL by FC or spontaneous onset of labor (n=553).

STUDY II

The characteristics of study II are described in Table 6 and Figure 14. The data were collected from the medical records.

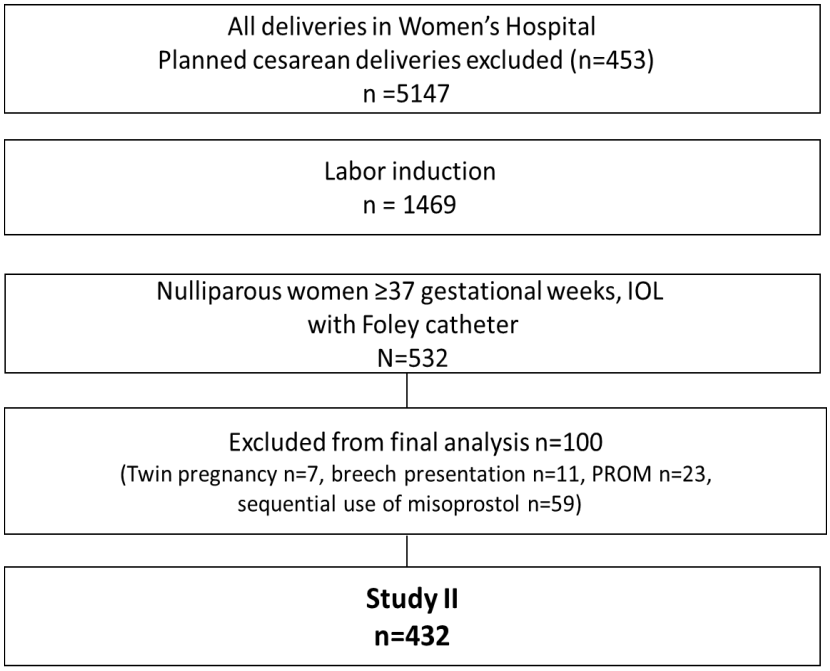


Figure 14. Flow chart of the nulliparous women undergoing IOL by FC (n=432) (II).

STUDY III

Table 6 and Figure 15 describe the characteristics of the multicenter study III. The randomization was done by sealed envelopes in a 1:1 ratio. This study was open-label because the nature of the intervention made masking impossible. After 2.5 years of the study, an interim analysis was performed. Since no differences between the groups were found, and patient enrollment was slower than expected, the trial was stopped.

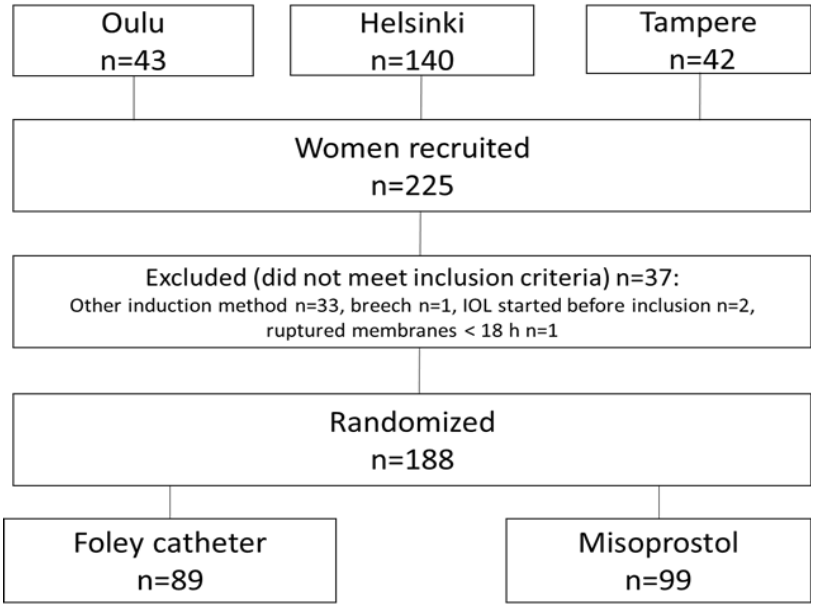


Figure 15. Flow chart of the women randomized to IOL by FC or misoprostol after PROM at term (n=188) (III).

STUDY IV

Study IV characteristics are described in table 6 and Figure 16. Prior to IOL, all women underwent a cardiotocography (CTG) and an ultrasonographic assessment of fetal biophysical profile including amniotic fluid volume. The women with reassuring test results were then offered an option for outpatient IOL. Maternal satisfaction was measured by a questionnaire during postpartum care.

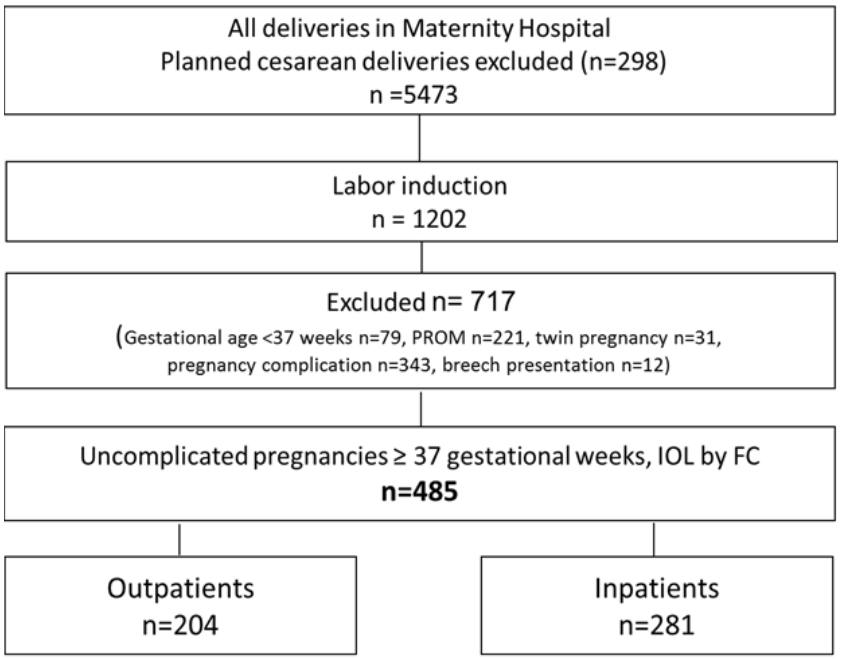


Figure 16. Flow chart of the women undergoing outpatient or inpatient IOL by FC (n=485) (IV).

STUDY V

Table 6 describes the characteristics of study V. None of the participants had regular contractions or any evidence of rupture of membranes at the time of enrollment. One woman ruptured the membranes during insertion of the FC, and was excluded. Thus, the final study population consisted of 34 nulliparous women.

METHODS

DATA COLLECTION FROM MEDICAL RECORDS

Clinical data on the study populations were collected from hospital patient records (I–V), by interviews (III–V), and from statistical survey form by the National Institute for Health and Welfare assessing maternal height, weight, BMI, smoking, assisted reproductive in vitro fertilization (IVF) treatment, and history of previous pregnancies (I–V). Data on IOL, and delivery and neonatal outcomes were collected from the hospital patient records (I–V).

Maternal characteristics (I–V)

Maternal characteristics, and delivery and neonatal outcome parameters evaluated in studies I–V are presented in Table 7.

Table 7. Maternal characteristics and labor outcome parameters of studies I–V

Maternal characteristics	Delivery and neonatal outcomes
Maternal age	Mode of delivery
Height	Indication for CS
Weight	Prophylactic antibiotic use
Pre-pregnancy BMI	Oxytocin administration
IVF	Epidural and/or spinal analgesia
Smoking	Fetal scalp blood sampling
Pregestational diabetes	Meconium-stained amniotic fluid
Gestational diabetes	Uterine hyperstimulation
Insulin dependent gestational diabetes	Fetal tachycardia
Gestational age	Placental retention
PROM	Sphincter injury
Bishop score	Postpartum hemorrhage
Indication for labor induction	Fever ≥38°C during labor
History of previous CS	Maternal intrapartum infection
	Maternal postpartum infection
	Birth weight
	Apgar score
	Umbilical artery blood pH and base excess (BE) values
	Gender
	Neonatal infection
	Admission to neonatal care unit

In all studies included in this thesis, BMI 30 kg/m² was defined as a cut-off for obesity. GDM was diagnosed by a 2-hour oral glucose tolerance test during the first or the second trimester, and 5.3, 10.0, and 8.6 mmol/L were used for 0-, 1-, and 2-hour cut-off values (104). Women who were diagnosed with GDM but had normoglycemia and normal fetal growth while on dietary care, were analyzed as uncomplicated pregnancies in studies I and IV. Women smoking during any trimester were defined as smokers.

The type and length of pregnancy were based on the results of first trimester ultrasound screening in all cases. Prolonged pregnancy was defined as gestational age ≥ 41^{+5} weeks, and post-term pregnancy as gestational age ≥ 42^{+0} weeks. All women were induced at the latest by 42^{+1} gestational weeks if spontaneous labor had not commenced.

Cervical ripeness was defined by the Bishop score, with Bishop score < 6 indicating an unripe cervix, and Bishop score ≥ 6 representing a ripe cervix. All women had a Bishop score < 6 at the start of IOL. PROM was diagnosed by clinical examination or by a positive rapid vaginal dipstick test (ActimProm, Medix Biochemica, Espoo, Finland).

The main indications for labor induction followed the hierarchy of PROM, post-term pregnancy, hypertensive disorders, pregestational or gestational diabetes, intrahepatic cholestasis of pregnancy, and other indications. When there was more than one indication for CS, the primary indication was categorized by using the following hierarchy: fetal distress, infection, failure to progress, failed induction, and other indications.

Delivery outcome parameters (I–V)

The time intervals (hours) describing different phases of the induced deliveries were collected from hospital records. The duration of the FC retention was defined as the interval from FC insertion to its expulsion or removal. The induction to delivery interval was defined as the time from insertion of FC (I–V) or administration of the first misoprostol dose (III) to delivery. The first stage of labor was defined as the interval from regular contractions to start of pushing (303). The second stage of labor was defined as the interval from start of pushing to delivery (303).

Regular contractions were defined as contractions every 3–5 minutes with cervical dilation of a minimum of 3 cm. Uterine hyperstimulation was defined as > 5 contractions in a 10-minute period, or a contraction lasting longer than 3 minutes in a combination with fetal heart rate changes (III). Failed induction was diagnosed after ruptured membranes and 6–12 hours of oxytocin administration without cervical change (304). Labor arrest in the

first stage of labor was defined as failure to progress despite ruptured membranes and a minimum of 4 hours of adequate uterine activity without cervical change (304).

Maternal and neonatal outcomes (I–V)

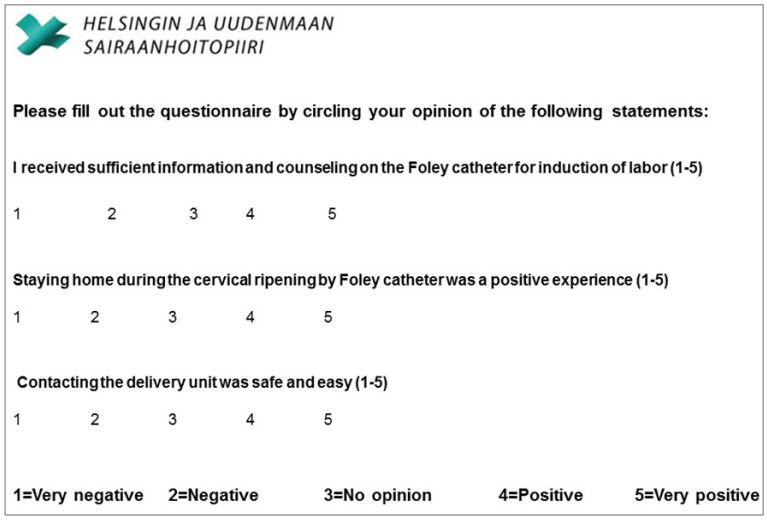
Maternal infections were categorized as intrapartum (during labor) and postpartum (from delivery to discharge). The criteria for intrapartum infection (I–II, IV–V) were maternal fever (≥ 38°C) during labor, fetal tachycardia (≥ 160 bpm), uterine tenderness, purulent amniotic fluid or vaginal discharge, total white cell count > 20 E9/L, and histopathological diagnosis of chorionamnionitis if clinically indicated. At least two of these criteria had to be met in combination with administration of antibiotics. For study III, maternal fever ≥ 38°C alone was used as a definition for intrapartum infection. Postpartum infections included endometritis, wound infections, and puerperal fever of unknown origin (I–V). Postpartum endometritis was defined as uterine tenderness, purulent vaginal discharge, total white cell count > 10 e9/L. The infections were categorized according to the following hierarchy: intrapartum infection, postpartum endometritis, and other postpartum infections. The woman was diagnosed with either intrapartum infection or postpartum endometritis, while intrapartum infection and other postpartum infections could occur in the same woman.

Neonatal infections (I–II, IV) were categorized as blood culture positive sepsis, clinical sepsis, and suspected sepsis. Neonatal clinical sepsis was defined as a blood culture negative infection with symptoms and signs consistent with sepsis (including respiratory distress, apnea, tachycardia, poor perfusion, low blood pressure, fever, hypo- or hyperglycemia, irritability, feeding problems, lethargy, and convulsions), abnormal blood test values (such as elevated levels of C-reactive protein, leukocytosis or leukopenia, increased neutrophil precursor counts, and thrombocytopenia), and a positive response to a minimum of a 5-day antibiotic treatment. The cases defined as suspected sepsis had to have at least one symptom and one abnormal blood test result, and a positive response to antibiotic treatment. During data collection, the diagnoses of neonatal infections were confirmed and categorized from patient records by a neonatologist (I–II, IV). For study III, any clinical suspicion of neonatal infection was used as the definition of neonatal infection.

Maternal satisfaction with induction of labor

Maternal satisfaction with outpatient IOL experience was measured after delivery using a Likert scale questionnaire with ratings 1–5 (very negative –

negative – no opinion – positive – very positive) (Figure 17) (IV) (305). The questionnaire was attached to the patient records when the decision on outpatient IOL was made. The women filled in the questionnaires during their stay in the postpartum ward and returned the completed forms to the mail boxes of the ward. The correlation of maternal satisfaction and labor outcome parameters was not included in the analysis.


HELSINGIN JA UUDENMAAN
SAIRAANHOITOPIIRI

Please fill out the questionnaire by circling your opinion of the following statements:

I received sufficient information and counseling on the Foley catheter for induction of labor (1-5)

1 2 3 4 5

Staying home during the cervical ripening by Foley catheter was a positive experience (1-5)

1 2 3 4 5

Contacting the delivery unit was safe and easy (1-5)

1 2 3 4 5

1=Very negative 2=Negative 3=No opinion 4=Positive 5=Very positive

Figure 17. Questionnaire used to measure maternal satisfaction during postpartum care in women who underwent outpatient IOL by FC (translated from Finnish to English) (IV).

MANAGEMENT OF LABOR INDUCTION

Cervical ripening by Foley catheter in inpatient care (I–V)

When mechanical cervical ripening was used for IOL, a single balloon FC (Rusch 2-way Foley Couvelaire tip, catheter size 22 Ch, Teleflex Medical, Athlone, Ireland) was inserted through the cervix towards the space between the amniotic membrane and lower uterine segment blindly during vaginal examination, or by direct visualization during a speculum examination. The balloon reservoir was inflated with 40–50 ml of saline and retracted so that it rested on the internal os. Transvaginal ultrasound was performed to assure balloon placement if needed. Light traction was applied, and the catheter was taped on the inner aspect of the thigh. A midwife monitored for balloon expulsion every 2–4 hours, and light traction was reapplied if necessary. The FC was retained for a maximum of 24 hours (I–II, IV–V), or in case of PROM for 8 hours with prophylactic antibiotic treatment (III). If spontaneous expulsion of the balloon did not occur within 24 hours, the FC was removed.

After spontaneous expulsion or removal of FC, the cervix was assessed. If the cervix was ripened to a Bishop score of ≥ 6, amniotomy was performed and continuous fetal monitoring was started. The timing of amniotomy after FC expulsion or removal varied from immediate to 12 hours, depending on the time of expulsion, inpatient or outpatient setting of IOL, and delivery unit capacity. If the cervix remained unripe with Bishop score < 6 after FC expulsion or removal, further management of cervical ripening was considered by the obstetrician in charge.

Cervical ripening by Foley catheter in outpatient care (IV)

The idea of a procedure for outpatient IOL was introduced to obstetricians and midwives by presentations and staff meetings. Written information and practical training on various clinical situations with outpatient FC induction were offered. In study IV, all women with an uncomplicated pregnancy, reassuring cardiotocography, and a normal fetal biophysical profile were offered an option for outpatient IOL. All procedures for FC induction were similar to those described in the chapter Cervical ripening by Foley catheter in inpatient care (page 52). Parturients who chose outpatient IOL were discharged after receiving counseling regarding the IOL management, discomfort, pain relief, and probability of balloon expulsion, and after signing an informed consent form. They were advised to check for balloon expulsion by pulling the catheter, and to contact the delivery unit after balloon expulsion. If the balloon was expulsed during the nighttime, the outpatients were asked to return to the delivery unit the following morning, unless they had any concerns or PROM occurred. In addition, oral and written instructions with 24-hour contact information were provided, and the women were advised to immediately contact the delivery unit in case of bleeding, severe pain, fever, ruptured membranes, or decreased fetal movements. Non-expulsed FCs were removed after a maximum of 24 hours, similarly to inpatient procedure.

Cervical ripening by misoprostol (III)

Synthetic 100 μg misoprostol tablets (Cytotec®, Piramal Healthcare UK Limited, Northumberland, England) divided into two (50 μg each) were administered orally every 4 hours for cervical ripening. Cardiotocography and uterine contractions were recorded for 30 minutes prior to misoprostol administration, for 60 minutes after the medication, and in case of regular contractions. If regular contractions did not occur following three doses of misoprostol, oral dose was increased to 100 μg or induction was continued by vaginal administration of 25–50 μg doses every 4 hours.

Oxytocin induction and augmentation (I–V)

After reaching Bishop score ≥ 6, oxytocin induction was started in the absence of regular contractions. The timing of oxytocin induction was initiated by local hospital policy, delivery unit capacity, and the preference of the managing obstetrician, varying between 2 and 24 hours after spontaneous or artificial rupture of membranes. In cases with prior misoprostol use, administration of oxytocin was started at the earliest 4 hours after the last dose of misoprostol. Oxytocin 5 IU (8.3 μg) (Syntocinon; Novartis, Copenhagen, Denmark) was diluted in 500 ml isotonic saline or in 5% glucose infusion. The administration was initiated at 15 ml/h, and increased by 5 ml every 15 minutes, or by 10 ml every 30 minutes, until regular contractions were achieved, or until the maximum dose of 90 ml/h for 6 hours was reached.

Oxytocin augmentation during labor, initiated by a midwife or an obstetrician, was routinely used in studies I–V. If uterine activity was insufficient (less than three contractions in a 10-minute period, or < 200 Montevideo units according to intrauterine pressure catheter monitor), oxytocin was continuously infused until 3–4 contractions occurred per 10 minutes, or ≥ 200 Montevideo units were achieved, or the progression of labor was deemed adequate. Intrauterine pressure catheter was used per obstetrician preference.

Group B streptococcus screening and antibiotic prophylaxis (I–V)

GBS (Streptococcus agalactiae) was tested by a culture from vaginal and perianal specimen collected at prenatal visit 4 weeks prior to delivery, or at admission. During studies I, II, and IV, a risk-group based strategy for GBS screening was used. In study III, all women with FC induction after term PROM were tested for GBS. In study V, a rapid qualitative in vitro GBS test (Xpert® GBS, Cepheid, Sunnyvale, California, USA) was performed in all cases after collecting the biomarker samples.

Administration of antibiotics to GBS-positive women was started after 18 hours from PROM or amniotomy, or at the start of regular contractions (I–II, IV). In study III, all women received prophylactic antibiotics at the initiation of IOL by FC or misoprostol. In study V, antibiotic prophylaxis was in case of positive GBS result started immediately following rupture of membranes. Benzylpenicillin was routinely used for antibiotic prophylaxis with the first dose of 4 million units intravenously, followed by 2.5 million units every 4 hours until delivery. In case of a penicillin allergy, clindamycin 900 mg was administered every 8 hours intravenously. In study III, intravenous

cefuroxime 1.5 g, or in case of allergy clindamycin 900 mg every 8 hours, was used for all women.

CERVICAL BIOMARKER SAMPLES AND ASSAYS (V)

For the cervical biomarker analyses in study V, 4 cervical swab samples were collected prior to insertion and after expulsion of the FC, with a maximum delay of 10 minutes before insertion and after expulsion. The samples were obtained by rotating a sterile swab in the inner walls of the cervical canal for 15 seconds during speculum examination. The swabs were then each swirled in their respective extraction solution for 15 seconds. The sample solutions were frozen and stored at −20°C until the analysis of IGFBP-1, phIGFBP-1, MMP-2, MMP-8, MMP-9, TIMP-1, and TIMP-2 concentrations. The same physician examined all women and collected all samples. All samples were analyzed in the same laboratory (Medix Biochemica, Espoo, Finland), which was blinded to the outcome of labor induction.

IGFBP-1 and phIGFBP-1 concentrations

Concentrations of cervical IGFBP-1 and phIGFBP-1 were quantitated by using monoclonal antibodies in two immunoenzymometric assays (IEMA) (Medix Biochemica, Espoo, Finland). The IGFBP-1 assay employs monoclonal antibody 6305, and detects the non-phosphorylated and less phosphorylated isoforms of IGFBP-1 (306). The phIGFBP-1 assay employs monoclonal antibody 6303, and recognizes the highly phosphorylated forms of IGFBP-1 (307). Analyses were performed according to the manufacturer's instructions (Medix Biochemica, Espoo, Finland). All samples were measured in duplicate, and the two assays were performed in parallel for each set of samples. The results were read from the standard curve, and the mean value of the results was reported. The detection limit of the assay was 0.3 μg/L, and the intra- and inter-assay variations were 4.6% and 6.4%, respectively. One plate allows the determination of 40 samples in duplicate, and a standard curve for each plate was utilized. A comparison of standard curves for the plates used during the study period of December 2014 and June 2015 ensured that no variation of the results occurred.

MMP-8 concentrations

MMP-8 concentration was measured with a solid-phase IEMA (MMP-8 IEMA, Medix Biochemica, Espoo, Finland) (308). The MMP-8 IEMA is a quantitative enzyme immunoassay using two monoclonal antibodies, 8706 and 8708, against human MMP-8 (Medix Biochemica, Espoo, Finland).

Microplate wells are coated with one monoclonal antibody against MMP-8, and the other antibody is conjugated to horseradish peroxidase, forming the enzyme conjugate used to detect the presence of MMP-8. Analyses were performed according to the manufacturer's instructions (Medix Biochemica, Espoo, Finland), and the solution absorbance in the wells was measured at 414 nm with a microplate reader (Multiskan, Thermo Fisher Scientific, Vantaa, Finland). All analyses were performed in duplicate, and the mean absorbance value for each duplicate set was read from a standard curve for MMP-8. One plate allows the determination of 40 samples in duplicate, and a standard curve for each plate was used. A comparison of standard curves for the plates used during the study period of December 2014 and June 2015 ensured that no variation of the results occurred. The results were reported as the mean value of MMP-8. The intra-assay and inter-assay coefficients of variation for MMP-8 were both lower than 6%, and the detection limit used for the assay was 0.4 ng/ml.

MMP-2, MMP-9, TIMP-1, and TIMP-2 concentrations

MMP-2, MMP-9, TIMP-1, and TIMP-2 analyses were carried out using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Biotrak ELISA Systems; GE Healthcare Life Sciences, Chicago, Illinois, USA for MMP-2 and TIMP-1, and Quantikine ELISA Kit; R&D Systems, Minneapolis, Minnesota, USA for MMP-9 and TIMP-2). All experimental procedures were performed according to manufacturer's instructions. All samples were measured in duplicate, and the assays were performed in parallel for each set of samples. The results were read from the standard curve, and the mean value of the results was reported. The intra- and inter-assay coefficients of variation for MMP-2 were < 7% and < 13%, for MMP-9 <3% and <8%, for TIMP-1 <12% and <6%, and for TIMP-2 <7% and <8%, respectively. The detection limits used were 0.37 ng/ml for MMP-1, 0.16 ng/ml for MMP-9, 1.25 ng/ml for TIMP-1, and 0.064 ng/ml for TIMP-2. The balance between the MMP-8 and TIMP-1 quantities was estimated on the basis of the molar ratio.

STATISTICAL ANALYSES (I–V)

The data analyses in this thesis were performed by using the Statistical Package for Social Sciences (SPSS) PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) (studies I, II), IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY, USA) (studies III, IV), and IBM SPSS Statistics for Windows, Version 22.0 (study V). A p-value less than 0.05 was considered statistically significant. A post-hoc power analysis was performed

by simulations using R software (II). In study III, the sample size was determined by power analysis.

Categorical variables were compared by Pearson's Chi-square test or Fisher's exact test when appropriate (I–V). Unpaired comparisons of continuous variables were carried out by Student's t-test if the data were normally distributed, and by Mann–Whitney U test in case the data did not follow a normal distribution (I–V). Labor outcomes of nulliparous and multiparous women were analyzed separately in studies I and IV. The Kaplan-Meier survival curve was used for analysis of induction to delivery interval (III). Univariate logistic regression analysis, represented by ORs with 95% CIs, was performed to estimate the RR for CS (studies I, II). Multivariate logistic regression analyses were performed to control for possible confounding factors (Table 8), and for calculating adjusted ORs and their 95% CIs for CS and maternal and neonatal infections (II, IV). Correlations between the cervical biomarker concentrations and labor outcomes were analyzed by using Pearson's correlation coefficient (V).

Table 8. Maternal and delivery related confounding factors used in the multivariate regression analyses in studies II and IV assessing risk factors for CS and maternal and neonatal infections (II, IV)

Risk factor	Study II	Study IV
Maternal age ≥37 years	x	x
IVF	x	x
Smoking	x	x
Nulliparity		x
History of previous CS		x
BMI ≥30	x	x
GDM (insulin and non-insulin dependent)	x	x
Hypertensive disorder	x	
Post-term pregnancy (≥42 weeks)		x
Outpatient setting		x
Bishop score ≤3 at the start of IOL	x	x
Cervical effacement >2 cm at the time of amniotomy	x	
Cervical dilation ≤3 cm at the time of amniotomy	x	
Amniotomy in ≤2 h or >2 h after balloon expulsion	x	
Amniotomy ≤12 h or >12 h after balloon expulsion	x	
Oxytocin induction	x	x
Oxytocin administration in ≤3 h or >3 h after amniotomy	x	
Oxytocin administration in ≤12 h or > 2 h after amniotomy	x	
Early epidural analgesia (prior to regular contractions or at cervical dilation ≤3 cm)	x	

RESULTS

FOLEY CATHETER INDUCTION IN PROLONGED AND POST-TERM PREGNANCIES (I)

The clinical characteristics of the women with prolonged and post-term pregnancies are shown in Table 9. The women undergoing IOL were more often nulliparous and post-term, and more often had a Bishop score ≤ 3 at 41+5 gestational weeks (Table 9).

Table 9. Clinical characteristics of the women with prolonged or post-term pregnancy (n=553) (I)

	FC induced labor (n=303)	Spontaneous labor (n=250)	*p*-value
Maternal age ≥35 years	21 (65)	28 (70)	0.07
Nulliparous	81 (244)	50 (126)	<0.001
BMI ≥30	11 (34)	9 (22)	0.28
GDM	9 (27)	9 (22)	0.96
Bishop score ≤3 at 41^{+5} weeks	49 (148)	15 (38)	<0.001
Gestational age	41.8 [0.14]	41.8 [0.13]	0.05
Post-term (≥42^{+0})	65 (197)	26 (65)	<0.001

Data presented as % (n) or mean [SD]. SD = standard deviation.

Only 10% of the women who presented with an unfavorable cervix at 41+5 gestational weeks had an improved Bishop score ≥ 6 during expectant management from 41+5 to 42+1 gestational weeks. The nulliparous women with Bishop score ≤ 3 more often needed oxytocin induction after FC expulsion (50% vs. 38%; p=0.01), and more often failed to achieve vaginal delivery following IOL (44% vs. 31%; p=0.04) compared to nulliparous women with Bishop score > 3. In contrast, most multiparous women achieved vaginal delivery regardless of the Bishop score (92% vs. 100%; p=0.09).

MATERNAL DELIVERY OUTCOMES

The median (range) time the FC was retained was 9(0.3–30) h in nulliparous women, and 5(0.3–24) h in multiparous women (I). The median (range) time from the start of regular contractions to vaginal delivery was shorter in induced labor than in spontaneous labor (11[3–34] h vs. 13[3–35] h; p=0.004). Maternal delivery outcomes are presented in Table 10.

Table 10. Maternal delivery outcomes of nulliparous and multiparous women with FC induced and spontaneous labors at 41+5 to 42+1 gestational weeks (n=553) (I)

	Nulliparous			Multiparous		
	IOL (n=244)	**Spontaneous (n=126)**	***p*-value**	**IOL (n=59)**	**Spontaneous (n=124)**	***p*-value**
CS	37 (91)	9 (11)	<0.001	3 (2)	1 (1)	0.20
Fetal distress	16 (38)	5 (6)	0.42	–	–	–
Infection	3 (7)	–	0.34	–	1 (1)	–
Failure to progress	19 (46)	4 (5)	0.29	3 (2)	–	–
Vacuum extraction	18 (45)	24 (30)	0.55	7 (4)	2 (3)	0.21
PPH ≥1000 ml						
Vaginal delivery	9 (21)	10 (13)	0.56	7 (4)	8 (10)	0.80
CS	14 (33)	2 (3)	0.93	2 (1)	–	–
Intrapartum infection	6 (15)	2 (3)	0.13	2 (1)	1 (1)	0.54
Postpartum infection	4 (9)	2 (2)	0.26	2 (1)	–	–
Placental retention	3 (8)	3 (4)	0.49	3 (2)	3 (4)	0.93
Sphincter injury	0.4 (1)	4 (5)	0.97	–	1 (1)	–
Laparotomy	1 (2)	–	–	–	–	
Hysterectomy	–	–	–	–	–	–

Data presented as % (n). PPH = Postpartum hemorrhage.

The CS rate of nulliparous women was higher in induced labor compared to spontaneous labor (37% vs. 9%; p<0.001) (Figure 18). In multiparous women, this difference was not seen (Figure 18). Nulliparous women had an OR of 6.2 (95% CI 3.2–12.1) for induction failure and CS.

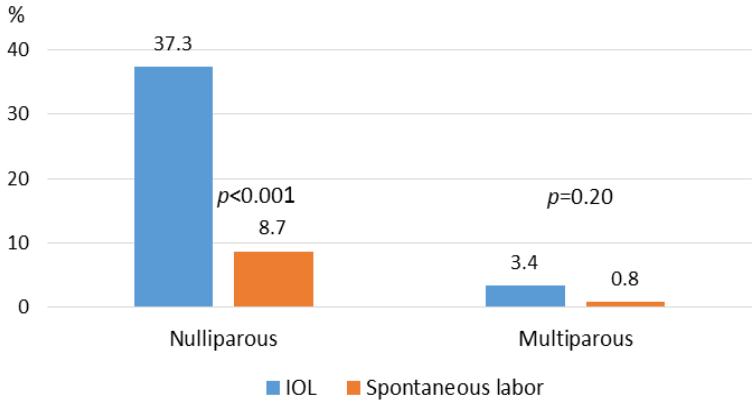


Figure 18. CS rates following IOL and spontaneous onset of labor in prolonged and post-term pregnancies of nulliparous and multiparous women (I).

The maternal intrapartum infection rates were not significantly different between induced and spontaneous labors (6% vs. 2%; p=0.13 in nulliparas, and 2% vs. 1%; p=0.54 in multiparas). The rates of postpartum infection or postpartum hemorrhage were not significantly different between the groups (Table 10). Two laparotomies were performed for women who delivered by CS following IOL; one due to an infection and the other due to postpartum hemorrhage (Table 10).

NEONATAL OUTCOMES

The neonatal outcomes are summarized in Table 11. The umbilical cord blood gas values, Apgar scores, and neonatal care admission rates were not significantly different between the groups of induced and spontaneous labor (Table 11). Neonatal infection was more often suspected following IOL than spontaneous labor in nulliparous women (8% vs. 2%; p=0.04), but the rates of clinical neonatal sepsis were similar between the groups (Table 11). In multiparous women no difference between IOL and spontaneous onset of labor was detected (3% vs. 2%; p=0.60) (Table 11). No cases of blood culture positive neonatal sepsis were found.

Table 11. Neonatal outcomes in FC induced and spontaneous deliveries at 41+5 to 42+1 weeks (n=553) (I)

	Nulliparous			Multiparous		
	IOL (n=244)	**Spontaneous (n=126)**	***p*-value**	**IOL (n=59)**	**Spontaneous (n=124)**	***p*-value**
Apgar score 1 min <7	9 (22)	7 (9)	0.50	5 (3)	4 (5)	0.75
Apgar score 5 min <7	3 (8)	1 (1)	0.23	–	1 (1)	0.53
Umbilical artery pH <7.05[1]	2 (5)	4 (5)	0.32	5 (3)	1 (1)	0.09
Umbilical artery BE ≤−12.0[1]	3 (7)	5 (6)	0.40	2 (1)	1 (1)	0.52
Neonatal infection	8 (19)	2 (3)	0.04	3 (2)	2 (2)	0.60
Suspected sepsis	5 (13)	2 (2)	–	3 (2)	1 (1)	–
Clinical sepsis	2 (5)	1 (1)	–	–	1 (1)	–
Unknown origin	0.4 (1)	–	–	–	–	–
Admission to NICU	12 (30)	10 (12)	0.45	–	1 (1)	0.49
Admission to neonatal ward	3 (7)	2 (2)	0.43	3 (2)	4 (5)	0.83

Data presented as % (n). [1]11 missing values in nulliparous women.

LABOR INDUCTION BY FOLEY CATHETER IN NULLIPAROUS WOMEN WITH TERM PREGNANCY (II)

Table 12 shows the clinical characteristics of the nulliparous women undergoing labor induction by FC.

Table 12. Clinical characteristics of the nulliparous women undergoing IOL by FC (n=432) (II)

Clinical characteristic	% (n)
Maternal age ≥35 years	20 (86)
BMI ≥30	15 (64)
GDM	19 (81)
Bishop score ≤3	48 (209)
Gestational age	41.0 [1.4]
Post-term (≥42^{+0})	17 (73)
Indication for IOL	
Post-term pregnancy	62 (266)
Hypertensive disorders	13 (56)
Gestational diabetes	7 (29)
FGR	5 (23)
Oligohydramnion	4 (19)
Intrahepatic cholestasis	4 (16)
Other*	5 (23)

Data presented as % (n) or mean [SD]. SD = standard deviation.

*Other: decreased fetal movements n=8, large for gestational age fetus n=4, fetal disease (cardiac malformation, Catch-22) n=2, maternal disease (back pain, heart transplantation, difficulty urinating, ulcerative colitis) n=3, pregestational diabetes type 1, n=3, psychosocial reasons n=3.

CHARACTERISTICS OF LABOR INDUCTION

Spontaneous expulsion of the FC occurred in 90% of the women (unpublished data). Prior to expulsion of the FC, spontaneous rupture of membranes occurred in 6% of the women, and in 11% contractions started spontaneously. Following expulsion of the FC, amniotomy was performed in 88% of the cases, and spontaneous rupture of membranes occurred in 11% of the women. Altogether, 12% of the women had an unripe cervix (Bishop score < 6) after FC expulsion and underwent subsequent cervical ripening by misoprostol. Of the women undergoing IOL by FC, 42% needed oxytocin for inducing contractions, while 57% started spontaneous contractions. Early

epidural or spinal analgesia was started prior to regular contractions or cervical dilation of 3 cm in 3% of the women.

The duration of FC induced labor in nulliparous women resulting in vaginal delivery is presented in Figure 19 (unpublished data). The median induction to delivery interval was 29.5 (interquartile range 20–36, minimum–maximum 7–71) hours (Figure 19).

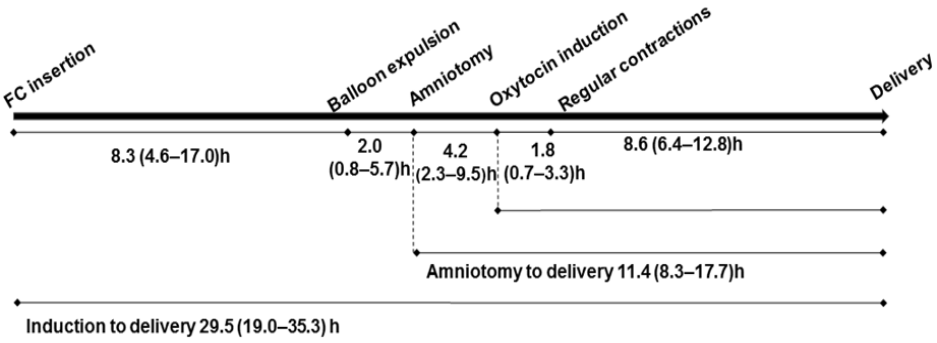


Figure 19. Induction to vaginal delivery intervals in nulliparous women undergoing IOL by FC. Presented as hours; median (interquartile range) (II).

DELIVERY OUTCOMES

The delivery outcomes are shown in Table 13. The CS rate in nulliparous women undergoing IOL by FC was 39%, and 46% in the women who needed subsequent use of misoprostol after FC. The most common indication for CS was failure to progress; failed induction 7% (n=32), and labor arrest 12% (n=53) (Table 13).

Table 13. Delivery outcomes of nulliparous women undergoing IOL by FC (n=432)

Delivery outcome	% (n)
Cesarean section	39 (169)
Fetal distress	15 (63)
Infection	3 (12)
Failure to progress	20 (85)
Other[1]	2 (9)
Vacuum extraction	16 (71)
Postpartum hemorrhage ≥1000 ml	21 (92)
Suspected intrapartum infection	6 (27)
Postpartum infection	4 (17)
Placental retention	3 (14)
Grade III perineal tear	1 (3)
Laparotomy	1 (5)
Hysterectomy	– –
Apgar score 1 min <7	9 (40)
Apgar score 5 min <7	4 (17)[2]
Umbilical artery pH <7.05	2 (10)[3]
Umbilical artery BE ≤−12.0	2 (9)[3]
Neonatal infection	9 (38)
Suspected sepsis	5 (21)
Clinical sepsis	3 (12)
Unspecified infection	1 (5)
Admission to NICU	2 (9)
Admission to neonatal ward	16 (67)

Data presented as % (n). 1Other: bleeding n=1, preeclampsia n=3, umbilical cord prolapse n=1, maternal exhaustion n=2, failed vaginal instrumental delivery n=2. Missing values: 2n=4, [3]n=23.

The rate of maternal intrapartum infection was 6% (Table 13). Two cases (0.5%) of blood culture positive maternal sepsis occurred. Postpartum infection rate was 4%, the most common postpartum infection being endometritis (2%). The overall rate of neonatal infections was 9%, and 3% with a diagnosis of clinical sepsis (Table 13).

RISK FACTORS FOR CESAREAN DELIVERY

The univariate and multivariate analyses of risk factors for CS after IOL are presented in Table 14. Advanced maternal age ≥ 37 years (OR 1.9), obesity (OR 1.8), gestational diabetes (OR 1.9), and Bishop score ≤ 3 (OR 1.6) were associated with an increased risk of CS following IOL in nulliparous women

(Table 14). After multivariate logistic regression analysis, the factors associated with an increased risk of CS were need for oxytocin induction (OR 2.9) and need for early epidural analgesia (OR 9.9) (Table 14).

Table 14. Univariate and multivariate analyses of risk factors for CS after IOL by FC in nulliparous women (n=432) (II)

	Study population (n=432)	CS (n=169)	Univariate analysis		Multivariate analysis	
	% (n)	% (n)	OR (CI 95%)	*p*-value	OR (CI 95%)	*p*-value
Maternal age ≥37 (years)	10 (43)	14 (23)	1.9 (1.0−3.6)	0.04	0.6 (0.3−1.3)	0.22
IVF [1]	4 (19)	5 (9)	1.4 (0.6−3.6)	0.45	0.7 (0.2−2.1)	0.52
Smoking	14 (61)	14 (24)	1.0 (0.6−1.8)	0.97	1.0 (0.5−2.0)	0.95
BMI ≥30[2]	15 (64)	20 (33)	1.8 (1.1−3.1)	0.03	0.7 (0.4−1.3)	0.23
Gestational diabetes	19 (81)	25 (42)	1.9 (1.2−3.1)	0.01	0.6 (0.3−1.1)	0.12
Bishop score ≤3 at IOL start[1]	48 (206)	55 (93)	1.6 (1.1−2.4)	0.02	1.3 (0.8−2.1)	0.21
Cervical effacement >2 cm at amniotomy	7 (32)	9 (16)	1.5 (0.6−2.1)	0.85	1.1 (0.5−2.5)	0.84
Cervical dilation ≤3 cm at amniotomy	4 (19)	78 (132)	1.6 (0.8−3.4)	0.19	0.8 (0.4−1.6)	0.52
Amniotomy >12 h after balloon expulsion	11 (47)	11 (19)	0.9 (0.5−1.7)	0.79	1.1 (0.5−2.1)	0.87
Need for oxytocin induction	44 (188)	61 (103)	3.3 (2.2−4.9)	<0.001	2.9 (1.9−4.5)	<0.001
Early epidural analgesia	3 (15)	9 (15)	11.2 (2.5−50.5)	0.002	9.9 (2.1−47.5	0.004

[1]Missing values 2. [2]Missing values 4.

RISK FACTORS FOR MATERNAL INFECTIOUS MORBIDITY

Maternal infections were not associated with FC retention time, early or delayed timing of amniotomy, or early or delayed timing of oxytocin induction. The duration of labor was longer in cases of intrapartum infection compared to women with no infection (15[7–25] h vs. 12[0.6–35] h; p=0.015). Maternal infections were more common in women who delivered by CS compared to women who delivered vaginally (intrapartum infection

OR 7.7, 95% CI 2.9–20.8; p<0.001, and postpartum infection OR 3.9, 95% CI 1.4–11.4; p=0.007).

In univariate analysis, gestational diabetes was associated with an increased risk of intrapartum infection (OR 3.3) (Figure 20), and this association remained significant after multivariate regression analysis (OR 4.3, 95% CI 1.7–11.0; p=0.002). No significant risk factors were identified for postpartum infections.

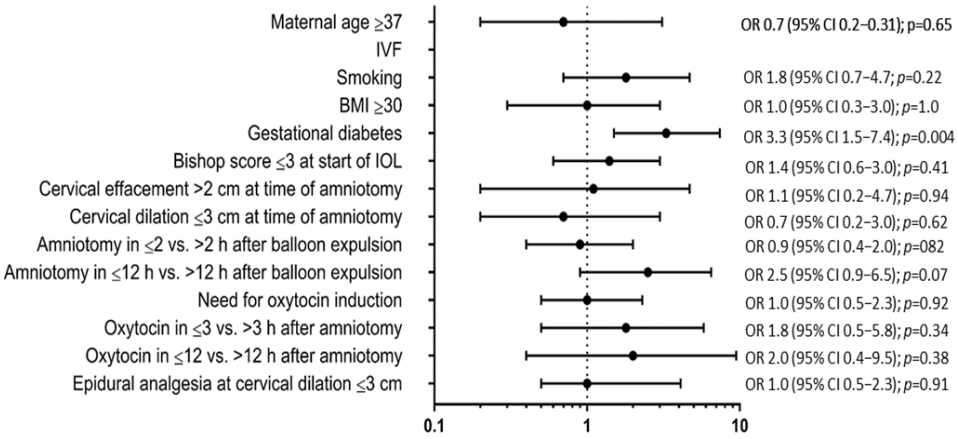


Figure 20. Univariate analysis of ORs for maternal intrapartum infection in nulliparous women undergoing IOL by FC (II).

RISK FACTORS FOR NEONATAL INFECTIOUS MORBIDITY

Neonatal infections occurred more often following CS than vaginal delivery (OR 5.0, 95% CI 2.4–10.6; p<0.001 for clinical sepsis and OR 18.2, 95% CI 2.3–142.6; p=0.001 for suspected sepsis). More cases of clinical neonatal infection were observed in women who received oxytocin administration > 12 hours after amniotomy compared to ≤ 12 hours after amniotomy (16% vs. 7%; p=0.04), but this association did not remain significant after logistic regression analysis.

Maternal age ≥ 37 years (OR 4.9), gestational diabetes (OR 4.6), and early epidural analgesia (OR 6.0) were associated with an increased risk of neonatal clinical infection (Figure 21). After multivariate regression analysis, only the association with early epidural analgesia remained significant (OR 10.5, 95% CI 1.4–76.0; p=0.02).

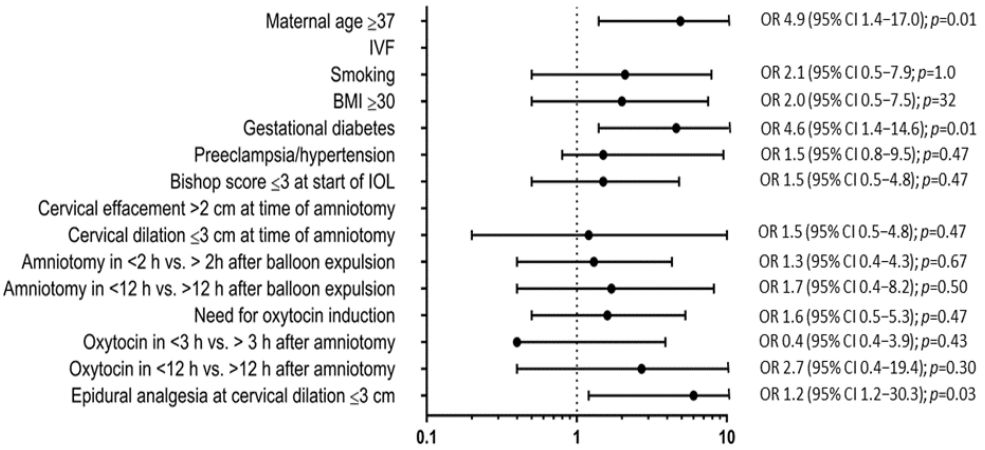


Figure 21. Univariate analysis of ORs for neonatal infection following IOL by FC in nulliparous women (II).

COMPARISON OF FOLEY CATHETER AND ORAL MISOPROSTOL FOR INDUCTION OF LABOR IN WOMEN WITH PREMATURE RUPTURE OF MEMBRANES AT TERM (III)

A total of 47% (n=89) of the women underwent IOL by FC and 53% (n=99) by misoprostol after PROM at term. Table 15 shows the clinical characteristics of the study population.

Table 15. Clinical characteristics of the women undergoing IOL by FC or oral misoprostol after PROM at term (n=188) (III)

	FC (n=89)	Misoprostol (n=99)	*p*-value
Maternal age ≥35 years	21 (19)	19 (19)	0.41
Nulliparous	74 (66)	78 (77)	0.53
BMI ≥30	15 (13)	18 (18)	0.51
Bishop score ≤3 at the start of IOL	25 (22)	33 (33)	0.20
Gestational age	39.9 [1.2]	39.8 [1.2]	0.71
Duration of PROM	29.0 [18–42]	30.0 [18–168]	0.04
GBS-positive	20 (18)	19 (19)	0.89

Data presented as % (n), mean [SD], or median [range]. SD = standard deviation.

FC was retained for a median (range) time of 6(0.6–18) h. Of the women undergoing IOL by misoprostol, 49% (n=49) needed one dose, 30% (n=30) needed two doses, and 20% (n=20) needed three or more doses of misoprostol. Oxytocin was more often needed for inducing contractions following the use of FC compared to use of misoprostol (42% vs. 18%; p<0.001). However, oxytocin augmentation during labor was as frequent in both groups (88% vs. 86%; p=0.72). The use of opioids (27% vs. 39%; p=0.07) and epidural or spinal analgesia (83 vs. 85; p=0.76) was not significantly different between the induction methods.

DELIVERY OUTCOMES

The delivery outcomes are presented in Table 16. The CS rates were not significantly different between the groups (24% vs. 18%; p=0.36). The rates of maternal intrapartum infections, postpartum infections, and neonatal infections were similar (Table 16). All women were screened for GBS, and 20% were positive. One case of intrapartum infection following misoprostol induction occurred in a GBS-positive woman, while all other maternal and neonatal infections occurred in GBS-negative women. There were no cases of laparotomy or hysterectomy. The induction to delivery interval was similar in both groups (22 h in FC group vs. 24 h in misoprostol group; p=0.31).

Table 16. Delivery outcomes of the women undergoing IOL by FC (n=89) and misoprostol (n=99) (III)

	FC (n=89)	Misoprostol (n=99)	*p*-value
CS	24 (21)	18 (18)	0.36
Failure to progress	17 (15)	8 (8)	0.07
Fetal distress	6 (5)	10 (10)	0.26
Intrapartum infection	1 (1)	0	0.47
Postpartum hemorrhage ≥1000 ml	13 (12)	13 (13)	0.89
Fetal tachycardia	7 (6)	9 (9)	0.55
Hyperstimulation	2 (2)	4 (4)	0.69
Intrapartum infection	2 (2)	2 (2)	–
Postpartum endometritis	1 (1)	2 (2)	–
Apgar score 1 min <7[1]	2 (2)	2 (2)	1.00
Apgar score 5 min <7[1]	–	–	–
Umbilical artery pH <7.05[2]	1 (1)	2 (2)	0.50
Umbilical artery BE ≤−12.0[2]	–	3 (3)	0.25
Neonatal infection	1 (1)	5 (5)	0.22
Admission to neonatal ward	8 (7)	9 (9)	0.76

Data presented as % (n).[1]Missing values 1. [2]Missing values 7.

OUTPATIENT COMPARED TO INPATIENT SETTING OF LABOR INDUCTION BY FOLEY CATHETER (IV)

Table 17 presents the characteristics of the study IV population (n=485). The most common IOL indication for both groups was prolonged or post-term pregnancy (89% [n=182] of outpatients and 90% [n=253] of inpatients), but more post-term women ended up in the inpatient group (16% vs. 34%; p<0.001, Table 17).

Table 17. Characteristics of the inpatients and outpatients undergoing IOL by FC (n=485) (IV)

	Outpatients (n=204)	Inpatients (n=281)	*p*-value
Maternal age ≥35 years	22 (44)	21 (58)	0.44
Nulliparous	64 (131)	64 (181)	0.96
BMI ≥30	16 (32)	15 (42)	0.82
Bishop score ≤3 at the start of IOL	43 (88)	37 (104)	0.09
Gestational age	41.7 [0.9]	41.7 [0.9]	0.97
Post-term pregnancy (≥42^{+0})	16 (32)	34 (95)	<0.001
History of previous CS	15 (31)	16 (46)	0.73

Data presented as % (n) or mean (SD). SD = standard deviation.

The reasons for contacting the delivery unit during outpatient cervical ripening are shown in Table 18, expulsion of the balloon (59%) being the most common reason. The return rate to hospital for reasons other than expulsion of the balloon, onset of labor, or reaching 24 hours of cervical ripening was 7% (Table 18). The median (range) retention time of FC was longer in outpatients than in inpatients (10[0.1–27] h vs. 7[0.1–26] h; p<0.001). FC expulsion occurred during nighttime in 13% (n=36) of the inpatients and 23% (n=47) of the outpatients, whose amniotomy was postponed for 8–12 hours to the following morning.

Table 18. Reason for contacting the delivery unit during outpatient cervical ripening (n=204)

Reason for contacting	% (n)
Balloon expulsion	59 (121)
Reaching 24 hours of cervical ripening	25 (50)
Onset of labor	9 (18)
Rupture of membranes	2 (4)
Other[1]	5 (11)

[1]Suspected rupture of membranes n=3, vaginal bleeding n=3, difficulty urinating n=2, decreased fetal movements n=2, rupture of the balloon n=1.

DELIVERY OUTCOMES

The maternal and neonatal outcomes are summarized in Table 19. No cases of home delivery, placental abruption, intrauterine fetal death, or severe pain occurred in inpatient or outpatient IOL by FC. The rates of CS were not significantly different between outpatients and inpatients (32% vs. 32%; p=0.82). Duration of labor was similar between the inpatients and outpatients, but the median (range) induction to delivery interval was longer in outpatients than in inpatients (31[4–82] h vs. 25[3–71] h; p<0.001). The rates of maternal and neonatal infections, postpartum hemorrhage, or neonatal care admission were not significantly different between the groups (Table 19).

Table 19. Maternal and neonatal outcomes of outpatients and inpatients undergoing IOL by FC (IV)

	Primiparous			Multiparous		
	Outpatients (n=115)	**Inpatients (n=163)**	***p*-value**	**Outpatients (n=70)**	**Inpatients (n=94)**	***p*-value**
CS	38 (44)	39 (64)	0.87	21 (15)	20 (19)	0.85
PPH ≥1000 ml						
Vaginal delivery	7 (8)	9 (15)	0.47	10 (7)	6 (6)	0.38
CS	15 (17)	13 (22)	0.65	4 (3)	5 (5)	1.00
Intrapartum infection	7 (8)	6 (9)	0.62	6 (4)	2 (2)	0.40
Postpartum infection	6 (7)	2 (4)	0.21	3 (2)	2 (2)	1.00
Apgar score 1 min <7	10 (12)	10 (16)	0.87	10 (7)	5 (5)	0.26
Apgar score 5 min <7	4 (5)	4 (7)	0.98	4 (3)	3 (3)	0.71
Umbilical artery pH <7.05	3 (3)	1 (2)	0.65	4 (3)	3 (3)	0.74
Umbilical artery BE ≤−12.0	3 (3)	2 (4)	1.00	3 (2)	2 (2)	1.00
Neonatal infection	10 (12)	8 (13)	0.48	−	5 (5)	0.07
Admission to NICU	2 (2)	3 (5)	0.49	3 (2)	−	0.25
Admission to neonatal ward	16 (18)	12 (19)	0.33	6 (4)	9 (8)	0.50

Data presented as % (n). PPH =Postpartum hemorrhage

MATERNAL SATISFACTION ON OUTPATIENT PROCEDURE

Of the 112 women (55%) who returned the Likert scale questionnaire after delivery, 85% were satisfied with outpatient induction (very positive 71%, positive 15%, no opinion 10%, negative 0%, very negative 5%), and 91% were satisfied with the contact information and counseling provided (very positive 74%, positive 16%, no opinion 2%, negative 2%, very negative 5%).

CERVICAL INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1 AND MATRIX METALLOPROTEINASES IN LABOR INDUCTION BY FOLEY CATHETER (V)

CLINICAL CHARACTERISTICS AND DELIVERY OUTCOMES

The characteristics and delivery outcomes of the study V population (n=34) are summarized in Table 20. The median (range) gestational age was 41.9 (40.0–42.1) weeks, and 47% of the women were post-term (Table 20). Half of the women had Bishop score ≤ 3 at the insertion of FC.

Table 20. Characteristics and delivery outcomes of study V population (n=34)

Clinical characteristic/delivery outcome	% (n)
Maternal age	31 [4]
BMI ≥30	15 (5)
Gestational diabetes	26 (9)
Bishop score ≤3 at start of IOL	50 (17)
Post-term pregnancy (≥42^{+0})	47 (16)
Vaginal delivery	56 (19)
CS	44 (15)
Fetal distress	6 (2)
Labor arrest	18 (6)
Failed induction	15 (5)
Other[1]	6 (2)
Postpartum hemorrhage ≥1000 ml	24 (8)

Data presented as % (n) or mean [SD]. SD = standard deviation.

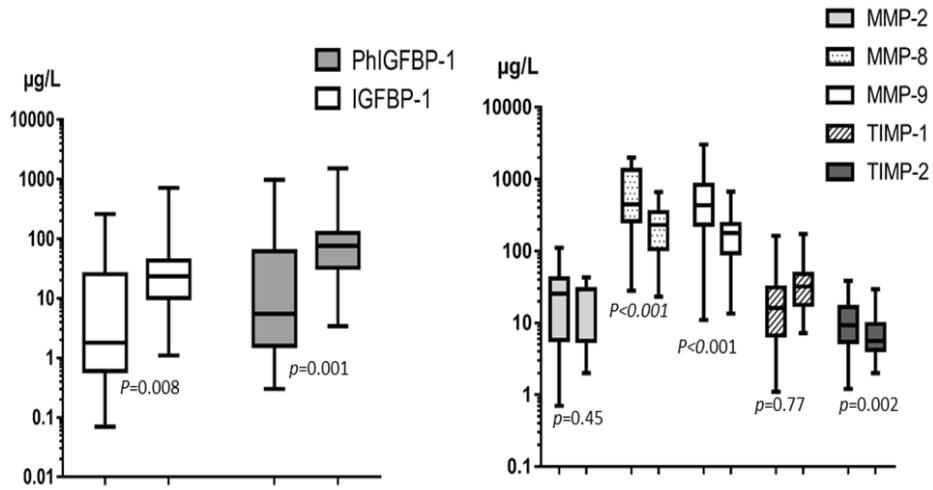
[1]Umbilical cord prolapse n=1, epileptic seizure.

CONCENTRATIONS OF CERVICAL BIOMARKERS

The concentrations of IGFBP-1 and phIGFBP-1 increased, while the concentrations of MMP-8 and MMP-9 decreased during cervical ripening by FC in nulliparous women (Figure 22). MMP-2 concentration remained low with no significant change during FC retention. The concentration of TIMP-1 did not significantly change, whereas the TIMP-2 concentration decreased during FC induced cervical ripening (Figure 22).

The highest increase of IGFBP-1 and phIGFBP-1 concentrations was observed in women who started spontaneous contractions. At start of IOL,

the median MMP-8 concentration was higher in women with Bishop score ≤ 3 compared to women with Bishop score > 3 (593 µg/L vs. 408 µg/L; p=0.02). Also, the MMP-8 concentrations decreased more in women with Bishop score ≤ 3 compared to women with Bishop score > 3 (443 µg/L vs. 209 µg/L; p=0.01). The concentrations of these selected cervical biomarkers were not significantly different between the women who delivered vaginally and the women who delivered by CS due to failure to progress.



Biomarker	FC insertion	FC expulsion	*p*-value
phIGFBP-1	6 (0.3–976)	76 (3–1530)	0.008
IGFBP-1	2 (0.1–261)	24 (1–718)	0.001
MMP-2	9 (1–39)	6 (2–30)	0.45
MMP-8	446 (28–1998)	230 (23−661)	<0.001
MMP-9	433 (11–3019)	178 (14–667)	<0.001
TIMP-1	16 (1–162)	32 (7–172)	0.88
TIMP-2	26 (1–111)	19 (1–539)	0.002

Figure 22. Concentrations (median; range) of cervical biomarkers in nulliparous women at FC insertion and expulsion. IGFBP-1 and pHIGFBP-1 increased, whereas MMP-8, MMP-9, and TIMP-2 decreased during FC induced cervical ripening.

DISCUSSION

MANAGEMENT OF LABOR INDUCTION BY FOLEY CATHETER

Similar to our study IV, several protocols suggest that outpatient cervical ripening is safe and feasible for women with uncomplicated pregnancies (24, 220, 309-311). Outpatient cervical ripening shortens the hospitalization period, optimizes the delivery unit capacity, and may decrease health care costs (26, 36). Antenatal care episodes in Helsinki University Hospital (Maternity hospital) decreased by 16% after introducing the outpatient protocol (IV), although we did not assess the health care costs during study IV. One of the key questions is the readmission rate of the outpatients. In our study IV, the return rate to hospital for reasons other than labor, rupture of membranes, balloon expulsion, or reaching 24 hours of home cervical ripening, was 7%, as also reported previously (24). We believe this low was due to the detailed counseling and 24-hour contact information provided during the study IV.

Our results suggest that FC can safely remain in the cervical canal for 24 hours in women with intact amniotic membranes (I–II, IV–V), and at least 8 hours with antibiotic prophylaxis in women with PROM (III). In previous studies, FC retention time of 12–24 hours is frequently described (199, 312), although a recent Dutch study used a maximum of 96 hours with FC replacement every 24–48 hours, with no increase in the rates of maternal and neonatal infectious morbidity (22). In our study II, the duration of FC remaining in the cervical canal had no association with infectious morbidity. In contrast, a previous study reported an increase in cervical pathogenic microbes, such as GBS, Candida albicans and Candida glabrata, and Gardnerella vaginalis during FC retention (101).

Our study suggests that early or delayed amniotomy following balloon expulsion had no association with the mode of delivery (II). This is in line with a previous study reporting no difference in CS rate following early amniotomy at < 4 cm of cervical dilation in nulliparous women (228). However, a recent retrospective cohort study on 546 nulliparous women concluded that amniotomy within one hour of FC expulsion, compared to delay of 4 hours or more, was associated with shorter induction to delivery interval and a higher frequency of vaginal deliveries within 24 hours (230).

The oxytocin administration rate during labor is approximately 47% in Finland, while in Helsinki University Hospital it is 60% (4). In our study, the rate of oxytocin usage was approximately 85% (I–V). The rate of oxytocin

usage was high both in induced and spontaneous labors (I). Unfortunately, we did not differentiate between oxytocin use in the first and the second stages of labor. Oxytocin was more often needed for labor induction following the use of FC compared to misoprostol (III), as also noted in previous studies (17, 18). A recent study suggests that discontinuing oxytocin during the active phase of labor may improve delivery outcomes but increase the duration of the active phase of labor by an average of 40 minutes (240). In our study, oxytocin administration was determined by the managing midwife and obstetrician without a strict protocol, and some women may have been unnecessarily treated with continuous oxytocin during the active phase of labor. High rate of oxytocin use and discontinuous administration may also partly explain some of the CS due to fetal distress during our studies I–V.

OUTCOMES OF LABOR INDUCTION BY FOLEY CATHETER

CESAREAN DELIVERY

The highest CS rates in our study were observed in nulliparous women with prolonged and post-term pregnancies (I–II, V), which is in line with previous reports (262, 263). In our study I, the rate of CS in induced labor at or beyond 41+5 weeks was sixfold compared to spontaneous labor. In contrast, IOL in multiparous women more often resulted in vaginal delivery (I, IV). Previously IOL, regardless of the method, has been associated with a three- to eightfold increase in CS rate compared to spontaneous labor at or beyond term (261), but more recent studies have demonstrated a reduction in CS following IOL at term compared to expectant management (27-31). In our study I, the groups were different with a selection bias of more nulliparous and post-term women ending up in the induction group. Additionally, we focused on a narrow time frame between 41+5 and 42+1 gestational weeks. Thus, our results (I) are inapplicable for further conclusions on timing of IOL with regard to CS rates.

Our results show no difference in the CS rates between FC and misoprostol induced labors (III), as also previously demonstrated (19, 20, 173). Interestingly, a lower CS rate of 4.5% with no increase in infections has been observed with an expectant management policy of 48 hours after PROM (97). In our study, the overall rate of CS was lower in IOL following PROM (III) compared to other indications (24% vs. 33%; $p<0.001$) (III, IV–V). In our study, PROM appears to have a positive impact on the progress of induced labor in women with an unfavorable cervix. It may be contemplated that

perhaps PROM occurred as a result of a biochemical activation process, which led to the process of cervical ripening and rupture of membranes, thus resulting also in more successful labor induction in these women. The rate of CS was not significantly different between inpatients and outpatients (IV), which is in accordance with previous studies (24, 26, 288, 310).

MATERNAL INFECTIOUS MORBIDITY

The median (range) maternal infection rates of intrapartum infections 5(2–6)% and postpartum infections 3(1–4)% in our studies I–V are consistent with the previously shown 7% rate of chorionamnionitis, and 3.5% rate of postpartum endometritis following labor induction (16). The rate of maternal infections is higher in induced compared to spontaneous labor (0.2–1.5%) (313). An older systematic review has linked FC with an increased risk of infections (174), but in more recent studies FC has not been associated with increased infectious morbidity compared to PGs (16, 18, 19, 165, 173). The rates of maternal infections were not different between the groups of FC and misoprostol (III), as also previously reported (16). Furthermore, outpatients and inpatients undergoing IOL by FC had similar rates of infectious maternal morbidity (IV), which is in accordance with previous studies (24, 26, 310).

The use of FC in women with ruptured amniotic membranes has raised concerns over infectious morbidity. In our study III, however, the maternal infection rates were the lowest following IOL by FC in cases of term PROM. On the other hand, prophylactic antibiotics were used for all women in our study III, which may have led to a reduced rate of infections. Another factor related to low infectious morbidity may have been the shorter duration of induced labor following PROM compared to IOL in non-PROM cases (22 h vs. 30 h) (II, III). Similar reassuring results on IOL by FC after PROM at term have been previously reported by a small Swedish pilot study (n=18) and a retrospective cohort study (n=122) (314, 315).

The highest rate of maternal infections was seen in nulliparous women (II). Unfortunately, the placental histopathological diagnosis of chorionamnionitis was not available in all cases. Duration of labor, duration of ruptured membranes, use of internal fetal monitoring, presence of meconium, number of vaginal examinations, use of prophylactic antibiotics, and GBS screening protocols are factors associated with rates of infectious morbidity (313). In our study, gestational diabetes was associated with maternal infections (II). Similar results were reported by a Danish study (n=2492), in which gestational and pregestational type 2 diabetes were associated with an increased risk of postpartum infections (316). Maternal infections were also associated with prolonged labor, CS, and nulliparity

(III), as also noted previously (317). Increased risk of chorionamnionitis has been demonstrated in nulliparous women remaining in the latent phase for more than 12 hours (284).

NEONATAL INFECTIOUS MORBIDITY

In our studies I–IV, the median (range) rate of neonatal clinical sepsis following IOL was 1.8(1–3) %, which parallels the results of previous studies (16). No blood culture positive neonatal sepsis cases occurred during our studies I–V, whereas a sepsis incidence of approximately 1 per 1000 live births has been previously reported (318). The rates of neonatal infections are known to vary by geographic region, resource use, and management practices, such as GBS screening or use of prophylactic antibiotics.

The neonatal infection rates were similar in the groups of FC and misoprostol IOL (III), as also reported by a recent review and meta-analysis (16). Consistent with previous studies, outpatient cervical ripening by FC did not result in increased neonatal infectious morbidity compared to inpatient cervical ripening (IV) (24, 26, 310). Furthermore, the neonatal infection rate was low (1%) in women undergoing IOL by FC following term PROM ≥ 18 hours. Our results add to the limited data on the use of FC in women with term PROM, and suggest that with regards to neonatal infectious morbidity, FC seems a safe and feasible method of IOL.

In nulliparous women, the incidence of neonatal infections was higher in induced compared to spontaneous labor (I). However, the rates of clinical neonatal sepsis were similar between these groups, whereas the rate of suspected neonatal infections was higher in induced labors (I). We speculate that the use of FC, a relatively new method at the time of the study, may have resulted in a lower threshold for starting antibiotics in cases of prolonged induction to delivery intervals, and to more neonates being admitted for observation. Unfortunately, further comparisons between spontaneous and induced labors are limited, since the rates of suspected neonatal infections are not included in most studies, and data on the rates of blood culture negative neonatal infections following spontaneous labor are not available.

The majority of neonates diagnosed with infection in our studies I and II were delivered by CS. Neonatal infection may have occurred in the absence of maternal infection, and maternal infection did not always lead to neonatal infection, although maternal chorionamnionitis may increase the risk of neonatal infection by 1–4% (319). Early epidural analgesia was associated with an increased risk of neonatal infection in our study II, but this may rather be related to prolonged latent phase of induced labor, which is a known risk factor for infectious morbidity.

OTHER DELIVERY OUTCOMES

Maternal and neonatal outcomes were similar between induced or spontaneous labor in prolonged or post-term pregnancy (I), IOL by FC or misoprostol following PROM at term (III), and between inpatients and outpatients (IV). IOL itself has been associated with increased admissions to neonatal unit (93, 284), but this was not seen in our studies I–V. Moreover, admissions to NICU and to neonatal unit were similar between induced and spontaneous labor, between FC and misoprostol (III), and between outpatients and inpatients (IV), as also shown in previous studies (18, 310). In accordance with previous studies, most women were satisfied with outpatient IOL, and found contacting the delivery unit feasible (220, 288, 289).

A retrospective cohort study by Mackeen et al. reported shorter induction to delivery interval (12.3 h vs. 22.6 h; $p<0.01$) in women undergoing IOL by FC compared to misoprostol following PROM at term (314). In our study III, no difference in the induction to delivery interval was found between these two methods. The induction to delivery interval was longer in outpatients than in inpatients (IV), as also previously noted (24). This may be explained by the fact that amniotomy was in outpatients often delayed to the next morning in case of FC expulsion at night. However, the durations of the first and second stages of labor were similar in outpatients and inpatients (IV).

FACTORS ASSOCIATED WITH SUCCESS OF LABOR INDUCTION BY FOLEY CATHETER

Advanced maternal age, obesity, gestational diabetes, and an unfavorable cervix were risk factors for CS in our study II, as also reported by several previous studies (86, 87, 261, 270). We also noticed that the cervix further ripened from unfavorable to favorable only in every tenth woman during expectant management from 41+5 to 42+1 gestational weeks (I). We used the Bishop score to assess the degree of cervical ripeness, with a score ≥ 6 being a marker for a favorable cervix. Since the Bishop score was originally derived from multiparous women (48), a more preferable concept for favorable cervix in nulliparous women could be Bishop score ≥ 8 (5). It may also be speculated that despite an improved Bishop score following FC expulsion, the cervical ripening process, such as remodeling of collagen, had not yet commenced (320). Furthermore, higher cervical collagen concentrations have been reported in women with failure to progress compared to women with normal progress of labor (320). It has been suggested that initiating cervical ripening gradually and earlier in nulliparous women with

unfavorable cervices may improve delivery outcomes, although no studies have yet addressed the issue.

We found that the need for oxytocin induction and early epidural analgesia were associated with an increased risk of CS in nulliparous women (II), as also noted in a previous study (263). However, this may be explained by the fact that factors associated with early request for epidural analgesia, such as IOL, oxytocin use, and nulliparity, are all also linked to increased risk of CS (321).

The most common indications for CS following IOL by FC were failed induction and labor arrest (I–V), as also previously reported (12, 173, 199). Previous studies conclude that before considering an induction failed, at least 12 hours of latent phase in the setting of ruptured membranes and oxytocin administration should be allowed for nulliparous women, and 15 hours for multiparous women (282, 284, 286). Furthermore, transition to active labor occurs only at 6 cm of cervical dilation following IOL by FC (285). In our studies I–V, oxytocin was administered predominantly for 6–12 hours, the timing of oxytocin administration altered, and the definitions for failed induction and labor arrest varied. Therefore, in some cases failed induction may have been diagnosed too early. We speculate that some CSs performed due to suspected labor arrest may have been partly due to physician related factors, such as medical concerns or false interpretation on progress of induced labor, and patient related factors, such as maternal exhaustion and preference for CS. Also, some CSs might have been avoided if there had been a standardized management protocol for labor induction.

Post-term pregnancy is associated with increased rates of perinatal complications and operative delivery (28, 32, 33), as also seen in our studies I–II, IV–V. A recent retrospective cohort study comparing expectant management and elective IOL between 38 and 42 gestational weeks suggested that the curve for CS risk was U-shaped with the nadir at 39 gestational weeks (322). In Finland, the first fetal monitoring in uncomplicated pregnancy is scheduled at 41+5 gestational weeks, and IOL is carried out between 41+5 and 42+1 gestational weeks. Routine IOL at 41 gestational weeks would increase the rates of labor induction and use of health care resources. On the other hand, earlier IOL may decrease cesarean deliveries, perinatal complications, and episodes of neonatal care, thus eventually decreasing total health care costs (27, 28).

CERVICAL IGFBP-1 AND MMPS IN FOLEY CATHETER INDUCTION (V)

Our results suggest that IGFBP-1, phIGFBP-1, MMP-8, MMP-9, and TIMP-2 are involved in the process of cervical ripening. However, the changes in these cervical biomarker concentrations showed no correlation with CS due to labor arrest or failed induction, thus appearing not suitable for predicting the outcome of labor induction in clinical use. The study investigated only nulliparous women, since the concentrations of phIGFBP-1 and MMP-8 have been shown to differ between nulliparous and multiparous women (323, 324).

In our study, the IGFBP-1 concentrations increased during cervical ripening without predicting the induction to delivery interval, as also seen previously (64). The presence of cervical phIGFBP-1 may predict successful vaginal delivery (65), but this was not observed in our study V. However, IGFBP-1 and phIGFBP-1 concentrations increased more during FC induced cervical ripening in women who started spontaneous contractions, as also previously demonstrated (65).

In contrast to a previous study by Lim et al., which showed an increasing trend (69), the MMP-8 and MMP-9 concentrations decreased during FC induced cervical ripening in our study. In addition, the starting levels and the decrease were also greater in women with less ripe cervices. Our results suggest that the decrease in MMP-8 and MMP-9 concentrations may reflect reduced defensive potential during cervical ripening (325). In our study, the TIMP-2 concentrations also decreased, which may reflect interaction with MMPs, and the homeostatic regulation of extracellular matrix remodeling by TIMPs (67). Furthermore, in the study by Lim and colleagues, the study design and sampling technique differed from ours, and the correlations between biomarkers and IOL outcomes were not analyzed (69).

STRENGTHS AND WEAKNESSES OF THE STUDY

The strengths of the study include a well-defined study population of a tertiary care unit with approximately 14 000 deliveries annually, uniform dating of pregnancy by first trimester ultrasound, systematically recorded hospital- and registry-based data, and extensive experience of the use of FC. To our best knowledge, study III is the largest RCT on use of FC after PROM at term. In study V, the sampling technique and management of cervical ripening were performed by the same obstetrician (V).

The major limitation of studies I and II is the retrospective design. The study design (I) may have led to a selection bias of more post-term and nulliparous women ending up in the IOL group. Another obvious weakness is the lack of power analyses in determining the sample sizes (I, II), although this can be explained by the fact that we chose a cohort of one year. Also, the approach of focusing on the narrow time frame between 41+5 and 42+1 weeks may to some extent offset the lack of power in study I. In study III, the main limitation was the relatively small number of patients enrolled. Furthermore, unfortunately we did not assess patient satisfaction (III). We also acknowledge the lack of randomization on the setting of IOL (IV), and regret not assessing the economic impact of the outpatient procedure (IV). However, this was a pilot study emphasizing feasibility, and also emphasizing maternal preference on the setting of IOL (IV). The main limitation of the study V was the small sample size. Also, there may have been inter-individual variation in vaginal bacterial flora and cervical mucus cellularity reflected in the biomarker concentrations (V). We are also aware that characteristics and practice patterns demonstrated in the studies may not be applicable to other settings. Also, the management of labor induction may have been influenced by lack of standardized protocol, as well as delivery unit capacity, human resources, and logistic issues.

FUTURE ASPECTS

The rates of labor induction are anticipated to rise as the methods of fetal monitoring improve, and vaginal delivery, including the role of vaginal microbiome during labor, will be promoted over non-medically indicated cesarean deliveries. After discovering the exact mechanism of labor onset, related to the telomere loss and cell-free fetal DNA theory, prediction of successful labor induction will hopefully become common practice. The concentrations of cell-free fetal DNA, cervical collagen, myometrial oxytocin receptors, and biochemical mediators, measured from maternal serum, cervical tissue, and amniotic fluid, might in the future help to analyze the optimal timing of IOL and delivery. Additionally, several bedside screening tests for activation of the trigger for parturition, and success of labor induction, may be developed. Labor induction may become digitalized, as small cervical, myometrial and amniotic electrodes connected to a wireless transmitter could be used to follow the progress of labor induction and labor, as well as to predict the delivery outcome. Instead of comparing the use of PGs and balloon catheters, combined use might be the method of choice in the future. The pharmaceutical industries may release new balloon catheters secreting continuous or pulsed low dose PGs. As the new methods evolve, the

obstetricians can regulate PG dosage and balloon pressure from a distance, depending on the information a sensor attached to the cervical ripening device sends to the patient's medical record. Furthermore, fetal cardiotocography may be remotely simultaneously monitored in a digital fashion.

However, as we wait for the knowledge and techniques to evolve, the high rate of CS in nulliparous women today is of concern and requires further assessment. One may speculate that in the absence of the underlying biochemical trigger leading to cervical ripening and onset of labor, IOL fails to result in successful vaginal delivery regardless of the management practice. Further studies on suitable biomarkers for bedside screening on the success of IOL are needed. On the other hand, optimal timing of IOL may also decrease the rates of CS, perinatal complications, and health care costs. Use of FC after PROM remains one of the questions to be investigated further. We were also encouraged by the pilot study on outpatient IOL, and a randomized trial on the setting of labor induction including a cost analysis could substantiate these findings.

CONCLUSIONS

1. Labor induction with FC in prolonged or post-term pregnancy does not increase maternal or neonatal morbidity compared to spontaneous onset of labor, but is associated with an increased rate of cesarean delivery in nulliparous women.

2. IOL by FC is associated with a high rate of CS in term nulliparous women. Advanced maternal age ≥ 37, obesity, gestational diabetes, Bishop score ≤ 3, need for oxytocin induction, and request for early epidural analgesia are associated with an increased risk of cesarean delivery. Gestational diabetes and early epidural analgesia are associated with infectious morbidity in these pregnancies.

3. FC and oral misoprostol can both be used for IOL in women with term PROM with no difference in the rates of cesarean delivery, or maternal or neonatal infectious morbidity when prophylactic antibiotics are used.

4. IOL by FC appears safe and feasible as an outpatient procedure, and results in no difference in the rate of CS, or maternal and neonatal infectious morbidity compared to inpatients. Most women are satisfied with outpatient IOL.

5. The concentrations of cervical biomarkers IGFBP-1 and phIGFBP-1 increase, whereas MMP-8, MMP-9, and TIMP-2 concentrations decrease during FC induced cervical ripening in nulliparous women. However, these changes do not predict the outcome of labor induction, and thus appear not suitable for clinical practice.

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