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LABOR INDUCTION AT TERM AND BEYOND

EFFECTS ON VAGINAL DELIVERY RATE, ADVERSE OUTCOMES, AND CHILDBIRTH EXPERIENCES

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DOCTORAL THESIS

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Undergoing a spontaneous onset of labor at the optimal time
by choice is impossible.

This thesis is for anyone with an interest in labor induction.

ABSTRACT

One in three labors in Finland is induced. Compared with spontaneously initiated labor, induced labor increases the risk of cesarean section (CS) and a negative childbirth experience. Waiting for a spontaneous onset of labor is not always feasible, however, and labor induction may be needed to protect maternal or fetal health. When labor induction is compared with expectant management, the associations with CS rates and childbirth experiences may differ.

This thesis explores how labor induction affects CS rates and adverse outcomes in women in light of the common pre-labor risk factors of prior CS for labor dystocia or failed labor induction, group B streptococcus (GBS) colonization, nulliparity, and late- or post-term pregnancy. This thesis also aims to discover ways to ameliorate the childbirth experience in women who undergo labor induction.

Five original articles form the basis of this thesis. Two of the articles detail retrospective cohort studies (I and II), and two are about a single prospective cohort study (III–IV). Study V (submitted) describes a randomized controlled multicenter trial.

Study I showed that 72.9% of women who had previously undergone a CS for labor dystocia or failed labor induction succeeded in a trial of labor. Traditional risk factors for CS, such as labor induction and a lack of prior vaginal delivery, were also identified as risk factors in our study. The rate of repeat CS was twofold in women with a prior failed labor induction (41.0%) compared with women who had previously experienced labor dystocia in the first (24.4%) or second stage of labor (26.9%, p = 0.003). The greatest rate of CS, 48.1%, was found in women with a history of prior failed labor induction who underwent labor induction in their current pregnancy.

Study II showed that, in terms of infection, labor induction by balloon catheter was safe in GBS-positive women with intact membranes when prophylactic antibiotics were administered at the onset of labor or membrane rupture. In our study, the rate of maternal intrapartum infection was lower in GBS-positive women than in GBS-negative women, at 4.7% vs. 8.3% (p = 0.01). The rates of maternal postpartum infection and neonatal infection were similar in the two groups. A prolonged duration of ruptured membranes (≥ 12 hours) was associated with all types of infection assessed.

Studies III and IV showed that women who underwent labor induction had relatively positive childbirth experiences. The negative experiences of women with their first birth were mainly associated with the same delivery-related factors that affected the parous women: CS and hemorrhage. The nulliparous women, however, scored lower on assessments of their own capability to give birth. Thus, the confidence and agency of such women should be enhanced through antenatal education. The choice of labor induction method—balloon

catheter or misoprostol—had no effect on childbirth experiences, but women treated with balloon catheters were more content with the method chosen and stated that they would choose the same method in a future pregnancy.

Study V identified a reduced rate of operative delivery in nulliparous women with unripe cervices if they underwent labor induction at 41+0 gestational weeks compared with expectant management and labor induction at 41+5 to 42+1 gestational weeks (30.6% vs. 45.6%, p = 0.003). The rates of CS (16.7% vs. 24.1%, p = 0.07) and adverse neonatal outcomes (9.7% vs. 14.4%, p = 0.16) did not differ between the groups, and no perinatal deaths occurred. Of the women who completed a vaginal delivery, the rates of operative delivery by vacuum extraction were lower in the early induction group than in the expectant management group (16.8% vs. 28.4%, p = 0.02). In addition, fewer women in the early induction group had hemorrhage ≥ 1,000 ml (12.2% vs. 20.8%, p = 0.03). Of the women who had been through expectant management, 45.6% had a spontaneous onset of labor.

In conclusion, offering a trial of labor after CS to women with a history of prior CS for labor dystocia or failed labor induction may be encouraged, although a failed labor induction in the prior pregnancy or the need for labor induction in the current pregnancy lower the success rate of vaginal delivery. An effective labor induction protocol leading to as high a rate of vaginal delivery as possible and a preparedness to respond to postpartum hemorrhage are paramount for avoiding negative childbirth experiences in women undergoing labor induction. In addition, enhancing nulliparous women's confidence in their capacity and preparedness for labor and delivery could result in better experiences. Balloon catheter induction is safe in terms of infectious morbidity. It may also result in more positive views of the labor induction process, although the childbirth experiences associated with this practice seem to be similar to those of women who undergo labor induction via misoprostol. Practices for managing late-term pregnancy in the Finnish maternity care system should be assessed, as offering early induction at 41+0 gestational weeks may result in lower rates of operative delivery than the current protocol of implementing expectant management up to 41+5–42+1 gestational weeks. However, as perinatal outcomes were reassuring with both management options, expectant management may still be chosen if preferred by the pregnant woman.

TIIVISTELMÄ

Suomessa joka kolmas synnytys käynnistetään. Käynnistetyssä synnytyksessä on suurempi riski keisarileikkaukselle ja huonolle synnytyskokemukselle, kun vertailukohtana on spontaanisti käynnistynyt synnytys. Joskus synnytyksen spontaania käynnistymistä ei kuitenkaan voida jäädä odottamaan, vaan äidin tai lapsen etu puoltaa käynnistystä. Tämä väitöskirja tutkii käynnistyksen vaikutuksia keisarileikkauksen ja muiden synnytyskomplikaatioiden esiintyvyyteen ja synnytyskokemukseen.

Väitöskirja perustuu viiteen alkuperäisartikkeliin. Näistä kaksi on takautuvia kohorttitutkimuksia (I ja II), kaksi on kirjoitettu etenevästä kohorttitutkimuksesta (III–IV), ja yksi on satunnaistettu monikeskustutkimus (V, julkaisuarviossa).

Tutkimuksen I tulosten perusteella aiemmin epäonnistuneen käynnistyksen tai pysähtyneen synnytyksen vuoksi keisarileikatuista synnyttäjistä suurin osa, 72,9%, synnytti alakautta jatkossa. Aiempi epäonnistunut käynnistys sekä käynnistys nykyisessä synnytyksessä olivat kuitenkin merkittäviä riskitekijöitä alatiesynnytyksen epäonnistumiselle.

Tutkimuksen II tulosten perusteella B-ryhmän streptokokkibakteerin (GBS) kantajilla ei ollut riskiä synnyttäjän tai vastasyntyneen infektioiden lisääntymiseen, kun synnytys käynnistettiin balonkimenetelmällä sikiökalvojen ollessa käynnistyksen alussa ehjät. GBS-bakteerin kantajilla oli synnytyksen aikaisia infektioita jopa vähemmän kuin ei-kantajilla (4,7% vs. 8,3%, p = 0,01), mahdollisesti liittyen kantajille synnytyksen käynnistyttyä tai lapsiveden mentyä aloitettuun antibioottiprofylaksiaan.

Tutkimuksen III–IV tulosten perusteella synnyttäjät kokivat käynnistyksellä alkaneet synnytyksensä melko positiivisena, ja suurin riski huonolle kokemukselle liittyi synnytyskomplikaatioihin: keisarileikkaukseen ja tavanomaista suurempaan verenvuotoon. Ensisynnyttäjien kokemusta omasta pärjäävyydestään tulisi kuitenkin vahvistaa. Balonki- ja misoprostolikäynnistysmenetelmiä verratessa synnytyskokemukset olivat yhtä hyvät, mutta balongilla käynnistetyt olivat tyytyväisempiä itse käynnistysmenetelmään.

Tutkimuksen V tulosten perusteella pitkittyneen ensiraskauden käynnistysajankohdan varhentaminen raskausviikolta 41+5–42+1 raskausviikolle 41+0 saattaisi vähentää toimenpidesynnytysten osuutta, sillä varhaisemmin käynnistetyistä 30,6% synnytti imukuppi- tai keisarileikkausavusteisesti, kun seurantaryhmässä vastaavan toimenpidesynnytyksen koki 45,6%, p = 0,003. Kohtukuolemia ei tapahtunut eikä keisarileikkausten tai huonovointisten vastasyntyneiden osuuksissa ollut eroja. Liki puolella seurantaryhmäläisistä synnytys käynnistyi itsekseen. Varhaisemman käynnistyksen mahdollistamista kaikille sitä toivoville ensisynnyttäjille tulisi arvioida jatkossa Suomessa.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Place K, Kruit H, Tekay A, Heinonen S, Rahkonen L: Success of trial of labor in women with a history of previous cesarean section for failed labor induction or labor dystocia: A retrospective cohort study. BMC Pregnancy Childbirth. 2019; 19: 176.

II Place K, Rahkonen L, Nupponen I, Kruit H: Vaginal streptococcus B colonization is not associated with increased infectious morbidity in labor induction. Acta Obstet Gynecol Scand. 2021; 100: 1501–1510.

III Place K, Rahkonen L, Verho-Reischl N, Adler K, Heinonen S, Kruit H: Childbirth experience in induced labor: A prospective study using a validated childbirth experience questionnaire (CEQ) with a focus on the first birth. PLoS One. 2022; 17: e0274949.

IV Place K, Kruit H, Rahkonen L: Comparison of primiparous women's childbirth experience in labor induction with cervical ripening by balloon catheter or oral misoprostol–A prospective study using a validated childbirth experience questionnaire (CEQ) and visual analogue scale (VAS). Acta Obstet Gynecol Scand. 2022; 101: 1153–1162.

V Place K, Rahkonen L, Tekay A, Väyrynen K, Orden M-R, Vääräsmäki M, Uotila J, Tihtonen K, Rinne K, Mäkikallio K, Heinonen S, Kruit H: Labor induction at 41+0 gestational weeks or expectant management for the nulliparous woman: the Finnish randomized controlled multicenter trial. Submitted.

All publications were originally published as open access. The articles are referred to in the text by these Roman numerals.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AROM	Artificial rupturing of membranes
AOR	Adjusted odds ratio
BC	Balloon catheter
BMI	Body mass index
CEQ	Childbirth Experience Questionnaire
CI	Confidence interval
CS	Cesarean section
CTG	Cardiotocography
EHR	Electronic health record
GBS	Group B streptococcus
GDM	Gestational diabetes
GW	Gestational weeks
HUS	Helsinki University Hospital
IQR	Interquartile range
IVF	In vitro fertilization
NICU	Neonatal intensive care unit
OR	Odds ratio
PROM	Premature rupture of membranes
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SD	Standard deviation
SWEPIS	Swedish Post-term Induction Study
TOLAC	Trial of labor after cesarean
VAS	Visual analog scale
VBAC	Vaginal birth after cesarean

1 INTRODUCTION

When the safety and well-being of a mother or her fetus are compromised by letting a pregnancy continue, labor induction or cesarean section (CS) without a trial of labor is required. Today, one in three labors in Finland is induced.[1] The frequency of induced labor has increased worldwide in recent years, as indications for labor induction have increased, and more pregnancies are affected by conditions that warrant induction.[1,2]

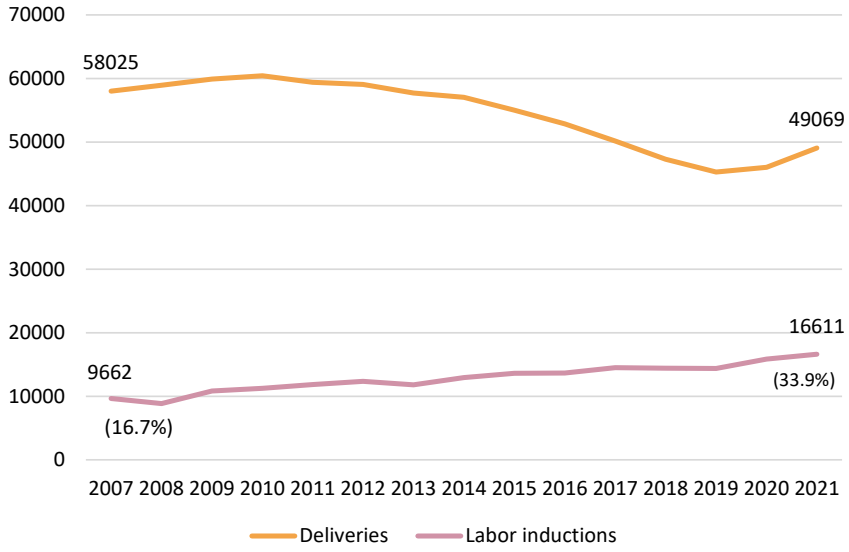


Figure 1 The rates of delivery and labor induction in Finland between 2007 and 2021. Data collected from the Finnish Institute for Health and Welfare, "Perinatal statistics – Parturients, deliveries and newborns 2021."[1]

Historically, labor induction was thought to lead to a greater frequency of CS, but recent research has suggested that optimal timing and management of labor induction can increase the probability of successful vaginal delivery; however, there is controversy over this point.[3,4]

Vaginal delivery is the safest mode of delivery for both the mother and baby,[5,6] but in some cases, a CS can save the lives of both. In many countries, the frequency of CS has increased in recent decades,[7] partly for reasons that cannot be considered medically justified. In Finland, the CS rate is currently 20%.[1] The causes of the rise in CS frequency are complex, but the increasing rates of labor induction have often been blamed.

Safe labor and delivery as well as low maternal and neonatal mortality and morbidity are considered the standard in our high-resource maternity care system, and women anticipate a positive childbirth experience. Among the public, the maternal childbirth experience has become an increasingly important factor when assessing the care provided, and there is an increasing emphasis on the active role of the parturient in the process.

Emergency CS is perhaps the most important cause of negative childbirth experiences.[8] Thus, reducing the frequency of unsuccessful vaginal deliveries that lead to CSs is one possible means of promoting positive childbirth experiences.

This thesis explores how labor induction can be used to increase the prevalence of successful vaginal deliveries and, in addition, how labor induction affects childbirth experiences and adverse outcomes. The specific focus was on first births, which comprised 42.5% of all deliveries in Finland in 2021.[1]

2 REVIEW OF THE LITERATURE

2.1 LABOR ONSET

The exact mechanism underlying the onset of labor has not yet been established, but the role of the fetus has become increasingly important in recent research.[9] It has been suggested that the human parturition cascade is a complex interplay between fetal maturation, the hormonal systems of both the mother and fetus, the maternal uterus, and the placenta.[10,11] Due to these factors, levels of endogenous maternal prostaglandin and other inflammatory mediators rise, which ripens the cervix and produces uterine contractions.[12,13]

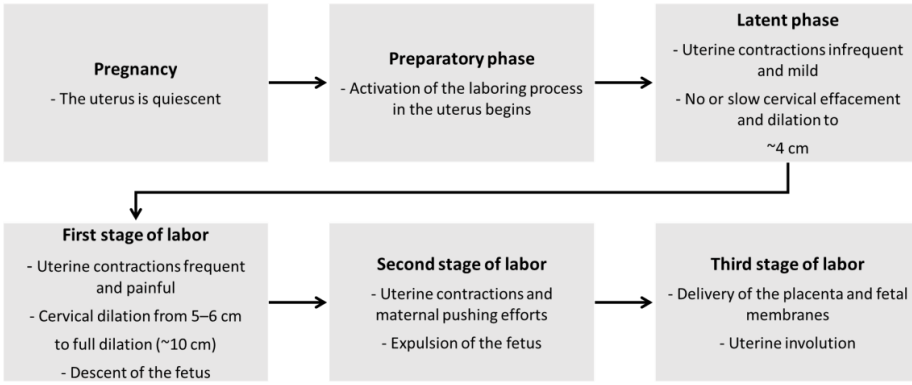
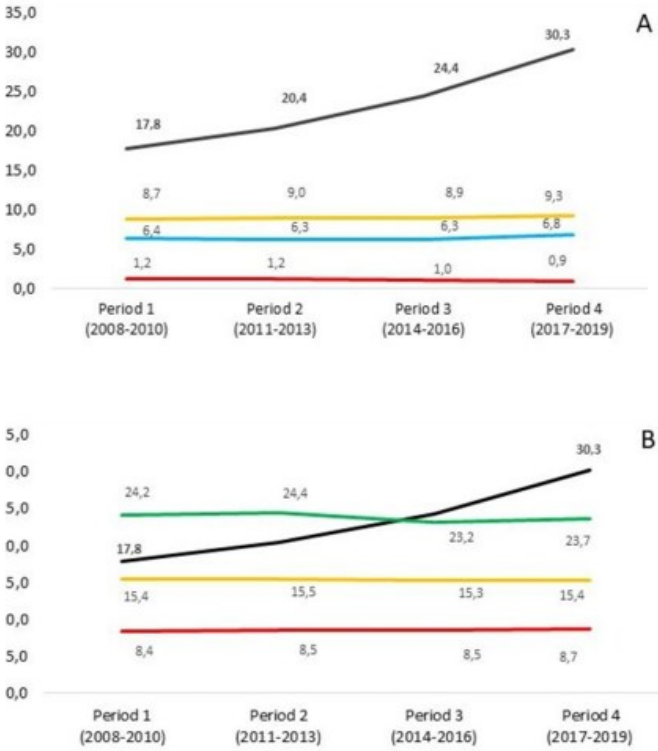


Figure 2 The stages of labor.

Labor may also be induced by stimulating uterine contractions to achieve vaginal delivery before the natural, spontaneous onset of labor.[14] Traditionally, induced labor has been associated with a higher CS rate than spontaneously initiated labor.[3,15,16] For example, a Finnish study revealed a CS rate of 30.7% in women whose labor was induced at ≥ 41+5 gestational weeks (GW), whereas women who experienced a spontaneous onset of labor in the same weeks had a CS rate of 4.8%.[17] The increased risk of CS has thus indicated that labor induction should be offered to women only if medically necessary. However, in the comparison of labor induction and expectant management, effects on the CS rates may be different.[4] In Finland, the increased frequency of labor induction in recent years has not been associated with an increased rate of CS (Figure 3), which is consistent with recent international research.[3,4]



In Figure 3A: labor induction in black, emergency CS in yellow, planned CS in blue, crash emergency CS in red.

In Figure 3B: labor induction in black, CS following labor induction in yellow, CS following labor induction in nulliparas in green, CS following labor induction in multiparas in red.

Figure 3 Rates of labor induction and cesarean section in Finland between 2008 and 2019. Copied from Kruit H, Gissler M, Heinonen S, Rahkonen L: Breaking the myth: The association between the increasing incidence of labour induction and the rate of caesarean delivery in Finland–A nationwide Medical Birth Register study. BMJ Open. 2022; 12: e060161.

2.2 DELIVERY MODE

Vaginal delivery is healthier than a CS for both the mother and the neonate.[5] As a CS is a major surgery, maternal complications—such as infection, postpartum hemorrhage, and venous thromboembolism—are more common, and injuries of the adjacent organs (the bladder, bowels, and ureters) are possible.[18] In addition, a history of CS leads to an increased risk of potentially life-threatening complications in subsequent pregnancies, such as an abnormally attached placenta and uterine rupture.[5] A prior CS often leads to a repeat CS, and the risks are known to increase as the number of CSs increases.[5] Safely preventing the first CS is thus essential.

The mode of delivery not only affects the mother and her subsequent pregnancies but also the neonate. Respiratory problems, although usually mild and transient, are more common among those born via CS.[5] Additionally, the mode of delivery shapes the neonatal microbiome, which may affect the health of the individual long into adulthood.[6,19]

2.3 PREDISPOSING FACTORS FOR CESAREAN SECTION AND ADVERSE OUTCOMES

Common risk factors for CS include nulliparity, advanced maternal age, and obesity, and the rates of childbearing women ≥ 35 years of age, as well as those with a body mass index (BMI) ≥ 30, have increased in Finland in recent years, as shown in Figure 4.[1]

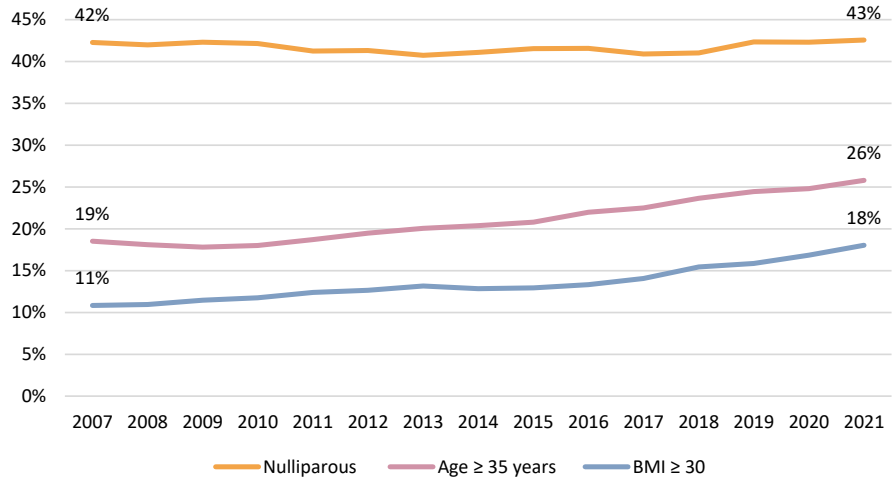


Figure 4 The rates of parturients in groups at risk of cesarean section in Finland between 2007 and 2021. Data collected from the Finnish Institute for Health and Welfare, "Perinatal statistics – Parturients, deliveries and newborns 2021."[1]

2.3.1 PARITY

Nulliparous women underwent 42.5% of all deliveries in Finland in 2021.[1] These women are at higher risk of perinatal mortality and likelier to have an emergency CS than women who have already given birth.[3,15,16,20] In Finland, 16.5% of nulliparous women and 6.5% of parous women underwent emergency CS in 2021.[1] The incidences of crash emergency CS were 1.1% and 0.6%, respectively. In addition, compared with parous women, nulliparous women are at higher risk of operative vaginal delivery (16.9% vs. 4.1%) and other complications, such as anal sphincter injury (1.8% vs. 0.4%) and hemorrhage requiring blood transfusion (4.7% vs. 2.1%).[1]

2.3.2 ADVANCED MATERNAL AGE

In many Western countries, women choose to become pregnant later than would perhaps be biologically optimal.[21] In Finland, women who delivered their first child in 2021 were 30 years old on average,[1] and of all deliveries in

Finland in 2021, 25.8% were by women 35 years old or older (Figure 4).[1] In studies, advanced maternal age is often classified as ≥ 35, ≥ 37, or ≥ 40 years of age.

Advanced maternal age is associated with increased rates of perinatal and maternal mortality, adverse neonatal outcomes, maternal chronic illnesses, and pregnancy-related conditions, such as gestational diabetes (GDM) and hypertension.[21–24] Compared with younger women, advanced maternal age has also been suggested to increase the frequency of CS and operative vaginal delivery, regardless of whether the onset of labor is spontaneous or induced.[25,26]

2.3.3 OBESITY

Obesity is a growing health issue globally. In 2021, 45.3% of all Finnish women who gave birth were overweight, with a pre-pregnancy BMI ≥ 25, while 18.4% were obese, with a BMI ≥ 30 (Figure 4).[1] Obese women are at increased risk of perinatal death and CS.[22,27,28] In addition, pregnancy complications such as GDM and preeclampsia are more common among obese women.[29]

2.3.4 PRIOR CESAREAN SECTION

A successful trial of labor after cesarean (TOLAC) ending with a vaginal birth after cesarean (VBAC) is associated with the lowest maternal morbidity rate for women with a history of prior low transverse CS.[30–33] The maternal and neonatal risks of an unsuccessful TOLAC that ends with an emergency or crash emergency CS are, however, greater than the risks of a scheduled repeat CS.[31,33] The American College of Obstetricians and Gynecologists (ACOG) suggests that women with a 60%–70% likelihood of achieving a VBAC via a TOLAC experience the same or less maternal morbidity than women who undergo an elective repeat CS.[33]

A 2023 study of the Finnish National Birth Register found that 77.0% of women who had undergone a CS in their first pregnancy underwent a TOLAC in their second pregnancy. In comparison, of the women who had undergone a prior vaginal delivery and were currently in their second pregnancy (the control group), nearly all (97.2%) underwent a trial of labor.[34] In the same study, 69.3% of the women who underwent a TOLAC and 96.8% of the women in the control group completed a successful vaginal delivery in their second pregnancy ($p < 0.001$). The rates of vacuum delivery (16.0% vs. 3.0%, $p < 0.001$), and neonatal intensive care unit (NICU) admission (13.2% vs. 6.8, $p < 0.001$) were higher in the TOLAC group than in the control group. In addition, although the rate of perinatal mortality was low in both groups, it was higher in the TOLAC group than in the control group (0.5% vs. 0.3%, $p < 0.001$).[34]

According to a recent Finnish cohort study, the risk factors for a failed TOLAC include a prolonged gestational age, an unripe cervix at admission, and a lower mean intrauterine pressure as measured by an intrauterine pressure

catheter during labor.[35] In the same study, 74% of women had a successful VBAC, and this rate was unaffected by labor induction.[35] In many other studies, labor induction has been associated with a reduced success rate of VBAC when compared with a labor of spontaneous onset.[36–39]

A history of prior vaginal delivery is the best predictor of a successful TOLAC.[30,35,40] The indication for the previous CS and the cervical status and head station recorded during the previous CS also influence the success rate.[40–45] Women with a history of nonrecurring CS indication, such as a breech presentation or fetal distress, have higher chances of a successful TOLAC than women who previously underwent CS for non-progressing labor, i.e., labor dystocia.[42,43] Acknowledged risk factors for a repeat CS include obesity, advanced maternal age, lower maternal height, and greater neonatal birthweight.[36,46–55]

The success rate of a TOLAC can be predicted using nomograms and calculators, but their use is limited when considering a TOLAC of a woman with a prior failed labor induction or labor dystocia.[56–58] In extant research, the rates of VBAC among women with a previous CS for labor dystocia vary between 42% and 77% (Table 1).

In addition, there are scarce data on the effect of labor induction on the VBAC rate among women with a history of CS for labor dystocia. Thus, labor induction may be discouraged for these women. In the few studies performed, the rates of successful VBAC following labor induction in the current labor vary between 42% and 58% if the indication for the previous CS was labor dystocia (Table 1).

In Finland, labor is induced in women with a history of CS for the same indications as in women without a uterine scar. In a nationwide Norwegian study, women who had undergone a prior CS constituted 12% of all labor induction cases. In the same study, the indication for labor induction was most often premature rupture of membranes (PROM, 21%) or prolonged/post-term pregnancy (15%).[59]

In addition to its health benefits, a TOLAC is suggested to be more cost-effective than a repeat planned CS.[60] If long-term consequences are considered, a TOLAC appears more economical than a repeat planned CS if the VBAC success rate is 47% or more.[61]

Table 1. Outcomes of trials of labor after previous cesarean section due to labor dystocia.

Study	Design	N	Vaginal delivery	Labor induction	Vaginal delivery following labor induction	Uterine rupture
Bujold 2001 [62]	Retrospective	868	68%	27%		2%
Landon 2005 [43]	Prospective	4,630	64%		58%	
Peaceman 2006 [63]	Retrospective	3,182	54%			
Yokoi 2012 [64]	Retrospective	177	77%			
Abildgaard 2013 [40]	Retrospective	355	52%	13%		
Obeidat 2013 [44]	Retrospective	37	49%			0%
Lewkowitz 2015 [45]	Retrospective	238	49%	21%	47%	
Soni 2015 [65]	Prospective	131	73%			
Bhide 2016 [66]	Retrospective	399	42%			
Mizrachi 2017 [37]	Retrospective	231	67%	5%	42%	
Maykin 2017 [67]	Retrospective	196	63%			
Lindblad Wollmann 2018 [38]	Prospective	979	56%		44%	
Levin 2022 [39]	Retrospective	168	64%	11%	42%	2%

The most feared complication after a prior CS is uterine rupture, the rate of which varies from less than 1% to 2%–3% in different studies (0%–2% in Table 1). In a nationwide Norwegian study of women who underwent labor induction, the rate was 2.2% in women with a prior CS.[59]

For women with a history of CS, the primary method of initiating cervical ripening is to use a balloon catheter (BC) as, according to many studies, prostaglandins increase the risk of uterine rupture, unlike BCs.[68–70] In a Finnish cohort study, the rate of uterine rupture was 0.3% in women in whom labor was induced by a BC and 0.8% in women in whom labor began spontaneously ($p = 0.47$).[71] Contrarily, in a smaller Finnish cohort study, cervical ripening via BC was a risk factor for uterine rupture in univariate analysis, as was an unfavorable cervix.[35]

2.3.5 FETAL FACTORS

Macrosomia is often defined as a birth weight ≥ 4,000 g or ≥ 4,500 g at any stage of pregnancy, although differences in definitions exist.[72] Macrosomia increases the risk of neonatal and maternal morbidity as well as emergency CS.[72] In the case of vaginal delivery, macrosomic neonates are at risk of birth trauma and shoulder dystocia. For this reason, CS without a trial of labor may be recommended at an estimated fetal weight of ≥ 5,000 g in a pregnancy not affected by diabetes or ≥ 4,500 g in the case of pregnancies marked by diabetes.[72] Unfortunately, fetal weight estimations made using ultrasound may be inaccurate, and no clear evidence exists of a correct management protocol for macrosomia.[73–77] In the future, estimating fetal weight using magnetic resonance imaging could be beneficial, as it may be better than ultrasound at accurately detecting fetuses that are large for their gestational age.[78,79]

The fetal lie and presentation also affect the success of vaginal delivery. In the case of a transverse lie, for example, vaginal delivery is not feasible. In breech presentation cases, many women choose elective CS due to the increased risk of adverse perinatal outcomes associated with vaginal delivery, and an estimated four of ten women experiencing a breech presentation and aiming for vaginal delivery eventually have an emergency CS.[80] Additionally, in otherwise optimal cephalic presentations, a suboptimal fetal head position (other than occiput anterior) or compound presentation (fetal extremities presenting alongside the presenting part) may necessitate CS if these issues are not resolved in expectant management or through obstetric maneuvers.[81,82]

If the fetus is afflicted by inadequate placental function or some other factor affecting intrauterine well-being, the stress caused by uterine contractions may rapidly lead to fetal compromise.[83,84] These fetuses may often be identified during pregnancy based on factors such as intrauterine growth restriction or circulatory adaptation to chronic hypoxia.[84,85] Sometimes, a CS without a trial of labor is chosen to avoid the stress of uterine contractions. In a trial of vaginal delivery monitored using cardiotocography (CTG), a gradual decline in fetal well-being may be suspected, and an emergency CS for fetal distress may consequently be performed.[83]

2.4 TRADITIONAL INDICATIONS FOR LABOR INDUCTION

The choice between labor induction and CS without a trial of labor requires an assessment of all aspects of the mother-fetus pair, including the odds of successful vaginal delivery following labor induction and the fetus's resources for tolerating the stress of uterine contractions during the trial of vaginal delivery. Additionally, labor induction may not be feasible in cases in which prompt delivery is needed, as it may take several hours or even days until delivery is achieved.

The contraindications for labor induction are similar to those of vaginal delivery and include a transverse fetal lie, placenta previa, umbilical cord prolapse, maternal human immunodeficiency virus (HIV) infection with a high viral load, active primary genital herpes infection, pelvic deformity, uterine rupture, and history of a classical CS.[14,86]

2.4.1 DURATION OF PREGNANCY

Prolonged pregnancy is a common indication for labor induction. Additionally, pregnancy duration must be acknowledged when considering labor induction due to any indication, as the gestational age at delivery greatly affects the neonatal outcome.

In Finland, the gestational age, and thus the estimated due date, is determined by the fetal crown-rump length (CRL) in the first ultrasound screening, which is offered to all pregnant women at GW 11+0–13+6 according to the last menstrual period.[87]

The average length of human gestation is 40 weeks—280 days—and a pregnancy that has lasted 40+0 weeks is considered due.[87] Babies born prematurely, before 37+0 GW, are at increased risk of respiratory and neurodevelopmental issues, and the severity of these problems is largely determined by the gestational age.[88–91] The GW between 37+0 and 38+6 are considered early term, and although babies born at this time usually thrive, some problems, such as developmental delays, may still exist.[89,90,92] For this reason, labor induction or CS without a medical indication before 39+0 GW are not recommended.[14] The full term, 39+0 to 40+6 GW, is considered the optimal time for delivery,[14,93–95] and most elective CSs and labor inductions are scheduled for these weeks. A late-term pregnancy is determined as between GW 41+0 and 41+6, and a post-term pregnancy begins at GW 42+0. Whether labor should be induced or expectantly managed in women at ≥ 41+0 GW is an ongoing debate addressed in this thesis.

Risk factors for a post-term pregnancy include nulliparity, prior post-term pregnancy, obesity, and a male fetus.[96] Genetic predisposition is also suggested to have an effect.[97]

The ongoing research on post-term pregnancy has led to changes in management guidelines and thus a gradual decline in the number of post-term deliveries in Finland. In 2021, 1.8% of all pregnancies continued to 42+0 GW, while in 2007, the rate was 5.4% (Figure 5).[1]

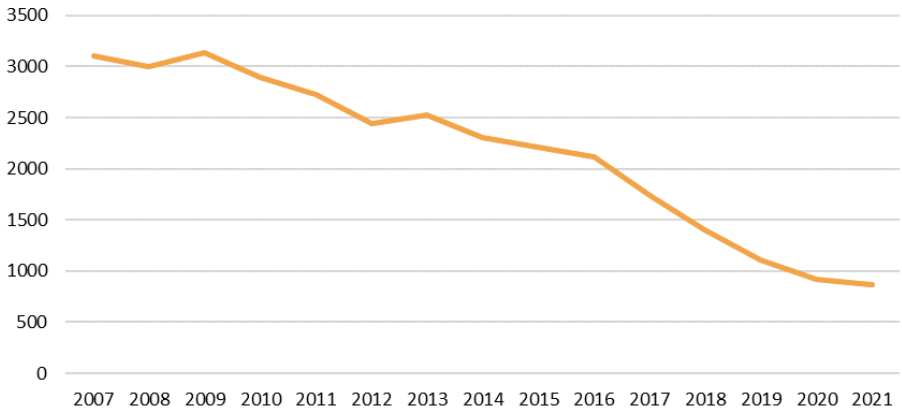


Figure 5 Post-term deliveries (≥ 42+0 gestational weeks) in Finland between 2007 and 2021. Data collected from the Finnish Institute for Health and Welfare, "Perinatal statistics – Parturients, deliveries and newborns 2021."[1]

Neonatal and maternal risks increase with advancing gestational age in term pregnancies and even more in post-term pregancies.[98–103] In post-term pregnancies, the rates of perinatal death and other neonatal complications, such as asphyxia, meconium aspiration, umbilical cord complications, pneumonia, septicemia, bone fractures, peripheral nerve injuries, and even childhood metabolic impairments and disabilities, have been observed to be higher compared with term deliveries.[92,98,100,104]

The risk increase at term is gradual. For example, the umbilical artery pH and base excess (BE) values decrease, and the incidence of meconium-stained amniotic fluid increases in a continuous rather than threshold-based fashion after 37 GW.[105] In a recent systematic review and meta-analysis of 15 million pregnancies in high-income countries, the prospective risk of stillbirth gradually increased with gestational age, from 0.11 to 3.18 per 1,000 deliveries from 37 to 42 weeks.[100] Additionally, neonatal mortality increased after 41 GW and significantly after 42 GW (Figure 6).[100]

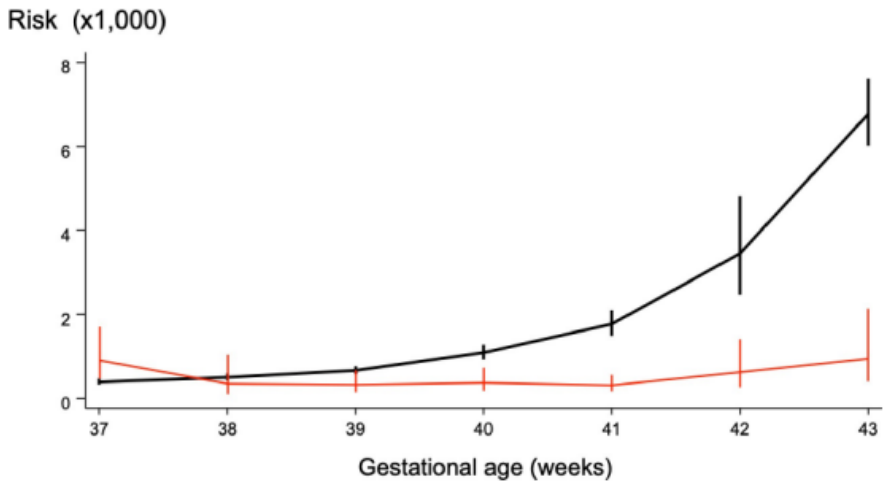


Figure 6 Prospective risk of stillbirth (black line) per 1,000 pregnancies and risk of neonatal death (red line) per 1,000 deliveries by gestational age in pregnancies continued to term. Copied from Muglu J, Rather H, Arroyo-Manzano D, Bhattacharya S, Balchin I, Khalil A, Thilaganathan B, Khan KS, Zamora J, Thangaratinam S: Risks of stillbirth and neonatal death with advancing gestation at term: A systematic review and meta-analysis of cohort studies of 15 million pregnancies. PLoS Med. 2019; 16: e1002838.

Obstetric complications such as postpartum hemorrhage, cephalopelvic disproportion, cervical injuries, shoulder dystocia, and postpartum infection have also been found to be higher in studies that compared post-term to term deliveries.[98] In pregnancies that lasted more than 39–40 weeks, observed maternal and obstetric complications include prolonged labor, anal sphincter injury, postpartum hemorrhage, chorioamnionitis, and endometritis.[99] In addition, the rates of operative vaginal delivery and CS increase after 39–40 weeks,[99] an effect also seen in studies of post-term women.[98]

In a Finnish study, one in three nulliparous women who underwent labor induction for a post-term pregnancy had a CS (37.3%),[17] a rate that can be regarded as rather high compared with the average CS risk of ~20%–25% for a nulliparous woman.[1] In Finland to date, the risks related to late- and post-term pregnancy have not outweighed the possibly increased risk of CS due to an earlier induction, and expectant management until the break-up point of ~42 GW has thus been the rule followed in the hope of making successful vaginal delivery more likely.[106] In many countries, Finland included, labor induction is initiated at 41+5–42+1 GW in uncomplicated pregnancies.[93,106]

2.4.2 TERM PRE-LABOR RUPTURE OF MEMBRANES

Following spontaneous PROM, six in ten women begin uterine contractions and eventually undergo labor within the next 24 hours.[107] When the fetal membranes are ruptured, a route appears for infectious pathogens to travel from the maternal birthing canal to the fetus. In some cases, however, PROM may itself be caused by inflammation or infection.[108] To prevent infection after PROM, labor is induced if the contractions have not started spontaneously after a period of expectant management, as labor induction, compared with expectant management, has been suggested to decrease the rates of neonatal sepsis and maternal infection.[109] The most important predictors of neonatal infection are clinical chorioamnionitis and maternal colonization by group B streptococcus (*Streptococcus agalactiae*, GBS).[110–112]

2.4.2.1 Group B streptococcus

The prevalence of GBS in pregnant women ranges between 10% and 30%.[113] One in two infants born to GBS-colonized women may become colonized themselves in a vaginal delivery, and among these children, 1%–2% develop a clinical infection.[114] Although GBS is rarely harmful in the general population, it is the leading cause of severe neonatal infections, such as sepsis, pneumonia, and meningitis.[111] In addition, GBS can cause maternal morbidity.[115] The risk of intrapartum chorioamnionitis and post-partum endometritis is twofold in women colonized with GBS compared with women with no colonization.[115]

Maternal risk factors for severe neonatal infection include preterm delivery, young age, bacteriuria during pregnancy, fever during labor, a long interval between the rupture of membranes and birth, heavy GBS colonization, and a history of a previous GBS-related neonatal infection.[111,116] However, not all severe neonatal infections occur in high-risk cases. Thus, many guidelines currently promote universal screening and provision of antibiotic prophylaxis to all GBS-positive women instead of selective screening and restriction of antibiotic prophylaxis to high-risk women.[116,117]

Colonization may be permanent or transitory and GBS screening via rapid onsite testing at the onset of labor or just before labor induction may thus be beneficial compared with a traditional culture-based screening at 35 to 37 GW.[118,119] Antibiotic prophylaxis administered at the onset of labor, preferably at least four hours before birth, prevents neonatal sepsis.[120]

Cervical ripening with a BC has been shown to increase the number of bacteria, including GBS, in the cervix,[121] but no evidence of an association with clinical infection has been presented. Nevertheless, concerns have been raised about an association between infectious morbidity and BC.[122]

2.4.3 DIABETES

Pre-pregnancy diabetes, whether type 1 or 2, imposes multiple risks on the developing fetus, including risks of congenital malformation, excessive or impaired growth, and stillbirth.[123] Pregnancies affected by GDM—which currently include more than one in five pregnancies in Finland[3]—are also at increased risk of complications such as macrosomia.[123] The severity and rate of complications related to diabetes are greatly affected by the degree of glycemic control and, in the case of GDM, by whether the onset occurs in an early stage of pregnancy or later.[123]

In the case of pre-pregnancy diabetes, the optimal timing for labor induction is based on the assessment of glycemic control, pregnancy complications, and fetal well-being and growth.[124,125] In the case of GDM, studies advise against early-term induction and support expectant management until 39 to 41 GW, although no clear consensus exists.[126–128] Elective CS instead of labor induction is advised if the estimated fetal weight is 4,500 g or more.[72]

2.4.4 PREECLAMPSIA AND HYPERTENSION

Preeclampsia, a multisystem pregnancy disorder that causes maternal blood pressure to rise, may cause placental malfunction and thus fetal growth restriction or stillbirth.[129–131] Preeclampsia can progress into eclampsia with maternal seizures as well as blood coagulopathies, cerebral hemorrhage, kidney failure, and even maternal and fetal death.[129–131]

Labor induction for preeclampsia is advised after 37 GW or even earlier if needed for maternal benefit.[128,130] Labor induction is also advised for maternal hypertension even without other signs of preeclampsia, as induction may result in a reduced rate of adverse maternal outcomes compared with expectant management. [132,133]

2.4.5 TWIN GESTATION

Twin pregnancies are at increased risk of complications such as intrauterine growth restriction (IUGR) and perinatal mortality, which are often caused by impairments in placental function.[134–138] Moreover, spontaneous preterm deliveries are common, and in the case of pregnancies continuing to term without contraindications for a vaginal delivery, labor induction is started earlier than in the case of singleton pregnancies. It is often recommended that dichorionic twins be delivered from 37 to 38 GW and monochorionic diamniotic twins from 34 to 37 GW.[134,139] The recommendation for monochorial monoamniotic twins is CS between 32+0 and 33+6 GW.[134,139]

2.4.6 OTHER PREGNANCY-RELATED FACTORS

Acknowledged medical indications for labor induction include concern over the well-being of the fetus (IUGR, reduced fetal movements, nonreassuring CTG readings, or signs of circulatory impairment in ultrasound examination), blood group immunization, pre-term PROM, intrahepatic cholestasis of pregnancy, suspected nondiabetic fetal macrosomia, and maternal medical conditions.[14] However, for many common indications presented above, strong supporting evidence from research is lacking.[14,128]

2.4.7 NON-PREGNANCY-RELATED FACTORS

Some maternal factors are considered relative reasons for labor induction in that labor induction should not be commenced before 39 GW.[14] These inductions are often subject to criticism but may greatly increase maternal well-being. Relative indications for labor induction include fear of labor, a complication in a prior labor or delivery, prevention of fetal malposition after a successful external version, family reasons, or a long distance to the hospital.[14]

2.5 NEW INDICATIONS FOR LABOR INDUCTION

2.5.1 LATE-TERM PREGNANCY

2.5.1.1 Current guidelines on labor induction

The WHO recommends labor induction at 41 GW instead of the traditional 42 GW,[106,140] whereas other guidelines, such as those of the British National Institute for Health and Care Excellence (NICE), ACOG, and the French National College of Obstetricians and Gynecologists (Collège National des Gynécologues et Obstétriciens Français, CNGOF) recommend individual assessments and allow more time for expectant management. These national guidelines suggest labor induction either between 41+0 and 42+0 (NICE) or between 41+0 and 42+6 GW (ACOG and CNGOF).[14,141,142]

In the Nordic countries, the Danish Society of Obstetrics and Gynecology (Dansk Selskab for Obstetrik og Gynaecologi) recommends labor induction between 41+3 and 41+5 GW, and the Norwegian Society of Gynecology and Obstetrics (Norsk Gynekologisk Forening) between 42+0 and 42+2 GW.[143,144] In Sweden, the National System for Knowledge-Driven Management Within Swedish Healthcare (Nationellt System för Kunskapsstyrning och Hälso-och Sjukvård) instructed in 2021 that women should give birth by 42+0 GW.[145]

All the guidelines presented above also discuss monitoring practices for late-term pregnancies. In Finland, routine monitoring is currently not advised or widely practiced until 41+5 GW in low-risk pregnancies.

2.5.1.2 Comparison of labor induction at 41 gestational weeks with expectant management until 42 gestational weeks

In a 2020 systematic review and individual participant data meta-analysis of randomized trials by Alkmark et al. (3 trials, n = 5,161), labor induction at 41 weeks improved perinatal outcomes compared with expectant management until 42 weeks, with no effect on the rate of CS.[146] A decrease in the risk of severe adverse perinatal outcomes was, however, seen only in nulliparous women and not in multiparous women.

The systemic review by Alkmark et al. included a large Swedish randomized controlled trial (RCT) of 2,762 women, the Swedish Post-Term Induction Study (SWEPIS), in which five stillbirths and one neonatal death (for a perinatal mortality rate of 0.4%) occurred in the expectant management group, while there was no perinatal mortality in the early induction group.[102] The study was stopped early due to these perinatal deaths. In the SWEPIS, neonatal admission to NICU was reduced in the early induction group, as were the rates of macrosomia (≥ 4,500 g), small-for-gestational-age infants, and neonatal jaundice requiring phototherapy or exchange transfusion. The rates

of maternal preeclampsia, gestational hypertension, and eclampsia were lower but the rate of endometritis was higher in the early induction group. The rates of CS and instrumental vaginal delivery were similar in the two groups.

The Dutch INDEX study (INDuction of labor at 41 weeks versus EXpectant management until 42 weeks) of 1,801 women, included in Alkmark's review, found a reduced risk of adverse perinatal outcomes (defined as perinatal mortality or morbidity: a 5-minute Apgar score < 7, meconium aspiration syndrome, plexus brachialis injury, intracranial hemorrhage, or NICU admission) in the early induction group, with similar rates of CS.[147] The third RCT included in the review was conducted in Turkey and contained 600 women. It found no difference in the CS rate, but neonatal morbidity was lower in the early induction group.[148]

Although these trials suggest that labor induction at 41+0 GW or earlier would be beneficial without an increase in the rate of CS, conflicting findings exist.[149,150] In a cohort study conducted alongside the INDEX in which women were able to choose whether to be induced at 41 weeks or managed expectantly until 42 weeks, the rates of CS were higher in the nulliparous women in whom labor was induced earlier.[150] No significant differences in other adverse outcomes were observed in that study, unlike in the INDEX RCT.[147,150] Women who prefer induction to expectant management may view their lives and pregnancies differently than those who prefer expectant management and may even have different predispositions for adverse outcomes; it is possible that these differences affect the results of studies that explore the timing of labor induction.[150,151]

2.5.2 TERM PREGNANCY

As the optimal time for delivery is likely GW 39 to 40,[14,93,94] research on labor induction at term has recently been a hot topic in the obstetric community. Two review articles with meta-analyses published in 2014 suggested, controversially at the time, that labor induction at term reduces the risk of CS.[152,153] The other paper also found a reduced risk of fetal death and admission to the NICU.[153]

A 2018 Cochrane review found a reduced risk of perinatal death, NICU admission, and CS but an increase in operative vaginal birth if labor was induced after 41 weeks instead of expectant management being implemented.[154] A newer (2020) Cochrane review of labor inductions at or beyond 37 weeks also identified a significant reduction in perinatal death rate if labor was induced compared with expectant management being applied, although the absolute rates were small (0.4 vs. 3 deaths per 1,000).[4] In this newer review, the rates of NICU admission and CS were also lower, but unlike in the 2018 review, there was no increase in the rate of operative vaginal birth. In the 2020 review, the optimal timing of labor induction was not determined, but individualized risk profiling and support for women in making an informed choice were advised.

In a 2019 cohort study, nulliparous women with labor induced at 39 weeks had a decreased likelihood of CS, whereas the rate was unchanged in multiparous women. In both groups, the rate of pregnancy-related hypertension was lower.[133] In a review article published the same year, the rate of CS was not altered by a 39-week induction compared with expectant management up to 41–42 weeks, but the rates of meconium-stained amniotic fluid and macrosomia were lower.[155]

As nulliparous women are at greater risk of CS and perinatal mortality than parous women,[3,20] focusing research on interventions for nulliparous women seems reasonable. In the 2018 ARRIVE (A Randomized Trial of Induction Versus Expectant Management) trial of 6,106 low-risk nulliparous women, the rates of CS and hypertensive disorders were reduced in the 39-week induction group compared with the expectant management group.[156] The rates of adverse perinatal outcomes were not significantly different. A subsequent meta-analysis of six cohort studies also found a reduced risk of CS in nulliparous women with labor induced at 39 weeks compared with those who pursued expectant management, and the risks of maternal peripartum infection and perinatal adverse outcomes, including mortality, were lower.[157]

A recent cohort study that explored the impact of the ARRIVE trial and included both nulliparous and parous women showed that implementing a more liberal induction policy at 39 weeks did not increase the rate of CS, but the admission-to-delivery interval was longer in the post-implementation period than it was before the more liberal protocol was implemented.[158] Additionally, the rate of maternal chorioamnionitis increased, whereas there were no differences in other maternal or neonatal morbidities.[158]

In a study of low-risk multiparous women who underwent labor induction at 39 weeks, the rates of CS and maternal morbidity were lower compared with expectant management, and the neonatal results did not differ.[159]

Debate is ongoing internationally over how to interpret the results of the studies of low-risk women with labor induced at 39 weeks but has not, so far, widely affected management guidelines.

2.5.3 WOMEN OF ADVANCED AGE

Labor induction at term has been suggested to either lower or not affect the rate of CS among women ≥ 35 years old.[160,161] As women of advanced maternal age are at increased risk of perinatal and maternal morbidity and mortality,[21–24] labor induction at 40+0 GW may be recommended to diminish the risks associated with late- and post-term pregnancy, although no effect of such induction on short-term maternal or neonatal outcomes has been shown.[162]

2.5.4 OBESE WOMEN

As obese women are at increased risk of perinatal death and CS,[22,27,28] they may also be seen as a risk group for whom term labor induction may be viewed as reasonable because it has the benefit of avoiding post-term pregnancy. Several retrospective studies have shown that term labor induction reduces the rate of CS in obese women compared with expectant management.[163–166] In addition, according to these studies, the risks of macrosomia, NICU admission, and other perinatal and maternal adverse outcomes are lower when labor induction occurs at term.[163–166] However, contradictory results of an increased risk of CS and neonatal intensive care unit admission have also been presented.[167]

In the case of pregnancies continuing to the late term or after it, labor induction is suggested to be as safe and reasonable a management option for obese women as it is for non-obese women, as the rates of labor complications are largely comparable, although the CS rates among obese women are higher.[168]

2.6 FACTORS THAT PREDICT SUCCESSFUL LABOR INDUCTION

The best simple, clinical predictor of successful labor induction seems to be a ripe (dilated, effaced, softened) cervix at the start of labor induction, i.e., a Bishop score ≥ 6 (Table 2).[35,169,170] It has been suggested that with a score of 8 or higher, the odds of a vaginal delivery are similar to those of a spontaneous onset of labor.[14]

Table 2. Modified Bishop scores, where each aspect of the cervix is assessed, and the scores are added together to form the final score.[171]

Score	Dilation (cm)	Length (cm)	Consistency	Position	Station (from the ischial spines)
0	< 1	> 4	Firm	Posterior	-3
1	1–2	2–4	Moderate	Mid-line	-2
2	3–4	1–2	Soft	Anterior	-1–0

No biochemical marker or ultrasound finding has proven to be decisive in studies of factors that predict successful labor induction, and the more recent studies suggest their use mainly as part of more complex prediction models yet to be discovered.[172–174] The ultrasound factors suggested to predict success include the cervical length and angle and the distance between the fetal head and the maternal perineum.[173] Other potentially beneficial predictive factors studied include the quantitative elastography of the cervix and biochemical markers such as the cervicovaginal fetal fibronectin.[174,175]

2.7 METHODS OF LABOR INDUCTION

The primary method chosen for labor induction is mostly determined by the ripeness of the cervix. If the cervix is unripe, i.e., the Bishop score is < 6 (Table 2), it is recommended that it first be ripened using a BC or prostaglandin medication. When the cervix is ripe, i.e., the Bishop score is ≥ 6, labor induction is started or continued by artificially rupturing the fetal membranes and/or administering intravenous oxytocin infusion.

Although not officially considered part of labor induction, membrane sweeping at 39 GW and beyond could be offered to all women hoping for vaginal delivery, as it may help in avoiding formal induction and shorten labor with minimal risks.[176] Alternative methods that have been used to stimulate labor without increasing complications but that are unsupported by scientific evidence include nipple stimulation, acupuncture, and raspberry leaf tea.[177]

2.7.1 BALLOON CATHETER

In this procedure, the tip of a balloon catheter is inserted through the cervix against the fetus's head during a vaginal examination, and the balloon is filled with saline. The catheter is then attached to the maternal thigh to provide light traction. The BC mechanically dilates the lower uterine segment and cervix, and it also stimulates the release of endogenous prostaglandin and production of hyaluronic acid, which augment cervical softening.[178–180]

Two different types of BC exist, with either a single or double balloon system. The amount of substance used to inflate the balloon varies between 30 and 80 ml. The only BC with an indication for labor induction is the Cook® double balloon catheter (Cook Medical LLC, Bloomington, USA), in which the balloons are placed on both sides of the cervix: one in the lower uterine segment and the other in the vagina.

No significant improvement in outcomes has been noted if a double balloon catheter is used rather than a single balloon catheter, but women using the single balloon have been reported to be more satisfied with their induction.[181–184] In addition, the Cook® double balloon catheter is more costly than single balloon catheters (for example, the Rüsh 2-way Foley, Couvelaire tip, catheter size 22 Ch, Teleflex Medical, Athlone, Ireland).[183] Thus, off-label use of single balloon catheters is common.

Cervical ripening by BC can be carried out in low-risk women in an inpatient or outpatient setting, as both settings are safe and effective.[185–188] In the few studies done on women's experiences, outpatient setting has been suggested to be viewed positively.[186,188,189]

2.7.2 PROSTAGLANDINS

Misoprostol, a prostaglandin E1 analog, was originally developed for gastric protection but has, until very recently, been used as an off-label medication for labor induction, postpartum hemorrhage, and medical abortion (Cytotec®, Piramal Healthcare UK Limited, Northumberland, England).[190] When used in labor induction, misoprostol can be administered either orally or vaginally, with the oral route producing higher and faster peak serum values than the vaginal route.[191] As the oral route seems to have a better safety profile when used for labor induction, this route is currently preferred.[190,192] Vaginal administration may, however, stimulate vaginal delivery faster than oral administration.[193]

The WHO recommends that misoprostol be administered either orally, at 25 µg every 2 hours, or vaginally every 6 hours.[194] A 2021 Cochrane review also suggested a 25-µg dose and prioritized the oral route to balance efficacy and safety.[192]

Since 2021, a brand of oral misoprostol with an indication for labor induction (Angusta®, Norgine Danmark, Valby, Denmark) has been available in Finland as 25-µg tablets. However, the labeled product is more expensive than the traditional off-label product. Thus, off-label use is still common, although this product is only available in 200-µg tablets that must be cut, leading to uneven doses.

Traditionally, misoprostol has been administered in the inpatient setting only, and routine CTG tracings have been recorded after administration or at the onset of contractions.[14] Lately, outpatient use has also become possible, as studies suggest that it is both safe and effective and may reduce the time spent in the hospital.[195–197]

Dinoprostone is a prostaglandin E2 analogue with an indication for labor induction. In Finland, dinoprostone is currently available as a vaginal insert (Propess®, Ferring GmbH, Kiel, Germany) and is less widely used than misoprostol. Internationally, dinoprostone use is a popular method of labor induction, and it is available in multiple forms, such as vaginal gels and pessaries.[198,199]

2.7.3 CHOICE OF CERVICAL RIPENING METHOD

The cervical ripening methods most used in Finland—BC and misoprostol—are both safe and effective, and their use is relatively interchangeable.[200,201] However, if the cervix is extremely unripe, placing the BC can be challenging, and in the case of a low-lying placenta, the balloon can cause bleeding. Misoprostol may, in turn, cause uterine hyperstimulation and tachysystole and thus fetal distress and meconium-stained amniotic fluid.[202]

Misoprostol is contraindicated for women with a history of CS, as many studies report that it increases the risk of uterine rupture,[68,70] which BC does not.[69]

Most women using a BC can be treated as outpatients, but women using misoprostol have, until recently, been treated as inpatients, as previously discussed.[14,185–188,195–197]

Research on the concurrent use of BC and misoprostol has indicated reassuring safety and effectiveness profiles with no effect on the CS rate.[203–205] In addition, concurrent use has been suggested to stimulate vaginal delivery faster than using either method on its own, perhaps even resulting in lower rates of neonatal NICU admission.[203–205] Administering misoprostol vaginally instead of orally may accelerate vaginal delivery even further.[206]

2.7.4 ARTIFICIAL RUPTURING OF THE MEMBRANES

Artificial rupturing of the membranes (AROM, amniotomy) is usually performed with a fetal scalp electrode, which enables reliable CTG monitoring afterwards. Sometimes, a small hook can be used instead. AROM is thought to increase levels of endogenous prostaglandins and thus promote cervical ripening and uterine contractions.[207] The membranes can also be artificially ruptured for labor augmentation.[208] In Finland, if labor induction is initiated via BC, AROM is recommended 1–3 hours after expulsion of the BC whenever feasible to benefit from the prostaglandin rise first induced by the BC, and further enhanced by the prostaglandin rise caused by the membrane rupture.[178,207]

2.7.5 OXYTOCIN

Oxytocin is a hormone secreted by the maternal hypothalamus and released into the bloodstream via the pituitary gland in a pulsatile fashion.[209] Towards the end of a pregnancy, the number of oxytocin receptors in the uterus increases.[210] Oxytocin stimulates uterine contractions and is thus essential for normal labor.[14]

Exogenous oxytocin infused intravenously can be used in labor induction or augmentation if the contractions produced by spontaneously initiated labor are determined to be too weak.[14,211,212] Protocols vary, and higher doses may cause uterine hyperstimulation followed by adverse neonatal outcomes, although higher doses may also shorten labor duration and yield a lower rate of CS.[211,213–215]

The 2022 European guidelines on oxytocin use for the induction and augmentation of labor recommend that oxytocin infusion be started at least one hour after rupturing the membranes and, if misoprostol is used for cervical ripening, no sooner than four hours after the last dose.[14,212] The aim of infusion is to provoke 3–4 contractions every 10 minutes. The instructions also advise continuous CTG use until delivery.[212] In the recommendation, it is advised to start the infusion (Syntocinon® 1 ml = 8.3 µg = 5 IU combined with 500 ml saline) at 12 ml/h and gradually increase it over the next 7 hours up to

180 ml/h (in the case of a previous uterine scar, a starting dose of 6 ml/h and augmentation during the next 4.5 hours up to 60 ml/h are advised).[212]

According to a Cochrane systemic review, after the active phase of labor has started, discontinuing oxytocin infusion may help reduce the rate of uterine tachysystole and CS.[216] A diagnosis of failed labor induction should not be made before 12 to 15 hours of oxytocin infusion.[217]

2.8 TIMING LABOR BY TIMING THE INDUCTION

Delivery during daytime (office hours) is often suggested to be better than delivery during evening or nighttime, perhaps because, in most hospitals, the highest numbers of staff work during daytime, intuitively enabling better care.[218,219] Studies of neonatal morbidity do not, however, support this assumption.[220–223]

The best time to induce labor in order to yield daytime delivery has been under investigation. For multiparous women, oxytocin induction initiated in the morning may help avoid nighttime delivery.[224] With a BC induction, the suggested optimal starting time for nulliparous women is the afternoon or evening, while for multiparous women, it is the morning.[225] However, based on the results of a study of optimal labor induction timing in light of staffing for labor anesthesia and obstetric care (~ during the daytime), Warner et al. suggested that labor induction should be started at 2:00 am for nulliparous women and at 4:00–5:00 am for multiparous women,[218] which seems impractical, as obstetric staffing is usually at its lowest at night. At present, most inductions in Finland are started during the daytime, as a consensus on the topic is lacking since prior research is scarce and has reached diverse conclusions.

2.9 THE CHILDBIRTH EXPERIENCE

2.9.1 WHY IT IS IMPORTANT

The childbirth experience profoundly affects the mother's health and well-being.[226] For many women, the experience is positive. If the experience is negative, however, it may lead to fear of childbirth in the following pregnancy as well as anxiety, postpartum depression, and even posttraumatic stress disorder.[227–229] It may also impair bonding with the baby and affect the couple's relationship.[230–232]

In high-resource countries in which maternal and neonatal mortality and morbidity rates are low, the maternal childbirth experience has become a significant factor in the assessment of the quality of maternity care.[233] A positive childbirth experience is anticipated by women, and safety and psychosocial well-being are equally valued.[233]

Many European countries, Finland included, have birth rates below the replacement rate of 2.1,[234] and at present, Finland's population structure is among the oldest in Europe.[235] In 2022, the fertility rate was 1.32, which is the lowest known number in Finnish history (recorded since 1776).[236]

A negative childbirth experience has been claimed to delay or prevent women from wanting to have more children,[237–239] so a positive childbirth experience should be of interest to Finland, which already struggles to maintain a welfare state. A recent cohort study estimated that a negative childbirth experience in the first birth might contribute to a decline of 400 potential childbirths in Finland every year.[239] Thus, supporting women in childbirth should be a priority for our decision-makers.

2.9.2 EVALUATING THE EXPERIENCE

Childbirth experiences can be assessed using interviews or structured questionnaires, the answers to which can be converted into numerical scores. The results can be used to identify those women with negative experiences and give them more support after their labor and delivery. Although women recall their deliveries fairly well, their assessment of the experience may be altered by the time of the survey.[240]

A 2017 review found 36 questionnaires designed to measure the mother's childbirth experience from various angles and suggested that the following seven were valid and reliable for further use: (1) the Childbirth Experience Questionnaire (CEQ), (2) the Maternal Satisfaction Scale for Cesarean Section, (3) the Responsiveness in Perinatal and Obstetric Health Care Questionnaire, (4) the Pregnancy and Maternity Care Patients Experiences Questionnaire, (5) the Childbirth Perception Scale, and (7) the Wijma Delivery Expectancy/Experience Questionnaire.[241–248]

The two most used methods of evaluating childbirth experiences in Finland are the Visual Analog Scale (VAS) and the CEQ, discussed in the next two

chapters.[249] Although the VAS and CEQ have previously been studied together in assessing childbirth experience, they have not been compared with each other before our study.[250–252]

2.9.2.1 The Visual Analog Scale

A VAS is a visual tool that can be used to assess scalable phenomena. In the hospital setting, it is most often used to measure pain levels, but it can also be used to evaluate the childbirth experience.[253] When the VAS is used, the individual just points to the place on the scale that reflects their view of the matter assessed, and the corresponding number from 0 to 10 (or 0 to 100 if assessed on a 100-mm scale) is recorded as the score. At HUS Helsinki University Hospital (HUS Helsingin yliopistollinen sairaala), the VAS is used to measure satisfaction with childbirth after the birth; zero represents the most negative experience possible, and ten represents the most positive experience possible.[254]

Figure 7 Example of a VAS scale.

The VAS is simple to use, and it indicates quite easily and rapidly whether the childbirth experience has been extremely negative or positive. However, as the childbirth experience is multifactorial, a simple digit can only express it very narrowly. Unfortunately, prior research is scarce regarding the question of which specific aspects of the multifactorial experience women assess when giving a single-unit response to the question about their childbirth experience.[255] However, Mäkelä et al. showed in a recent study that despite being a simple tool, the VAS is suitable for screening for post-traumatic stress disorder when measured twice after birth (< 1 week postpartum and a few months later) with a cutoff value of 50 mm.[256]

2.9.2.2 The Childbirth Experience Questionnaire

The CEQ is a multidimensional questionnaire created to explore the childbirth experience more profoundly than, for example, the VAS.[248] In Finland, it has mainly been used for research purposes.

The CEQ was created and validated in Sweden, whose cultural environment and obstetric practices are very similar to those of Finland. The questionnaire has been validated in Finnish as well as many other languages and populations.[248,249,257]

The questionnaire consists of 22 items (questions) that are grouped into four domains: “own capacity,” “professional support,” “perceived safety,” and “participation” (Table 3). The results are presented on a scale of 1 to 4, from the most negative to the most positive experience possible.

The CEQ items are scored followingly: three items are assessed on a VAS (scale: 0–100 mm, items: 20–22) and the rest on a four-point Likert scale (totally agree = 4, mostly agree = 3, mostly disagree = 2, and totally disagree = 1). The VAS scale scores are changed to categorical values (0–40 mm = 1, 41–60 mm = 2, 61–80 mm = 3, and 81–100 mm = 4). All negatively worded statements (items 3, 5, 8, and 9) and one item on labor pain (item 20) are reversed so that higher scores ultimately reflect a more positive experience, as for all the other items. The domain scores are computed as the means of the individual scores within the domain, and the total CEQ score is computed similarly.[248,249]

Table 3. The CEQ items and the four domains.

	Own capacity
1	Labor and birth went as I had expected
2	I felt strong during labor and birth
4	I felt capable during labor and birth
5	I was tired during labor and birth
6	I felt happy during labor and birth
19	I felt that I handled the situation well
20	As a whole, how painful did you feel your childbirth was? (VAS)
21	As a whole, how much control did you feel you had during childbirth? (VAS)
	Professional support
13	My midwife devoted enough time to me
14	My midwife devoted enough time to my partner
15	My midwife kept me informed about what was happening during labor and birth
16	My midwife understood my needs
17	I felt very well cared for by my midwife
	Perceived safety
3	I felt scared during labor and birth
7	I have many positive memories from childbirth
8	I have many negative memories from childbirth
9	Some of my memories from childbirth make me feel depressed
18	My impression of the team’s medical skills made me feel secure
22	As a whole, how secure did you feel during childbirth? (VAS)
	Participation
10	I felt I could have a say whether I could be up and about or lie down
11	I felt I could have a say in deciding my birthing position
12	I felt I could have a say in the choice of pain relief

Abbreviations: VAS: visual analog scale

The CEQ was renewed after our studies were conducted, and the CEQ2 differs in some items in the domains "professional support" and "participation."[258] The renewed version may not exceed its predecessor in usability, however, and it has not been validated in Finnish, unlike the original CEQ.[249,258]

2.9.3 RISK FACTORS FOR A NEGATIVE EXPERIENCE

Some risk factors for a negative childbirth experience are known already before labor, and some are caused by the events of the labor and delivery itself. For example, poor health (self-reported), untreated fear of labor, being under psychiatric care during pregnancy, and a lack of antenatal education or partner support may subject the woman to a negative experience.[259–262]

Pregnant women often hope for a natural birth, and an emergency or crash emergency CS appears to be a major intrapartum risk factor for a negative childbirth experience—maybe even the most important one.[8,248,249,257,260,263–267] Previous research also shows that women with a strong preference for a vaginal delivery who eventually end up undergoing a CS are at risk of postpartum depression.[268] Other labor-related risk factors for a negative experience include operative vaginal delivery (vacuum extraction or forceps use), long labor (≥ 12 hours), oxytocin use, maternal complications, hemorrhage, and neonatal complications, such as admission to the NICU.[248,249,257,260,263–267] Daytime delivery has been suggested to be associated with a more positive childbirth experience, although in a recent Finnish study, multiparous women reported a preference also for nighttime delivery.[223]

Nulliparity is another well-known pre-labor risk factor for a negative childbirth experience,[260,263,264] as is labor induction.[8,263,264] In post-term pregnancies, the negative effect of labor induction may not, however, be as notable.[269]

In the SWEPIS, in which women either underwent labor induction at 41 GW or pursued expectant management until 42 GW,[102,251] the childbirth experiences were positive overall and similar across the groups, with no differences in the domains "own capacity," "perceived safety," and "professional support." However, in the "participation" domain, the women in the induction group reported higher scores than those in the expectant management group. In the SWEPIS, 86% of the participants randomized to the induction group truly underwent labor induction, whereas in the expectant management group, the induction rate was only 33%. The CS rates were similar in the two groups: 10.4% in the induction group and 10.7% in the expectant management group.[102]

It has been suggested that although labor induction may have a negative effect on the childbirth experience, this effect is weaker than the effect of the mode of delivery. In a recent Finnish cohort study, successful, unassisted vaginal delivery after induction was experienced as more positive than operational delivery (CS or vacuum-assisted) of spontaneous onset.[8] In the same study, 25% of nulliparous women who underwent labor induction and

then had a CS had a negative childbirth experience (VAS ≤ 5). Given the increased risk of CS after labor induction compared with spontaneous onset, the question of the individual's CS risk in relation to induction becomes even more relevant, as an unsuccessful attempt not only affects the physical but also the psychological well-being of the woman.

A phenomenological study of the labor induction experiences reported in the SWEPIS described how the women felt that their labor became *another journey* instead of the one intended—the one with spontaneous onset.[270] They also felt like they had lost something important about giving birth by not completing a natural birth. The advantages of labor induction for these women were that the labor would finally start after the long wait and that it was easier to account for practicalities such as caring for elder children or pets (*planning the unplannable*). At the time of labor induction, the women experienced *being a guest at the labor ward,* or not really having their own space, for they were not giving birth yet but were still at the hospital and under scrutiny; a homier environment would have been preferred. The women also handed over the control of their labor to the staff (*someone else controlling the labor*) and thus had to put aside their preferences and comply with hospital guidelines and routines. The women also reported that the induction became part of the labor (*overshadowed on how it turned out*) and felt like their bodies had been forced into labor even if they were not ready for it. The women also expressed disappointment with their bodies for not initiating spontaneous labor and pondered whether waiting for a while longer would have been beneficial.

In conclusion, the impact of labor induction on mental well-being seems complex. Thus, the individual views of the pregnant woman must be taken into account when deciding whether to induce.

2.10 COST OF LABOR INDUCTION

It has been suggested that an increase in the rate of labor induction will lead to higher costs. This is mainly due to the need for more personnel to take care of the women during labor induction, as the latent phase is, indeed, longer in these women than in those who enter labor spontaneously.[15,271]

Intuitively, the increase in cost is real, but this view oversimplifies the mathematics of overall cost and cost-effectiveness, which also considers quality aspects. The higher costs caused by labor induction in a department of obstetrics and gynecology may avoid an adverse neonatal outcome such as asphyxia, which could lead to severe neurologic impairment. Thus, avoiding this adverse event could lead to reduced costs in the NICU and in the department of pediatrics and pediatric neurology. In years to come, this initial cost increase from labor induction might even lead to a decreased use of social security payments if it prevents severe neurologic impairment.

A common factor assessed in studies of health care economics is the quality-adjusted life year (QALY), which estimates the years of life to be achieved after an intervention and also weights each year by a quality-of-life score ranging from one (perfect health) to zero (dead).[272] The incremental cost-effectiveness ratio (ICER), which defines the cost per QALY gained, can then be used to decide whether or not an intervention is cost-effective and affordable.[273]

The threshold at which the ICER demands a new intervention, i.e., the arbitrary amount of money the system is willing to pay for a single QALY, is a matter of politics more than medicine. In the United Kingdom, for example, the cost-effectiveness threshold has traditionally been £20,000 to £30,000, and in the United States of America, it is $50,000.[274,275] In Finland, the threshold has not been determined, at least to the author's knowledge.

In some studies, labor induction has been suggested to be cost effective compared with expectant management, but the labor costs have been identified as higher than those of expectant management.[276–278] For example, calculations for nulliparous women undergoing labor induction at 39 weeks suggest that induction is cost-effective, but only for women with an unripe cervix, who have a lower incremental cost per QALY than women with a ripe cervix.[277] This was linked to reducing the risk of CS and stillbirth associated with prolonged pregnancy, which is more likely among women with an unripe cervix compared with women with a ripe cervix.[277] Another study that made the same comparison between induction at 39 weeks and expectant management concluded that induction was cost-effective but had an ICER of $87,692 per QALY.[278]

Elsewhere, analyses of the SWEPIS have identified induction as cost-effective, mainly due to the reduction in perinatal mortality.[276] In the SWEPIS, the mean cost per birth was €4,108 in the induction group and €4,037 in the expectant management group. The ICER was €623 per QALY gained in favor of early induction.[276]

3 AIMS

This thesis explores the associations between labor induction and successful vaginal delivery, adverse obstetric and neonatal outcomes, and childbirth experiences. The specific aims are as follows:

1) Evaluate the success of TOLACs, including labor induction, in women with a history of a prior CS for failed labor induction or labor dystocia and compare delivery outcomes according to the stage of labor at the time of the previous CS.

2) Evaluate the safety of labor induction via BC in terms of maternal and neonatal infectious morbidity in women with and without GBS colonization.

3) Investigate whether nulliparity itself or factors related to labor induction and labor and delivery outcomes explain the increased risk of a negative childbirth experience in nulliparous women.

4) Compare the childbirth experiences of women whose labor was induced by BC or oral misoprostol using the CEQ.

5) Investigate the optimal timing of labor induction in nulliparous late- and post-term women with an unripe cervix by comparing labor induction at 41+0 GW and expectant management with labor induction at 41+5–42+1 GW.

4 SUBJECTS AND METHODS

4.1 SUBJECTS

This thesis consists of five original publications: two retrospective cohort studies (Study I, which focused on TOLACs, and Study II, on GBS), two publications based on a single prospective cohort study (Studies III–IV, which discussed childbirth experiences, SYNKO), and a randomized, controlled non-inferiority trial (Study V, concerning late- and post-term labor induction, SYKE). A comparison of the study settings is presented in Table 5.

Studies I–IV were conducted at the Department of Obstetrics and Gynecology of HUS, Finland. Study V was a clinical multicenter study coordinated by HUS that included five additional Finnish hospitals: Tampere University Hospital, Turku University Hospital, Oulu University Hospital, Kuopio University Hospital, and Central Finland Central Hospital.

4.1.1 ETHICS

The institutional review board at HUS approved the study protocols of all studies recounted in this thesis (Table 4).

Table 4. Details of study protocol approvals by the HUS institutional review board.

	Reference number	Date
Study I: TOLAC	HUS/42/2017	2.14.2017
Study II: GBS	HUS/400/2016	12.9.2016
Studies III–IV: SYNKO	HUS/3172/2018	12.5.2018
	HUS/154/2019	3.11.2019
Study V: SYKE	HUS/1978/2016	3.16.2017

The study protocol for Study V (SYKE) was registered in the ISRCTN registry (ISRCTN 83219789, available at https://doi.org/10.1186/ISRCTN83219789).

In the retrospective studies, informed consent was not required (Studies I and II). In the prospective Studies III–V, the participating women gave their written informed consent after receiving written and oral information about the study.

Table 5. Comparison of the study settings.

	Study I TOLAC	**Study II GBS**	**Studies III–IV SYNKO**	**Study V SYKE**
N	660	1,959	711 / 362	381
Design	Retrospective cohort	Retrospective cohort	Prospective cohort	Randomized controlled trial
Study period	1.1.2013–1.1.2015	1.1.2014–12.31.2017	1.1.2019–1.31.2020	3.1.2018–3.1.2022
Subjects	Parous women with a prior CS for labor dystocia	Nulliparous and parous women with intact membranes	Nulliparous and parous women / Nulliparous women	Nulliparous women with intact membranes
Onset of labor	Labor induction or spontaneous onset of labor	Labor induction	Labor induction	Labor induction or spontaneous onset of labor
Primary method of labor induction	BC, misoprostol, or artificial rupturing of the membranes	BC	BC, misoprostol, or artificial rupturing of the membranes / BC or oral misoprostol	BC, oral misoprostol, concurrent use of both
Main research question	What is the success rate of trial of labor after earlier CS for labor dystocia or failed labor induction?	Does labor induction by BC increase the risk of infection in women with GBS colonization?	Why are nulliparous women at risk of a negative childbirth experience? / Is the labor induction method associated with the childbirth experience?	Is labor induction at 41+0 GW a better choice than expectant management until 41+5–42+1 GW?
Main outcome	The rate of repeat CS and recurring failed labor induction or labor dystocia	The rates of maternal intra- and postpartum infection and neonatal infection	The childbirth experience as evaluated using the CEQ after labor induction	The rates of CS and a composite of adverse neonatal outcomes

Abbreviations: TOLAC: trial of labor after cesarean, GBS: group B streptococcus, CS: cesarean section, BC: balloon catheter, GW: gestational weeks, CEQ: Childbirth Experience Questionnaire

4.1.2 RECRUITMENT OF PARTICIPANTS

4.1.2.1 Studies I and II: TOLAC and GBS

In these retrospective studies, eligible women were identified in the hospital's electronic health records (EHRs) by using diagnosis codes and categorization tools to identify patients who had undergone labor induction.

4.1.2.2 Studies III–IV: SYNKO

In these two prospective studies, all women scheduled for labor induction were offered the opportunity to participate when they arrived at the HUS labor induction unit.

4.1.2.3 Study V: SYKE

In this prospective study, pregnant women received information on the study either from their primary caregivers (outpatient maternity care units) or at the prenatal maternity clinics at the hospital. All women who were interested in participating in the study contacted the researchers online themselves (in the Helsinki area) or were referred to the hospital by their primary caregivers (in other areas). During the study period, additional information on late- and post-term pregnancy, labor induction, and the study protocol was offered on the study website to support informed decision-making. All interested in the study were also able to contact the researchers through the website and ask for more information.

All women included in the study visited an antenatal clinic at 41+0 GW to have their well-being and that of the fetus checked through clinical and ultrasound examinations. They also underwent CTG monitoring, and preeclampsia screening based on blood pressure measurement and urine sampling.

At the 41+0-week screening visit, women were randomized by date of labor induction: early induction the same day or expectant management until 41+5–42+1 (the current treatment protocol for late-term pregnancy in Finland), with equal randomization ratios of 1:1. For the randomization, we used a custom-made online randomization site with randomly selected block sizes of 5, 10, and 20.

If the women randomized for expectant management had any concerns about the safety of continuing expectant management, or if the treating obstetrician deemed it necessary, the women were treated according to their needs. In addition, all participating women had the opportunity to withdraw their consent to participate in the study and thus not include their data in the analyses. The data were subjected to intention-to-treat analysis.

4.1.3 STUDY POPULATIONS

4.1.3.1 Study I: TOLAC

The inclusion criteria were designed to select women who had a viable singleton term pregnancy, cephalic presentation, and a lower-segment transverse CS for failed labor induction or labor dystocia in a previous pregnancy. The exclusion criteria ruled out women with a scheduled repeat CS, preterm delivery, breech presentation, or twin pregnancy in the current pregnancy. Women undergoing labor induction and women with spontaneously occurring labor were both included in the study. Figure 8 presents the study population.

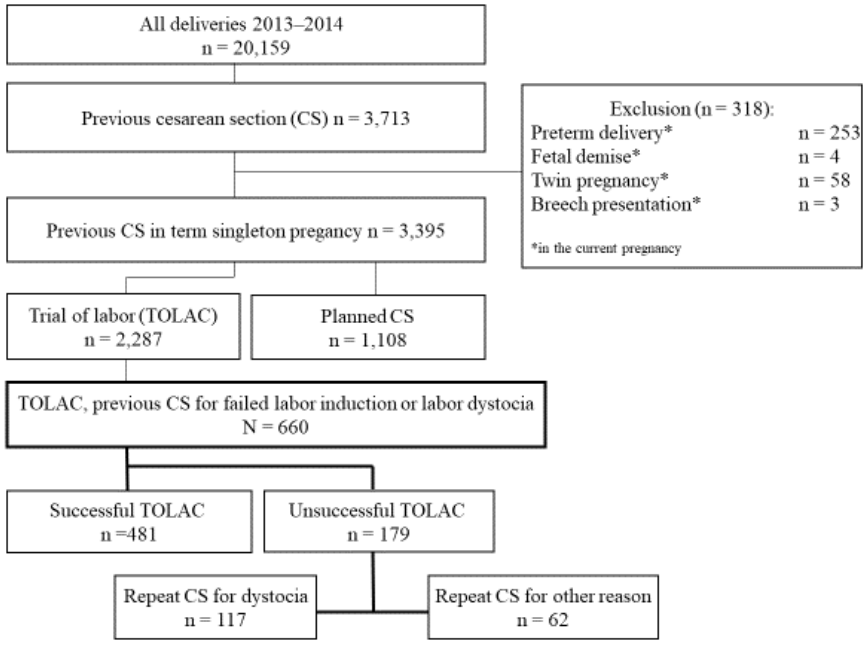


Figure 8 Formation of the study population: pregnant women with a previous CS due to failed labor induction or labor dystocia who underwent a TOLAC at HUS (N = 660).

4.1.3.1 Study II: GBS

The inclusion criteria were designed to select women who underwent labor induction using a BC in a viable singleton term pregnancy and demonstrated cephalic presentation, an unripe cervix (Bishop score < 6), and intact fetal membranes. The exclusion criteria ruled out those with unknown or erroneous results in pre-labor GBS testing (of vaginal and perineal samples). Figure 9 shows the study population.

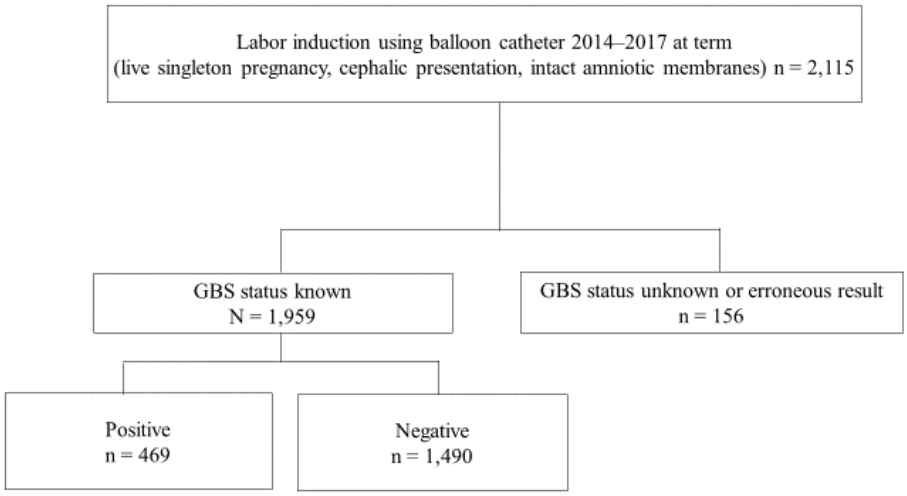


Figure 9 Formation of the study population: pregnant women with an unripe cervix, intact fetal membranes, and a known GBS-testing result at the time of labor induction who underwent labor induction by balloon catheter at HUS (N = 1,959).

4.1.3.2 Studies III–IV: SYNKO

The inclusion criteria were designed to select women undergoing labor induction in a viable singleton pregnancy who had a sufficient written and oral understanding of Finnish, Swedish, or English. Additional inclusion criteria were set for Study IV to recruit nulliparous (at recruitment) women whose labor was induced using a BC or oral misoprostol. The exclusion criteria ruled out cases of multifetal gestation and preterm birth (< 34 GW). Figures 10 and 11 show the study populations.

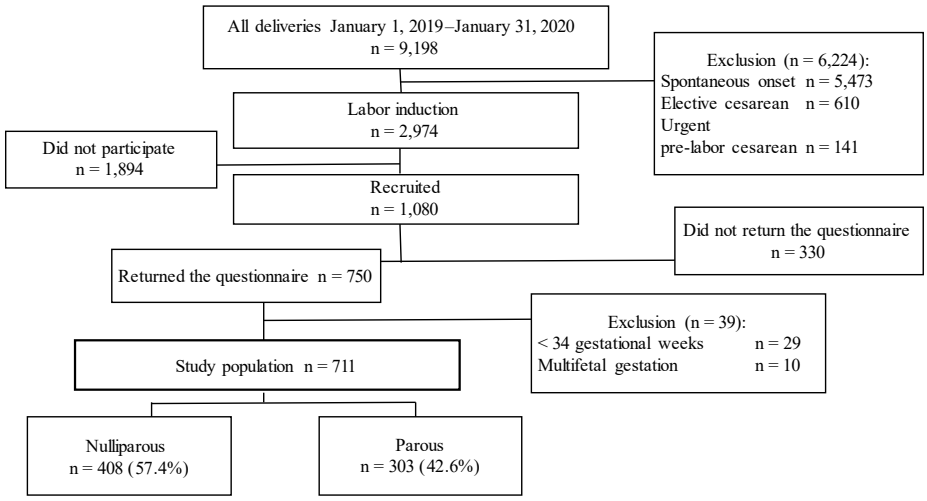


Figure 10 Formation of the study population: pregnant women undergoing labor induction at HUS (N = 711).

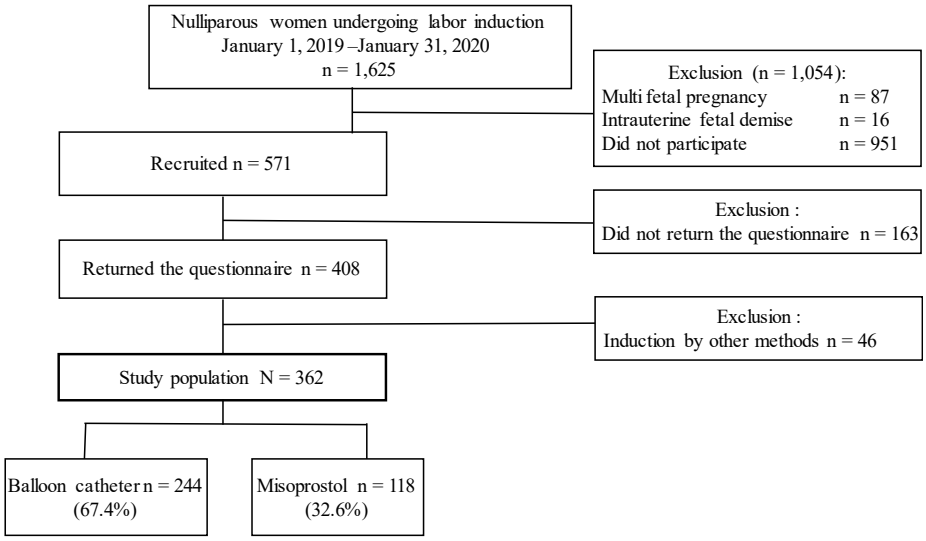
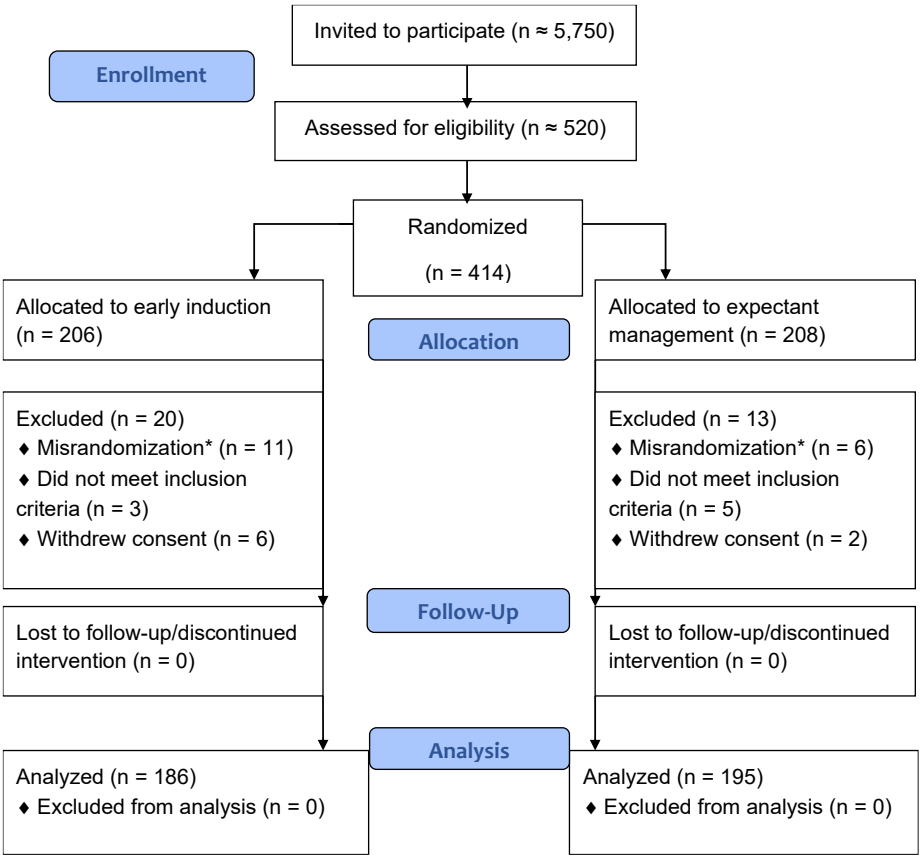


Figure 11 Formation of the study population: nulliparous pregnant women with an unripe cervix undergoing labor induction by balloon catheter or oral misoprostol at HUS (N = 362).

4.1.3.3 Study V: SYKE

The inclusion criteria were designed to select women at 41+0 GW (as confirmed by ultrasound in the first-trimester screening at GW 11+0–13+6) with nulliparity, an age ≥ 18 years, a viable singleton pregnancy with a cephalic presentation, an unripe cervix (Bishop score < 6), and intact fetal membranes. The exclusion criteria ruled out estimated fetal weights > 4,500 g or < 10% / < -1.5 standard deviations (SDs), uterine scarring, placenta previa, suspicion of maternal vaginal infection or chorioamnionitis, maternal HIV or hepatitis B or C infection, prenatally detected severe fetal malformation, and pregnancy complications requiring intervention and thus preventing expectant management. Figure 12 visualizes the study population.



*Misrandomization: A randomization event recorded in the randomization system without an existing patient file due to erroneous use of the randomization tool.

Figure 12 Formation of the study population: pregnant nulliparous women with an unripe cervix undergoing labor induction at 41+0 or expectant management until 41+5–42+1 gestational weeks (N = 381).

4.2 METHODS

4.2.1 SAMPLE SIZE CALCULATIONS

In Studies I and II, sample size calculations were not performed, as these were retrospective cohort studies.

The prospective study of SYNKO, reported in III and IV, was intended to be a one-year cohort study and thus required no sample size calculation before commencing.

In Study V (SYKE), the recruitment target was 400 women. This was based on an estimate of a 40% reduction in the CS rate, from ~38% (the CS rate in nulliparous women with labor induced for a post-term pregnancy at HUS) to ~20% (the overall rate in nulliparous women), [1,17] which required a sample of 198 women (significance level: 0.05, power: 80%). As it was evident that some women in the expectant management group would experience spontaneous onset of labor, the figure determined by the power calculation was doubled to form the recruitment target. The final number of randomizations in the study was 414, of which 206 were in the early induction group and 208 were in the expectant management group (Figure 12).

4.2.2 DATA COLLECTION

In all studies, data on the study population's characteristics and labor and delivery outcomes were obtained from individual patient charts in the hospital's EHRs and collected in an Excel file. In Studies III–IV (SYNKO), data on childbirth experiences were collected using the CEQ questionnaire.

4.2.3 PRE-LABOR FACTORS

The maternal characteristics recorded included age, gestational age, height, and pre-pregnancy weight and BMI; IVF history, smoking habits, fear of childbirth, and indication for labor induction; presence of pregestational diabetes (type 1 and 2) or GDM; and Bishop score at the start of labor induction. In Study I, a retrospective inquiry, information was also recorded about the stage of labor at which previous CSs for labor dystocia had been performed.

Gestational diabetes was diagnosed if an oral glucose tolerance test yielded any of the following blood plasma values: a fasting value ≥ 5.3 mmol/l, 1-hour value ≥ 10.0 mmol/l, or 2-hour value ≥ 8.6 mmol/l. A fear of labor was diagnosed if the woman was referred to the antenatal clinic for or reported such a fear and it required additional psychosocial support during pregnancy.

In Study I, information on maternal GBS carrier status or antibiotics usage was not available. In other studies, GBS presence was tested using a rapid qualitative in vitro test (XPert® GBS, Cepheid, Sunnyvale California, United

States of America) of vaginal and perineal samples. In Studies II–IV, the test was taken at admission for labor induction, and in Study V (SYKE), at the 41+0 screening visit.

In the case of two error signals in recurrent samplings in the XPert® GBS test, the women were treated as GBS positive. However, in Study II, on GBS, women with erroneous or unknown results were excluded.

All GBS-positive women received antibiotic prophylaxis during labor, with benzylpenicillin being the recommended option. In Study II, the women received 4 million units of benzylpenicillin intravenously, followed by 2.5 million additional units every 4 hours until delivery. In Studies III–V, the recommended dose was 5 million units followed by 2 million more every 4 hours. In the case of penicillin allergy, the women were administered 1.5 g of cefuroxime or 900 mg of clindamycin every 8 hours intravenously. Prophylaxis was initiated at the onset of labor or spontaneous or artificial membrane rupture.

4.2.4 LABOR INDUCTION

In Studies II (GBS) and III–IV (SYNKO), all participants experienced labor induction. In Studies I (TOLAC) and V (SYKE), the rates of labor induction were 34.2% and 76.7%, respectively.

The indications for labor induction in Studies I–IV were obtained from the EHRs. In Study V (SYKE), all women in the early induction group underwent labor induction for late-term pregnancies (41+0 GW). Most women randomized for expectant management and then induced at 41+5–42+1 GW had no other reasons for induction than post-term pregnancy.

In Studies I–IV, the method of labor induction was chosen by the obstetrician and patient. In Study V (SYKE), the method was determined by randomization into three treatment arms based on the use of BC, oral misoprostol, or concurrent BC and misoprostol, with equal randomization ratios of 1:1:1. The assessment of induction methods in the SYKE trial is part of another study, and these results are not discussed in this thesis.

In Studies I–IV, if the cervix remained unripe (Bishop score < 6) 24 hours after the primary method of labor induction was initiated, the obstetrician determined the next method of continuation. In Study V (SYKE), if the cervix remained unripe after 72 hours of cervical ripening according to the randomized treatment protocol, the obstetrician determined the method of continuation.

4.2.4.1 Balloon catheter

In all studies, a single 40–80-ml BC was used, retained for a maximum of 24 hours at a time until spontaneous expulsion or removal. In Studies I–IV, a Cook® double balloon catheter may have been used instead of the standard

single balloon catheter, as it was available at the discretion of the treating obstetrician during the time of the research. However, data on the types of balloons used were not collected, as no difference in the delivery outcomes of single and double BC use has been discovered.[181]

All low-risk women were offered an outpatient protocol and asked to return to the hospital if they had any concerns, after the balloon expulsion or after 24 hours of the balloon staying in place. Inpatient treatment was chosen if the pregnancy was considered high-risk (due, for example, to pregestational diabetes or nonreassuring CTG) or if the woman preferred it.

In the case of PROM and labor induction via BC (which was feasible in all studies but Study II), prophylactic antibiotics were used, and the balloon retention time was limited to eight hours. Data on antibiotic administration are lacking for Study I (TOLAC), but at the time of the study, the antibiotic commonly used in the case of PROM and BC use was a single 1.5-g dose of cefuroxime. In Studies III–V, 5 million units of benzylpenicillin administered intravenously, followed by 2 million units every 4 hours until delivery was instructed for the women with PROM. If the woman was not a GBS carrier, the antibiotic prophylaxis was discontinued after BC expulsion. If the woman was a GBS carrier, the prophylaxis was continued in accordance with protocol.

4.2.4.2 Misoprostol

In Studies I–IV, a vast majority of the women in whom labor was induced by misoprostol were orally administered 50 μg of misoprostol (Cytotec®) every 4 hours until the achievement of regular contractions and/or a Bishop score ≥ 6. In some women, misoprostol may have also been administered vaginally (25 μg of Cytotec® every 4 hours), and in Studies III–IV (SYNKO), as 25 μg orally every 2 hours (Angusta®). In Study III, the use of a dinoprostone vaginal insert (Propess®) was also possible at the discretion of the treating obstetrician. In Study V (SYKE), all participants whose labor was induced by misoprostol received 50-μg doses (Cytotec®) every 4 hours until observance of regular contractions and/or a Bishop score ≥ 6. All women whose labor was induced using prostaglandins were treated as inpatients.

4.2.4.3 Balloon catheter and misoprostol use: consecutive and concurrent

In Studies I–IV, consecutive use of BC and misoprostol was possible. In the case of consecutive use, the first procedure was recorded as the primary method.

In Studies I, II, and IV, BC and misoprostol were not used concurrently, but in Study III, they may have been. In Study V (SYKE), women assigned to the combination group were treated with a single 40–80-ml balloon catheter retained for a maximum of 24 hours at a time and simultaneous oral

misoprostol at 50 μg every 4 hours until the onset of regular contractions and/or a Bishop score ≥ 6.

4.2.4.4 Artificial rupturing of the membranes and oxytocin infusion

In Studies I and III, AROM was used as the primary method of labor induction for women with a ripe cervix. For those women who underwent labor induction after PROM and with a ripe cervix, oxytocin infusion was the primary method used. In Studies II, IV, and V, which consisted solely of women with an unripe cervix, the membranes were ruptured, and intravenous oxytocin infusion was initiated once the cervix was ripe.

In the retrospective studies, I and II, AROM was performed 2–12 hours after BC expulsion, and oxytocin was initiated 2–12 hours after membrane rupture according to the judgment of the treating obstetrician. In Studies III–V, AROM was performed 1–3 hours after BC expulsion. In the absence of adequate contractions, oxytocin infusion was initiated 1–3 hours after membrane rupture. If misoprostol was used for cervical ripening, oxytocin was initiated no sooner than 4 hours after the last dose in all studies to prevent uterine hyperstimulation.[14] In all studies, the oxytocin infusion was intended to generate 3–4 90–140-second contractions every 10 minutes and, eventually, cervical progress.[212]

A low-dose oxytocin protocol was used in the retrospective studies, I and II, and a high-dose protocol was used in the prospective studies, III–V.[215] In both protocols, oxytocin was initiated at 15 ml/h. In the low-dose protocol, the infusion was augmented every 30 minutes up to 90 ml/h within 4.5 hours and continued up to 6 hours if contractions did not begin. This was followed by a break of 2–6 hours before another round of infusion began. In the high-dose protocol, the infusion was augmented every 20 minutes up to 120 ml/h within 4 hours and continued for up to 12 hours.

In the low-dose oxytocin protocol, failed labor induction was diagnosed after 2 sets of 6-hour oxytocin infusions, and in the high-dose protocol, after a single 12-hour infusion.[215] At the onset of labor, the infusions were decreased or stopped. Earlier interventions due to concerns about fetal well-being or other issues were also conducted as needed in all studies.

4.2.5 LABOR AND DELIVERY MANAGEMENT

In all studies, labor and delivery were managed according to the hospital protocol. Continuous CTG tracing and oxytocin augmentation were routinely used during labor.

4.2.6 DELIVERY OUTCOMES

Delivery outcomes recorded included oxytocin use for labor induction and augmentation, epidural and spinal analgesia, and mode of delivery, categorized as unassisted vaginal, operative vaginal by vacuum extraction, or CS. Indications for CS included fetal distress, failed induction, labor dystocia, and other indications, such as preeclampsia, infection, and hand/foot presentation. The other delivery-related factors recorded were the induction-to-delivery interval, the duration of labor, episiotomy, and the following delivery complications: shoulder dystocia, sphincter injury, postpartum hemorrhage, uterine rupture, manual removal of a retained placenta, and intra- and post-partum infection.

The interval between the start of labor induction and birth is referred to as the induction-to-delivery interval. The latent phase of labor was not recorded for the women who experienced a spontaneous onset of labor. The first stage of labor was defined to begin at the time of regular contractions and cervical dilation of 4–6 cm. The second stage of labor was defined to begin at a cervical dilation of 10 cm and maternal pushing efforts and end with the delivery of the neonate, which also determined the endpoint of the labor.

Failed labor induction was diagnosed if the labor did not start despite ruptured membranes and > 12 hours of oxytocin administration.[217] Labor dystocia was diagnosed in the first stage of labor if no progress was observed when the cervical dilation was ≥ 6 cm, the membranes were ruptured, and adequate contractions had been occurring for ≥ 4 hours, and in the second stage of labor if delivery failed at a cervical dilation of 10 cm despite ≥ 1 hour of active pushing or by a failed operative vaginal delivery.[279]

Uterine rupture was diagnosed by a complete rupture of the uterine wall, excluding only fenestrations. Shoulder dystocia was defined if obstetric maneuvers were, in the judgment of the treating obstetrician in the EHR, needed to deliver the neonate after delivery of the head.

Postpartum hemorrhage was defined as maternal hemorrhage ≥ 1,000 ml in Studies I, II, and V. In the SYNKO studies, postpartum hemorrhage was defined as an abnormally large hemorrhage in vaginal delivery but not in CS (≥ 1,500 ml in Study III and ≥ 1,000 ml in Study IV).

In all studies, maternal intrapartum infection was diagnosed if two of the following occurred: a fever ≥ 38 °C, a fetal heart rate > 160 beats per minute, a white blood cell count ≥ 15 e9/l, uterine tenderness, or purulent discharge.[280] Maternal postpartum infections included endometritis (if two of the following were present: a fever ≥ 38 °C, a white blood cell count ≥ 15 e9/l, uterine tenderness, or purulent vaginal discharge), clinical wound infection, septicemia, deep abdominal or pelvic infection, urinary tract infection, or puerperal fever of unknown origin.[281]

In Study II (GBS), the women were followed up for one week after delivery, and in Study V (SYKE), the women were followed up until discharged from the postpartum unit. In Study I (TOLAC) and Studies III–IV (SYNKO), the follow-up period was not specified.

4.2.7 NEONATAL OUTCOMES

The neonatal outcomes recorded included gestational age at birth, sex, birthweight, Apgar score at 5 minutes, umbilical artery pH, and umbilical artery BE; the presence of macrosomia (≥ 4,500 g in Studies I–IV and ≥ 4,000 g in Study V) or infection; and NICU admission status.

A determination of adverse neonatal outcomes required at least one of the following: a 5-minute Apgar score < 7, NICU admission, umbilical artery blood pH < 7.05, or BE < -12.0.

All neonatal infections were confirmed and categorized by a neonatologist. In Study II (GBS), the neonatal infections were further divided into blood culture-positive sepsis, clinical sepsis, suspected sepsis, and other suspected infections. Clinical neonatal sepsis was diagnosed if the neonate exhibited the following signs or symptoms: fever, respiratory distress or apnea, tachycardia, poor perfusion, low blood pressure, seizures, hypo- or hyperglycemia, feeding problems, lethargy or irritability, abnormal blood values (leukocytosis, leukopenia, increased neutrophil precursors, thrombocytopenia, or C-reactive protein < 20 mg/l), and a positive response to a minimum of five days of antibiotic treatment notwithstanding a blood culture that remained negative. Suspected sepsis was diagnosed if the neonate exhibited at least one symptom of sepsis, had at least one abnormal blood value, and responded positively to antibiotic treatment.

4.2.8 ASSESSMENT OF THE CHILDBIRTH EXPERIENCE

4.2.8.1 The Childbirth Experience Questionnaire

In Studies III–IV (SYNKO), we used a multidimensional tool, the CEQ, to evaluate the childbirth experience.[248,249] The questionnaire was handed to the women upon admission to the labor induction unit after they were provided with information about the study and gave their written informed consent. The questionnaire was available in Finnish, Swedish, and English, and the women were asked to return it by mail or email within one month after their childbirth.

In Study IV, with the permission of the authors of the original CEQ questionnaire, we added six items on labor induction. One of the newly added items, *I was satisfied with the timing of the labor induction chosen for me,* was set on a three-point Likert scale (to indicate a wish that it had occurred earlier, a wish that it had occurred later, or satisfaction with the timing). The other five items added were scored on a four-point Likert scale (totally agree = 4, mostly agree = 3, mostly disagree = 2, totally disagree = 1). These five items comprised a new, unvalidated "induction" domain. Notably, this experimental domain was not included in the analyses of the total CEQ scores in Study IV.

Table 6. The items added to the CEQ, which formed an unvalidated "induction" domain in Study IV.

I am satisfied with the labor induction method chosen for me
I would select the same labor induction method again in my next pregnancy
The information I received about labor induction was clear and sufficient
I was happy with the staff of the labor induction unit
I was satisfied with the pain relief I received in the labor induction unit

The CEQ was originally validated in primiparous women who experienced a spontaneous onset of labor, but it has since been used in studies that included multiparous women and labor induction. To the author's knowledge, it has not been previously used or validated in a population solely consisting of women who experienced induced labor. Although we did not perform a validation study, we assessed the usability of the CEQ in our study population by examining the questionnaire's floor and ceiling effects, i.e., the percentages of the most negative and most positive responses given. In this approach, if 15% or more of respondents choose an extreme response (very positive or very negative), a questionnaire is considered to be unsuitable for use within the population, as no distinction between these respondents is possible.[282]

In the CEQ, we defined the childbirth experience as negative if all the woman's domain scores were in the most negative quartile of the scores assigned in the study population.[283]

4.2.8.2 The Visual Analog Scale

The VAS ratings of the overall childbirth experience were recorded, following standard practice at HUS, and the results were compared with the CEQ scores in Study IV. At HUS, a VAS score < 5 or a numerical rating scale (NRS) score ≤ 4 represents a negative childbirth experience, and these women may receive additional support after discharge.[254]

4.2.9 STATISTICAL ANALYSES

We performed statistical analyses using IBM's SPSS Statistics for Windows, versions 25–28. To compare categorical variables, we used a Chi-square test and Fisher's exact test as appropriate, and the data are presented as numbers and percentages. For continuous variables, we used the t-test when the data followed a normal distribution and the Mann-Whitney U test when they did not. We present these data using the mean and SD or median and interquartile range (IQR) as appropriate. In this thesis, the CEQ results from Studies III–IV are presented only as means and SDs for clarity, as most items followed a normal distribution. The median and IQR values can be found in the original articles.

To calculate odds ratios (OR) for different outcomes and events in the studies, we used logistic regression analysis. In the studies with relatively large sample sizes (I, II, and III), we also calculated adjusted odds ratios (AORs) with a 95% confidence interval (CI) to control for possible confounding factors. In the studies with many potential confounding factors (II and III), we used stepwise logistic regression to choose which factors to include in the final multivariable analyses. All variables used in the final multivariable analyses are shown in the tables unless stated otherwise. In Study IV, multivariable analysis was not feasible due to the small sample size, while in Study V, it was omitted due to adherence to the registered study protocol.

In Study V, we also present the results of the primary outcomes using risk ratios (RRs) with a 95% CI.

A p-value < 0.05 was considered statistically significant. Missing data, if they existed, were handled by pairwise exclusion when possible and in logistic regression by listwise exclusion.

In Study II, in addition to SPSS, we used R software to perform receiver operating characteristic (ROC) curve analyses to find cut-off values for continuous time factors predictive of infection. We used the Youden criterion, and an area under the ROC curve (AUC) > 0.75 was considered significant.[284]

In Study V, we assessed the safety of continuing the trial in November 2019[102] by conducting an interim analysis halfway to achieving the recruitment target. In the final study report, we submitted the data to intention-to-treat analysis. In addition, we performed exploratory analyses in which only women strictly following study protocol for the initiation date of labor induction and women undergoing spontaneous onset of labor before their scheduled late induction were included.

5 RESULTS

Table 7. Key characteristics and outcomes of all studies.

	I TOLAC	II GBS	III SYNKO	IV SYNKO	V SYKE
	n = 660	n = 1,959	n = 711	n = 362	n = 381
Nulliparous, rate (n)	0%	52.7% (1,033)	57.4% (408)	100%	100%
Age in years, mean (SD)	32.1 (4.7)	31.4 (5.4)	33.6 (5.0)	32.9 (5.2)	28.7 (5.3)
Pre-pregnancy BMI, kg/m², median (IQR)	24.3 (7.0)	24.2 (6.8)	24.0 (6.2)	24.0 (6.0)	24.9 (6.0)
Labor induction, rate (n)	34.2% (226)	100%	100%	100%	75.9% (289)
Gestational age at labor induction in weeks, median (IQR)	40.4 (2.3)	41.0 (2.4)	40.3 (2.4)	40.6 (2.4)	41.0 (0.72)
Vaginal delivery, rate (n)	72.9% (481)	75.9% (1,486)	77.2% (549)	67.1% (243)	79.5% (303)
Cesarean section, rate (n)	27.1% (179)	24.1% (473)	22.8% (162)	32.9% (119)	20.5% (78)
Oxytocin use in induction or augmentation, rate (n)	92.0% (607)	79.1% (1,550)	80.7% (574)	90.3% (327)	74.0% (282)
Epidural or spinal analgesia, rate (n)	87.1% (575)	79.9% (1,565)	80.6% (573)	87.6% (317)	87.7% (334)
Birthweight in grams, mean (SD)	3,706 (455)	3,597 (504)	3,591 (505)	3,560 (507)	3,724 (398)

Abbreviations: TOLAC: trial of labor after cesarean, GBS: group B streptococcus, SD: standard deviation, BMI: body mass index, IQR: interquartile range

5.1 STUDY I: TOLAC

Women who completed a successful TOLAC—i.e., a vaginal delivery after earlier CS for prior failed labor induction or labor dystocia—were compared with women who did not complete a TOLAC and underwent a repeat CS.

5.1.1 MATERNAL CHARACTERISTICS

Of the 660 women included in the study, 481 (72.9%) delivered vaginally. The women with a repeat CS and an unsuccessful TOLAC were shorter and more obese; more often had post-term pregnancy, diabetes, and no prior vaginal delivery; and more often underwent labor induction (Table 8) compared with women who completed the TOLAC.

Table 8. Differences between maternal characteristics of 481 women with a completed TOLAC and 179 women with an unsuccessful TOLAC in Study I (TOLAC), N = 660.

	Successful TOLAC		**Unsuccessful TOLAC**		
	n = 481	**72.9%**	**n = 179**	**27.1%**	**p-value**
Height < 160 cm	97	20.2	50	27.9	**0.03**
Body mass index ≥ 35 kg/m²	34	7.1	19	10.6	**0.01**
Diabetes, any type	121	25.2	63	35.2	**0.01**
Prior vaginal delivery	124	25.8	17	9.5	**< 0.001**
Post-term pregnancy (≥ 42 gestational weeks)	35	7.3	29	16.2	**0.001**
Labor induction	143	29.7	83	46.4	**< 0.001**

Abbreviations: TOLAC: trial of labor after cesarean

5.1.2 OUTCOMES

The primary outcome, a successful TOLAC, was compared in three study groups: (1) women who had experienced prior labor dystocia in the first stage of labor, (2) women who had experienced it in the second stage of labor, and (3) women with prior failures of labor induction. The secondary outcomes were compared in the groups with successful and unsuccessful TOLACs.

A total of 481 women (72.9%) had successful TOLACs. The rate of a successful TOLAC was the highest among women with a prior CS in the first (75.6%) or second (73.1%) stages of labor and the lowest among women with a prior failed labor induction (59.0%, p = 0.003; Table 9).

The rates of oxytocin use and epidural or spinal analgesia did not differ between the study groups with successful or unsuccessful TOLACs. Also, no significant difference in adverse primary neonatal outcome rate was observed (6.9% in successful TOLAC and 8.9% in unsuccessful TOLAC cases, p = 0.37).

Table 9. Primary and secondary outcomes in Study I (TOLAC), N = 660.

		n	Rate
Primary outcomes	**Successful TOLAC**	179/660	27.1%
	Prior dystocia in the first stage of labor	384/508	75.6%
	Prior dystocia in the second stage of labor	38/52	73.1%
	Prior failed labor induction	59/100	59.0%
Secondary outcomes	Uterine rupture	4	0.6%
	Postpartum hemorrhage ≥ 1,000 ml	126	19.1%
	Intrapartum infection	19	2.9%
	Postpartum infection	16	2.4%
	Adverse neonatal outcome	49	7.4%

Abbreviations: TOLAC: trial of labor after cesarean

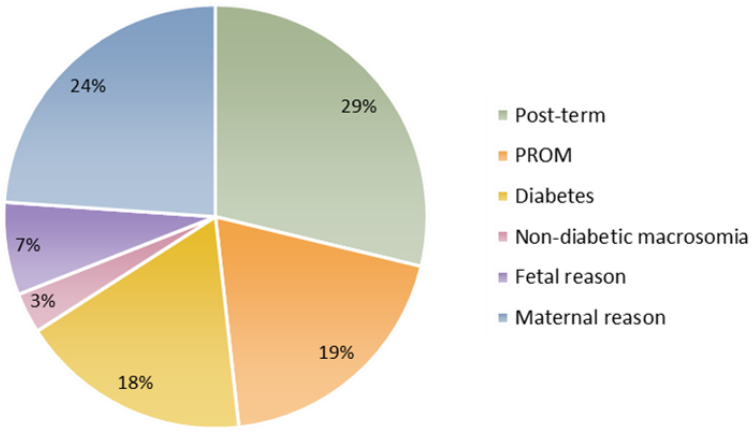
The rates of intrapartum infection were higher among the women with an unsuccessful TOLAC than among those with a successful TOLAC (8.4% [n = 15] vs. 0.8% [n = 4]); p < 0.001), but the rate of postpartum infection did not differ between the groups. Additionally, the rates of postpartum hemorrhage ≥ 1,000 ml (30.2% [n = 54] vs. 15.0% [n = 72], p < 0.001) and birthweight ≥ 4,500 g (7.3% [n = 13] vs. 3.3% [n = 16], p = 0.03) were higher among the women with an unsuccessful TOLAC. The rates of adverse neonatal outcomes were similar. A multivariable model of the risk factors that predicted a failed TOLAC is presented in Table 10.

Table 10. Risk factors for a repeat CS (n = 179) in Study I (TOLAC), N = 660.

	AOR	CI (95%)	p-value
Height < 160 cm	1.7	1.1–2.7	**0.01**
No prior vaginal delivery	4.9	2.7–9.0	**< 0.001**
Maternal age ≥ 37 years	1.6	1.0–2.7	**0.05**
More than 2 years since the previous CS	1.6	1.1–2.4	**0.02**
Diabetes, any type	1.7	1.0–2.6	**0.03**
Labor induction for PROM	2.1	1.0–4.1	**0.04**
Labor induction for non-diabetic macrosomia	5.9	1.2–29.2	**0.03**
Labor induction due to fetal reasons	4.2	1.5–12.2	**0.007**
Birthweight ≥ 4,500 g	2.4	1.1–5.5	**0.03**

Additional factors adjusted for: maternal age ≥ 37 years, IVF use, smoking history, BMI ≥ 35 kg/m², medication-dependent gestational diabetes, post-term pregnancy, labor induction for post-term pregnancy, labor induction for diabetes, labor induction for a maternal reason.
Abbreviations: CS: cesarean section, PROM: premature rupture of membranes

Of the women, 226 (34.2%) underwent labor induction in their current pregnancy. The primary methods used for labor induction were similar in women with successful or unsuccessful TOLACs: BC was used for 59.7%, misoprostol for 8.8%, and AROM and oxytocin for 31.4% of the women. Figure 13 presents the indications for labor induction, which were also similar across the study groups.



Diabetes: pregestational diabetes (type 1 and 2) or gestational diabetes.
Fetal reason: oligohydramnios, polyhydramnios, nonreassuring CTG, intrauterine growth restriction, blood group immunization, reduced fetal movements, prevention of fetal malposition after successful external cephalic version, or gastrointestinal anomalies.
Maternal reasons: preeclampsia, intrahepatic cholestasis of pregnancy, maternal medical condition, exhaustion, psychosocial reasons, or complications in an earlier pregnancy, such as previous intrauterine death or shoulder dystocia.
Abbreviations: PROM: premature rupture of membranes

Figure 13 Indications for labor induction in Study I (TOLAC), N = 660.

The rate of successful TOLACs in women undergoing labor induction was 63.3% (n = 143), which is lower than the 77.9% (n = 338) rate for women who had a spontaneous onset of labor ($p < 0.001$). Of the 77 women who underwent (a failed) labor induction in a prior pregnancy and attempted it in the current pregnancy, 40 (51.9%) had a successful TOLAC.

For women who had not completed a prior vaginal delivery, the rate of successful TOLACs was 68.8% (n = 357), which is lower than the 87.9% (n = 124) rate for women with a history of prior vaginal delivery ($p < 0.001$). Table 11 shows a comparison of TOLAC success rates by onset of labor and history of prior vaginal delivery.

Table 11. Comparison of rates of successful TOLACs according to history of prior vaginal delivery and labor induction in the current pregnancy in Study I (TOLAC), n = 660.

	TOLAC success rate in women with no history of prior vaginal delivery		**TOLAC success rate in women who completed a prior vaginal delivery**		**p-value**
	n = 519	78.6%	n = 141	21.4%	
TOLAC success rate in women with induced labor n = 226, 34.2%	104 / 180	57.8%	39 / 46	84.8%	**p < 0.001**
TOLAC success rate in women with spontaneous onset of labor n = 434, 65.8%	253 / 339	74.6%	85 / 95	89.5%	**p = 0.002**
p-value	**p < 0.001**		p = 0.42		

Abbreviations: TOLAC: trial of labor after cesarean

Four cases (0.6%) of uterine rupture occurred, all in women who had not completed a prior vaginal delivery. All these women had a repeat CS in the current pregnancy. One of the women had a prior CS for failed labor induction, and three of the women had a prior CS for labor dystocia in the first stage of labor. One of the ruptures occurred following induction via AROM and oxytocin and three after a spontaneous onset of labor. There were no cases of hysterectomy.

5.2 STUDY II: GBS

Women with intact amniotic membranes who underwent labor induction by BC were divided into a group who tested positive for GBS and a second group who tested negative. Their characteristics were then compared.

5.2.1 MATERNAL CHARACTERISTICS

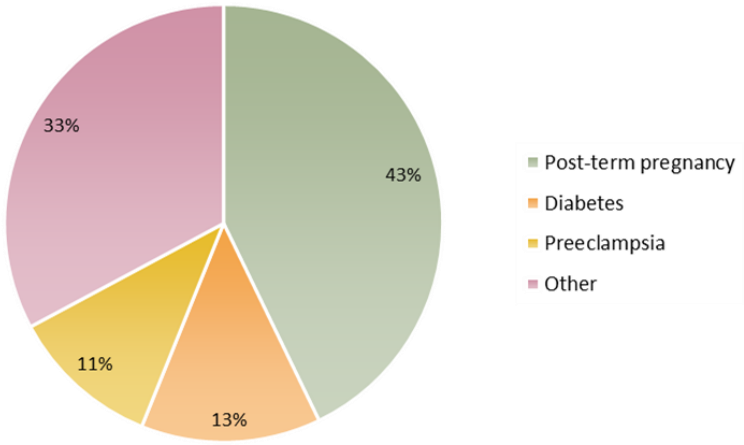
A total of 1,959 women were included in the study, of whom 469 (23.9%) were GBS positive at the time of delivery. The GBS-positive women were older and more often obese than the GBS-negative women (Table 12).

Table 12. Differences between maternal characteristics of 469 GBS-positive and 1,490 GBS-negative women in Study II (GBS), N = 1,959.

	GBS positive		**GBS negative**		
	n = 469	**23.9%**	**n = 1,490**	**76.1%**	**p-value**
Maternal age ≥ 37 years	97	20.7	233	15.6	**0.01**
Body mass index ≥ 35 kg/m²	46	9.8	92	6.2	**0.01**

Abbreviations: Abbreviations: GBS: group B streptococcus

All women underwent labor induction by BC. Figure 14 presents the indications for labor induction, which were similar in the groups compared.



Diabetes: pregestational diabetes (type 1 and 2) or gestational diabetes.
Other: oligohydramnios, complications in a previous pregnancy, fetal anomalies, reduced fetal movements, maternal medical condition unrelated to pregnancy, blood group immunization, nonreassuring CTG, prevention of fetal malposition after successful external cephalic version, fetal arrhythmia, or polyhydramnios.

Figure 14 Indications for labor induction in Study II (GBS), N = 1,959.

5.2.2 OUTCOMES

The rates of oxytocin use, and epidural or spinal analgesia did not differ between the study groups. The rates of operative vaginal delivery (11.5%) and CS (24.1%) were also statistically similar. The neonatal admission rate to the NICU was the same, 1.1%, in the two groups.

The overall rate of maternal intrapartum infection was 7.4%, and it was lower in the GBS-positive group than in the GBS-negative group (Table 13). There were seven women who had intrapartum sepsis, all in the GBS-negative group. The pathogens found in blood cultures were *Staphylococcus aureus* (n = 2), GBS (n = 1), *Enterococcus fecalis* (n = 1), *Granulicatella elegans* (n = 1), *Staphylococcus epidermidis* (n = 1), and *Streptococcus anginosus* (n = 1).

The rate of maternal postpartum infection was 3.9%, and the rate of neonatal infection was 3.3%. Both rates were similar across study groups (Table 13). No cases of maternal postpartum sepsis occurred, but one newborn (0.05%) tested positive for sepsis in a blood culture (unspecified coagulase-negative staphylococcus) in the GBS-negative group. No difference in the rates of adverse neonatal outcomes was seen in the groups (Table 13).

Table 13. Primary and secondary outcomes in Study II (GBS) among 1,959 mother–newborn pairs.

		GBS positive		**GBS negative**		
		n = 469	**23.9%**	**n = 1,490**	**76.1%**	**p-value**
Primary outcomes	Maternal intrapartum infection	22	4.7	123	8.3	**0.01**
	Maternal postpartum infection	14	3.0	63	4.2	0.23
	Neonatal infection	14	3.0	51	3.4	0.66
Neonatal outcomes	5-minute Apgar score < 7	21	4.5	45	3.0	0.13
	Umbilical artery pH < 7.05	9	1.9	26	1.7	0.80
	Umbilical artery base excess < -12.0	13	2.8	34	2.3	0.55
	NICU admission	5	1.1	16	1.1	1.0

Abbreviations: GBS: group B streptococcus, NICU: neonatal intensive care unit

Antibiotics were administered to 99.1% of the GBS-positive women and, in 86.1%, at least four hours before delivery, as recommended. The antibiotics most often used were benzylpenicillin (76.8%), cefuroxime (17.2%), and clindamycin (3.6%). Of the GBS-negative women, 14.7% received antibiotics during labor, all for suspected infection. Antibiotics were administered for intrapartum infection in 44.7% of the women, and 65.3% received them at the discretion of the treating obstetrician for elevated body temperature or infection markers (leucocytes, C-reactive protein). Notably, all women who underwent CS received prophylactic antibiotics—most often, a single dose of cefuroxime—which was not counted in this study as a use of antibiotics.

The median delivery-related intervals are shown in Table 14. No differences in any of them were seen between the GBS-positive and GBS-negative women.

Table 14. Delivery-related intervals in Study II (GBS), n = 1,959.

Interval from balloon insertion to expulsion in hours, median (IQR)	5.6 (6.7)
Interval from induction to delivery in hours, median (IQR)	23.8 (21.3)
Interval from rupture of membranes to delivery in hours, median (IQR)	10.4 (11.4)
Duration of labor in hours, median (IQR)	6.6 (2.3)

Abbreviations: IQR: interquartile range

The median duration of labor was longer in nulliparous women who delivered vaginally and had an intrapartum infection compared with those without an infection (13.0 h vs. 8.7 h, $p < 0.001$). In addition, the rates of induction-to-delivery interval ≥ 24 h (70.4% vs. 52.8%, $p = 0.02$) and of membrane-rupture-to-delivery interval ≥ 12 h (68.2% vs. 49.5%, $p = 0.02$) were higher among the nulliparous, infected women who delivered vaginally than among those not infected.

The interval from BC insertion to expulsion was not associated with infectious morbidity, but in GBS-positive women, an interval of > 6.5 h showed an association with postpartum endometritis in the ROC curve, with an AUC of 0.72 (Figure 15).

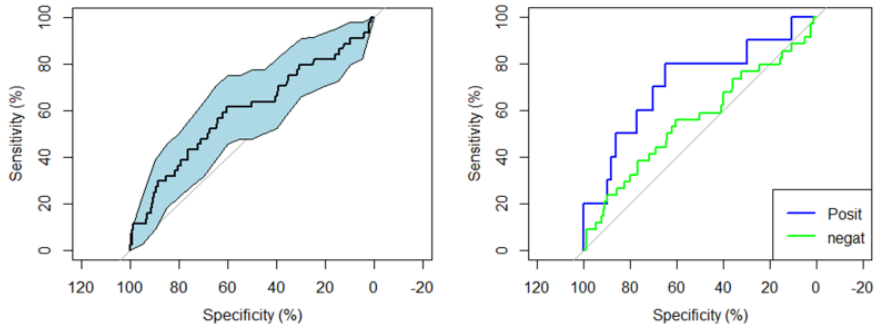


Figure 15 Effect of balloon-insertion-to-expulsion interval on postpartum endometritis in all women (AUC 0.60) and in GBS-positive and GBS-negative women (AUC 0.72 and 0.56, respectively) in Study II (GBS), N = 1,959.

For induction-to-delivery interval and duration of labor, no clinically relevant cut-off value was found for increased risk of infection. The rupture-of membranes-to-delivery interval, at > 13.3 h, showed some association with intrapartum infection in all women, with an AUC of 0.72 (Figure 16). In GBS-positive women, no correlation was found, but in GBS-negative women, the cut-off value was 12.7 h, with an AUC of 0.76.

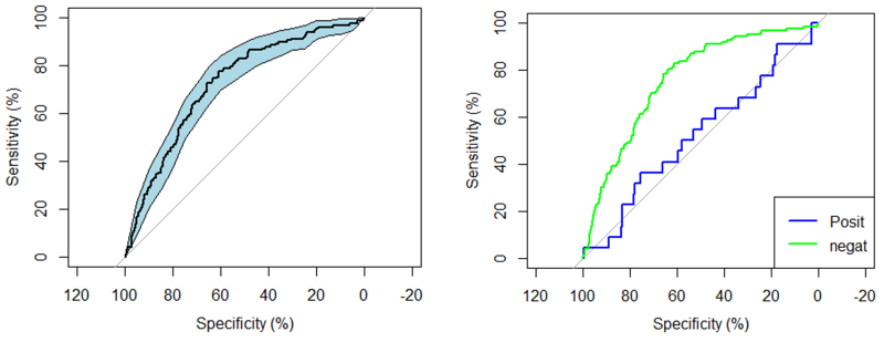


Figure 16 Effect of rupture-of-membranes-to-delivery interval on intrapartum infection in all women (AUC 0.72) and in GBS-positive and GBS-negative women (AUC 05.2 and 0.76) in Study II (GBS), N = 1,959.

The risk factors associated with maternal intrapartum infection were nulliparity, a gestational age ≥ 41+0 weeks, a Bishop score < 3 at the start of induction, and a rupture-of-membranes-to-delivery interval ≥ 12 h (Table 15). GBS positivity was negatively associated with maternal intrapartum infection, and the AOR of GBS negativity for intrapartum infection was 1.8 (CI [95%] 1.1–2.9, p = 0.02).

Table 15. Risk factors for maternal intrapartum infection (n = 145) in Study II (GBS), N = 1,959.

	All women (N = 1,959)		
	AOR	**CI (95%)**	**p-value**
Group B streptococcus positivity	0.6	0.3–0.9	**0.02**
Previous cesarean section	2.0	1.0–4.1	0.06
Age ≥ 37 years	0.8	0.5–1.4	0.52
In vitro fertilization use	0.7	0.3–1.6	0.39
Smoker	1.3	0.8–2.2	0.27
Nulliparity	2.7	1.5–4.9	**0.001**
Body mass index ≥ 35 kg/m²	1.0	0.5–2.1	1.0
Gestational diabetes	1.3	0.9–2.0	0.17
Gestational age ≥ 41+0 weeks	1.6	1.1–2.3	**0.02**
Bishop score < 3	1.6	1.1–2.3	**0.007**
Rupture of membranes to delivery ≥ 12 h	3.6	2.4–5.5	**< 0.001**

Abbreviations: AOR: adjusted odds ratio, CI: confidence interval

The risk factors associated with maternal postpartum endometritis were rupture-of-membranes-to-delivery interval ≥ 12 h and CS (Table 16).

Table 16. Risk factors for maternal postpartum endometritis (n = 44) in Study II (GBS), N = 1,959.

	All women (N = 1,959)		
	AOR	**CI (95%)**	**p-value**
Group B streptococcus positivity	0.9	0.4–1.9	0.83
Body mass index ≥ 35 kg/m²	1.9	0.6–6.1	0.28
Gestational diabetes	1.8	0.9–3.4	0.10
Rupture of membranes to delivery ≥ 12 h	2.6	1.3–5.2	**0.01**
Cesarean section	3.0	1.6–5.7	**< 0.001**

Abbreviations: AOR: adjusted odds ratio, CI: confidence interval

The risk factors associated with neonatal infection were nulliparity, GDM, rupture-of-membranes-to-delivery interval ≥12 h, and maternal intrapartum infection (Table 17).

Table 17. Risk factors for neonatal infection (n = 65) in Study II (GBS), N = 1,959.

	All women (N = 1,959)		
	AOR	**CI (95%)**	**p-value**
Group B streptococcus positivity	1.1	0.6–2.1	0.76
Nulliparity	2.2	1.2–4.3	**0.02**
Body mass index ≥ 35 kg/m²	0.2	0.03–1.4	0.10
Gestational diabetes	1.9	1.1–3.3	**0.03**
Gestational age ≥ 41+0 weeks	1.6	0.9–2.9	0.11
Rupture of membranes to delivery ≥ 12 h	1.9	1.1–3.5	**0.03**
Maternal intrapartum infection	7.3	4.2–12.7	**< 0.001**

Abbreviations: AOR: adjusted odds ratio, CI: confidence interval

5.3 STUDY III–IV: SYNKO

In Study III, on childbirth experience in induced labor, nulliparous women were compared with parous women. In Study IV, also on childbirth experience in induced labor, nulliparous women who underwent labor induction via BC were compared with nulliparous women who underwent labor induction via misoprostol.

5.3.1 MATERNAL CHARACTERISTICS

A total of 1,080 women were recruited, of whom 750 returned the CEQ survey questionnaire; thus, the response rate was 69.4%. In Study III, 711 women met the study criteria, and of these, 408 (57.4%) were nulliparous and 303 (42.6%) were parous.

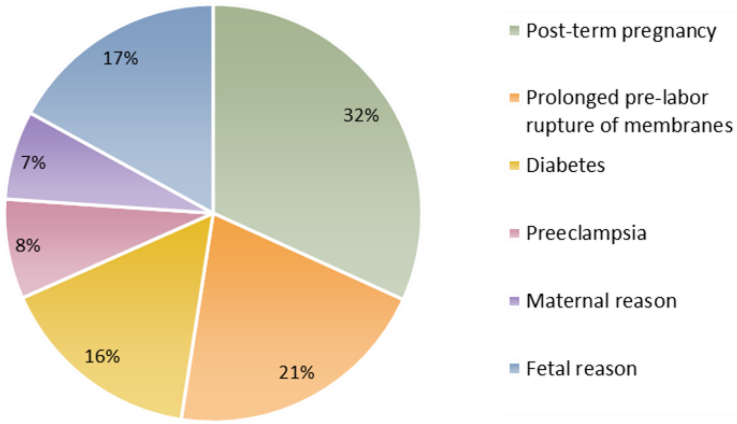
The nulliparous women more often had late- or post-term pregnancies (≥ 41+0 GW), had a Bishop score < 3 at the start of labor induction, and underwent cervical ripening, while the parous women more often had GDM (Table 18).

Table 18. Maternal characteristics that were statistically different across the groups compared in Study III (SYNKO), N = 711.

	Nulliparous		**Parous**		
	n = 408	**57.4%**	**n = 303**	**42.6%**	**p-value**
Maternal age ≥ 37 years	90	22.1	110	36.3	**< 0.001**
Gestational diabetes	108	26.5	106	35.0	**0.01**
Gestational age ≥ 41+0 weeks	182	44.6	96	31.7	**< 0.001**
Bishop score at the start of labor induction < 3	203	49.8	124	40.9	**0.02**
Cervical ripening	366	89.7	253	83.5	**0.02**

The most common method used for labor induction was BC (59.8% in nulliparous women and 71.9% in parous women, $p < 0.001$).

Figure 17 presents the indications for labor induction in Study III. Nulliparous women more frequently had labor induced due to post-term pregnancy (37.5% vs. 24.1%, $p < 0.001$) or PROM (25.2% vs. 14.5%, $p < 0.001$), and parous women more frequently had labor induced due to diabetes (22.4% vs. 11.0%, $p < 0.001$) and maternal (12.9% vs. 2.5%, $p < 0.001$) or fetal issues (20.5% vs. 14.5%, $p = 0.04$). The rates of labor induction for preeclampsia were similar in the two groups.



Diabetes: pregestational diabetes (type 1 and 2) or gestational diabetes.
Maternal reason: fear of childbirth, mother's request, medical condition unrelated to pregnancy, substance abuse.
Fetal reason: IUGR, cholestasis in pregnancy, breech presentation, macrosomia, oligohydramnios, fetal heart defect or other anomaly, successful external cephalic version for unstable lie, blood group immunization, decreased fetal movements, other unspecified risks in pregnancy, complications in an earlier pregnancy or delivery, polyhydramnios.

Figure 17 Indications for labor induction in Study III (SYNKO), N = 711.

In Study IV, a total of 571 women were recruited, of whom 408 returned the CEQ survey questionnaire. Thus, the response rate was 71.5%. Of these women, 362 met the study criteria: 244 (67.4%) underwent cervical ripening by BC and 118 (32.6%) by misoprostol.

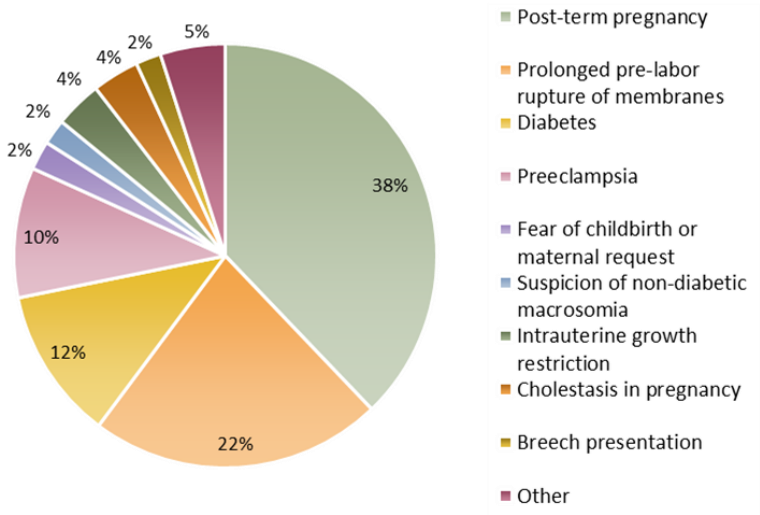
The women who had labor induced by BC were leaner, of more advanced gestational age, and had a riper cervix before labor induction (Table 19).

Table 19. Maternal characteristics that were statistically different across the groups compared in Study IV (SYNKO), N = 362.

	Balloon catheter		**Misoprostol**		
	n = 244	**67.4%**	**n = 118**	**32.6%**	**p-value**
Body mass index (median, IQR) kg/m²	24.0	5.0	25.7	7.7	**0.01**
Gestational age at the start of labor induction, weeks (median, IQR)	41.0	2.3	40.3	1.9	**0.003**
Bishop score at the start of labor induction (median, IQR)	4.0	3.0	3.0	2.0	**< 0.001**
Bishop score < 3 at the start of labor induction	118	48.4	81	68.6	**< 0.001**

Abbreviations: BMI: body mass index, IQR: interquartile range

Figure 18 presents the indications for labor induction in Study IV. Women with post-term pregnancies more often had labor induced by BC (45.5% vs. 22.0%, p < 0.001), and women with PROM more often had labor induced by misoprostol (43.2% vs. 12.3%, p < 0.001). In the other indications, no differences between the two methods were detectable.



Diabetes: pregestational diabetes (type 1 and 2) or gestational diabetes.
Other: oligohydramnios, fetal heart defect, reduced fetal movements, blood group immunization, maternal medical condition unrelated to pregnancy, substance abuse, other unspecified risks in pregnancy, successful external cephalic version for unstable lie.

Figure 18 Indications for labor induction in Study IV (SYNKO), N = 362.

5.3.2 OUTCOMES

Tables 20, 21, and 22 show different comparisons of delivery outcomes within the SYNKO study: nulliparous women vs. parous women (III) and labor induction by balloon catheter vs. misoprostol (IV) in nulliparous women.

In Study III, oxytocin use in labor induction or augmentation, epidural or spinal analgesia, episiotomy, intrapartum infection, operative vaginal delivery, and CS were more common in nulliparous than parous women (Table 20). The indications for CS did not differ (Table 21), nor did the neonatal results, apart from the higher rate of neonatal infection among the nulliparous women compared with the parous women (Table 22).

In Study IV, oxytocin use for labor induction was more common in women with labor induced by BC compared with misoprostol (47.8% vs. 30.5%, p = 0.002). However, oxytocin use in general, including for labor augmentation, was equally common in the groups (Table 20). The indications for CS and the neonatal outcomes were similar in the two groups (Tables 21 and 22).

Table 20. Delivery outcomes in Studies III and IV (SYNKO), N = 711 / 362.

	Study III, N = 711					Study IV, N = 362				
	Nulliparous		Parous			Balloon catheter		Misoprostol		
	n = 408	57.4%	n = 303	42.6%	p-value	n = 244	67.4%	n = 118	32.6%	p-value
Oxytocin use	369	90.4	205	67.7	**< 0.001**	222	91.0	105	89.0	0.55
Epidural or spinal analgesia	358	88.0	215	71.0	**< 0.001**	214	88.1	103	87.3	0.83
Unassisted vaginal delivery	205	50.2	257	84.8	**< 0.001**	122	50.0	56	47.5	0.65
Operative vaginal delivery	72	17.6	15	5.0	**< 0.001**	42	17.2	23	19.5	0.60
Cesarean section	131	32.1	31	10.2	**< 0.001**	80	32.8	39	33.1	0.96
Episiotomy	97	24.4	24	8.3	**< 0.001**	58	24.2	24	20.3	0.44
Manual removal of retained placenta	7	1.7	11	3.6	0.11	5	2.0	2	1.7	1.0
Sphincter injury	10	2.5	3	1.0	0.15	6	2.5	3	2.5	1.0
Intrapartum infection	30	7.4	8	2.6	**0.006**	20	8.2	6	5.1	0.28
Postpartum infection	13	3.2	4	1.3	0.11	8	3.3	3	2.5	1.0
Hemorrhage in vaginal delivery ≥ 1,500 in study III / ≥ 1,000 ml in study IV	29	7.1	22	7.3	0.94	35	21.3	21	26.6	0.36
Induction to delivery ≥ 24 h	264	64.7	91	30.0	**< 0.001**	161	66.0	96	81.4	**0.003**
Duration of labor ≥ 12 h	168	41.2	24	7.9	**< 0.001**	93	38.3	52	44.4	0.26

Table 21. Indications for cesarean section in Studies III (n = 162 / 711) and IV (n = 119 / 362) (SYNKO).

	Study III, n = 162					Study IV, n = 119				
	Nulliparous		Parous			Balloon catheter		Misoprostol		
	n = 131	80.9%	n = 31	19.1%	p-value	n = 80	40.2%	n = 39	32.8%	p-value
Fetal distress	42	32.1	9	29.0	0.74	23	28.8	15	38.5	0.29
Failed induction	43	32.8	14	45.2	0.20	29	36.3	11	28.2	0.38
Labor arrest	39	29.8	5	16.1	0.13	25	3.3	9	23.1	0.35
Other	7	5.3	3	9.7	0.41	3	3.8	4	10.3	0.21

Other reasons: nulliparous: infection n = 2; preeclampsia n = 3; hand presentation n = 1; foot presentation n = 1; multiparous: umbilical cord prolapse n = 2; infection n = 1, Balloon catheter: preeclampsia n = 1; infection n = 1; hand presentation n = 1, misoprostol: preeclampsia n = 2; infection n = 1; foot presentation n = 1.

Table 22. Neonatal outcomes in Studies III and IV (SYNKO), N = 711 / 362.

	Study III, N = 711					Study IV, N = 362				
	Nulliparous		Parous			Balloon catheter		Misoprostol		
	n = 408	57.4%	n = 303	42.6%	p-value	n = 244	67.4%	n = 118	32.6%	p-value
Pre-term (< 37 gestational weeks)	10	2.5	10	3.3	0.50	6	2.5	4	3.4	0.61
Macrosomia (≥ 4500 g)	12	2.9	11	3.6	0.60	9	3.7	2	1.7	0.30
Apgar 5 min < 7	21	5.2	10	3.3	0.22	11	4.5	8	6.9	0.36
Umbilical artery pH ≤ 7.05	5	1.2	3	1.0	0.76	3	1.2	2	1.7	0.66
Umbilical artery base excess ≤ -12.0	6	1.5	3	1.0	0.57	3	1.2	3	2.5	0.40
Neonatal intensive care unit admission	65	15.9	39	12.9	0.25	41	16.8	19	16.1	0.87
Infection	9	2.2	1	0.3	**0.04**	7	2.9	0	0	

In Study III, the delivery-related intervals were longer among the nulliparous women than among the parous women: the median induction-to-delivery intervals were 31.2 (IQR 25.0) hours vs. 14.1 (IQR 18.7) hours ($p < 0.001$), and the median labor durations were 10.8 (IQR 7.5) hours vs. 4.7 (IQR 4.1) hours ($p < 0.001$).

In Study IV, the median induction-to-delivery interval was shorter in women with labor induced by BC than in women who underwent induction via misoprostol, at 31.4 (IQR 21.6) hours vs. 36.9 (IQR 27.6) hours ($p < 0.001$), and more women who used a BC completed vaginal delivery within 24 hours from the start of induction (29.5% vs. 13.6%, $p < 0.001$).

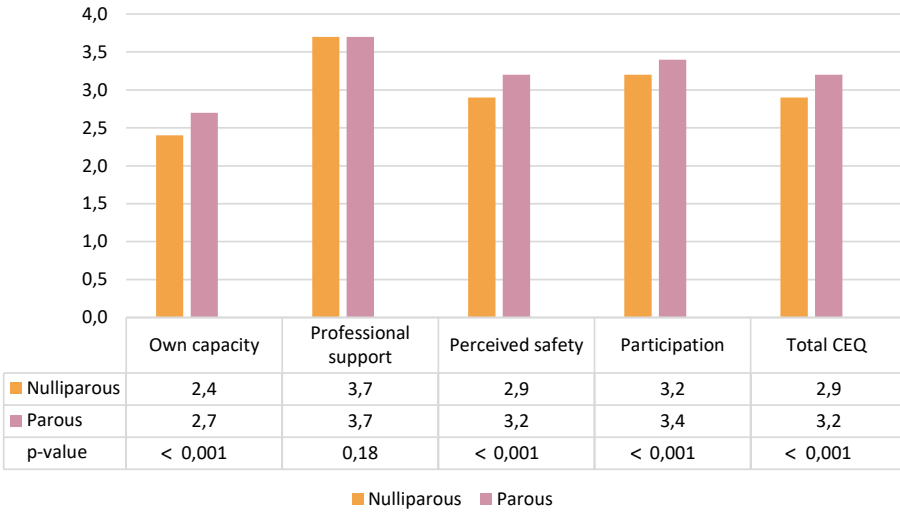
In Study III, 34.3% of the women delivered during the night, 24.5% during the day, and 41.2% during the evening (Table 23). The nulliparous women most often delivered during the night or evening, and the parous women most often delivered during the evening (Table 23). Compared by parity, the daytime delivery rates were higher among the nulliparous women, and the evening delivery rates were higher among the parous women.

Table 23. Delivery intervals in Study III (SYNKO), N = 711.

	Study III, N = 711				
	Nulliparous		**Parous**		
	n = 408	**57.4%**	**n = 303**	**42.6%**	**p-value**
Delivery during the night (00:00–07:59)	152	37.3	92	30.4	0.06
Delivery during the day (08:00–15:59)	115	28.2	59	19.5	**0.008**
Delivery during the evening (16:00–23:59)	141	34.6	152	50.2	**< 0.001**

5.3.2.1 The childbirth experience in Study III

The mean total CEQ score was 3.0 (SD 0.5), lower in the nulliparous women than in the parous women (Figure 19 and Table 24). The domain scores for "own capacity," "perceived safety," and "participation" were also all lower among the nulliparous women than among the parous women, but the score for "professional support" did not differ between the groups.



	Own capacity	Professional support	Perceived safety	Participation	Total CEQ
Nulliparous	2,4	3,7	2,9	3,2	2,9
Parous	2,7	3,7	3,2	3,4	3,2
p-value	< 0,001	0,18	< 0,001	< 0,001	< 0,001

Figure 19 Mean CEQ domain scores in Study III (SYNKO), N = 711.

Table 24. Mean CEQ domain scores in Study III (SYNKO), N = 711.

	Nulliparous (n = 408)		Parous (n = 303)		
	Mean	**SD**	**Mean**	**SD**	**p-value**
Own capacity	2.4	0.6	2.7	0.6	**< 0.001**
Professional support	3.7	0.5	3.7	0.5	0.18
Perceived safety	2.9	0.7	3.2	0.7	**< 0.001**
Participation	3.2	0.8	3.4	0.7	**< 0.001**
Total CEQ	2.9	0.5	3.2	0.5	**< 0.001**
Number of items responded to	21.8	1.3	21.7	1.5	0.70

Abbreviations: CEQ: Childbirth Experience Questionnaire, SD: standard deviation

On the individual items of the CEQ, the nulliparous women had lower scores in all items in "own capacity" and in all but one item in "perceived safety" and "participation" (Table 25). No differences in individual items in "professional support" were detectable.

Table 25. CEQ item descriptions in Study III (N = 711).

		Nulliparous (n = 408)		Parous (n = 303)		
	Item	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Own capacity						
Labor and birth went as I had expected	1	2.4	1.0	2.9	0.9	**< 0.001**
I felt strong during labor and birth	2	2.6	0.9	3.0	0.8	**< 0.001**
I felt capable during labor and birth	4	2.6	0.8	3.0	0.8	**< 0.001**
I was tired during labor and birth	5	1.8	0.9	2.3	1.0	**< 0.001**
I felt happy during labor and birth	6	2.5	0.8	2.8	0.8	**< 0.001**
I felt that I handled the situation well	19	3.3	0.8	3.4	0.7	**0.004**
As a whole, how painful did you feel your childbirth was? (VAS)	20	2.0	0.9	2.2	1.0	**0.01**
As a whole, how much control did you feel you had during childbirth? (VAS)	21	1.8	0.9	2.2	1.0	**< 0.001**
Professional support						
My midwife devoted enough time to me	13	3.8	0.5	3.7	0.6	0.96
My midwife devoted enough time to my partner	14	3.7	0.6	3.7	0.6	0.22
My midwife kept me informed about what was happening during labor and birth	15	3.7	0.6	3.7	0.6	0.12
My midwife understood my needs	16	3.7	0.6	3.7	0.6	0.50
I felt very well cared for by my midwife	17	3.8	0.5	3.8	0.5	0.73
Perceived safety						
I felt scared during labor and birth	3	2.5	1.0	2.7	1.0	**0.04**
I have many positive memories from childbirth	7	2.8	0.9	3.2	0.8	**< 0.001**
I have many negative memories from childbirth	8	2.5	1.0	3.0	0.9	**< 0.001**
Some of my memories from childbirth make me feel depressed	9	2.9	1.1	3.3	1.0	**< 0.001**
My impression of the team's medical skills made me feel secure	18	3.7	0.7	3.7	0.6	0.93
As a whole, how secure did you feel during childbirth? (VAS)	22	3.2	1.0	3.4	0.9	**0.02**
Participation						
I felt I could have a say whether I could be up and about or lie down	10	3.3	0.9	3.5	0.9	**0.01**
I felt I could have a say in deciding my birthing position	11	2.9	1.1	3.3	0.9	**< 0.001**
I felt I could have a say in the choice of pain relief	12	3.5	0.8	3.5	0.8	0.15

Abbreviations: SD: standard deviation, VAS: visual analog scale

A negative childbirth experience, defined in the CEQ by all the individual domain scores being in the most negative quartile of scores given, was detected in 7.3% (52 of 711) of the women: 8.8% (36 of 408) of the nulliparous and 5.3% (16 of 303) of the parous women (p = 0.08). In the multivariable analysis, a negative experience was associated with a CS and a hemorrhage ≥ 1,500 ml in vaginal delivery.

Table 26. Factors associated with a negative CEQ result (n = 52) in Study III (SYNKO), N = 711.

	AOR	**CI (95%)**	**p-value**
Nulliparity	1.2	0.6–2.4	0.63
Cervical ripening	1.0	0.4–2.7	0.97
Oxytocin use in labor induction or augmentation	1.5	0.6–3.8	0.38
Epidural use	0.6	0.3–1.2	0.15
Cesarean section	6.7	1.9–9.3	**< 0.001**
Hemorrhage ≥ 1,500 ml in vaginal delivery	2.8	1.1–7.5	**0.03**
Induction to delivery ≥ 24 h	0.9	0.4–1.8	0.68
Duration of labor ≥ 12 h	1.2	0.6–2.4	0.66
Daytime delivery	1.5	0.9–2.8	0.20

All variables significantly associated with a negative experience in Table 27 were chosen for this multivariable model.
Abbreviations: AOR: adjusted odds ratio, CI: confidence interval.

Table 27 shows the results of the multivariable analyses of factors associated with negative results in the individual CEQ domains. In these analyses, CS was associated with a negative experience in all domain scores of the CEQ, and a hemorrhage ≥ 1,500 ml in a vaginal delivery was associated with a negative experience in "own capacity" and "perceived safety."

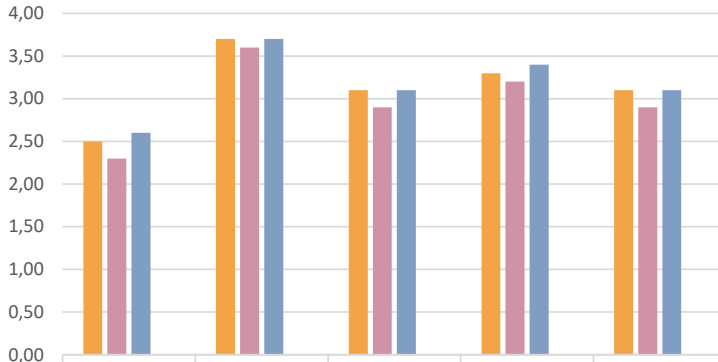
Nulliparity was associated with a negative experience in "own capacity." Cervical ripening was associated with a negative experience in "professional support," and oxytocin use in labor induction or augmentation was associated with a negative experience in "participation." Interestingly, the effect of epidural or spinal analgesia was negative on "own capacity" but positive on "professional support" and "participation." Daytime delivery negatively affected "own capacity" and "professional support."

Table 27. Factors associated with negative results in individual CEQ domains in Study III (SYNKO), N = 711.

	Own capacity (n = 212. 29.9%)			**Professional support (n = 206. 29.1%)**			**Perceived safety (n = 111. 15.6%)**			**Participation (n = 354. 50.2%)**		
	AOR	**CI (95%)**	**p-value**	**AOR**	**CI (95%)**	**p-value**	**AOR**	**CI (95%)**	**p-value**	**AOR**	**CI (95%)**	**p-value**
Nulliparity	1.6	1.0–2.4	**0.03**	1.0	0.7–1.5	0.89	1.1	0.7–1.9	0.72	1.4	1.0–2.0	0.09
Maternal reason for labor induction	0.5	0.2–1.3	0.15	0.6	0.3–1.3	0.17	0.1	0.02–1.0	0.05	1.5	0.8–2.9	0.20
Cervical ripening	1.4	0.8–2.7	0.24	2.0	1.1–3.5	**0.02**	1.7	0.7–3.8	0.24	1.4	0.9–2.4	0.15
Oxytocin use	0.9	0.5–1.5	0.67	1.2	0.7–1.9	0.56	1.3	0.7–2.7	0.41	2.1	1.4–3.5	**< 0.001**
Epidural or spinal analgesia	1.9	1.1–3.2	**0.03**	0.5	0.3–0.8	**0.004**	1.2	0.6–2.4	0.53	0.4	0.3–0.6	**< 0.001**
Operative vaginal delivery	1.0	0.6–1.8	0.94	1.3	0.8–2.4	0.31	0.8	0.4–1.7	0.56	1.6	1.0–2.7	0.07
Cesarean section	3.2	2.0–5.0	**< 0.001**	2.2	1.4–3.5	**< 0.001**	3.7	2.2–6.4	**< 0.001**	2.6	1.6–4.0	**< 0.001**
Maternal complication	1.1	0.6–1.9	0.73	1.1	0.7–2.0	0.63	1.4	0.8–2.7	0.25	0.8	0.5–1.4	0.54
Hemorrhage ≥ 1,500 ml in vaginal delivery	2.2	1.2–4.3	**0.02**	1.4	0.7–2.6	0.37	2.7	1.2–5.9	**0.01**	1.1	0.6–2.1	0.68
Induction to delivery ≥ 24 h	0.9	0.6–1.4	0.57	0.6	0.4–1.0	0.05	1.1	0.6–1.9	0.86	0.8	0.6–1.2	0.33
Duration of labor ≥ 12 h	1.5	1.0–2.3	0.06	1.2	0.8–1.9	0.33	1.1	0.5–1.8	0.90	0.9	0.6–1.4	0.61
Neonate transferred to the NICU	1.3	0.8–2.1	0.32	0.9	0.5–1.4	0.57	1.7	1.0–2.9	0.06	1.4	0.9–2.3	0.14
Daytime delivery	1.7	1.2–2.5	**0.008**	1.8	1.3–2.7	**0.002**	1.6	1.0–2.5	0.07	1.1	0.7–1.6	0.67

Abbreviations: AOR: adjusted odds ratio, CI: confidence interval, NICU: neonatal intensive care unit

Lower CEQ scores in daytime delivery were observable for all women compared with other times of day in "own capacity," "professional support," "perceived safety," and total CEQ score (Figure 20), and the results were similar in nulliparous and parous women.



	Own Capacity	Professional Support	Perceived Safety	Participation	Total CEQ
Night	2,50	3,70	3,10	3,30	3,10
Day	2,30	3,60	2,90	3,20	2,90
Evening	2,60	3,70	3,10	3,40	3,10
p-value (Day vs others)	< 0,001	< 0,001	< 0,001	0,06	< 0,001

Figure 20 Effect of time of day on mean CEQ scores in Study III, N = 711.

5.3.2.2 The childbirth experience in Study IV

The mean total CEQ score in this study, which consisted solely of nulliparous women, was 2.9 (SD 0.6). Comparing by method of cervical ripening, no differences were detectable in the domain scores (Figure 21) or the individual items.

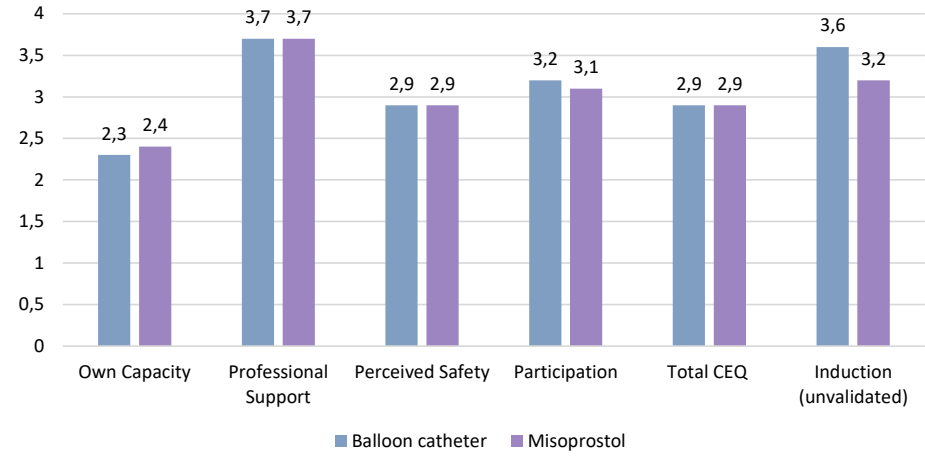


Figure 21 Mean CEQ domain scores and additional unvalidated "induction" domain score in Study IV (SYNKO), N = 362.

In the analysis of the unvalidated "induction" domain, the mean score for women with BC was 3.6 (SD 0.6), and for women with misoprostol, it was 3.2 (SD 0.6, $p < 0.001$). Women who used a BC were satisfied more often with the labor induction method chosen for them and would select the same method in the next pregnancy compared with women who used misoprostol (Table 28). In the item on the timing of labor induction (not included in the "induction" domain), 77.9% of the women were satisfied (78.3% of the women who used BC and 77.1% who used misoprostol, $p = 0.80$).

Table 28. Description of the unvalidated "induction" domain items in Study IV (SYNKO), N = 362.

	Balloon catheter (n = 244)		**Misoprostol (n = 118)**		
	Mean	**SD**	**Mean**	**SD**	**p-value**
I am satisfied with the labor induction method chosen for me	3.5	0.7	3.2	0.8	**< 0.001**
I would select the same labor induction method again in my next pregnancy	3.3	0.9	2.7	1.0	**< 0.001**
The information I received about labor induction was clear and sufficient	3.4	0.8	3.3	0.8	0.10
I was happy with the staff of the labor induction unit	3.7	0.6	3.6	0.7	0.15
I was satisfied with the pain relief I received in the labor induction unit	3.2	0.9	3.0	1.1	0.17

Abbreviations: SD: standard deviation

A negative childbirth experience affected 5.8% (21 of 362) of the women: 5.3% (13 of 244) who used a BC and 6.8% (8 of 118) who used misoprostol (p = 0.58). Using VAS scores 0–4 as an indicator, 10.5% (38 of 362) of the women had a negative childbirth experience: 11.1% (27 of 244) who used a BC and 9.3% (11 of 118) who used misoprostol (p = 0.59).

Table 29 shows a comparison of negative childbirth experiences as assessed using the VAS and CEQ. The women with VAS scores of 0–4 more often had negative childbirth experiences based on the total CEQ and in the individual domains "own capacity," "professional support," and "perceived safety" compared with women with VAS scores of 5–10. In the "participation" domain, a negative childbirth experience was equally common in the groups with VAS scores of both 0–4 and 5–10.

Table 29. Comparison of indicators of a negative childbirth experience.

	VAS 0–4 (n = 38)		**VAS 5–10 (n = 324)**		
	n	**%**	**n**	**%**	**p-value**
Negative: own capacity (n = 112)	28	73.7	80	25.9	**< 0.001**
Negative: professional support (n = 113)	18	47.4	90	29.1	**0.02**
Negative: perceived safety (n = 115)	32	84.2	77	24.9	**< 0.001**
Negative: participation (n = 100)	9	23.7	86	27.9	0.58
Negative score in all domains (n = 21)	5	13.2	14	4.5	**0.03**

Abbreviations: VAS: visual analog scale

5.3.2.3 Assessment of CEQ usability in the SYNKO study population by floor and ceiling effect

In Study III, a floor effect was seen in 50.0% (4 of 8) of the items in the nulliparous and 37.5% (3 of 8) of the items in the parous group in the "own capacity" domain. No floor effect was seen in the items in "professional support," and in the items in "perceived safety" and "participation," it was only seen in the nulliparous group, with 33.3% (2 of 6 and 1 of 3, respectively) of the items, and not in the parous group.

In Study IV, a floor effect was seen in 62.5% (5 of 8) of the items in "own capacity" and none of the items in "professional support" for both methods of labor induction. In "perceived safety," a floor effect was seen in 33.3% (2 of 6) of the items in the BC group and 50.0% (3 of 6) of the items in the group who used misoprostol. In "participation," 33.3% (1 of 3) of the items showed a floor effect among all women.

In both studies, the ceiling effects were pronounced in three of the four CEQ domains: "professional support," "perceived safety," and "participation." In Study III, all items in these domains showed a ceiling effect among all women, and in Study IV, all did so but for one item in the "perceived safety"

domain among women with labor induced via BC (number 8: *I have many negative memories from childbirth*). In Study III, the domain "own capacity" showed a ceiling effect in 25.0% (2 of 8) of the items in the nulliparous and 62.5% (5 of 8) of the items in the parous group. In Study IV, the domain "own capacity" showed a ceiling effect in 12.5% (1 of 8) of the items among women who used a BC and 25.0% (2 of 8) of the items among women who used misoprostol.

In the unvalidated "induction" domain, a floor effect was detectable for the item *I would select the same labor induction method again in my next pregnancy* in women undergoing labor induction by misoprostol, and a ceiling effect was detectable in all items (Table 30) for both methods of labor induction.

Table 30. Floor and ceiling effects in the additional items on labor induction in Study IV (SYNKO), N = 362

	Balloon catheter (n= 244)		**Misoprostol (n = 118)**	
	Floor %	**Ceiling %**	**Floor %**	**Ceiling %**
I am satisfied with the labor induction method chosen for me	1.7	63.5	3.4	42.7
I would select the same labor induction method again in my next pregnancy	6.2	48.1	15.5	20.7
The information I received about labor induction was clear and sufficient	4.6	58.9	4.3	49.6
I was happy with the staff of the labor induction unit	1.2	73.6	3.4	66.7
I was satisfied with the pain relief I received in the labor induction unit	7.5	47.3	12.2	45.2

5.4 STUDY V: SYKE

Nulliparous women randomized for labor induction at 41+0 GW were compared with nulliparous women randomized for expectant management and labor induction at 41+5–42+1 GW.

5.4.1 MATERNAL CHARACTERISTICS

A total of 381 women were included in the study, of whom 186 (48.8%) were assigned to the early induction group and 195 (51.2%) to the expectant management group. The mean estimated fetal weight on ultrasound examination was 3,688 (SD 314) g at the 41+0 GW screening visit. There were no differences between the groups in maternal characteristics.

Women in the early induction group had no other indication for labor induction than a prolonged pregnancy duration, similar to most women in the expectant management group who underwent labor induction at 41+5–42+1 GW. Some of the women in the expectant management group who had labor induced before their scheduled time were induced earlier by their own request, due to PROM, or for other reasons that required an intervention.

5.4.2 OUTCOMES

In the expectant management group, 45.6% (n = 89) of the women had a spontaneous onset of labor. The women in the early induction group delivered four days sooner on average than the women who were managed expectantly: the median GW were 41+1 (IQR 0.14) in the early induction group and 41+5 (IQR 0.43) in the expectant management group ($p < 0.001$).

The women who underwent early induction had a lower rate of operative delivery than the women who practiced expectant management, at 30.6% vs. 45.6% (RR 0.7 [95% CI 0.5–0.9], $p = 0.003$). The CS rates were 16.7% in the early induction group and 24.1% in the expectant management group, which does not yield a statistically significant difference (RR 0.7 [95% CI 0.5–1.0], $p = 0.07$; Table 31). Of the women who completed a vaginal delivery, the rates of operative delivery by vacuum extraction were lower in the early induction group than in the expectant management group (16.8% vs. 28.4%, $p = 0.02$; Table 31).

The rate of hemorrhage ≥ 1,000 ml was lower in the early induction group than in the expectant management group (Table 31), and among women who completed vaginal delivery compared with those who underwent CS (13.1% vs. 30.1%, $p < 0.001$). The rates of manual removal of a retained placenta, anal sphincter injury, and maternal infection were similar in the groups, but one woman in the expectant management group had eclampsia.

No perinatal deaths occurred, and the rates of adverse neonatal outcomes were similar in the groups who experienced early induction and expectant management, at 9.7% vs. 14.4% (RR 0.7 [95% CI 0.4–1.2], $p = 0.16$; Table 31).

No statistical difference between the groups was observed for mean neonatal weight, but more neonates weighted ≥ 4,000 g in the expectant management group (Table 31).

Table 31. Delivery outcomes in Study V (SYKE), N = 381.

	Early induction		**Expectant management**		
	n = 186	**48.8%**	**n = 195**	**51.2%**	**p-value**
Vaginal delivery	155	83.3	148	75.9	0.07
Unassisted vaginal delivery	129	83.2	106	71.6	**0.02**
Vacuum extraction	26	16.8	42	28.4	**0.02**
Cesarean section	31	16.7	47	24.1	0.07
Fetal distress	6	19.4	12	25.5	0.53
Failed induction	10	32.3	14	29.8	0.82
Labor arrest in the first stage	7	22.6	12	25.5	0.77
Labor arrest in the second stage	6	19.4	7	14.9	0.61
Other indication	2	6.5	2	4.3	0.67
Hemorrhage ≥ 1,000 ml	22	12.2	38	20.8	**0.03**
Hemorrhage ≥ 1,000 ml in vaginal delivery	16	10.6	22	15.8	0.19
Hemorrhage ≥ 1,000 ml in cesarean section	6	20.7	16	36.4	0.15
Manual removal of a retained placenta	5	2.6	7	3.6	0.62
Anal sphincter injury	5	2.7	10	5.1	0.22
Intrapartum infection	6	3.2	8	4.1	0.79
Postpartum infection	8	4.3	15	7.7	0.17
Adverse neonatal outcome	18	9.7	28	14.4	0.16
Apgar 5 min < 7	4	2.2	9	4.6	0.19
Umbilical artery pH ≤ 7.05	5	2.9	3	1.7	0.45
Umbilical artery base excess ≤ -12.0	7	4.1	4	2.3	0.35
Neonatal intensive care unit admission	11	5.9	21	10.8	0.09
Neonatal weight, g (mean, SD)	3,691	345	3,756	441	0.11
Neonatal weight ≥ 4,000 g	31	16.8	57	29.5	**0.004**

Protocol violations in the early induction group (included in analyses): spontaneous onset of labor before induction (n = 2) and labor induction at 40+6 (n = 1).
Protocol violations in the expectant management group (included in analyses): labor induction at 41+0 (n = 1), labor induction at 41+2 (n = 3), labor induction at 41+3 (n = 1), labor induction at 41+4 (n = 5), and cesarean section at 41+2 after eclampsia at home (n = 1).
Abbreviations: SD: standard deviation

In the exploratory analyses, the women who underwent early induction and those who experienced spontaneous labor in the expectant management group had statistically similar rates of unassisted vaginal delivery and CS (Table 32), whereas the women in the expectant management group who underwent labor induction at 41+5–42+1 GW had the lowest rate of unassisted vaginal delivery and the highest rate of CS among all groups (Table 32). The rates of adverse neonatal outcomes were not statistically different among the groups, nor were the rates of vacuum-assisted vaginal deliveries.

Table 32. Exploratory analyses of the mode of delivery and adverse perinatal outcome by type of labor onset in Study V (SYKE), n = 367.

	Early induction			**Expectant management**					
				Spontaneous onset			**Late induction**		
	n = 183	**49.9%**	**p-value** (compared with spontaneous onset)	**n = 89**	**24.3%**	**p-value** (compared with late induction)	**n = 95**	**25.9%**	**p-value** (compared with early induction)
Unassisted vaginal delivery	127	69.4	0.48	58	65.2	**0.004**	42	44.2	**< 0.001**
Operative vaginal delivery	26	14.2	0.09	20	22.5	0.82	20	21.1	0.15
Cesarean section	30	16.4	0.38	11	12.4	**< 0.001**	33	34.7	**< 0.001**
Adverse neonatal outcome	18	9.8	0.53	11	12.4	0.30	17	17.9	0.06

Early induction: labor induction at 41+0, spontaneous onset: uninduced onset at 41+1–41+5, late induction: labor induction at 41+5–42+1.
Those who experienced a protocol violation regarding the time of labor induction were excluded from the analyses.

6 DISCUSSION

This thesis explores how labor induction affects rates of vaginal delivery and adverse outcomes among women with the common pre-labor risk factors of prior CS, GBS colonization, nulliparity, and late- or post-term pregnancy. This thesis also explores the childbirth experience in women who undergo labor induction.

Labor induction rates have increased globally in recent years, and in Finland today, one in three women who enter labor are induced to do so.[1] Reasons for the increase vary, but older mothers and high obesity rates no doubt affect these recent developments.

Indications for labor induction seem to be on the rise along with increases in research, advancements in prenatal care, and rising awareness in the pregnant population of the possible risks associated with various aspects of pregnancy and related background factors. These new indications seem to either promote a possible benefit (such as lowering the risk of intrapartum CS) or aim to avoid unlikely harm (such as stillbirth), whereas the traditional indications can often be seen as avoiding likely harm (such as eclampsia). As indications for labor induction are more prone to be controversial in the case of these new indications, the role of the parturient in the decision-making process is even more essential than with the traditional indications for induction.

Additionally, induced labor usually requires more time and effort from both the woman in labor and the personnel taking care of her than a labor of spontaneous onset.[158] If labor induction was offered to more women than it currently is, this would require more personnel, especially when using labor induction methods that require surveillance in the hospital setting. However, implementing outpatient labor induction protocols more widely could help address this problem. Thus, the increasing rate of labor induction is not only a question of medicine but also of economics and psychology, and the current increase in the rate is evidently causing concern in the medical community.

6.1 TRIAL OF LABOR AFTER CESAREAN

6.1.1 MAIN FINDINGS

In our study, seven of ten women with past labor dystocia or a prior failed attempt at induction succeeded in their TOLAC, which suggests that a TOLAC is a feasible option to a scheduled repeat CS in these women with a prior CS. The success rate was very similar in a recent Finnish cohort study by Hautakangas et al. that placed a focus on uterine contractility and uterine rupture.[35] In our study, the rate of repeat CS was twofold in women with a prior CS for failed labor induction compared with women whose indication for their prior CS was labor dystocia in the first or second stage of labor (two in five vs. one in four women).

The rate of postpartum hemorrhage was rather high in our study compared with earlier research, but in agreement with other studies, the rate was naturally higher in the women who underwent an unsuccessful TOLAC compared with women who completed a VBAC. [200,285,286] The rates of maternal infection were consistent with previous studies, and our finding of a greater rate of maternal intrapartum infection in women who underwent a repeat CS was consistent with the higher rates of maternal morbidity and endometritis found among women who did not complete a TOLAC compared with women with success in a TOLAC.[30,285,287] In our study, the rates of adverse primary neonatal outcomes were rare, as in previous studies.[34,62,285]

Prior vaginal delivery is the greatest predictor of VBAC,[49] as evidenced by our study, in which nine of ten women who had a history of prior vaginal delivery had a successful TOLAC, while only seven of ten women who did not have a history of prior vaginal delivery had a successful TOLAC. The VBAC rate in the women with no history of prior vaginal delivery in our study was very similar to the rate in the 2023 Finnish Birth Register study, held in a comparable setting.[34]

Labor induction, compared with spontaneous labor, has previously been shown to negatively affect the success rate of TOLACs.[39,43,286,288] In our study, a negative effect of labor induction was only observed in women with no history of prior vaginal delivery, but not in women who had delivered vaginally in the past. Of the women with no history of prior vaginal delivery, six in ten had a successful TOLAC if labor was induced, whereas in the case of spontaneous labor, seven in ten women with no history of prior vaginal delivery achieved a successful TOLAC. In the study by Hautakangas et al., labor induction did not affect the VBAC rate, but the study did not compare the rates by history of prior vaginal delivery.[35]

In addition to the risk factors of no previous vaginal delivery and labor induction, a maternal height < 160 cm, neonatal macrosomia (≥ 4,500 g), and labor induction for suspected neonatal macrosomia were also associated with a failed TOLAC in our study. This finding is consistent with previous studies suggesting that lower maternal height is a risk factor for failed induction and

CS[54,55] and that a birth weight of > 4,000 g increases the risk of recurrent CS.[46–48] In addition, women with diabetes were at increased risk of a failed TOLAC, consistent with previous literature.[289] Additional risk factors for a repeat CS were a maternal age ≥ 37 years (p = 0.05) and a gap of more than two years since the previous CS. Advanced maternal age is a known risk factor for CS, and the older women may have also had a longer period between labor incidences than women with shorter intervals.[25,26] In addition, labor induction for PROM or fetal issues was associated with CS. In such pregnancies, CS for infection or fetal distress may be more common.[50,289,290,291]

The uterine rupture rate was less than one percent in our study, making it lower than the rate recorded by Hautakangas et al. Although labor induction is often suggested to increase the rate of uterine rupture,[35,286–288,290,291] this was not evident in our study, in which three of the four uterine ruptures occurred after a spontaneous onset of labor and only one occurred after labor induced by AROM and oxytocin infusion.

As discussed earlier, the method of choice for cervical ripening in women with a history of previous CS is a balloon catheter. Hautakangas et al. found, on the contrary, that a balloon catheter instead of misoprostol increased the risk of uterine rupture in univariable analysis. This effect may, however, be due to unfavorable cervices requiring cervical ripening, or even to the oxytocin used for labor augmentation.[35,288] Moreover, in our study, some women received misoprostol despite a uterine scar, and no uterine ruptures occurred. In our study, the women with uterine ruptures had not completed prior vaginal delivery, as in Hautakangas et al.[35] Prior vaginal delivery has also been suggested to decrease the risk of uterine rupture.[287,292]

6.1.2 STRENGTHS AND WEAKNESSES

The retrospective design is undeniably the major weakness of this study. The strengths include the relatively large sample size and the systematic and detailed EHR system used at our hospital, which enabled accurate data collection.

In the retrospective studies included in this thesis, the labor induction management practices were somewhat dependent on the treating obstetrician, unlike in the prospective studies, wherein the renewed hospital guidelines on labor induction were in use. This variation in management practices reflects the reality in labor wards, where protocols and personnel change over time. It may, however, be seen as a weakness of this study.

The design of Study I, which did not include women who delivered via a planned CS, may have caused bias, as women who were estimated to have a low probability of completing a VBAC may have been advised to have a repeat CS instead of a TOLAC. We regret not having data on neonatal birthweights from the earlier deliveries via CS, as increased birthweight in a subsequent pregnancy has been suggested to increase the risk of repeat CS.[63,293] In addition, we lacked data on estimated fetal weight at TOLAC, which, unlike

the actual birthweight, may be determined pre-labor. In the case of labor induction, estimated fetal weight is a key factor in the assessment of candidacy for vaginal delivery and, thus, is almost invariably noted. As a surrogate to estimated fetal weight, we used birthweight, which is available only after delivery. However, comparing the birthweight of a past delivery through CS due to labor dystocia to the estimated fetal weight in the current pregnancy has not been proven useful in predicting VBAC.[39] We also lacked data on cervical dilation at the prior CS. In previous studies, greater cervical dilation at the time of CS increased the likelihood of a successful TOLAC in the subsequent pregnancy.[40,44,45]

6.1.3 INTERPRETATION

Women with a single prior lower-segment CS are usually successful in TOLACs in Finland; hence, liberally offering TOLACs seems reasonable. However, the traditional risk factors associated with CS are also applicable to these women. No previous vaginal delivery, labor induction, lower maternal height, diabetes, advanced maternal age, obesity, and fetal factors such as macrosomia or vulnerability to infection or intrapartum distress may all increase the risk of CS for these women.

As the maternal and neonatal risks of an unsuccessful TOLAC are higher than the risks of a scheduled repeat CS,[31,33,294] individual assessment and discussion with the pregnant woman about her preferences regarding the upcoming labor and delivery are paramount. This is especially true if multiple risk factors are present.

The ACOG suggests that women with a 60%–70% likelihood of achieving VBAC experience the same or less maternal morbidity than women who have an elective repeat CS.[33] In our study, the only two subgroups not advised to have a TOLAC based on this figure were 1) the women with no history of prior vaginal delivery undergoing labor induction in their current pregnancy and 2) all women with a history of failed labor induction who also underwent labor induction in their current pregnancy. Whether or not these rates of six in ten or five in ten women with a VBAC justify a TOLAC should be decided individually.

As the rate of labor induction is on the rise, the rate of women with a history of CS for labor dystocia or failed labor induction may also be on the rise. As many pregnancy complications that call for labor induction are likely to also affect the next pregnancy (such as diabetes, preeclampsia, or prolonged pregnancy), some of these women will be assessed for a repeat trial of labor induction. Hence, for these women with a history of failed labor induction, among whom the TOLAC success rate was 52%, opting for an elective CS may seem a reasonable choice for many obstetricians and pregnant women alike, although the opposite conclusion may also be reached. It is, thus, important to acknowledge the psychological factors that motivate the choice of delivery plan among these women and to be supportive of their decision.

6.2 INFECTIOUS MORBIDITY IN LABOR INDUCTION BY BALLOON CATHETER

6.2.1 MAIN FINDINGS

Labor induction by BC appears safe in GBS-positive women with intact amniotic membranes when prophylactic antibiotics are administered at the onset of labor or the rupture of membranes. In our study, the rate of maternal intrapartum infection was lower in GBS-positive women than in GBS-negative women, and the rates of maternal postpartum and neonatal infection did not differ by GBS status.

The prevalence of GBS in our study population was in line with previous research.[113,295] Some characteristics of GBS-positive women, such as obesity, were consistent with previous studies,[296] while others, such as advanced maternal age, were not.[295]

To our knowledge, no prior studies have focused on BC use among GBS-positive women. One study suggested that membrane stripping is safe in women colonized with GBS,[297] but, on the contrary, another study found an increase in cervical pathogenic microbes such as GBS, *Candida albicans*, *Candida glabrata*, and *Gardnerella vaginalis* during BC retention. [121] Studies (other than ours) on infectious morbidity in GBS-positive women are still lacking. However, a recent Finnish cohort study by Kruit et al. that explored BC use among women with PROM found that GBS positivity was not associated with an increased risk of maternal or neonatal infection when prophylactic antibiotics were used.[298]

In our search for an optimal cut-off point for the duration from ruptured membranes to delivery, the ≥ 12 h interval used in previous literature proved to be a good candidate, demarcating the point at which infection risk begins to increase.[299,300] In multivariable analyses, an interval from the rupture of membranes to delivery ≥ 12 h was associated with maternal intra- and post-partum infection and neonatal infection. Our results are in line with previous studies, in which a prolonged duration of membrane rupture has been associated with infectious morbidity.[109,300,301]

The prophylactic antibiotics given to GBS-positive women may explain the lower rate of maternal intrapartum infection in our study, as no differences were detected between the GBS-negative and GBS-positive women in the duration of ruptured membranes, duration of labor, or induction-to-delivery interval. Interestingly, in a 2015 meta-analysis of PROM, no differences in infectious morbidity were seen in the groups who received prophylactic antibiotics and those who received none if the latency period from PROM to delivery was < 12 h. [299] Only at a latency of ≥ 12 hours did women who received prophylactic antibiotics exhibit a lower rate of chorioamnionitis and endometritis than women who received no prophylaxis.[299]

The antibiotic protocol for GBS colonization was very well followed in our study population, and the one percent without adequate prophylaxis delivered

shortly after admission to the labor ward, which explains the failure to follow protocol. The criteria for intrapartum infection were met for less than 50% of the GBS-negative women who received antibiotics, and the others received them at the discretion of the treating obstetrician for elevated body temperature or elevated infection markers. As antibiotic use affects both the mother and the fetus, this use should be carefully assessed.[302–305] However, given that the GBS-negative women in our study had a greater risk of intrapartum infection, antibiotic use in case of a prolonged duration of ruptured membranes could be beneficial if signs of infection are present, even if not all criteria for infection are strictly fulfilled.

Additional risk factors for maternal intrapartum infection included GBS negativity, nulliparity, gestational age at delivery ≥ 41 weeks, and a very unripe cervix (Bishop score < 3) at the start of labor induction. These factors are consistent with earlier studies, except for the interesting association with GBS negativity.[157,306] Also echoing previous studies, CS was associated with post-partum endometritis.[306,307] The association of maternal intrapartum infection, nulliparity, a longer rupture-of-membranes-to-delivery interval (≥ 12h), and GDM with neonatal infection is also in line with previous research.[308,309]

In our study, the duration of BC retention was not linked to infectious intrapartum or neonatal morbidity, but a retention time ≥ 6.5 h showed a trend toward a higher risk of post-partum endometritis in GBS-positive women. The reasonable conclusion to draw from this, in light of the known increase in pathogenic microbes during BC retention,[121] is to favor a swift labor-induction process with minimal delays and remain aware of the potentially increased risk of postpartum endometritis in women with a prolonged duration of BC retention.

6.2.2 STRENGTHS AND WEAKNESSES

The major weakness of this study is the retrospective design. Additionally, excluding women who underwent labor induction via misoprostol may be seen as a weakness that introduces bias, as women regarded as having a high risk of infection may have been treated with misoprostol instead of a BC.

The most important strengths of this study are the relatively large sample size and the systematic and detailed EHRs used for data collection. The universal rapid screening testing for GBS, which enabled correct diagnoses of carrier status to be made at the time of delivery with relative accuracy, and the comprehensive antibiotic prophylaxis are regarded as important strengths. The variation in labor induction management practices adopted for the retrospective studies can either be seen as a strength or a weakness, as discussed previously.

6.2.3 INTERPRETATION

Regarding maternal and neonatal infectious morbidity, labor induction via BC is safe in women colonized with GBS when prophylactic antibiotics are administered at the onset of labor or membrane rupture. According to our findings, the optimal time from rupture of membranes to delivery is < 12 h, at least in women not protected by antibiotics. Hence, cervical ripening should be initiated well before AROM. Moreover, as increasing BC retention time may subject women to infectious morbidity, BCs should be removed from the vagina as soon as the cervix has been ripened and the BC can be pulled through the cervix. Fortunately, the importance of avoiding unnecessary breaks in labor induction has been widely acknowledged, and many labor induction guidelines today aim for an efficient and effective protocol.

Antibiotic resistance is a global problem, and antibiotics should only be given with good reason. However, penicillin, the first-line prophylaxis for GBS, is a narrow-spectrum antibiotic that can potentially prevent a life-threatening neonatal infection. Hence, using penicillin instead of more broad-spectrum antibiotics such as cefuroxime or clindamycin might decrease the probability of antibiotic resistance and prevent infections.[114,310–312] Challengingly, many women report an allergy to penicillin when admitted to the labor ward but are, in fact, penicillin tolerant if tested properly. This leads to an unnecessary use of broad-spectrum antibiotics. Hence, there should be greater awareness of allergy diagnoses and testing before labor in primary health care.[313–315]

6.3 THE CHILDBIRTH EXPERIENCE

6.3.1 MAIN FINDINGS

Women with induced labor rated their labor and delivery experiences relatively positively, with the parous women scoring slightly higher than the nulliparous women.

In the multivariable analyses, emergency or crash emergency CS was the factor most associated with a negative childbirth experience, which is consistent with earlier research.[260,266,316] This negative impact of CS on the childbirth experience emphasizes the importance of safely preventing the primary CS—a goal that is conventionally justified for medical and monetary reasons.[5,279,317] Surprisingly, operative vaginal delivery was not associated with a negative childbirth experience in our study. Perhaps in the context of labor being induced and already medicalized, additional need for an obstetrician is noted less negatively than in a labor of spontaneous onset.[263]

Of the other potential maternal complications assessed in this study, only postpartum hemorrhage ≥ 1,500 ml after vaginal delivery was associated with a negative childbirth experience. This association of dissatisfaction with childbirth has also been seen in prior studies.[263,265,316] The association was pronounced in the domains "own capacity" and "perceived safety," perhaps due to the physiological effects of hemorrhage (tachypnea, tachycardia, weakness, sweating). Such a state may, no doubt, make the woman feel fearful and out of control. Effective prevention of postpartum hemorrhage and empathetic support during and after the acute emergency are thus paramount.

According to our study, nulliparous women, like parous women, mainly have negative childbirth experiences due to labor- and delivery-related factors. The only domain in which nulliparity was associated with a negative childbirth experience in the multivariable analyses was "own capacity," in which the nulliparous women less often reported that they felt strong and capable, and that labor and birth went as expected.

In earlier studies, antenatal education and birth preparedness have been associated with greater satisfaction, improvement in the sense of control and confidence in giving birth, and lower rates of fear of birth, depression, anxiety, and stress.[316,318,319] At the time of our studies, public prenatal classes offered to nulliparous women in the HUS area were very brief and medically oriented, at times comprising only a few hours of online videos or group classes led by a public care nurse. As this may not provide women with adequate support, the decline in public prenatal classes has led to a booming market of private paid classes, which are only available for women with a special interest in the topic and the necessary financial resources. These classes often focus on the woman's inner strength, nonmedical methods of pain relief, relaxation, and methods of making labor an empowering experience.

The importance of prenatal information and classes has newly been emphasized in our maternity care,[320] but in some hospitals, most classes are

offered only on request and only to women with a fear of labor. Thus, many women who do not express their fear or have not really thought about labor at the time of inquiry are left without support. The recent developments in the HUS area on the subject are nonetheless noted with delight, although proper universal prenatal classes are still lacking in this area.

In Study IV, which compared BC and misoprostol use by nulliparous women, the childbirth experiences were similar across the groups. Our results are comparable to those of the SWEPIS, in which no differences in CEQ scores between the two methods were found.[250]

In the assessment of labor induction, however, women preferred BCs over misoprostol, which contrasts with two earlier studies in which women preferred misoprostol over BCs in a future pregnancy.[201,321] One reason for the preference for BCs in our study may be the shorter labor-induction-to-delivery interval in women who use a BC, which may have been due to a higher Bishop score at the start of labor induction. Although the negative effect, noted in other studies, of a longer induction-to-delivery interval or longer labor on childbirth experience was not seen in our research,[257,264,316] the shorter intervals may still be one reason why BCs were favored.

The effect of labor induction location is also one explanation for the differences in preference for BC or misoprostol. In our study, most women who used BCs were offered outpatient protocol, and all women who used misoprostol were treated as inpatients. Previously, outpatient induction by BC has been suggested to be preferred by women compared with inpatient induction by dinoprostone,[322] and many women prefer to stay home during early induction.[188,323] However, a recent Finnish study on BC induction found that women who underwent induction as outpatients were slightly less satisfied and more anxious than women in the inpatient setting, although both groups had generally good experiences of induction and would choose BC induction again in a subsequent pregnancy.[189] Offering outpatient induction should not, therefore, prevent women from staying at the hospital if desired.

In Study III, in which labor induction by AROM and oxytocin was also possible, cervical ripening was associated with a negative experience in "professional support," highlighting the need for providing information and personal support during the induction process, which may take several hours or even days.[316]

Being able to choose the induction method used has been suggested to lead to better satisfaction in labor induction, with no differences when comparing between methods.[316,324] In our study, the choice of method was based on joint decision-making by the obstetrician and the woman. Some women with labor induced by misoprostol may have preferred BC but, due to a very unripe cervix and failed BC placement, were administered misoprostol instead, possibly leading to a worse experience.

Oxytocin use has previously been shown to negatively affect the childbirth experience, especially in the "own capacity" domain.[248,249,257,260,325] In previous studies, augmentation of labor has mainly yielded negative results for

"perceived safety."[248,249,257,325] In our study, "participation" was the only domain negatively affected by oxytocin use; this association was also identified in the original validation study of CEQ, unlike in some other studies.[248,249,257,325] As many studies on childbirth experience mainly consist of women who spontaneously enter labor, these differences in results may imply that the way women enter labor (spontaneously or via induction) also modifies women's experiences of some aspects of labor management and other events during the labor.

The negative impact of oxytocin use in "participation" may be associated with the intravenous lines necessary, which prevent free movement during labor and make staying in bed an easier option compared with being up and about. In the studies included in this thesis, a vast majority of the women were administered oxytocin, making the possible hindrance of movement a very common problem in the labor ward. Thus, helping women stay active despite intravenous lines is one factor that might improve women's perceptions of being active participants in their own labor.

The "own capacity" domain was negatively affected by epidural or spinal analgesia use, echoing an earlier Swedish study.[325] It is well known that some women prefer nonmedical pain-relief methods over medical ones and tend to revere unmedicated labor. As labor progresses, however, most women opt for epidural or spinal analgesia, as seen in our studies, in which eight or nine of ten women chose this form of pain relief. This change of plans in pain relief may negatively affect the woman's perception of their self-capability. However, in our study, epidural or spinal analgesia use was a protective factor against negative experiences in "professional support" and "participation." We hypothesize that the positive effect of efficient pain relief methods in these domains is related to allowing women to better observe their surroundings and interact with the staff when their focus is not solely on the labor pain.

Lower CEQ scores in daytime delivery were observable for all women compared with other times of day in "own capacity," "professional support," "perceived safety," and total CEQ score. Daytime delivery has previously been suggested to be better for reasons such as better staffing and improved experience, but no positive effect on the childbirth experience was seen in our study.[223,224] As our study included only women with induced labor, those who delivered during the daytime may have spent the previous night at the hospital, awake with painful contractions, which may lead to a more negative experience relative to women with a spontaneous onset of labor, who may have spent the previous night at home and perhaps even slept. It is also possible that administrative and educational events, as well as non-emergency operations that only take place in the daytime, prevent staff from attending to the woman in labor as well as at other times of the day. Additionally, midwives change shifts in the afternoon, leading to a change in midwife during labor, which interrupts the continuation of care.[325]

In Study IV, fewer women had negative childbirth experiences according to assessment with the CEQ than with the VAS. Thus, using a negative CEQ result

instead of a VAS score of 0–4 as a criterion for a negative childbirth experience would encourage fewer women to seek additional post-partum support.

A Swedish study published in early 2023 explored the question of what women consider when rating their childbirth experience if a single-item measure is used, such as a 10-point NRS or VAS.[255] The researchers compared CEQ2 results with NRS ratings and found that the NRS was mostly comparable to the CEQ2 item "perceived safety" and, to a lesser extent, to "own capacity" and "participation." The domain "professional support" did not seem to be a factor that women assessed when the NRS was used. In our study, the CEQ and VAS scores were comparable in the domains "perceived safety" and "own capacity," and somewhat in "professional support," but not in "participation." According to these findings, the VAS used at HUS seems to most accurately reflect the woman's perception of her capacity to give birth and the safety of the setting, but not the level of professional support or opportunity to be an active participant and decision-maker in her own labor and birth.

The overall childbirth experience may be neutral or even positive, even if some aspects of the experience are negative. This was also seen in our study, in which many women with VAS scores of 5–10 had a negative experience in at least one CEQ domain. The VAS being "too high" is perhaps partly due to the complex nature of the experience, but it may also be related to the survey being administered a day or two after delivery, when women often feel relieved that the labor is now over, regardless of possible hardships they encountered. The presence of a midwife may also influence the scoring if the women feel that they should be polite and report higher scores than they feel. In our study, the women filled out the CEQ in the privacy of their homes and returned it within one month after delivery, allowing them to thoroughly assess their experiences.

A previous study on the timing of CEQ administration showed that when the questionnaire was answered during the first week postpartum and again three months later, the total CEQ score and the two domains comparable to those of the VAS, "own capacity" and "perceived safety," showed similar results. [252] The scores in "professional support" and "participation" that were not comparable to the CEQ in our study decreased over time. Hence, administration of the simple, numerical VAS in the postpartum ward seems a useful substitute for a more profound CEQ a month later.

6.3.2 STRENGTHS AND WEAKNESSES

The strengths of the SYNKO study are the prospective design, relatively large sample size, and uniform protocol for labor induction and labor management. In addition, as in retrospective studies, meticulous data collection from EHRs is regarded as an important strength.

The recruitment efficiency is an obvious weakness of this study, since not all women who underwent labor induction participated, and not all women recruited answered the questionnaire, which may have led to bias. In our study, the response rates for the women recruited were 69%–72%. Traditionally, survey response rates above 60%–70% have been considered sufficient and reliable. [326] Hence, even though not all women who underwent labor induction were recruited, the response rates among the participants were good.

Not including women with a spontaneous onset of labor or elective CS could also be seen as a weakness, as could the lack of randomization in the method of labor induction. Furthermore, we did not have data on outpatient cervical ripening or the presence of a support person during labor. However, in Study III, 98% of the participants answered the item "My midwife devoted enough time to my partner," suggesting that they had someone with them for support.

In Study IV, the sample size did not allow for a multivariable analysis to be conducted to better evaluate the factors that created a negative childbirth result, which can be regarded as a weakness. However, the rates of many known risk factors for a negative childbirth experience, such as CS, extended labor, oxytocin use, maternal complications, hemorrhage, and neonatal complications, such as admission to NICU, were similar in the groups of women with cervical ripening via BC or misoprostol, [248,249,257,260,263–266] so we believe that the groups are comparable in terms of these possible confounding factors.

Surprisingly, the choice of a questionnaire also appears to be a weakness. The CEQ showed notable floor and ceiling effects, which means that it is not an optimal tool for distinguishing the most negative and most positive childbirth experiences in a population consisting solely of women undergoing labor induction. Still, while not optimal, the CEQ was better at identifying negative childbirth experiences, which seems to be the most important factor, given our goal of being able to direct additional support to the women who need it.

As there are no questionnaires especially developed for women undergoing labor induction, at least to the author's knowledge, the renewed version of the CEQ, the CEQ2, may be better than the original version.[258] The CEQ2 differs somewhat in the domains "professional support" and "participation," and it was used in a population with a very high rate of labor induction, namely that of the SWEPIS (which had a labor induction rate of 64.0%).[102] In future studies on labor induction, using the updated CEQ2 might be beneficial. Unfortunately, it is not yet available in Finnish.

The added items on labor induction used in Study IV would also not be useful in the future due to the extreme ceiling effect and the item wordings, which address women's satisfaction rather than the experience.

VAS scores are routinely recorded at HUS after childbirth, and they should be assigned using a visual scale. In real life, however, an NRS score, expressed in whole numbers, is sometimes sought instead. These two methods may seem interchangeable, and in the clinical setting, they may well be. For research purposes, however, inconsistent use of tools may result in discrepancies between analyses. In this thesis, the term VAS is used, as it is not possible to know exactly which method was used for each woman. This is another potential weakness of the study.

In addition, at HUS, VAS scores are collected only a few days postpartum, when women are often very tired and just feel relieved that the labor is over. Hence, the childbirth experience in its fullness may not have been fully processed, and some may therefore rate their experience as overly positive. [252]

6.3.3 INTERPRETATION

Good obstetric care is key in avoiding a negative childbirth experience, as seen in our study, in which CS and postpartum hemorrhage after vaginal delivery were the factors most associated with a negative childbirth experience. However, this is not all there is to it. Acknowledging labor induction, especially when cervical ripening is needed, as a potential cause of a negative childbirth experience emphasizes the need for adequate and repeated information and support for women during the process. The choice between BC and misoprostol may not be justified by differences in childbirth experiences, but some factors in the induction experience seem to differ, with BC appearing to be the favored option at present.

In our studies, daytime delivery did not seem to lead to a better childbirth experience for women who underwent labor induction and, hence, may not be a factor that should be emphasized in deciding the time of day to induce. The VAS, routinely administered to all women at HUS after delivery, seems to be a suitable tool for crudely evaluating the childbirth experience, and may best represent women's perceptions of their own capacity to give birth and the safety of the hospital setting. For a more profound analysis of the experience, the CEQ may not be the best tool for women who undergo labor induction, but it does pick out those with a negative experience. Moreover, assessing labor induction experiences using the items added to the CEQ in our study may not be recommended.

Creating an atmosphere of safety and self-capability in the labor ward begins in society and the health care system well before the woman sets foot in the hospital. Thus, every person, whether it be a journalist writing about a case of labor in which everything went wrong or a friend who does not get along with the midwife, should consider how their words affect women and families about to have children. This does not mean that realistic stories

should not be told at all, but rather that the unexpected and cruel nature of life and childbirth should be remembered, and stories adjusted accordingly: even today, labor and delivery are a threat to women's health, even to their lives, and not everything will go according to plan. Feeling safe and capable during childbirth is a paradox, but working towards achieving it should nonetheless be one of the priorities of modern obstetrics.

Another priority should be women-centered care, which focuses on the individual's preferences and a personalized evaluation of the possible risk factors present and eventually leads to informed and joint decision-making. This is not easy since obstetrics is an especially unpredictable field of medicine and pregnant women are often emotionally and psychologically vulnerable. In addition, as many women today are deprived of adequate information and preparedness for their labor, they may not have the resources needed for agency and shared decision-making.

Traditionally, childbirth has been both a physiological process and a social event, unlike today, when the tremendous advancements in maternal and neonatal care have made it a medical event that takes place inside hospital walls. There is no need to go back in time, abandon modern obstetrics, and return to the era of high maternal and neonatal mortality rates, but listening to voices not often heard in the medical community could still be beneficial. Supporting women's inner strength and capacity to give birth, even in very medicalized contexts, which an induced onset of labor essentially is, could be one important element of a better childbirth experience. Hence, whenever possible, listening to the woman and supporting her role as an active agent should be encouraged by our hospital protocols.[270] Moreover, we should be on the same team and work for and with women for the common goal: a safe delivery with a happy and healthy mother and an unharmed baby.

Midwives and obstetricians are key in improving the childbirth experience, and quality care is only possible with adequate staffing.[327] Thus, hospital processes and staffing should be organized accordingly.[226,328,329]

6.4 LATE-TERM LABOR INDUCTION FOR NULLIPAROUS WOMEN

6.4.1 MAIN FINDINGS

Labor induction at 41+0 GW yielded a reduced rate of operative deliveries compared with expectant management: seven of ten women in the early induction group completed an unassisted vaginal delivery, whereas five of ten women undergoing expectant management completed an unassisted vaginal delivery. The rates of CS were not statistically different in the groups. However, among those who completed a vaginal delivery, operative delivery by vacuum extraction was needed in nearly one in three women in the expectant management group, but only in one in six in the early induction group. In addition, more women in the expectant management group had hemorrhage ≥ 1,000 ml, which may be explained by the trend of rising CS rates relatively to early induction cases.

The rates of adverse neonatal outcomes were not statistically different in the groups who underwent early induction and expectant management. However, women in the expectant management group more often delivered a neonate weighing ≥ 4,000 g, presumably due to the four-day difference in gestational age at delivery.

In the exploratory analyses, those who spontaneously entered labor before the scheduled late induction at 41+5–42+1 GW in the expectant management group had the lowest rate of CS, at only one in ten women. However, statistically, the CS rate did not differ from that of the early induction group. When comparing the groups who underwent early induction and spontaneous onset, the rates of unassisted vaginal delivery, operative vaginal delivery, and adverse neonatal outcomes were statistically similar.

In the exploratory analyses, labor induction at 41+5 GW onwards led to the highest CS rate in our study, with one in three women having a CS—comparable to the study on which we based our power calculations.[17] Additionally, in this late induction group, the rate of unassisted vaginal delivery was the lowest, whereas the rates of operative vaginal delivery and adverse neonatal outcomes were not statistically different compared with the other two groups.

In earlier research, the rates of hypertension, preeclampsia, and eclampsia have been found lower in women who underwent earlier induction compared with those who pursued expectant management.[102,133] One case of eclampsia was also observed in the present study. This woman, according to the study protocol, had no signs or symptoms of preeclampsia at the initial visit at 41+0 GW, was randomized to undergo expectant management, had eclampsia at home at 41+2 GW, and then underwent CS the same day.

6.4.2 STRENGTHS AND WEAKNESSES

A major strength of our study is the clinically relevant study setting, in which the current treatment protocol in Finland, expectant management up to 41+5–42+1 GW, was compared to early induction at 41+0 GW, a standard already followed in some countries. Another important strength of our study was the study website, in which information on the study, labor induction, and late- and post-term pregnancy was available to all interested, including both pregnant women and maternity care professionals. We also encouraged participants to approach the researchers through our website for more information to support informed decision-making about whether to participate.

The multicenter setting, which included all five university hospitals and the largest central hospital in Finland, can also be considered a strength. The multicenter setting did, however, lead to some discrepancies in randomization and data collection, which is a weakness of this study and needs to be considered in future studies that use several study sites.

Our original recruitment target of 400 women and the final number of analyzed cases, 381, may be seen a weakness of the study, although our hypothesis that there would be no increase in the CS rate was validated, and we saw a reduction in the rate of operative delivery. The conclusion that there was no statistical difference in the CS rate may, however, be due to an insufficient sample size, as it could also be possible to infer a lower rate of CS in the early induction group.

We did, in fact, aim to recruit a larger number of participants after the interim data analysis, as during that time, in autumn 2019, all participating hospitals had started to recruit women, and the recruitment was progressing well. Unfortunately, not long after, organizational changes at some of the hospitals and the Covid-19 pandemic negatively affected our ability to recruit women in the registered study period, even though the recruitment was prolonged once due to the pandemic. Post hoc power calculations performed after closing the recruitment in spring 2022, showed that, for a statistical difference in CS rates to be apparent, 1,042 women should have been randomized (for a significance level of 0.05 and power of 80%). Hence, if there really was a difference in CS rates, prolonging the recruitment period would probably not have been sufficient to detect it.

One reason for the lower-than-expected CS rates may have been the new oxytocin regimen for labor induction implemented at the largest recruitment unit of the study, HUS, after the study that formed the basis of our power calculation.[17,215] In 2018 and afterwards, when the SYKE study was conducted, a high-dose oxytocin regimen instead of a low-dose regimen was followed for women undergoing labor induction. In a study comparing these two regimens, the old procedure resulted in a vaginal delivery rate of 47.9%, and the new regime in a vaginal delivery rate of 69.9%.[215] The standardized labor induction management protocols and concurrent rather than consecutive use of BC and

misoprostol may also have favorably affected the successful vaginal delivery rate in the SYKE study compared with those identified in earlier studies.

The recruitment method chosen may be the greatest weakness of our study, as many participants were required to contact the researchers themselves to be screened. On the one hand, this could lead to a healthy volunteer bias, as those who are interested in the well-being of their pregnancies and thus welcome an additional visit at the hospital often seem to be active and knowledgeable about health issues—perhaps more so than the general population. On the other hand, many women told us that their reason for participation was the desire to undergo earlier induction or ascertain the baby's well-being. These women may have therefore had real concerns about their pregnancies.

Maternal factors that affect preferences regarding late-term pregnancy management were explored in a Dutch study in which women themselves got to choose between labor induction at 41 GW or expectant management (in which the CS rate was higher in women with labor induced earlier, contradicting an RCT conducted simultaneously as well as our RCT).[147,150,151] In this study, the women who preferred induction at 41 GW reported more problems with quality of life and were more anxious than women who preferred expectant management.[151] The main reasons for choosing earlier induction were a *safe feeling*, the *pregnancy taking too long*, and them *knowing what to expect*. The main reason for the preference for expectant management was the *wish to give birth as naturally as possible*.

In conclusion, women are motivated by diverse factors that positively or negatively affect their decisions to participate in studies or choose their own management protocols. This makes the generalizability of research challenging, and the results of our study, for example, may better capture results for women who prefer earlier induction.

Excluding parous women and women with ripe cervices can also be seen as a weakness. Thus, the effects of earlier labor induction among these women cannot be evaluated based on our study.

We regret not collecting data on the women's blood pressure and other possible signs of preeclampsia development, as it would have been interesting to see whether higher blood pressure measurements and other signs of preeclampsia would have been more prominent in the expectant management group in the days following the initial 41+0 GW visit. In our study, women with preeclampsia were excluded and only one eclampsia case was detected, which did not allow for proper analysis of the effect of earlier induction on maternal hypertensive disorders. We also regret not collecting exact Bishop scores at the 41+0 GW visit, which may have allowed further analysis of the odds of spontaneous labor and other outcomes.

6.4.3 INTERPRETATION

Offering labor induction at 41+0 GW at the wish of the pregnant woman has already become common at some hospitals in Finland. According to our results, this opportunity should be considered more widely to make early induction possible for all women, which it currently is not. For example, in the HUS area, which manages one in three annual deliveries in Finland,[1] women are offered labor induction at 41+0 GW only if they specifically know to ask for it. Some delivery units in Finland, however, offer this opportunity to all women, which puts women in unequal positions concerning the management of late-term pregnancy. A national consensus on the matter should thus be established.

As discussed earlier, monitoring visits in late-term pregnancy are advised by many obstetric guidelines, but such recommendations are lacking in Finland. In our study, all women were screened at 41+0 GW. Of the women assessed, some did not fulfill the study criteria, i.e., they were assessed as not well enough for expectant management and were treated according to need. Without our study, these women would have had their first visits to the hospital only at 41+5 GW. Whether this would have led to worse pregnancy outcomes cannot be determined, but the national guidelines for late-term pregnancy management, which are currently inadequate, should, in the author's opinion, be reevaluated.

Ideally, Finnish women would be invited to the hospital at 41+0 GW, assessed for any threats to the well-being of their pregnancy, and treated according to need. If their pregnancies were identified as low-risk, they would be offered information on late- and post-term pregnancy and their management options. After information collection and personalized assessment, the women could make an informed choice about their preferred management option: early induction or expectant management. Women who preferred nonmedicalized labor and expectant management could still be offered this opportunity, but unlike today, they would be making an informed choice, and the well-being of their pregnancy would be ascertained. Ideally, women undergoing expectant management would be assessed as likely to undergo spontaneous labor and would thus avoid labor induction for post-term pregnancies, in which one in three nulliparous women fail and eventually have CS. If assessed as very unlikely to undergo a spontaneous onset of labor, early induction at 41+0 GW could be recommended. Predicting the odds of a spontaneous onset of labor is difficult, and as we are waiting for reliable predictive methods to be discovered, assessing cervical ripeness based on traditional Bishop scores may be our best tool.[35,169,170]

In studies of women's perceptions of their prolonged pregnancies, many find passing their due date stressful and wish for their labor to be induced.[151,330] Thus, offering early labor induction would probably lead to a higher rate of labor induction than the rate of 33.9% recorded in 2021.[1]

In a Dutch study in which women were allowed to choose the management protocol for their late-term pregnancies, 44.7% of the women preferred

induction at 41 GW, 42.1% preferred expectant management until 42 GW, and 12.2% did not have a preference.[151] If the percentages in Finland were like those in the Dutch study, early induction would be chosen by thousands of women in Finland annually, depending on the rate of late-term pregnancy, which has not, to the author's knowledge, been studied in Finland. In Sweden, the rate of late-term pregnancy has been estimated at around 20%.[331] Using these numbers and the number of deliveries in Finland in 2021, we might have around 4,000 additional labor induction cases in Finland annually. At HUS, the annual number of additional labor induction cases could be more than 1,000.

Organizational changes would surely be needed to enable this change in management practices. If, however, this would lead to fewer operative deliveries, it would allow the transfer of obstetricians from the labor ward and operating room to the antenatal clinic and labor induction unit. Moreover, if earlier induction led to better neonatal outcomes and more positive childbirth experiences, it would be a viable option to establish as the current protocol. Whether late-term hospital visits for all women are achievable in our healthcare system remains to be seen, as the current economic climate of cost reductions in public healthcare may not be favorable for these measures, no matter how beneficial they may be. Additionally, it is possible that only the women at high risk of CS and adverse perinatal outcomes, such as nulliparous women with unripe cervices, would benefit from this new protocol if cost-effectiveness is considered.[277] This is one factor that should be evaluated when creating Finnish guidelines for late-term pregnancy management.

Elective labor induction, i.e., labor induction without maternal or fetal indication at 39 weeks, was declared a reasonable option for pregnant women by the ACOG after the ARRIVE trial.[332,333] In Finland, this management option has not been much discussed, and to the author's knowledge, is not practiced. In Finland, women's preferences regarding labor induction without maternal or fetal indications have not been studied, but in an American study of women's preferences regarding labor induction before due dates, 99% were supportive of labor induction for fetal indications, and 96% were supportive of labor induction for maternal indications.[334] In the absence of fetal or maternal indications, 54% of the women were not interested in labor induction before the due date.[334] These women were often concerned about the potential fetal harm that labor induction without indication might cause.

Studies on the long-term effects of term labor induction on children's neurodevelopment are almost nonexistent. It has been suggested that labor induction between 37 and 41 GW is associated with decreased school performance in children at 12 years of age when compared with children born after a spontaneous onset of labor in the same weeks or even after later gestation.[335] Further research is, however, needed. Thus far, elective labor induction at 39 weeks is unlikely to be appealing in the Finnish maternity care system.

7 CONCLUSIONS

1) Women with a history of CS for failed labor induction or labor dystocia have relatively high rates of vaginal delivery in a following pregnancy: seven in ten of such women complete a VBAC. The Finnish practice of widely offering TOLACs for these women should, thus, be continued. General risk factors for CS, such as no previous vaginal delivery, labor induction, low maternal height, diabetes, or fetal factors, such as macrosomia or susceptibility to infection or intrauterine distress, may subject the woman to a repeat CS in this subgroup of parturients as well. Women with a history of prior failed labor induction currently undergoing labor induction seem to be at the highest risk of a failed TOLAC. However, even among these high-risk women, one in two succeed. How this figure is regarded should be discussed individually.

2) BC use for labor induction should not be discouraged among women who are GBS carriers: the rates of intrapartum infection may even be lower in GBS-positive women than in GBS-negative women, and the rates of postpartum infection or neonatal infection may be similar when prophylactic antibiotics are started at the onset of labor or membrane rupture. GBS-negative women afflicted by prolonged membrane rupture, on the contrary, seem to be at a heightened risk of intrapartum infection.

3) All women, nulliparous and parous, are at risk of a negative childbirth experience mainly due to labor and delivery-related factors, such as CS and hemorrhage. Thus, maximizing the odds of vaginal delivery through an efficient labor induction protocol and effectively treating postpartum hemorrhage through good obstetric care is also paramount in the childbirth experience. Additionally, directing women in whom labor is induced, who experience labor as very medicalized from the beginning, towards elements of physiological birth and women-centered care could be beneficial in building a positive childbirth experience. Enhancing nulliparous women's antenatal education could be one important way to support this, as nulliparous women's evaluations of their capability and preparedness for labor and delivery seem more negative than those of parous women.

4) All women, especially the nulliparous, should be offered late-term pregnancy visits to the hospital at 41+0 GW to assess the possibilities of early induction and expectant management. Early induction may be beneficial in increasing the probability of unassisted vaginal delivery, which could lead to a better childbirth experience in addition to increased maternal and neonatal medical benefits. If the relevant information is offered and the parturient chooses it, expectant management could remain a choice for those who wish to experience non-medicalized labor, as one in two women who undergo expectant management may have a spontaneous onset of labor, which contributes to a favorable CS rate and an absence of statistically significant increases in adverse neonatal outcomes.

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