# Labor induction strategies with misoprostol - Evaluating oral, sequential and outpatient protocols for improved outcomes

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## Evaluating oral, outpatient and sequential protocols for improved outcomes

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## Evaluating oral, outpatient and sequential protocols for improved outcomes

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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**Title and subtitle:** Labor induction strategies with misoprostol: Evaluating oral, outpatient and sequential protocols for improved outcomes

**Abstract:**

Induction of labor (IOL) is one of the most common interventions in obstetric practice today, initiated when awaiting spontaneous labor may pose risks to the mother or fetus. The increasing incidence of IOL globally has been influenced by advancements in fetal monitoring and evolving clinical guidelines. However, since there are variations in outcomes based on administration routes, protocols, and patient characteristics, there is a need for further investigation to optimize approaches. The overall aim of this thesis was to evaluate the bioavailability and pharmacokinetic parameters, safety, and clinical efficacy of different misoprostol formulations and induction protocols, focusing on optimizing IOL strategies for better maternal and neonatal outcomes.

Study I: This was a randomized pharmacokinetic study conducted on 72 women admitted for labor induction. The study compared the relative bioavailability of two different misoprostol formulations across two different administration routes. Bioequivalence between the two compared formulations could not be confirmed. However, the results demonstrated that the sublingual route resulted in 20–30% higher bioavailability and faster absorption compared to oral administration. These results suggest the need for careful consideration of dosing, formulation and administration routes in clinical practice.

Study II: A retrospective cohort study involving 2,404 women compared the clinical outcomes of oral misoprostol solution and sublingual misoprostol for labor induction at Skåne University Hospital in Lund during a 5-year period. The study found that sublingual misoprostol was associated with a higher rate of cesarean section among primiparous women (28.6% vs. 20.5%, $p<0.001$) compared to oral misoprostol solution. Sublingual was however associated with a higher rate of vaginal delivery within 24 hours for both primiparous and multiparous women. This highlights the need for tailored induction protocols based on parity and other risk factors.

Study III: This was a retrospective study evaluating outpatient versus inpatient labor induction with oral misoprostol in 564 women. The results indicated that outpatient induction significantly reduced the time from admission to delivery compared to inpatient induction (12.8 hours vs. 20.6 hours, $p<0.001$) without compromising delivery outcomes, suggesting that outpatient induction may be a viable option for certain low-risk pregnancies. The study was not large enough to detect differences in rare outcomes or safety.

Study IV: A retrospective study including 664 nulliparous women with post-term pregnancies examined the effectiveness of sequential labor induction using misoprostol and intracervical balloon catheters. The study found that the sequential method significantly reduced the induction-to-delivery interval (21.8 hours vs. 23.0 hours, $p=0.003$) without increasing maternal or neonatal complications, indicating a potentially safe and effective option in cases where a faster induction process is wanted.

**Key words:** Misoprostol, induction of labor, pharmacokinetics, cesarean, outpatient, sequential, oral, sublingual

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# Labor induction strategies with misoprostol

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*To the loves of my life, Bahareh, Adrian, Isabelle, and Oliver*

*What is and always will be my greatest creation, is you.*

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# List of scientific papers

This thesis is based on the following four papers, henceforth referred to in the text by their Roman numerals. The papers are appended in the end of the thesis with due permission from the publishers.

**I.** **A relative bioavailability study of two misoprostol formulations following a single oral or sublingual administration**
Amini, M., Reis, M. & Wide-Swensson, D.

Frontiers in Pharmacology. 11, 50, feb 12 2020

**II.** **Sublingual misoprostol vs. oral misoprostol solution for induction of labor: A retrospective study**
Amini, M., Wide-Swensson, D. & Herbst, A.

Frontiers in surgery. 9, 968372, sep 15, 2022

**III.** **Outpatient vs inpatient induction of labor with oral misoprostol: A retrospective study**
Hallén, N., Amini, M., Wide-Swensson, D. & Herbst, A.

Acta Obstetricia et Gynecologica Scandinavica. 102, 5, s. 605-611 7 s, 2023

**IV.** **Induction of labor in prolonged pregnancy in nulliparous women with unfavorable cervix: comparison of sequential oral misoprostol-intracervical balloon catheter with oral misoprostol alone**
Amini, M, Wide-Swensson, D & Herbst A.

Submitted manuscript

# Abstract

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**Conclusions**: The findings from these studies underscore the importance of individualized IOL strategies based on patient profiles, including the selection of appropriate misoprostol formulations and induction protocols. While misoprostol is effective for labor induction, careful consideration must be given to the administration route and combination with mechanical methods to optimize outcomes. This thesis supports the development of more standardized and tailored IOL protocols to improve safety and efficacy in diverse clinical scenarios.

# List of abbreviations

| | |
|---|---|
| IOL | Induction of labor |
| CS | Cesarean section |
| NMA | Network meta-analysis |
| NICU | Neonatal intensive care unit |
| FHR | Fetal heart rate |
| IUGR | Intrauterine growth restriction |
| PROM | Prelabor rupture of membranes |
| PPROM | Preterm prelabor rupture of membranes |
| ARM | Artificial rupture of membranes |
| BMI | Body mass index |
| IVF | In vitro fertilization |
| DFM | Decreased fetal movements |
| RR | Relative risk |
| OR | Odds ratio |
| BS | Bishop score |
| ICP | Intrahepatic cholestasis of pregnancy |
| EM | Expectant management |
| RCT | Randomized controlled trial |
| AMA | Advanced maternal age |

# Preface

My fascination with the specialty of obstetrics and gynecology began in 2012, when I was a medical student and my wife was pregnant with our first child, Adrian. This broad specialty, encompassing both surgical and medical branches, captivated me with its complexity. It requires consideration not only for the mother-to-be but also for the unborn child.

I vividly remember my rotation as a medical student in the OB/GYN department, particularly a moment sitting down with my now co-supervisor, Dag, at the delivery ward in Lund. We were conducting rounds of all the patients admitted to the ward, with a team of doctors, midwives, and fellow medical students, carefully assessing and discussing how we could best assist each woman in the labor process. Among the patients, several women were admitted for induction of labor, each with her own unique indication for the procedure.

During those discussions, one recurring theme was the variation in how women responded to the different methods, dosages, routes of administration, and protocols used at the clinic. Why did some women respond to only a few doses of the given drugs while others required more? Did the route of administration make a difference? How did the drugs behave in a full-term pregnant woman about to give birth? What was the best method? Is there a method that could be universally effective, or do we need to tailor our approach to each woman?

These questions sparked more curiosity than we had answers for that day. However, they lingered in my mind long after. In subsequent discussions with Dag, we realized our shared interest in uncovering the answers to these questions. With the additional guidance and expertise of my supervisor Andreas, we laid the groundwork for the thesis you are about to read.

# Introduction

Induction of labor (IOL) is one of the most common obstetric procedures today aimed at artificially initiating labor before its spontaneous onset to achieve vaginal delivery. It is utilized when the risk of continuing the pregnancy is greater than the risk of delivery. IOL is used for various maternal and fetal reasons. Indications for IOL include post-term pregnancy, premature rupture of membranes (PROM), preeclampsia, intrauterine growth restriction (IUGR), and various other maternal and fetal conditions. As a key component of modern obstetric practice, labor induction plays an important role in managing high-risk pregnancies and preventing adverse perinatal outcomes.

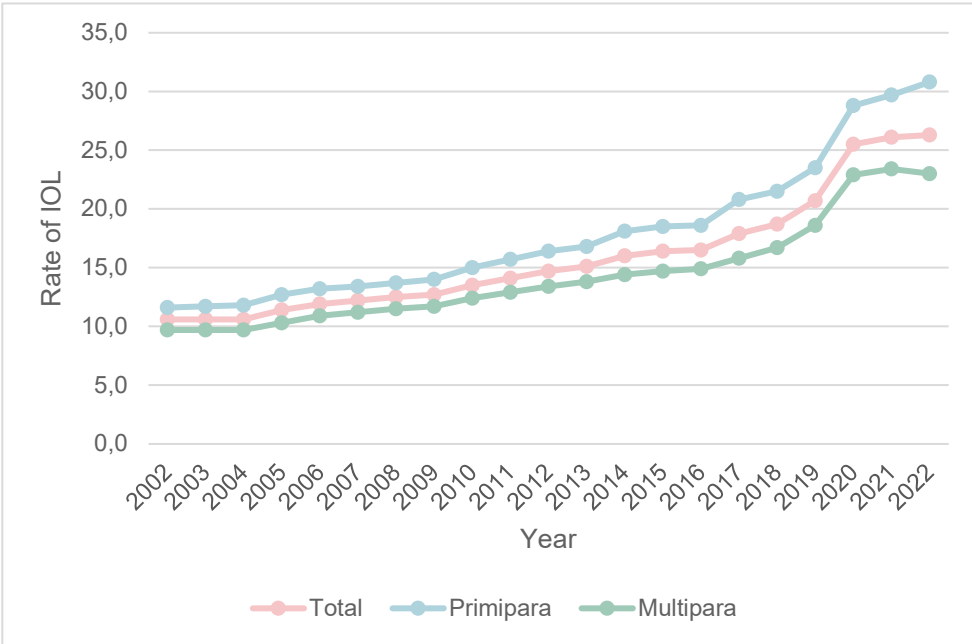


**Figure 1.** Induction of labor rate in Sweden between year 2002-2022. Graph reproduced with data from Socialstyrelsen (1).

The global incidence of labor induction has risen significantly, driven by advancements in medical knowledge, changing patient demographics, improved fetal monitoring techniques, and the increasing ability to diagnose and manage pregnancy complications. These developments have led to changes in clinical protocols, often recommending IOL over expectant management. For instance, in Sweden, the rate of labor induction has more than doubled since the early 1990s, with current estimates indicating that around 26% of all deliveries involve induction (1). In the United States and the United Kingdom, approximately one third of every woman undergo labor induction (2, 3). This shift reflects a broader recognition of the possible benefits of this intervention in for some indications in obstetric practice.

Misoprostol, a synthetic prostaglandin E1 analogue, has become a widely used agent for labor induction due to its effectiveness in cervical ripening and stimulating uterine contractions (4). However, despite its widespread use, significant variability in outcomes persists, depending on the formulation, protocol and route of administration. This variability emphasizes the importance and need for optimized and standardized protocols to ensure more predictable and safe outcomes.

Current research on misoprostol highlights several gaps, such as inconsistent findings on the relative efficacy of different administration routes, a lack of comparative studies on formulation bioavailability in term pregnant women, and limited data on the feasibility and safety of outpatient induction methods. Additionally, the combination of pharmacological and mechanical induction methods, such as the sequential use of misoprostol and Foley catheters, warrants further investigation, particularly in cases of labor induction where a quicker onset of labor is desired.

This thesis aims to address these gaps by evaluating the pharmacokinetics, efficacy, and safety of various misoprostol formulations and induction protocols. Specifically, the research explores the relative bioavailability of oral and sublingual misoprostol, compares clinical outcomes between different administration routes, assesses the practicality of outpatient induction, and investigates the benefits of sequential induction methods. The findings from this research may help to inform clinical guidelines, potentially improve labor induction outcomes, and contribute to a better theoretical understanding of the role of misoprostol in obstetric practice. Ultimately, this research aims to propose strategies that balance the benefits of timely delivery with minimizing associated risks, while recognizing that further studies are necessary to confirm and expand on these results.

To improve the process of IOL, it is important to first explore the rationale behind its use and the methods by which it is implemented. The following chapter aims to outline the most common indications for IOL, most of which are relevant to this thesis, offering a foundation for understanding when and why this intervention may be considered necessary.

# Indications for induction of labor

IOL is employed for various maternal and fetal indications, each aimed at improving outcomes for both the mother and the baby. When IOL is indicated for fetal reasons, the primary goal is to reduce perinatal morbidity and mortality, particularly the risk of intrauterine fetal death with post-term pregnancy, shoulder dystocia and brachial plexus injury with suspected macrosomia and fetal infection with PROM. On the maternal side, IOL is often used to mitigate the increased risks associated with conditions like preeclampsia or macrosomia, thereby reducing maternal morbidity and mortality. The following chapter will explore the rationale and supporting evidence for some of the most common indications for IOL relevant to this thesis, providing a detailed and balanced understanding of the clinical decision-making process.

## Post-term pregnancy

Post-term pregnancies, defined as those extending beyond 42 weeks of gestation, represent a significant concern in obstetric care due to the increased risks they pose to both the mother and fetus. These pregnancies, also referred to as postdate or prolonged pregnancies, occur in approximately 5-10% of all pregnancies. In Sweden, the incidence of post-term pregnancies is 7% (5). Gestational age >41 weeks was for many years in Sweden not considered an indication to induce labor. As gestation extends beyond the expected due date, the placenta may undergo senescence, reducing its capacity to efficiently provide nutrients and oxygen to the fetus (6). This decline in placental function is associated with several complications, including an increased likelihood of cesarean delivery, preeclampsia, fetal distress, and stillbirth (7). Furthermore, postdate fetuses are at a heightened risk for macrosomia, which complicates vaginal delivery and increases the likelihood of birth injuries and labor dystocia (8). Additionally, meconium aspiration syndrome, wherein the fetus inhales a mixture of meconium and amniotic fluid, is more prevalent in postdate pregnancies, leading to significant respiratory distress at birth (9). Such neonatal complications often necessitate intensive care, thereby placing additional demands on healthcare resources.

A comprehensive study which analyzed 76,761 post-term pregnancies in Sweden from 1982 to 1991, provided insights into the risks associated with extended gestation, particularly concerning the risk of stillbirth and neonatal mortality rates

as influenced by gestational age and maternal parity (10). The research revealed a significant increase in the risk of stillbirths among primiparous women as gestation extended beyond term, with the odds ratio (OR) for stillbirth rising from 1.50 at 41 weeks to 1.79 at 42 weeks and beyond. In contrast, multiparous women did not show a similar increase with advancing gestational age. Neonatal mortality rates were found to increase after 41 completed weeks for primiparous women, whereas, for multiparous women, a significant increase in neonatal mortality was observed only after 42 weeks. These findings underscore the heightened risk of adverse perinatal outcomes, particularly for primiparous women, as pregnancies continue into the post-term period.

A meta-analysis conducted by the Cochrane Institute, comparing labor induction at or beyond term with expectant management, included 34 RCTs involving more than 21,500 women (11). The analysis concluded that, compared to expectant management, IOL was associated with a significant reduction in perinatal deaths (RR 0.31, 95% CI 0.15 to 0.64), fewer neonatal intensive care unit (NICU) admissions (RR 0.88, 95% CI 0.80 to 0.96), fewer infants with Apgar scores below 7 (RR 0.73, 95% CI 0.56 to 0.96), and a reduced rate of cesarean sections (RR 0.90, 95% CI 0.85 to 0.95). The number needed to treat (NNT) to prevent one perinatal death was calculated to be 544. There were no significant differences between the groups regarding perineal trauma (RR 1.04, 95% CI 0.85 to 1.26) or postpartum hemorrhage (RR 1.02, 95% CI 0.91 to 1.15). There were also no differences regarding the need for operative vaginal birth (RR 1.03, 95% CI 0.96 to 1.10).

A more focused review including a total of 22 studies examining the outcomes of IOL at 41 weeks versus 42 weeks identified four RCTs that specifically matched the criteria for this comparison. The studies assessed key outcomes, including perinatal mortality, meconium aspiration syndrome, and CS rates. This review concluded that there is insufficient evidence supporting the induction of labor at 41 weeks over 42 weeks, underscoring the need for more adequately powered studies to determine the optimal timing for labor induction in late-term pregnancies (12).

A multicenter, randomized non-inferiority trial conducted by Keulen et al. compared induction of labor at 41 weeks with expectant management until 42 weeks in 1,801 low-risk women (13). The study found that adverse perinatal outcomes occurred in 1.7% of the induction group compared to 3.1% in the expectant management group (absolute risk difference of -1.4%, 95% CI -2.9% to 0.0%). The rate of cesarean sections was identical in both groups at 10.8%. The study concluded that while expectant management until 42 weeks did not meet the criteria for non-inferiority, the absolute risk of severe adverse outcomes was low in both groups, suggesting that induction at 41 weeks may offer slight benefits in reducing adverse perinatal outcomes.

In recognition of the limited evidence available for comparing outcomes between 41 weeks and 42 weeks, the **SWE**dish **P**ost-term **I**nduction **S**tudy (SWEPIS) was

specifically designed to address this gap (14). This trial involved 2760 women with low-risk singleton pregnancies, who were randomized into two groups: one undergoing IOL at 41 weeks and the other following expectant management until induction at 42 weeks. The study was terminated early due to a higher rate of perinatal mortality in the expectant management group compared to the induction group (6 deaths vs. 0 deaths). The primary outcome, a composite measure of various perinatal complications, did not significantly differ between the groups (2.4% vs. 2.2%, RR 1.06, 95% CI 0.65 to 1.73, p = 0.90). The study found no significant differences in the CS rate, need for instrumental delivery, or major maternal morbidity between the groups. However, the induction group experienced fewer NICU admissions, fewer cases of neonatal jaundice requiring therapy, and fewer instances of macrosomia compared to the expectant management group. A meta-analysis containing this study also concluded that IOL at 41 weeks compared to expectant management until 42 weeks reduced the primary composite outcome of mortality and severe neonatal morbidity (RR 0.43, 95% CI 0.21 to 0.91) with no significant difference in CS rates (15).

Further investigating the timing of IOL in postdate pregnancies, a Finnish RCT involving 381 nulliparous women with unripe cervical status was conducted. The findings demonstrated that the CS rate was lower in the induction group (16.7% vs. 24.1%, RR 0.7, 95% CI 0.5 to 1.0, p = 0.07). Additionally, the rate of operative vaginal delivery was significantly lower in the induction group (30.6% vs. 45.6%, p = 0.003), with fewer instances of postpartum hemorrhage ≥1000 mL (12.2% vs. 20.8%, p = 0.03), a rate of composite adverse neonatal outcomes of 9.7% in the induction group vs. 14.4% in the expectant management group (RR 0.7, 95% CI 0.4 to 1.2), and fewer neonates weighing ≥4000 g (16.8% vs. 29.5%, p = 0.004) compared to the expectant management group (16).

The evidence presented underscores the complexity of managing post-term pregnancies, particularly concerning the optimal timing of labor induction. In Sweden, the Swedish Society for Obstetrics and Gynecology (SFOG) currently recommends induction of labor at 41+0 to 41+6 weeks for uncomplicated pregnancies, based on the available evidence indicating a reduction in perinatal mortality with earlier induction (17).

## Premature rupture of membranes

Premature Rupture of Membranes is defined as the rupture of the fetal membranes before the onset of labor. When PROM occurs before 37 weeks of gestation, it is referred to as Preterm Premature Rupture of Membranes (PPROM). The incidence of PROM varies, occurring in approximately 8-10% of term pregnancies and 2-4% of preterm pregnancies (18). PROM presents several maternal and fetal risks. Maternal risks include infections such as chorioamnionitis and endometritis, which

can lead to sepsis. Fetal risks include respiratory distress syndrome and neonatal sepsis.

A study by Hannah et al., which involved 5041 women with term PROM compared induction of labor with oxytocin or prostaglandin E2 gel to expectant management (19). The primary outcome measured was neonatal infection, while secondary outcomes included the rate of CS and maternal satisfaction. The study found that neonatal infection rates were similar across the groups: 2.0% in the oxytocin induction group, 3.0% in the prostaglandin induction group, 2.8% in the expectant management group induced with oxytocin, and 2.7% in the expectant management group induced with prostaglandin. However, the incidence of clinical chorioamnionitis was significantly lower in the oxytocin induction group compared to the expectant management group (4.0% vs. 8.6%, $p < 0.001$). Postpartum fever occurred less frequently in the oxytocin induction group than in the expectant management group (1.9% vs. 3.6%, $p = 0.008$). The rates of CS did not significantly differ between the groups, ranging from 9.6% to 10.9%.

Building on this evidence, the secondary analysis of the TermPROM study compared the outcomes of immediate induction following PROM at term to those of delayed induction (initiated 24 hours after PROM) (20). The study, which compared 2,622 women undergoing immediate IOL versus 2,120 women with spontaneous labor, found that the rates of composite adverse neonatal outcomes, NICU admission and maternal infection were lowered with IOL within the first 15-20 hours compared to expectant management, without affecting CS rates. These findings suggest that while immediate induction of labor is generally preferred to minimize maternal infection risks and lower the CS rate, a brief period of expectant management, up to 15-20 hours, can be considered without significantly compromising neonatal safety.

Another secondary analysis of the Term PROM Study data, conducted by Seaward et al., aimed to identify significant predictors of neonatal infection among infants born to women with term PROM (21). The study found that the most significant predictors of neonatal infection included clinical chorioamnionitis (OR 5.89, 95% CI 3.68 to 9.43), positive maternal group B streptococcal status (OR 3.08, 95% CI 2.02 to 4.68), and the duration of time from membrane rupture to active labor. The risk of neonatal infection was increased when the interval from membrane rupture to active labor exceeded 24 hours (OR 1.97, 95% CI 1.11 to 3.48) and was higher when it extended beyond 48 hours (OR 2.25, 95% CI 1.21 to 4.18). This study supports the notion that while immediate induction of labor after PROM can reduce the risk of maternal and neonatal infections, particularly in cases involving maternal group B streptococcal colonization or clinical chorioamnionitis, a delay in labor induction up to 24 hours may be reasonable in the absence of these risk factors.

A Cochrane review assessing the effects of early planned birth (immediate IOL or within 24 hours) compared to expectant management for women with term PROM

found that early planned birth significantly reduces the risk of maternal infectious morbidity (chorioamnionitis and/or endometritis) compared to expectant management (RR 0.49, 95% CI 0.33 to 0.72). Neonates in the planned early group had a lower incidence of definite or probable early-onset neonatal sepsis (RR 0.73, 95% CI 0.58 to 0.92). There was no clear difference in the rate of caesarean section between the planned early birth and expectant management groups (RR 0.84, 95% CI 0.69 to 1.04) (22).

Further insights into the management of term PROM were provided by a retrospective study conducted by Pintucci et al., which evaluated the outcomes of 1,439 women with term PROM. The study aimed to determine the optimal waiting time for the onset of spontaneous labor within 48 hours of PROM, focusing on maternal and neonatal outcomes. The study found that active labor occurred spontaneously within 24 hours in 76.5% of women and within 48 hours in 90% of women. The overall incidence of CS was 4.5%, with a higher rate observed in women who underwent induction of labor compared to those who waited for spontaneous onset (OR 1.76, 95% CI 1.03 to 3.02). Additionally, the study reported a low incidence of clinical chorioamnionitis (2.3%) and neonatal infection (2.8%), even after 24 hours from PROM (23).

This study emphasizes that careful clinical management, including a strict analysis of maternal and fetal risk factors, can allow for expectant management of term PROM without a significant increase in maternal or neonatal morbidity. This approach may enhance the chances of vaginal delivery by allowing more time for cervical ripening, thereby reducing the need for cesarean sections.

Hjertberg et al. conducted a RCT comparing 12 versus 24 hours of expectant management in healthy nulliparous women with term PROM and a ripe cervix(24). The study found no increase in maternal or neonatal morbidity with 24 hours of expectant management. The CS rate was identical in both groups (4%), and there were no significant differences in neonatal infections. Spontaneous labor was more frequent in the 24-hour group (83% vs. 53%, $p < 0.005$), reducing the need for labor induction (17% vs. 47%, $p < 0.005$). These results suggest that in selected populations, extending expectant management beyond 24 hours may be safe and could reduce the need for interventions.

The evidence presented highlights the importance of carefully balancing the timing of labor induction after PROM to minimize the risks of both maternal and neonatal infections. While immediate induction of labor, particularly with oxytocin, is associated with reduced rates of clinical chorioamnionitis and postpartum fever, the findings also suggest that a short period of expectant management - up to 24 hours - may be a safe option in the absence of high-risk factors such as maternal group B streptococcal colonization or clinical chorioamnionitis.

In Skåne, clinical guidelines typically advocate for the induction of labor after 24 hours after PROM at term in the absence of risk factors (25). This recommendation

is based on the rationale that earlier induction helps to lower the risks of infection while balancing the need for avoiding unnecessary interventions. However, the evidence also supports that, in selected low-risk cases, expectant management beyond 24 hours can be considered without significantly increasing the risk of neonatal infection, provided that careful monitoring is maintained.

## Suspected macrosomia

Fetal macrosomia is defined as a condition where a newborn has an excessive birth weight, typically over 4,000 to 4,500 grams, regardless of gestational age. The incidence of macrosomia varies but is estimated to occur in about 5-10% of all pregnancies (26). Several factors contribute to the development of macrosomia, including maternal obesity, diabetes mellitus, excessive gestational weight gain, and prolonged pregnancy (27). Macrosomia presents significant risks for both the mother and the fetus during delivery. Maternal risks include an increased likelihood of cesarean delivery, perineal trauma and postpartum hemorrhage. Fetal risks include shoulder dystocia, brachial plexus injury and stillbirth (28).

When fetal macrosomia is suspected, the management of delivery becomes a critical decision point to reduce the associated risks for both the mother and the fetus. One approach that has been considered is IOL before the fetus reaches an excessive weight, thus potentially minimizing complications such as shoulder dystocia and the need for cesarean delivery.

However, the evidence supporting IOL for suspected macrosomia, is mixed. The Cochrane review by Boulvain et al. investigated whether IOL between 37 weeks and 40 weeks for suspected fetal macrosomia had any impact on CS rates or maternal or perinatal morbidity.

The review identified 4 RCTs involving a total of 1,190 women, 593 women in the IOL group and 597 women in the expectant management (EM) group. Compared to expectant management, IOL did not reduce the risk of CS (RR 0.91, 95% CI 0.76 to 1.09) or the need for instrumental delivery (RR 0.86, 95% CI 0.65 to 1.13). IOL was associated with a statistically significant reduction in the risk of shoulder dystocia (RR 0.60, 95% CI 0.37 to 0.98). The incidence of fractures (any type) was significantly lower in the IOL group (RR 0.20, 95% CI: 0.05 to 0.79). There was no significant difference between the IOL and expectant management groups in terms of brachial plexus injury (RR 0.21, 95% CI 0.01 to 4.28), but the overall occurrence of this outcome was low, making the effect difficult to estimate compared to the other outcomes (29).

The 2015 study by Boulvain et al., a large multicenter RCT, is pivotal in discussions of IOL for suspected macrosomic fetuses. This trial, involving 822 women, demonstrated that IOL at 37-38 weeks significantly reduced the risk of the composite outcome, which included shoulder dystocia, fractures, and other serious

neonatal morbidities (RR 0.32, 95% CI 0.15 to 0.71), and increased the likelihood of spontaneous vaginal delivery without raising the CS rate (30). Although this study was included in the Cochrane meta-analysis, its specific focus and robust findings highlight its importance in guiding clinical decisions regarding IOL for suspected macrosomia.

Ultrasound estimates of fetal weight can help guide delivery planning, although there are challenges in managing suspected macrosomia due to the margin of error in ultrasound predictions (31). This margin of error, ranging from 5-10%, could be a factor leading to inaccurate fetal weight estimations which can lead to unnecessary interventions, which is an important consideration when planning delivery for suspected macrosomia

There are no current Swedish national guidelines for this indication, although there is a regional guideline currently in the south of Sweden that support IOL when the estimated fetal weight exceeds 4,500 grams, typically recommending induction around 37-38 weeks of gestation (25). However, the decision to induce labor should still be individualized, considering the accuracy of fetal weight estimation, maternal health, obstetric history, maternal height, diabetes and other risk factors.

## Hypertensive disorders of pregnancy

Preeclampsia and gestational hypertension are hypertensive disorders that arise during pregnancy, defined by high blood pressure and, in the case of preeclampsia, significant proteinuria after 20 weeks of gestation. Hypertension during pregnancy is diagnosed when the systolic blood pressure reaches or exceeds 140 mmHg, and/or the diastolic blood pressure is 90 mmHg or higher. When blood pressure levels escalate to 160 mmHg systolic and/or 110 mmHg diastolic, it is classified as severe hypertension. Globally, preeclampsia affects 2% to 8% of all pregnancies, while gestational hypertension is more common, occurring in 6% to 17% of pregnancies (32).

**Preeclampsia** is a condition that arises typically after 20 weeks of gestation or postpartum in previously normotensive women. It is characterized by the development of hypertension and proteinuria, or by the onset of hypertension coupled with significant organ dysfunction, which may or may not include proteinuria.

**Gestational hypertension**, on the other hand, is defined by new-onset hypertension after 20 weeks of pregnancy without the presence of proteinuria or other preeclampsia-related symptoms of organ dysfunction.

Both conditions are associated with increased risks for both the mother and fetus, including the potential for severe complications such as eclampsia, placental abruption and IUGR. Management typically involves close monitoring,

antihypertensive therapy, and in severe cases, early delivery with IOL or CS to prevent maternal and fetal morbidity and mortality.

The HYPITAT trial investigated the outcomes of IOL compared to expectant monitoring in women with gestational hypertension or mild preeclampsia between 36 and 41 weeks of gestation. The study, involving 756 participants, found that IOL significantly reduced the risk of composite poor maternal outcomes, such as severe maternal morbidity and progression to severe disease. These outcomes were observed in 31% of women in the IOL group compared to 44% in the EM group (RR 0.71, 95% CI 0.59 to 0.86) (33).

When considering neonatal outcomes, the study reported no significant difference in composite adverse outcomes between the two groups. However, the incidence of arterial pH <7.05 was lower in the IOL group (RR 0.46, 95% CI 0.21 to 1.00). Additionally, the CS rate was non-significantly lower in the IOL group, with 14% of women undergoing CS compared to 19% in the expectant monitoring group (RR 0.75, 95% CI 0.55 to 1.04). Overall, these results suggest that IOL in women with gestational hypertension or mild preeclampsia at 36 to 41 weeks can lower maternal risks without significantly affecting neonatal outcomes.

The HYPITAT-II trial focused on the outcomes of immediate delivery versus expectant monitoring in women with hypertensive disorders of pregnancy between 34 and 37 weeks of gestation. This study, which included 703 women, found that while adverse maternal outcomes occurred in 1.1% of women in the immediate delivery group compared to 3.1% in the expectant monitoring group, this difference was not statistically significant (RR 0.36, 95% CI 0.12 to 1.11). On the other hand, neonatal respiratory distress syndrome was more prevalent in the immediate delivery group, affecting 5.7% of neonates compared to 1.7% in the expectant monitoring group (RR 3.3, 95% CI 1.4 to 8.2). The findings indicate that immediate delivery significantly increases the chances of neonatal respiratory distress, suggesting that routine immediate delivery may not be the best approach for late preterm hypertensive disorders (34).

The Cochrane review by Cluver et al. examined the effects of planned early delivery versus expectant management in women with hypertensive disorders of pregnancy from 34 weeks to term. The review found that early IOL was associated with a significantly lower risk of composite maternal mortality and severe morbidity compared to EM (RR 0.69, 95% CI 0.57 to 0.83). However, there was no significant difference in the CS rates between the IOL and EM groups (RR 0.91, 95% CI 0.78 to 1.07). Due to the high heterogeneity in the data, the review could not draw definitive conclusions about composite infant mortality and morbidity. Additionally, early IOL was also associated with an increased incidence of neonatal respiratory distress syndrome (RR 2.24, 95% CI 1.20 to 4.18) (35).

Another Cochrane review by Churchill et al. looked at early delivery versus expectant management for women with severe preeclampsia between 24 and 34

weeks of gestation. This review included six trials involving 748 women. The findings showed that there was insufficient evidence to determine whether early delivery improved maternal outcomes, as no maternal deaths were reported in the two studies that provided data on this outcome. Furthermore, early delivery likely made little or no difference in the incidence of HELLP syndrome (RR 1.09, 95% CI 0.62 to 1.91) or the risk of eclampsia (RR 0.98, 95% CI 0.06 to 15.58) (36).

Neonatal outcomes from this review indicated that infants in the early delivery group had a higher risk of intraventricular hemorrhage (RR 1.94, 95% CI 1.15 to 3.29) and respiratory distress syndrome (RR 2.30, 95% CI 1.39 to 3.81). These neonates were also more likely to require ventilation (RR 1.50, 95% CI 1.11 to 2.02) and had a lower gestational age at birth (mean difference -9.91 days, 95% CI -16.37 to -3.45 days). However, these babies were less likely to be small-for-gestational age (RR 0.38, 95% CI 0.24 to 0.61).

In summary, expectant management may be associated with better neonatal outcomes, particularly in reducing respiratory and neurological complications. The evidence was however not robust enough to provide definitive recommendations for clinical practice. Therefore, an individualized approach, considering the severity of preeclampsia and the gestational age is warranted.

## Diabetes

Diabetes, both preexisting (type 1 or type 2 diabetes) and gestational diabetes mellitus (GDM), significantly increases the risk of fetal macrosomia and intrauterine fetal death (37, 38).

A Cochrane review by Boulvain et al. investigated the outcomes of elective delivery versus expectant management in insulin-treated diabetic pregnant women at term. This review included one RCT involving 200 participants. The findings showed that elective induction of labor at 38 weeks significantly reduced the risk of macrosomia compared to EM (RR 0.56, 95% CI 0.32 to 0.98). The risk of shoulder dystocia was lower in the induction group, with no cases reported compared to three cases in the expectant management group, although this result did not reach statistical significance (RR 0.14, 95% CI 0.01 to 2.73). There was also no significant difference in the CS rate between the two groups (RR 0.81, 95% CI 0.52 to 1.26), and no other significant differences in maternal or neonatal morbidity were observed (39).

The GINEXMAL RCT by Alberico et al. explored immediate delivery by IOL versus EM in women with gestational diabetes between 38 and 39 weeks of gestation. The study, which included 425 women, reported no significant difference in the CS rates between the two groups, with 12.6% in the induction group and 11.7% in the expectant management group (RR 1.06, 95% CI 0.64 to 1.77). The incidence of shoulder dystocia was low and similar between groups, occurring in

1.4% of cases in the induction group compared to 0.5% in the EM group (RR 2.96, 95% CI 0.31 to 28.21). The trial concluded that for women with gestational diabetes at term, there were no clinically significant differences in maternal or neonatal outcomes between immediate delivery and expectant management, although the study's conclusions were limited by it being underpowered (40).

## Intrahepatic cholestasis of pregnancy

Intrahepatic Cholestasis of Pregnancy (ICP) is a liver disorder that occurs during pregnancy, typically in the third trimester, and is characterized by pruritus and elevated serum bile acids. The incidence of ICP varies depending on geography and ethnicity, affecting approximately 0.1-2% of pregnancies in Europe and North America, and up to 5% in South American populations (41). The causes of ICP are multifactorial, involving genetic, hormonal, and environmental influences (42). While the condition can cause significant discomfort for the mother, leading to increased risks of gallstones, gestational diabetes, and preeclampsia, its implications for the fetus are more severe. ICP is associated with a higher likelihood of preterm birth, fetal distress, meconium-stained amniotic fluid, and stillbirth (43).

A large study conducted in Sweden found that adverse fetal outcomes, such as spontaneous preterm deliveries, asphyxial events, and meconium stained amniotic fluid, were significantly correlated with bile acid levels exceeding 40 μmol/L (44).

Research by Puljic et al. demonstrated that the risk of fetal mortality increases with each additional week of expectant management beyond 36 weeks, with the risk rising from 4.7 per 10,000 at 36 weeks to 22.5 per 10,000 at 40 weeks, suggesting that early delivery may be necessary to mitigate these risks (45). Ovadia et al. showed that treatment with ursodeoxycholic acid significantly reduced the composite perinatal outcome (stillbirth or preterm birth) from 24.9% to 17.1% (aOR 0.60, 95% CI 0.39 to 0.91) (46).

The PITCHES trial examined the efficacy of ursodeoxycholic acid. While the treatment improved biochemical markers such as bile acids, it did not significantly reduce the risk of perinatal complications, including stillbirth (RR 0.85, 95% CI 0.62 to 1.15), preterm birth (RR 0.79, 95% CI 0.57 to 1.10), or neonatal unit admission (RR 0.81, 95% CI 0.58 to 1.13). Additionally, there was no significant difference in CS rates between the treatment and placebo groups (RR 1.00, 95% CI 0.68 to 1.46) (47). These findings suggest that while early delivery is an important strategy in managing ICP, pharmacological interventions may have limited impact on improving fetal outcomes.

## Intrauterine fetal growth restriction

Intrauterine Growth Restriction (IUGR) is a condition where a fetus does not grow to its expected size during pregnancy, typically defined as fetal weight below the 10$^{th}$ percentile for gestational age. The incidence of IUGR varies globally, affecting up to 10% of all pregnancies (48). Several factors contribute to the development of IUGR, including maternal hypertension, malnutrition, smoking, placental insufficiency, and fetal chromosomal abnormalities. IUGR is associated with heightened risks of adverse outcomes, such as perinatal mortality and significant morbidity (49).

The TRUFFLE study investigated early-onset IUGR between 26 and 32 weeks of gestation, involving 503 women. The study found that while perinatal death was relatively uncommon (8% in total), severe neonatal morbidity occurred in 24% of surviving live-born infants. The risk of such severe complications was notably higher among infants delivered at earlier gestational ages and with lower birth weights. Based on these findings, the study concluded that early delivery, though it may reduce the risk of stillbirth, is associated with a higher risk of significant neonatal morbidity (50).

The DIGITAT trial compared IOL with EM in women with suspected IUGR at term. The study, which included 650 women, found no significant difference in the primary outcome (composite adverse neonatal outcomes), between the two groups (5.3% in the IOL group vs. 6.1% in the EM group). The CS rate was also similar between the groups (14.0% vs. 13.7%). The study concluded that IOL and EM result in similar outcomes for term pregnancies complicated by suspected IUGR (51).

Determining the optimal timing for labor induction in cases of IUGR can be complex, as it depends on a variety of maternal and fetal factors. Based on current evidence, for most uncomplicated cases of IUGR, inducing labor at term appears to balance the maternal and neonatal risks effectively. This strategy considers both the potential advantages of prolonging pregnancy, and the risks associated with delaying delivery in compromised pregnancies.

## Twin pregnancy

Twin pregnancies occur in approximately 1–3% of all pregnancies worldwide, with higher rates in certain regions due to factors such as advanced maternal age, fertility treatments, and family history (52). These pregnancies are classified as either monochorionic (MC) or dichorionic (DC) based on chorionicity, which refers to the number of placentas. MC twins share a single placenta, while DC twins have two separate placentas. Chorionicity is a critical factor influencing the risks associated with twin pregnancies, with MC twins facing significantly higher risks of complications compared to DC twins.

Research shows that MC twins have a substantially higher risk of stillbirth and neonatal mortality compared to DC twins (53). A study by Glinianaia et al. found that the stillbirth rate in MC twins was found to be 44.4 per 1,000 births, compared to 12.2 per 1,000 in DC twins (RR 3.6, 95% CI 2.6 to 5.1). Similarly, neonatal mortality was higher in MC twins, with a rate of 32.4 per 1,000 live births, compared to 21.4 per 1,000 in DC twins (RR 1.5, 95% CI 1.04 to 2.2). These findings highlight the importance of close monitoring in twin pregnancies, especially those involving MC twins (54).

One study examining the risk of cesarean delivery following induction of labor in twin pregnancies found that induction was associated with an increased CS rate, 21% compared to 12% in spontaneous labor. The risk was particularly higher when cervical ripening agents were used (55). These findings suggest that although IOL may be necessary in managing twin pregnancies, it might raise the likelihood of cesarean delivery, particularly when the cervix is unfavorable at the time of induction. It is important to note that this study compared IOL to spontaneous labor in contrast to expectant management which would be a more appropriate comparison.

A Cochrane review by Dodd et al. analyzed the outcomes of elective birth at 37 weeks' gestation versus EM in women with uncomplicated twin pregnancies. The review included two RCTs involving 271 women. The findings indicated no significant differences between elective birth at 37 weeks and expectant management in terms of CS rates (RR 1.05, 95% CI 0.83 to 1.32), perinatal death or serious perinatal morbidity (RR 0.34, 95% CI 0.01 to 8.35), or maternal death or serious maternal morbidity (RR 0.29, 95% CI 0.06 to 1.38). Additionally, there were no significant differences in neonatal intensive care unit admissions (RR 1.03, 95% CI 0.37 to 2.88), low birth weight (<2500 g) (RR 1.28, 95% CI 0.93 to 1.75), or the occurrence of respiratory distress syndrome (RR 2.05, 95% CI 0.19 to 22.47) (56).

Regional guidelines in Skåne recommend elective delivery at 37 weeks to 38 weeks' gestation in uncomplicated DC twin pregnancies. For uncomplicated MC twin pregnancies, the recommendation is IOL at 36 weeks to 37 weeks (25).

## Maternal request

Maternal request for IOL without medical indications has become an increasingly common practice, contributing to the overall rise in induction rates in many countries. A study by Dögl et al. found that 10% of inductions in Norway were performed based on non-medical reasons, with maternal request being the most common indication, accounting for 35% of these cases. The study also reported that elective inductions had a CS rate of 13.8% compared to 16.9% in those with medically indicated inductions, although this difference was not found to be significant (57).

A systematic review by Dong et al. evaluated the outcomes of IOL before 40 weeks of gestation in low-risk pregnancies. The review found that elective IOL was associated with a reduction in the incidence of hypertensive disorders (RR 0.65, 95% CI 0.57 to 0.75) and a decrease in meconium-stained amniotic fluid (RR 0.45, 95% CI 0.23 to 0.89). However, it did not significantly reduce the CS rate (RR 0.95, 95% CI 0.81 to 1.11), suggesting that the potential impact on delivery mode remains unclear (58).

While maternal request for elective induction is a growing trend, the evidence suggests that while there may be some benefits, such as a reduced risk of hypertensive disorders, the impact on cesarean rates and perinatal outcomes is not substantial. Therefore, a cautious and individualized approach, involving shared decision-making and appropriate management of hospital resources, is recommended when considering IOL on maternal request, particularly in low-risk pregnancies.

## Suspected fetal compromise

Decreased fetal movement (DFM), oligohydramniosis, and other signs of suspected fetal compromise are critical concerns in obstetric practice, as they are often linked to adverse perinatal outcomes, including stillbirth, IUGR, and neonatal morbidity. Maternal reports of decreased fetal movement are among the most common reasons for antenatal visits, prompting immediate evaluation to rule out fetal distress or compromise (59).

A systematic review and meta-analysis by Bellussi et al. assessed the effectiveness of fetal movement counting as a tool to reduce perinatal mortality. The study, which included 468,601 fetuses, found no significant reduction in perinatal mortality between women who were instructed to monitor fetal movements and those who were not (RR 0.92, 95% CI 0.85 to 1.00). However, there was a slight increase in the rates of preterm birth, labor induction, and cesarean delivery among women who performed fetal movement counting. This suggests that while fetal movement monitoring may lead to more frequent medical interventions, it does not necessarily improve perinatal outcomes (60).

The AFFIRM trial investigated the effects of a care package aimed at raising awareness of DFM and standardizing the management of suspected fetal compromise. Involving 409,175 pregnancies, the trial did not find a significant reduction in stillbirth rates following the implementation of the DFM care package (aOR 0.90, 95% CI 0.75 to 1.07). However, there was a decrease in the proportion of small-for-gestational-age infants delivered at or beyond 40 weeks, alongside an increase in both cesarean sections and labor inductions, raising questions about the clinical utility of such interventions (61).

A Cochrane review by Bond et al. evaluated the outcomes of planned early delivery versus expectant management in pregnancies with suspected fetal compromise at term. This review, which included three trials with a total of 546 participants, found no significant differences in key neonatal outcomes, including perinatal mortality and major neonatal morbidity. Similarly, maternal outcomes - such as major maternal morbidity and CS rates - were comparable between the two groups. The review concluded that while early delivery did not show clear benefits in improving neonatal or maternal outcomes, it did reduce the likelihood of giving birth beyond >40 weeks of gestation (62).

Techniques such as fetal movement counting and standardized care packages for DFM may increase clinical interventions, but they do not consistently lead to improved perinatal outcomes (59). As such, management should carefully consider other risk factors that may help optimize outcomes.

## Elevated body mass index

Maternal obesity is widely recognized as a significant risk factor for adverse pregnancy outcomes, impacting both maternal and neonatal health. The relationship between elevated BMI and pregnancy complications has been well-documented across various studies. Women with a BMI greater than 30 were at increased risk of several complications, including postdates, induction of labor, CS, macrosomia and shoulder dystocia. The odds ratios for these outcomes were 1.4, 1.6, 1.6, 2.1, and 2.9, respectively, indicating a substantial increase in risk compared to women with a normal BMI (63). Additionally, the likelihood of developing conditions such as preeclampsia, gestational diabetes, cesarean delivery, macrosomia, and stillbirth increases in a nearly linear fashion as BMI rises (64-67).

A systematic review and meta-analysis by Krogh et al. examined full-term IOL versus expectant management in obese women. This analysis, which included data from four cohort studies involving over 1.3 million women, revealed that IOL at full term was associated with a significantly lower risk of cesarean delivery (19.7% vs. 24.5%; RR 0.71, 95% CI 0.63 to 0.81) compared to EM in obese women. Additionally, IOL was associated with a reduced risk of several adverse outcomes, including severe perineal lacerations, maternal infections, perinatal mortality, low Apgar scores, meconium aspiration syndrome, and macrosomia. However, the study also found an increased risk of instrumental vaginal delivery with IOL (RR 1.12, 95% CI 1.02 to 1.22). The quality of evidence was considered low to very low, suggesting that more high-quality research is needed to validate these findings (68).

Although the evidence regarding the optimal approach to IOL versus expectant management in obese women remains limited, a regional guideline in Skåne recommend IOL at 41 weeks for nulliparous women with a BMI greater than 30 (25).

## Advanced maternal age

Advanced maternal age (AMA), generally defined as 35 years and older at the time of delivery, has become increasingly common in developed countries due to sociocultural shifts such as delayed marriage and career prioritization. However, AMA is associated with heightened risks of pregnancy complications, including gestational diabetes, preeclampsia, and a higher likelihood of cesarean delivery (69).

Research consistently demonstrates that AMA is linked to a higher incidence of adverse pregnancy outcomes. For instance, Jacobsson et al. found that women aged 40–44 years and those aged 45 years or older had higher risks of perinatal mortality, IUFD and neonatal death, compared to younger women aged 20–29 years. Specifically, perinatal mortality was higher for women aged 40–44 (aOR 1.67, 95% CI 1.48 to 1.88) and for those aged 45 and older (aOR 2.45, 95% CI 1.51 to 3.98) (70).

A study by Fox et al. evaluated the effectiveness of antepartum surveillance combined with delivery at 41 weeks in reducing the risk of stillbirth in AMA patients. The study found that routine surveillance and planned delivery at 41 weeks significantly reduced the incidence of stillbirth in AMA patients to rates comparable with those in younger women. Specifically, stillbirth incidence beyond 36 weeks was 1.41 per 1,000 in AMA patients compared to 1.09 per 1,000 in younger women, a difference that was not found to be statistically significant (p=0.773). Patients aged >40 years had an incidence of stillbirth of 2.22 per 1,000 (71).

Knight et al. investigated the association between IOL and perinatal mortality in nulliparous women aged 35 years or older. Using data from 77,327 women, the study compared IOL at 39, 40, and 41 weeks with expectant management. Results showed that IOL at 40 weeks significantly reduced the risk of in-hospital perinatal death compared to expectant management (0.08% vs. 0.26%; aRR 0.33, 95% CI 0.13 to 0.80). The IOL group also had a lower risk of stillbirth and meconium aspiration syndrome. However, IOL at 40 weeks was linked to a slight increase in the risk of instrumental vaginal delivery (aRR 1.06, 95% CI 1.01 to 1.11) and emergency CS (aRR 1.05, 95% CI 1.01 to 1.09) (72).

These findings support the practice of IOL at term for nulliparous women aged over 40 years, as recommended in regional guideline from Skåne (25).

## In vitro fertilization

In vitro fertilization (IVF) has become a common method for addressing infertility, but pregnancies resulting from IVF are associated with a variety of risks, particularly concerning maternal and neonatal outcomes. The incidence of complications in IVF pregnancies is higher than in those conceived spontaneously. These risks are often attributed to the underlying infertility itself, the advanced

maternal age often seen in women undergoing IVF, and the IVF procedures themselves.

A meta-analysis by Pandey et al. highlighted the elevated risks associated with IVF pregnancies. Singleton pregnancies conceived through IVF or intracytoplasmic sperm injection (ICSI) were found to have a higher risk of preterm birth (RR 1.54, 95% CI 1.47 to 1.62), a higher risk of low birth weight (RR 1.39, 95% CI 1.27 to 1.53), and a higher risk of perinatal mortality (RR 1.87, 95% CI 1.48 to 2.37) compared to spontaneously conceived pregnancies (73). Additionally, IVF pregnancies were associated with an increased risk of hypertensive disorders (RR 1.41, 95% CI 1.28 to 1.56). A review by Silvestris et al. found that that pregnancy by oocyte donation is associated with gestational diabetes, and placental complications (74).

Donor oocyte pregnancies, which are often used in older women or those with diminished ovarian reserves, carry additional risks. Masoudian et al. found that pregnancies resulting from donor oocytes had a significantly higher risk of preeclampsia (OR 2.54, 95% CI 1.98 to 3.24) and gestational hypertension (OR 3.00, 95% CI 2.44 to 3.70), compared to other methods of assisted reproductive therapy (75). Additionally, Jeve et al. reported that donor oocyte pregnancies were associated with a higher risk of small-for-gestational-age (SGA) infants (OR 1.81, 95% CI 1.26 to 2.60) and a higher risk of CS (OR 2.71, 95% CI 2.23 to 3.30) (76).

The risk of stillbirth in IVF pregnancies varies with gestational age. Henningsen et al. found that the risk of stillbirth was significantly higher in IVF singletons before 28 weeks compared to spontaneously conceived singletons (aRR 2.08, 95% CI 1.55 to 2.78). The study also noted a higher risk of early neonatal death in IVF pregnancies (aRR 1.54, 95% CI 1.28 to 1.85) (77). However, after 28 weeks, the difference in the risk of stillbirth between IVF and spontaneously conceived pregnancies diminishes, indicating that while early gestational age poses a higher risk, proper clinical management can mitigate some of these dangers later in pregnancy. Hamilton et al focused on pregnancies conceived through infertility treatment and their outcomes at term. The study found that the risk of stillbirth and neonatal morbidity was reduced with timing of delivery at 39 weeks (78).

These findings highlight the need for careful monitoring and specialized care for IVF pregnancies, particularly in the early stages, to address the elevated risks of hypertensive disorders, preterm birth, low birth weight, and stillbirth. Patients undergoing IVF should be counselled on these risks, and close clinical management should be provided to optimize outcomes for both mother and child.

# Methods of induction of labor

This chapter will cover the primary pharmacological and mechanical methods of IOL, most of which are relevant to this thesis. A thorough understanding of these techniques is essential, as the chosen method can significantly impact both maternal and fetal outcomes. The methods explored include pharmacological agents like prostaglandins, such as misoprostol and dinoprostone, and oxytocin, which is widely used to stimulate uterine contractions. Additionally, mechanical methods such as the Foley catheter and membrane sweeping will be examined for their efficacy in cervical ripening and promoting labor progression.

Each method has distinct mechanisms of action, benefits, and potential risks, which will be analyzed in the context of current clinical practice.

## Pharmacological methods

The two main groups of pharmacological methods that will be described here are prostaglandins and oxytocin. Prostaglandins play a critical role as key mediators in both spontaneous labor and the induction of labor, functioning primarily through their effects on cervical ripening and the stimulation of uterine contractions. These compounds belong to the eicosanoid family, with a structure characterized by a 20-carbon unsaturated fatty acid backbone. Among the various types of prostaglandins, PGE1, PGE2, and PGF2α are the most relevant in labor due to their involvement in cervical ripening, uterine contractions, and membrane rupture (79).

Prostaglandins are synthesized through the cyclooxygenase (COX) pathway, where the COX-1 and COX-2 enzymes convert arachidonic acid into prostaglandin precursors. Their mechanism of action primarily involves binding to the prostaglandin E (EP) receptor family, which consists of four subtypes (EP1 to EP4) (80). Activation of these receptors mediates cellular responses that lead to smooth muscle contractions in the uterus. Additionally, the activation of metalloproteinases results in the degradation of collagen within the cervical connective tissue, facilitating cervical ripening (81).

The two main types of prostaglandins used for labor induction are Misoprostol (Prostaglandin E1, PGE1) and Dinoprostone (Prostaglandin E2, PGE2). Misoprostol is versatile in its routes of administration, and can be given orally,

vaginally, buccally, rectally or sublingually(82). Originally, it was used to treat and prevent intestinal ulcers caused by nonsteroidal anti-inflammatory drugs (83). Dinoprostone, by contrast, is available in various formulations, such as vaginal gels and pessaries.

## Oral misoprostol

Oral misoprostol has become increasingly popular for labor induction due to its proven effectiveness, ease of administration, and cost-efficiency. This section reviews the evidence supporting oral misoprostol's efficacy, safety, and optimal dosing regimens.

Oral misoprostol has been the subject of numerous reviews and meta-analyses. The most comprehensive recent analysis, a Cochrane review by Kerr et al., included 61 trials and over 20,000 women. This section will provide a detailed description of the findings from this review (84).

*Oral misoprostol compared to placebo*

Oral misoprostol demonstrates no significant difference in CS rates when compared to placebo (RR 0.81, 95% CI 0.59 to 1.11). The effect on uterine hyperstimulation accompanied by fetal heart rate changes remains inconclusive (RR 5.15, 95% CI 0.25 to 105.31). Vaginal births within 24 hours were not reported. However, there was a significantly reduced need for oxytocin augmentation with oral misoprostol compared to placebo (RR 0.46, 95% CI 0.38 to 0.55) (84).

*Oral misoprostol compared to vaginal dinoprostone*

When compared to vaginal dinoprostone, oral misoprostol may result in a lower rate of vaginal births within 24 hours (RR 0.93, 95% CI 0.87 to 1.00). However, it is significantly associated with fewer cesarean sections (RR 0.84, 95% CI 0.78 to 0.90) and a lower risk of uterine hyperstimulation with fetal heart rate changes (RR 0.49, 95% CI 0.40 to 0.59). No significant differences were observed in the need for oxytocin augmentation or neonatal outcomes, such as Apgar scores or NICU admissions (84).

*Oral misoprostol compared to vaginal misoprostol*

Compared to vaginal misoprostol, oral misoprostol was found to result in fewer vaginal births within 24 hours (RR 0.81, 95% CI 0.68 to 0.95) with a reduced risk of hyperstimulation with fetal heart rate changes (RR 0.69, 95% CI 0.53 to 0.92). Lower doses of oral misoprostol (10–25 μg) appeared to be less associated with uterine hyperstimulation with fetal heart rate changes than higher doses (50 μg), according to subgroup analysis. CS rates were the same with both methods (RR

1.00, 95% CI 0.86 to 1.16), though cesarean rates due to fetal distress were lower with oral misoprostol (RR 0.74, 95% CI 0.55 to 0.99) (84).

*Oral misoprostol vs. oxytocin*

Compared to intravenous oxytocin, oral misoprostol has a comparable effect on achieving vaginal delivery within 24 hours (RR 1.12, 95% CI 0.95 to 1.33). It was, however, associated with fewer cesarean sections (RR 0.67, 95% CI 0.50 to 0.90). There was no significant difference in hyperstimulation with fetal heart rate changes between the two methods (84).

*Oral misoprostol vs. mechanical methods*

In comparison to mechanical methods such as the transcervical Foley catheter, oral misoprostol might increase the likelihood of vaginal delivery within 24 hours (RR 1.32, 95% CI 0.98 to 1.79) and reduce CS rates (RR 0.84, 95% CI 0.75 to 0.95). Hyperstimulation with fetal heart rate changes showed no significant difference between these methods (84).

## Sublingual misoprostol

This section explores the clinical efficacy, safety, and optimal dosing regimens of sublingual misoprostol for labor induction, drawing on evidence from various studies to assess its role in obstetric practice.

*Sublingual misoprostol vs oral misoprostol*

Sublingual misoprostol used for IOL was first described by Shetty et al in 2002 (85). These results, along with other studies, have been analyzed in a Cochrane review by Muzonzini et al., which compared buccal/sublingual misoprostol to both oral and vaginal routes. The review included 3 trials involving 502 women.

The analysis found no significant difference in vaginal delivery not achieved within 24 hours with sublingual misoprostol compared to oral misoprostol (RR 0.87, 95% CI 0.68 to 1.11). Sublingual misoprostol had no difference in CS rates (RR 0.82, 95% CI 0.57 to 1.19) compared to oral misoprostol. The incidence of uterine hyperstimulation with fetal heart rate changes was evaluated, and no significant differences were found between the sublingual and oral routes (RR 1.39, 95% CI 0.28 to 6.96). In conclusion, the current body of research lacks sufficiently large studies to definitively determine whether true differences exist between sublingual and oral misoprostol for labor induction.

In another study that directly compared the sublingual, oral, and vaginal routes, sublingual misoprostol resulted in a shorter induction-to-delivery interval than oral administration (13.26 ± 3.27 hours vs. 16.06 ± 4.24 hours, $p = 0.003$). While the CS rates were lower for sublingual misoprostol, this difference was not statistically

significant (18.2% vs. 27.3%, p = 0.28). Additionally, the incidence of meconium-stained amniotic fluid was significantly lower in the sublingual group compared to the oral group (7.7% vs. 84.6%, p = 0.000) (86).

*Sublingual vs vaginal misoprostol*

The comparison between sublingual and vaginal administration routes has been addressed in a recent meta-analysis. Sublingual misoprostol was found to be associated with a shorter time to vaginal delivery when compared to vaginal misoprostol (mean difference of -1.11 hours, 95% CI -2.06 to -0.17). The CS rates between the two routes did not show a significant difference (RR 0.76, 95% CI 0.56 to 1.03) (87).

There were no significant differences regarding the risk of uterine tachysystole with sublingual misoprostol compared to vaginal misoprostol (RR 0.67, 95% CI 0.20 to 2.20). No differences in the risk of postpartum hemorrhage were found between the two routes (RR 3.00, 95% CI 0.12 to 72.59). NICU admissions were similar between the two routes (RR 1.00, 95% CI 0.68 to 1.47), and there was no significant difference in Apgar scores below 7 at 5 minutes (RR 0.92, 95% CI 0.43 to 1.94).

## Vaginal misoprostol

Vaginal misoprostol has largely been replaced by oral administration due to its ease of use, reduced need for vaginal examinations, and improved patient satisfaction. A Cochrane analysis examined the effects of vaginal misoprostol in comparison to placebo, vaginal dinoprostone, intracervical PGE2, and oxytocin (88).

When compared to placebo, vaginal misoprostol was significantly more effective in achieving vaginal delivery within 24 hours (RR 0.56, 95% CI 0.31 to 1.03). However, it was also associated with an increased risk of uterine hyperstimulation without FHR changes (RR 3.52, 95% CI 1.78 to 6.99). Additionally, the incidence of meconium-stained amniotic fluid was reduced with vaginal misoprostol compared to placebo (RR 0.81, 95% CI 0.67 to 0.98). Cesarean section rates showed no significant difference between the two groups (RR 0.99, 95% CI 0.84 to 1.16) (88).

## Dinoprostone

Dinoprostone, also known as PGE2, is a naturally occurring prostaglandin widely used in obstetrics for IOL. It facilitates labor by softening and dilating the cervix, making it a key component of labor induction. Dinoprostone is available in various formulations, including vaginal gels, inserts, and pessaries, which enhances its adaptability in obstetric practice.

Dinoprostone functions by binding to specific receptors on the smooth muscle cells of the uterus and cervix, promoting cervical ripening and initiation of uterine contractions. This prostaglandin works by increasing the collagenase activity in the cervix, which softens and dilates it. Additionally, dinoprostone stimulates the myometrium, leading to coordinated uterine contractions (89).

A Cochrane review by Thomas et al. included 70 RCTs involving 11,487 women, comparing PGE2 (all regimens) to placebo and other PGE2 forms, such as tablet, pessary, gel. While the number of studies reporting vaginal delivery not achieved within 24 hours was limited, no significant difference was found comparing PGE2 to placebo (RR 0.32, 95% CI 0.02 to 4.83). However, PGE2 significantly increased the risk of uterine hyperstimulation with FHR changes compared to placebo (RR 3.16, 95% CI 1.67 to 5.98). The CS rate was lower with PGE2, but the difference was not statistically significant (RR 0.91, 95% CI 0.81 to 1.02). NICU admission rates showed no significant difference (RR 0.94, 95% CI 0.78 to 1.14) (90).

*PGE2 vaginal tablet vs. PGE2 slow-release vaginal pessary*

No significant differences were noted in CS rates between the vaginal tablet and slow-release pessary (RR 1.13, 95% CI 0.64 to 1.99). Data on vaginal delivery not achieved within 24 hours was not available.

*PGE2 vaginal gel vs. PGE2 slow-release vaginal pessary*

Although there was no data on vaginal delivery not achieved within 24 hours, PGE2 gel was associated with a significant reduction in uterine hyperstimulation with FHR changes (RR 0.16, 95% CI 0.03 to 0.87). However, the dosages used in these trials differed considerably from current clinical practice, so these results should be interpreted cautiously.

The NICE Guideline NG207 presents a comprehensive review of both pharmacological and mechanical methods for IOL. It includes a network meta-analysis of 564 RCTs involving 29,056 women, examining outcomes such as vaginal delivery not achieved within 24 hours, uterine hyperstimulation with FHR changes, CS rates, and NICU admissions compared to placebo (91).

*PGE2 vaginal gel*

In comparison with placebo, PGE2 vaginal gel did significantly reduce the rate of vaginal deliveries not achieved within 24 hours (RR 0.17, 95% CI 0.08 to 0.34). However, the risk of uterine hyperstimulation without FHR changes was higher (RR 3.50, 95% CI 1.41 to 9.40). The CS rate was not significantly different from placebo (RR 0.85, 95% CI 0.75 to 1.01), but a significant difference emerged when adjusted for a Bishop Score <6. NICU admissions showed no significant differences (RR 1.41, 95% CI 0.93 to 2.14).

*PGE2 slow-release vaginal pessary*

The slow-release PGE2 vaginal pessary was notably more effective in achieving vaginal delivery within 24 hours compared to placebo (RR 0.21, 95% CI 0.09 to 0.43). However, it was associated with a higher risk of uterine hyperstimulation with FHR changes (RR 4.60, 95% CI 1.53 to 9.15). No significant differences were observed in CS rates (RR 0.84, 95% CI 0.68 to 1.03) or NICU admissions (RR 1.27, 95% CI 0.79 to 2.03).

*PGE2 intracervical gel*

Compared to placebo, PGE2 intracervical gel was significantly associated with a lower rate of vaginal deliveries not achieved within 24 hours (RR 0.22, 95% CI 0.11 to 0.43) and was associated with an increased risk of uterine hyperstimulation without FHR changes (RR 2.27, 95% CI 1.00 to 5.62). Cesarean section rates did not differ significantly from placebo (RR 0.91, 95% CI 0.77 to 1.08), and there were no notable differences in NICU admission rates (RR 1.27, 95% CI 0.83 to 1.96).

# Other pharmacological methods

## Oxytocin

Oxytocin is a peptide hormone produced in the hypothalamus and released in the posterior pituitary. It plays a central role in the regulation of labor as it stimulates uterine contractions and is widely used for IOL. During the later stages of pregnancy, there is an upregulation of oxytocin receptors in the uterus which in turn increase its sensitivity to endogenous and exogenous oxytocin (92). In addition to its direct role in stimulating contractions, oxytocin contributes to the Ferguson reflex, a positive feedback loop in which the stretching of the cervix and vagina during labor promotes further oxytocin release (93). Oxytocin's chemical structure closely resembles that of vasopressin, another pituitary hormone, which explains why, at high doses, oxytocin can exhibit mild antidiuretic effects (94).

A Cochrane review investigated the effect of intravenous oxytocin for cervical ripening and induction of labor, comparing it to both expectant management/placebo, vaginal PGE2 or intracervical PGE2. Oxytocin was less likely to be associated with vaginal delivery not delivered within 24 hours compared to EM (RR 0.16, 95% CI 0.10 to 0.25). However, when compared to vaginal PGE2, oxytocin was significantly less likely to achieve vaginal delivery within 24 hours (RR 1.77, 95% CI 1.31 to 2.38). This was also true when compared to intracervical PGE2 (RR 1.47, 95% CI 1.10 to 1.96). The CS rate was significantly higher with oxytocin compared to EM (RR 1.17, 95% CI 1.01 to 1.35; 24 trials; 6620 women). No significant differences were found with regards to serious neonatal morbidity or

death when comparing oxytocin to EM (RR 0.63, 95% CI 0.26 to 1.51). The authors found no significant differences in serious neonatal morbidity with oxytocin when compared to vaginal or intracervical PGE2 (95).

The question whether high-dose or low-dose oxytocin regimens can affect outcomes has been addressed in a meta-analysis by Moraes et al. The analysis included 21 trials involving 14,834 women, assessing outcomes CS rate, instrumental delivery and uterine tachysystole. No significant differences were found in the two groups with regards to delivery outcomes or neonatal outcomes. However, the rate of uterine tachysystole was significantly higher in the high-dose group (OR 1.61, 95% CI 1.23 to 2.11) (96). Similar results were found in a Cochrane review by Budden et al combining 9 trials, including 2,391 women comparing high-dose to low-dose regimens. No significant differences were found comparing the two regimens with regards to vaginal delivery not achieved within 24 hours (RR 0.94; 95% CI 0.78 to 1.14). The high-dose regimen was after adjusting for bias found to be associated with uterine tachysystole when compared to the low-dose regimen (RR 1.86, 95% CI 1.55 to 2.25) (97).

# Mechanical methods

*Balloon catheter*

Balloon catheters are a widely used mechanical method for IOL. They work by physically dilating the cervix, promoting the release of endogenous prostaglandins, which in turn aid in cervical ripening and the initiation of labor. Balloon catheters are particularly useful when pharmacological methods, such as prostaglandins, are contraindicated or when a controlled, gradual induction approach is preferred.

*Mechanism of action*

The primary mechanism of action of balloon catheters involves the mechanical dilation of the cervix. Once inserted, the balloon is inflated with saline or sterile water, applying direct pressure to the cervix. This pressure stimulates local prostaglandin production, promoting both cervical ripening and dilation. Additionally, the balloon can apply pressure to the lower uterine segment, which may help trigger uterine contractions.

*Types of balloon catheters available*

*Single-balloon catheter*

The most used single-balloon catheter in IOL is the Foley catheter, which features a single balloon that, once inserted through the cervix, is inflated with 30–80 mL of saline to apply pressure on the cervical os.

Research comparing low (30 mL) and high (60–80 mL) inflation volumes shows that higher inflation volumes tend to improve outcomes. A systematic review and meta-analysis by Berndl et al. demonstrated that while using a 60/80 mL balloon compared to 30 mL balloon did not significantly reduce CS rates (RR 0.94, 95% CI 0.65 to 1.38), it increased the likelihood of achieving a favorable cervix (RR 1.72, 95% CI 1.46 to 2.04) and reduced the risk of failure to deliver within 24 hours (RR 0.70, 95% CI 0.54 to 0.90). With 80 mL catheters, the likelihood of failure to delivery within 24 hours was further reduced (RR 0.57, 95% CI 0.40 to 0.81) (98).

Similarly, a meta-analysis by Schoen et al., which included 7 trials with 1,432 pregnancies, found that compared to a 30 mL balloon, a 60 mL balloon shortened the time from induction to delivery by nearly 4 hours (MD -3.9 hours, 95% CI -5.63 to -2.17) without increasing cesarean rates (RR 0.84, 95% CI 0.60 to 1.17). However, using an 80 mL balloon did not significantly reduce the time to delivery (99).

These findings suggest that higher-volume catheters offer greater efficacy in achieving favorable cervical conditions and timely delivery.

*Double-balloon catheter*

The Cook cervical balloon catheter is an example of a double-balloon design, with one balloon positioned inside the cervix and another outside, in the vaginal canal. Each balloon is typically inflated with 40–80 mL of saline. This dual-balloon configuration applies pressure from both sides of the cervix, aiding in dilation.

These catheters are usually left in place for 12 to 24 hours, allowing gradual dilation. Depending on the clinical scenario and cervical readiness, they may be used alone or in combination with other induction methods, such as oxytocin or amniotomy. Two meta-analyses have concluded that double-balloon catheters do not offer significant advantages over single-balloon catheters in terms of time to delivery, CS rates, or vaginal delivery rates. The Foley catheter remains popular due to its simplicity, cost-effectiveness, and availability, making it a preferred option compared to the double-balloon catheter (100, 101).

The Cochrane review by de Vaan et al summarized the outcomes for mechanical methods of IOL compared to other pharmacological methods. The review included 104 studies involving 20,055 women. The results from that review will be described below (102).

*Balloon catheter vs vaginal PGE2*

The balloon catheter did not significantly reduce the rate of vaginal delivery not achieved within 24 hours compared to vaginal PGE2 (RR 1.01, 95% CI 0.82 to 1.26). Cesarean section rates were also similar between the two methods (RR 1.00, 95% CI 0.92 to 1.09). However, balloon catheters significantly reduced the risk of uterine hyperstimulation with FHR changes (RR 0.35, 95% CI 0.18 to 0.67). Apgar

scores at 5 minutes and NICU admission rates showed no significant differences, but balloon catheters were more likely to require oxytocin augmentation (RR 1.54, 95% CI 1.35 to 1.76).

*Balloon catheter vs low-dose vaginal misoprostol*

When compared to low-dose vaginal misoprostol, balloon catheters were associated with a lower risk of uterine hyperstimulation with FHR changes (RR 0.39, 95% CI 0.18 to 0.85) but a higher CS rate (RR 1.28, 95% CI 1.02 to 1.60). There was no significant difference in the rate of vaginal delivery not achieved within 24 hours (RR 1.09, 95% CI 0.85 to 1.39) or serious neonatal morbidity/perinatal death. Balloon catheters required more oxytocin augmentation (RR 1.62, 95% CI 1.38 to 1.90).

*Balloon catheter vs low-dose oral misoprostol*

Balloon catheters had a higher rate of vaginal delivery not achieved within 24 hours compared to misoprostol (RR 1.28, 95% CI 1.13 to 1.46) but showed no significant difference in uterine hyperstimulation with FHR changes (RR 0.81, 95% CI 0.48 to 1.38). The CS rate was slightly higher with balloon catheters (RR 1.17, 95% CI 1.04 to 1.32). Other key outcomes, such as serious perinatal or maternal morbidity, NICU admission, and Apgar scores below 7 at 5 minutes, did not differ significantly between the two methods. However, balloon catheters were more likely to require oxytocin augmentation (RR 1.28, 95% CI 1.09 to 1.49).

*Single balloon vs double-balloon catheter*

The Cochrane analysis found no significant differences between single- and double-balloon catheters in terms of key outcomes like vaginal delivery within 24 hours, cesarean rates, the need for oxytocin augmentation, or NICU admissions. Other reviews and meta-analyses have confirmed these findings, indicating that single-balloon catheters are just as effective as double-balloon designs in terms of time to delivery, vaginal delivery rates, and CS rates (100, 101). Thus, the choice between single and double-balloon catheters may therefore depend more on clinician preference and specific patient factors than any substantial difference in efficacy.

*Risk of infection*

The potential for increased infection risk with balloon catheters in women with PROM remains a point of debate. Studies and meta-analyses on this topic have produced mixed results.

A systematic review and meta-analysis by McMaster et al., which included 26 randomized controlled trials with 5,563 women, found no significant increase in the risk of infection. Specifically, the use of transcervical Foley catheters did not raise the risk of chorioamnionitis (RR 0.96, 95% CI 0.66 to 1.38), endometritis (RR 1.03, 95% CI 0.66 to 1.6), maternal infections (RR 0.95, 95% CI 0.81 to 1.12), or neonatal

infections (RR 0.9, 95% CI 0.58 to 1.39) compared to locally applied prostaglandins (103).

In contrast, a review by Mackeen et al., focusing on the use of intracervical balloon catheters after membrane rupture, found a significantly higher risk of intra-amniotic infection (RR 3.2, 95% CI 1.17 to 8.70) when compared to oxytocin alone. A non-significant increase in intra-amniotic infection was also noted when comparing balloon catheters to vaginal prostaglandins (RR 1.84, 95% CI 0.91 to 3.73) (104).

# Other mechanical methods

*Membrane sweeping*

Membrane sweeping is a mechanical technique used to induce labor by separating the amniotic sac from the cervix, which can help stimulate the release of natural prostaglandins. One of its key advantages is its simplicity and low cost, as it can be performed without the need for hospitalization, making it an accessible option for many.

A Cochrane review found that membrane sweeping increases the likelihood of spontaneous labor (RR 1.21, 95% CI 1.08 to 1.34) and reduces the necessity for formal IOL (RR 0.73, 95% CI 0.56 to 0.94). The review did not reveal significant differences in CS rates (RR 0.94, 95% CI 0.85 to 1.04) or spontaneous vaginal births (RR 1.03, 95% CI 0.99 to 1.07). Importantly, the review also noted no significant effects on maternal or neonatal morbidity (105). In comparison with vaginal or intracervical prostaglandins, membrane sweeping showed no significant differences in outcomes like spontaneous labor onset, CS rates, or neonatal morbidity, although data were limited.

*Amniotomy*

Amniotomy, also known as artificial rupture of membranes (ARM), is a common method used to induce or accelerate labor. This procedure involves breaking the amniotic sac to release the amniotic fluid, which is thought to enhance uterine contractions due to the release of prostaglandins and pressure changes within the uterus.

Amniotomy works by stimulating the release of endogenous prostaglandins and increasing the pressure of the presenting part of the fetus on the cervix. The release of amniotic fluid is thought to facilitate stronger uterine contractions due to both the sudden shift in pressure within the uterus and the stimulation of prostaglandin release.

A Cochrane review by Bricker et al. evaluated the effectiveness of amniotomy in the context of labor induction. The findings suggested that while amniotomy may

reduce the duration of labor, it does not significantly affect the rates of cesarean sections or other medical interventions. Moreover, when used on its own, amniotomy does not appear to have a major impact on maternal or neonatal outcomes, though it can be beneficial as part of a broader induction strategy (106).

In practice, amniotomy's real utility emerges when it is used in conjunction with other methods or when the cervical status is favorable. For instance, a systematic review of 7 trials, which included 1,775 women, compared early amniotomy with induced labor. The results showed no significant difference in CS rates between the two groups (RR 1.09, 95% CI 0.80 to 1.49). However, early amniotomy was associated with a shorter induction-to-delivery interval (mean difference -3.62 hours, 95% CI -6.09 to -1.16). The review also noted no significant differences in terms of infectious morbidity, uterine hyperstimulation, or neonatal outcomes (107).

# Outpatient induction of labor

The global increase in labor induction rates has prompted a search for more efficient, comfortable, and cost-effective methods to manage growing trend. Studies, including the ARRIVE-trial, have shown reassuring results when comparing IOL to EM, suggesting that this trend will likely continue to grow (108). This trend has largely been driven by policy changes regarding the management of prolonged pregnancies and a growing awareness of the risks associated with post-term gestations. Evidence from Scandinavian RCTs, for instance, suggests that earlier inductions may help decrease the risk of stillbirth and other complications, without raising CS rates (14, 16). As induction rates rise, the need for methods that can accommodate this increase while minimizing the strain on healthcare systems becomes ever more pressing. Outpatient IOL has emerged as a promising alternative, allowing select women to undergo the early stages of labor induction at home rather than in the hospital. This approach may help reduce labor ward congestion and offer women a more comfortable experience. Several studies have compared inpatient and outpatient IOL, although the optimal strategy for outpatient induction remains a topic of debate (109).

*Pharmacological and mechanical methods in outpatient IOL*

Various pharmacological and mechanical methods have been evaluated for their effectiveness in outpatient IOL, as examined in both RCTs and systematic reviews. A Cochrane review, which included seven trials (six of which reported on 1,610 women), compared outpatient IOL to inpatient IOL using vaginal PGE2 or Foley balloon catheters. No significant differences in CS rate, uterine hyperstimulation or neonatal outcomes were found between outpatient and inpatient settings when using vaginal PGE2 or slow-release PGE2. However, in cases where a balloon catheter was used, the outpatient setting was linked to a lower CS rate, though the difference was not statistically significant (RR 0.64, 95% CI 0.41 to 1.01). Importantly, the quality of evidence in these trials was rated as low, indicating that these findings should be interpreted cautiously due to possible biases and imprecision (110).

A systematic review and meta-analysis comparing outpatient versus inpatient IOL across 12 studies involving 2,615 pregnancies, found no significant difference in cesarean delivery rates between the two groups (21.2% in the outpatient group vs. 21.5% in the inpatient group). Neonatal outcomes were also similar between the groups and for NICU admissions the rates were 5.6% and 6.6% respectively. The

outpatient group experienced a notably shorter hospital stay, averaging 282 minutes less. However, on a subgroup analysis, the authors found that the outpatient setting was associated with fewer cesarean deliveries when balloon catheters were used in both settings (RR 0.52, 95% CI 0.30 to 0.90) (111). A Portuguese RCT further highlighted this trend, finding that outpatient IOL using a Foley catheter was associated with a significantly lower CS rate for failed induction compared to the inpatient group (3% vs. 17%, p = 0.02), a difference that remained significant even after adjusting for factors such as maternal age, parity, and BMI (112).

Among various methods for outpatient cervical ripening analyzed in a meta-analysis, 25 μg vaginal misoprostol emerged as particularly effective, significantly reducing the time from intervention to delivery compared to placebo (mean difference 31.45 hours, 95% CI 51.13 to 11.77). Additionally, oral mifepristone at a dose of 50 mg offered the lowest odds of cesarean delivery (OR 0.19, 95% CI 0.04 to 0.92), without increasing risks of uterine hyperstimulation or low Apgar scores (113).

*Patient satisfaction with outpatient IOL*

In terms of patient satisfaction, studies indicate that women generally view outpatient IOL favorably. One RCT found no significant difference in satisfaction levels between multiparous women who underwent outpatient versus inpatient cervical ripening, with both groups reporting high satisfaction scores (114). A Norwegian study went further, revealing that women valued the comfort and sense of control they experienced at home, which contributed to a positive overall experience during outpatient IOL (115). Likewise, a systematic review underscored the importance of autonomy in outpatient settings, noting that women often associated greater control over their birthing process with a more positive experience (116). Another study reported that women appreciated the flexibility and comfort provided by outpatient cervical ripening, highlighting these aspects as key contributors to their overall satisfaction (117).

*Cost-effectiveness of outpatient IOL*

The cost-effectiveness of outpatient IOL has been the subject of conflicting findings. Some studies suggest that outpatient methods may reduce costs, while others indicate little to no financial advantage over inpatient IOL. For instance, Austin et al. found that while outpatient Foley catheter (OFC) induction reduced pre-delivery inpatient hours, leading to an incremental cost of $57 per hour saved, the overall cost savings were not realized. Women in the OFC group had higher average hospital costs ($6,524) compared to those in the inpatient prostaglandin gel group ($5,876), making OFC less cost-effective in this context (118). In contrast, Merollini et al. reported that outpatient balloon catheter IOL was indeed more cost-effective, with lower mean costs ($7,294) compared to inpatient prostaglandin IOL ($7,585). On the whole, outpatient IOL methods have the potential to lower inpatient hours and reduce costs, although the exact savings vary depending on the method used and the patient population being studied (119).

# Combined and sequential induction of labor

The approaches to IOL have evolved over time, with increasing evidence supporting the combined use of mechanical and pharmacological methods to boost both efficiency and safety. This chapter examines the use of combined methods, delving into their mechanisms, clinical outcomes and benefits.

*Overview and rationale*

The rationale for combining different methods of IOL lies in the potential for their complementary mechanisms of action to enhance overall effectiveness. Prostaglandins, such as misoprostol, chemically soften and ripen the cervix while stimulating uterine contractions, whereas mechanical methods like the Foley catheter physically dilate the cervix. Combining a mechanical IOL method like the Foley catheter with prostaglandins can create an additive effect. This combination may lead to a greater degree of cervical ripening and shorten the induction-to-delivery time. Prostaglandins can also address a common limitation of the Foley catheter, which in some cases dilates the cervix without significant effacement, improving the overall success of induction.

*Efficacy and time to delivery*

Several studies have demonstrated the significant advantages of combining intravaginal misoprostol with a Foley catheter for labor induction, particularly in shortening the induction-to-delivery interval. For example, Chung et al. found that this combination non-significantly reduced the time to active labor, though it was associated with a higher incidence of tachysystole compared to using the Foley catheter alone (120). Similarly, Aduloju et al. observed that this approach not only shortened the induction-to-delivery period but also increased the likelihood of vaginal delivery within 24 hours (121). Levine et al. demonstrated that the combination of misoprostol and Foley catheter led to faster time to delivery (16.2 hours vs. 21.4 hours, $p < 0.01$) and a higher likelihood of vaginal delivery within 24 hours (68% vs. 54%, $p = 0.02$) compared to single-agent methods (122).

Further supporting these findings, Carbone et al. reported a 3 hour reduction in the induction process when both a Foley catheter and vaginal misoprostol were used in

combination compared to vaginal misoprostol alone, with no significant increase in CS rates (123).

Moreover, a comprehensive meta-analysis confirmed that combining a Foley catheter with intravaginal misoprostol accelerates the time to delivery and enhances labor induction effectiveness compared to misoprostol alone (124). Sanchez-Ramos et al. conducted a network meta-analysis that included data from 61 RCTs involving 11,487 women. Their analysis showed that using a single-balloon catheter with vaginal misoprostol was the most effective strategy for achieving vaginal delivery within 24 hours, with a success rate of 87.5%. This approach also resulted in lower CS rates, underscoring the benefits of combining mechanical and pharmacological techniques for IOL (125).

Similarly, Chen et al. found that combining a Foley catheter with misoprostol reduced the time to delivery by 2.36 hours compared to misoprostol alone, with CS rates of 22.4% in the combination group versus 28.6% in the misoprostol-only group (126). Other reviews and meta-analyses have shown similar results (127-129).

The physical dilation caused by the Foley catheter can significantly enhance the cervical ripening effects of misoprostol. Studies indicate that using higher-volume Foley catheters (80 mL or 60 mL) in combination with misoprostol reduces the induction-to-delivery interval and decreases the need for additional misoprostol doses compared to lower-volume Foley catheters. In one study by Sharma et al., a higher volume catheter (80 mL) was associated with a shorter induction-to-delivery time compared to 60 mL (130, 131).

*Context-specific applications*

For example, in pre-eclamptic patients, Sharma et al. found that using a transcervical Foley catheter alongside sublingual misoprostol increased the rate of vaginal delivery within 24 hours compared to sublingual misoprostol alone (60.0% vs 41.4%, RR 1.46, 95% CI 1.03 to 2.06). Cesarean section rates were not significantly different between the two groups (132). Similarly, Poorhosseini et al. demonstrated that in patients with PROM, combining a Foley catheter with misoprostol significantly shortened the induction-to-delivery interval (10.83 hours vs. 13.10 hours, $p = 0.001$) without increasing the risk of infection. Furthermore, CS rates were non-significantly lower in the combination group (20.4% vs. 32%) (133).

*Safety and complications*

While combined methods improve the efficiency of IOL, careful consideration must be given to potential complications. Nasioudis et al. reported that combining mechanical dilation with misoprostol led to better neonatal outcomes, including lower NICU admission rates (RR 0.71, 95% CI 0.53 to 0.96) compared to misoprostol alone (127). However, the meta-analysis by Chen et al. also noted an increased risk of chorioamnionitis in the combination group (RR 2.07, 95% CI 1.04

to 4.13), although the risk of uterine tachysystole was lower with the combined approach (RR 0.58, 95% CI 0.38 to 0.91) (126). Chung et al. observed that while combining misoprostol with a Foley catheter slightly reduced the time to active labor, it was associated with a higher incidence of hyperstimulation compared to using the Foley alone (16.3% vs. 11.1%, $p = 0.02$), but lower than misoprostol alone (16.3% vs. 33.3%, $p = 0.02$) (120).

*Route of misoprostol administration*

The route of misoprostol administration can influence the safety and efficacy of combined methods. A study comparing buccal and vaginal administration of misoprostol in conjunction with a Foley catheter found both routes to be effective. However, the vaginal route was associated with a significantly shorter induction-to-delivery time (16.8 hours vs. 23.2 hours, $p < 0.001$), with no significant differences in cesarean rates or maternal/neonatal outcomes (134)

In conclusion, the combination of mechanical and pharmacological methods for IOL represents a significant advancement in obstetric practice, offering a more efficient and potentially safer approach to labor induction. The evidence from multiple studies supports the use of these combined methods to optimize labor outcomes, particularly in reducing the time to delivery and improving maternal and neonatal outcomes. While the combined approach generally offers improved efficacy, it requires careful patient selection and monitoring to mitigate potential risks such as infection. As ongoing research continues to refine these methods and standardize protocols, the combination of Foley catheters with misoprostol is likely to become an increasingly important tool in the management of labor induction.

# Key summary points

***Pharmacological Methods***

***Misoprostol (PGE1)***

•Oral misoprostol is associated with lower CS rates compared to vaginal dinoprostone.

•Sublingual misoprostol has faster action and higher bioavailability but may increase the risk of uterine tachysystole.

•Lower doses of misoprostol (10–25 μg) reduce the risk of uterine hyperstimulation and fetal heart rate abnormalities, while maintaining efficacy for induction.

•Oral misoprostol reduces the need for oxytocin augmentation compared to placebo.

***Dinoprostone (PGE2)***

•While effective for cervical ripening, dinoprostone carries a higher risk of uterine hyperstimulation with fetal heart rate changes when compared to mechanical methods.

•Vaginal formulations of dinoprostone (gel, pessary) show effectiveness but require close monitoring due to higher hyperstimulation risk.

***Oxytocin***

•Higher doses of oxytocin increase the risk of uterine tachysystole, particularly when combined with prostaglandins.

•It is less effective for cervical ripening but critical once contractions need stimulation after cervical ripening is achieved.

•Careful dosing of oxytocin is important to reduce hyperstimulation and fetal heart rate changes.

### *Mechanical Methods*

#### *Balloon Catheters*

•Lower risk of uterine hyperstimulation compared to pharmacological methods.

•Effective for patients with prior cesarean sections or when prostaglandins are contraindicated.

•Studies suggest that higher inflation volumes (60–80 mL) can improve outcomes, including shorter induction-to-delivery time and more favorable cervix conditions.

#### *Membrane Sweeping*

•Reduces the likelihood of formal IOL, decreasing the need for pharmacological interventions.

•Has little to no effect on cesarean rates but increases the chance of spontaneous labor onset.

#### *Amniotomy*

•Best used in combination with other methods like oxytocin when the cervix is ripe.

•Reduces induction-to-delivery time but does not significantly affect cesarean rates or maternal/neonatal morbidity.

#### *Combined Methods*

•Sequential or combined use of misoprostol with balloon catheter results in a shorter induction-to-delivery interval and is especially effective for patients with an unfavorable cervix.

# Pharmacokinetics of misoprostol

Misoprostol is a synthetic PGE1 analogue widely used in obstetrics and gynecology for various indications, including IOL medical management of miscarriage, and prevention and treatment of postpartum hemorrhage (135). Most studies regarding the pharmacokinetics of misoprostol have been conducted on healthy non-pregnant individuals or pregnant women undergoing termination of early pregnancy. Thus, no recent studies have been conducted on term pregnant women undergoing induction of labor. Understanding the pharmacokinetics of misoprostol is essential for optimizing its clinical use, ensuring efficacy, and minimizing adverse effects.

Key pharmacokinetic parameters include maximum plasma concentration ($C_{max}$), time to reach maximum concentration ($T_{max}$), area under the plasma concentration-time curve (AUC), and the time it takes for the plasma concentration of the drug to reduce by half (half-life; $t_{½}$). These parameters collectively describe the absorption, distribution, metabolism, and elimination of a drug.

*Absorption and routes of administration*

Misoprostol is rapidly absorbed after oral administration and is de-esterified into its active metabolite, misoprostol acid, which is responsible for its pharmacological effects (136) . The bioavailability of misoprostol varies significantly depending on the route of administration, which can influence both the drug's onset of action and its side effect profile.

*Oral administration*

Oral administration of misoprostol leads to a $T_{max}$ within 30 minutes, making it ideal for rapid intervention. However, plasma concentrations decline rapidly within 120 minutes (82, 137-139). The bioavailability can be influenced by factors such as food intake, which may delay absorption and reduce peak concentrations. While oral misoprostol is convenient and effective for fast action, it is also associated with gastrointestinal side effects, including nausea and diarrhea.

*Sublingual administration*

Sublingual administration results in even faster absorption than the oral route, with $T_{max}$ occurring within 25 minutes (82). This route bypasses the gastrointestinal tract, avoiding first-pass metabolism in the liver and thus providing higher bioavailability. While the rapid onset of action is beneficial, the sublingual route is also associated

with more pronounced side effects, such as shivering and fever, due to the higher peak plasma concentrations. Studies have shown that sublingual administration produces higher and more consistent plasma levels of misoprostol acid compared to vaginal administration, particularly in cases where vaginal bleeding may reduce absorption efficiency (140).

*Vaginal administration*

Vaginal administration, in contrast, leads to slower absorption but results in more sustained plasma levels. The drug is absorbed through the vaginal mucosa, with peak plasma concentrations reached within 60-75 minutes.(82, 138, 139). This slower absorption profile is often preferred for IOL because it provides a prolonged pharmacological effect with fewer systemic side effects. Vaginal misoprostol is favored for its localized action and the reduced likelihood of gastrointestinal issues.

*Buccal administration*

When administered buccally, misoprostol is placed between the cheek and teeth, allowing absorption through the buccal mucosa. Studies have shown that this route produces an absorption curve like that of vaginal administration, though with a lower AUC (139). The AUC is lower compared to sublingual administration (141). Compared to sublingual administration, buccal misoprostol provides lower peak plasma levels, making it a potential option in terms of efficacy and tolerability.

*Rectal administration*

The rectal route is primarily used in the context of postpartum hemorrhage (135). Rectal administration is associated with lower AUC compared to the vaginal and buccal routes (139).

*Distribution*

Misoprostol acid distributes extensively and rapidly throughout the body. The active metabolite binds to plasma proteins, primarily albumin, influencing its distribution and activity in various tissues, including the uterus.

Following this rapid distribution phase, a slower elimination phase occurs, allowing for sustained pharmacological effects. This distribution profile is important in determining dosing intervals and frequency, particularly in protocols requiring repeated doses for effective IOL or postpartum hemorrhage management.

*Metabolism*

Misoprostol undergoes extensive first-pass metabolism in the liver, where it is quickly converted to its active metabolite, misoprostol acid (142). The liver efficiently processes misoprostol, which explains its relatively short half-life and the need for frequent dosing in clinical applications.

The metabolism of misoprostol involves de-esterification, primarily by hepatic esterases, converting the prodrug into its active form. This rapid metabolic process allows for the quick onset of its therapeutic effects (82, 142).

*Elimination*

Misoprostol acid is eliminated primarily via the kidneys, with a smaller proportion excreted in the feces. The elimination half-life of misoprostol acid is approximately 40-60 minutes (141, 143). Due to its rapid metabolism and elimination, maintaining therapeutic levels often requires repeated dosing or sustained-release formulations. Given the short half-life, maintaining effective plasma concentrations requires careful consideration of dosing frequency route of administration and intervals.

*Clinical implications*

The knowledge of the pharmacokinetics of misoprostol, including its rapid absorption, widespread distribution, and metabolism by the liver followed by renal elimination, is important in managing its clinical effectiveness. Given its pharmacokinetic profile, consideration of the administration route and dosing regimen is essential to maximize therapeutic outcomes and minimize adverse effects. The choice of administration route could be tailored to the clinical scenario, with oral misoprostol being a route of preference for its convenience and rapid onset of action, despite its shorter duration and potential gastrointestinal side effects. In contrast, vaginal misoprostol may be more suitable for scenarios requiring a slower, sustained release with fewer systemic effects.

# Overall aims of the thesis

The overarching aim of this thesis is to investigate various aspects of induction of labor, particularly focusing on different methods and settings for administering misoprostol. The research aims to provide a detailed understanding of the efficacy, safety, and practical implications of these methods to improve obstetric outcomes and inform clinical practice. The specific aims of the thesis are as follows:

*Study I*

To investigate the relative bioavailability and pharmacokinetic profiles of two formulations of misoprostol administered via oral and sublingual routes.

*Study II*

To compare the effectiveness and safety of sublingual misoprostol versus oral misoprostol solution in inducing labor in term pregnant women.

*Study III*

To evaluate the feasibility, efficacy, and safety of outpatient induction of labor using oral misoprostol compared to inpatient induction in low-risk pregnancies.

*Study IV*

To evaluate whether the sequential use of oral misoprostol followed by the insertion of an intracervical balloon catheter reduces the induction-to-delivery interval in nulliparous women with prolonged pregnancy and an unfavorable cervix compared to oral misoprostol alone.

By addressing these aims, this thesis seeks to contribute to the field of obstetrics by offering insights that may enhance our understanding of induction of labor practices. The findings are intended to inform clinical guidelines, potentially improve patient outcomes, and support the development of more effective and patient-centered IOL strategies.

# Methodology

## Study I

*Study design and population*

This open-label, randomized, single-dose, comparative bioavailability study was conducted at the Department of Obstetrics and Gynecology, Skåne University Hospital in Lund and Malmö, Sweden, between 2014 and 2016. A total of 72 pregnant women were enrolled, all aged 18 years or older, with a singleton fetus in a cephalic position and a gestational age between 37 + 0 weeks and 42 + 0 weeks. Women were excluded if they had a known allergy to misoprostol or other prostaglandins, prior uterine scar, dead or anomalous fetus, liver or renal dysfunction, or multiple pregnancies.

*Interventions*

Participants were randomized into three groups to receive different doses and forms of misoprostol:

•Group A: Oral Angusta® 25 µg or Cytotec® solution (25 µg).

•Group B: Oral Angusta® 50 µg or Cytotec® solution (50 µg).

•Group C: Two tablets of Angusta® or Cytotec® 50 µg sublingually.

Blinding was maintained during the randomization process to avoid investigator bias. However, the treatment itself was not blinded due to the different administration forms requiring different preparations (e.g., tablet cutting for sublingual administration).

The oral misoprostol solution was prepared by dissolving one 200 µg tablet of Cytotec in 200ml of water, yielding 1 µg/mL.

*Primary and secondary outcomes*

The primary aim of this study is to evaluate the relative bioavailability by comparing the pharmacokinetic properties of two misoprostol formulations administered orally or sublingually, assessed through key pharmacokinetic parameters such as the area under the plasma concentration - time curve (AUC), maximum plasma concentration ($C_{max}$), time to reach maximum concentration ($T_{max}$), and elimination

half-life ($t_{½}$). Secondary outcomes included comparisons of these pharmacokinetic parameters between the different administration routes to evaluate their efficacy and safety profiles.

*Sampling and medical supervision*

Venous blood samples were collected at multiple time points post-administration (0, 5, 10, 20, 30, 40, 50, 75, 100, and 120 minutes, with additional samples at 180 and 240 minutes for Groups B and C). Blood samples were processed within 2 hours and stored at -20°C before being sent to York Bioanalytical Solutions, UK, for analysis. Throughout the study, patients were under continuous medical supervision at the labor ward, with tolerability assessed through monitoring adverse events and conducting physical examinations as needed.

*Drug analysis and pharmacokinetic evaluation*

Misoprostol acid concentrations in plasma were measured using a validated solid-phase extraction and liquid chromatography-tandem mass spectrometry method, with a detection range of 5–500 pg/ml. Pharmacokinetic parameters, including AUC, $C_{max}$, $T_{max}$, and $t_{1/2}$, were calculated using non-compartmental analysis via WinNonlin software (v. 6.3, Pharsight Corporation). Bioequivalence between test and comparator was assessed using dose-normalized ln-transformed AUC and $C_{max}$ values, with the 90% confidence interval for the geometric mean ratio required to fall within 80–125% to confirm bioequivalence. Relative bioavailability between oral and sublingual administration was calculated from preferably AUC, and otherwise from $AUC_{0-t}$.

*Statistical analysis*

Statistical analysis involved the use of the Kolmogorov-Smirnov test for normality, chi-square and Fisher's exact tests for comparison of categorical variables, and for comparison of normally distributed continuous variables the Student's t-test was used and for non-normally distributed continuous variables the Mann-Whitney U test was used. A p-value of $<0.05$ was considered statistically significant.

*Ethical considerations*

The study was conducted following ethical guidelines, with approval from the ethical review board of Lund (file record 2014/601) and the Swedish Medical Products Agency. All participants provided informed consent before enrollment. All data was un-identified and coded as to prevent identification. Participants undergoing IOL would receive an indwelling cannula as a regular procedure, and all blood samples were obtained through that cannula. Therefore, participants experienced no additional pain compared to standard procedure.

# Study II

*Study design*

This is a retrospective cohort study based on patients referred for IOL between January 1, 2013, and December 31, 2017, at the Department of Obstetrics and Gynecology, Skåne University Hospital, Lund, Sweden.

*Study population*

The study included women aged 18 years or older, carrying a live singleton fetus in a cephalic position, without major malformations, and who had not undergone previous cesarean delivery. These women were induced at a gestational age of ≥37+0 weeks using either oral or sublingual misoprostol. Patients induced by other primary methods, such as vaginal prostaglandin E2 gel or mechanical methods, were excluded from the study to focus on comparing the outcomes of sublingual and oral misoprostol administration.

*Interventions*

The two regimes compared in this study were:

•*Sublingual Misoprostol*: Cytotec® (Pfizer Inc., New York, USA) was administered as a quarter of a 200 µg tablet (50 µg) sublingually every 4 hours, with a maximum of 6 doses. Patients were instructed to keep the tablet sublingually for at least 5 minutes before swallowing.

•*Oral Misoprostol Solution:* A 200 µg tablet of misoprostol was dissolved in 100 ml of water to create a 2 µg/ml solution. Women received 10 ml (20 µg) for the first two doses, followed by 20 ml (40 µg) every 2 hours, up to a maximum of 12 doses.

*Primary and secondary outcomes*

The primary outcome was the CS rate, expressed as the inverse of the proportion of patients who delivered vaginally. Secondary outcomes included the induction-to-delivery interval, rate of vaginal delivery within 24 hours, incidence of postpartum hemorrhage (defined as blood loss >1,000 ml), Apgar score <7 at 5 minutes, and umbilical artery pH <7.10.

*Data collection*

Data was collected using a structured protocol form and extracted from electronic patient medical records (Obstetrix™). Collected data included demographic information (maternal age, body mass index, weight gain during pregnancy, and gestational age), modified Bishop's score before induction, and the specific indication for IOL. The data was anonymized and transferred to a Microsoft Excel™ spreadsheet for further analysis.

*Statistical analysis*

Statistical analyses were performed using SPSS software (version 24 for Apple OS X). The Kolmogorov-Smirnov test assessed the normality of continuous variables. The chi-square test was used for categorical variables, while the independent t-test and Mann-Whitney U test were employed for normally and non-normally distributed continuous variables, respectively. ANOVA was used to compare mean values.

To analyze the association between cesarean delivery and the method of induction, binary logistic regression was applied, adjusting for risk factors including maternal age, parity, gestational age, indication for induction, and Bishop's score. Results were presented as odds ratios (OR) with 95% confidence intervals (CI), and a p-value of $<0.05$ was considered statistically significant.

*Ethical considerations*

The study was approved by the regional ethics committee in Lund (file record: 2018/546). Due to the retrospective nature of the study, no treatment was given, and only patient charts were accessed and analyzed in an un-identified manner. Therefore, informed consent was not required and therefore waived.

# Study III

*Study design*

This retrospective study compared the outcomes of IOL with misoprostol administered at home versus in the hospital in low-risk pregnancies between January 1, 2019, and February 1, 2022, at the Department of Obstetrics and Gynecology, Skåne University Hospital, Lund, and Malmö, Sweden.

*Study population*

The study included low-risk term and post-term pregnant women with an unripe cervix, defined by a Bishop score ≤5, who received oral misoprostol for cervical ripening and IOL. Outpatient induction was offered to women meeting the inclusion criteria, which involved prolonged pregnancy, suspected large-for-gestational age fetus, or humanitarian reasons, while those with exclusion criteria (e.g., preterm gestation, hypertensive disorders, prior CS, see table 1 in the article) were not included.

*Study groups*

The study group consisted of women who began IOL at home and fulfilled the inclusion criteria, while the comparison group included women who underwent IOL

with misoprostol in the hospital. The comparison group was selected by matching outpatient IOL cases with hospital-based cases fulfilling the same inclusion criteria as the cases and according to labor unit, BMI, age, parity, and IOL indication.

*Protocol for outpatient IOL*

Eligible women underwent a clinical assessment, including vaginal examination, blood pressure measurement, fetal heart rate monitoring, and ultrasound to determine fetal presentation and amniotic fluid index. After consenting to outpatient IOL, patients received 5 tablets of misoprostol (Angusta®) 25 μg with a structured dosing schedule over 12 hours, starting in the evening and resuming the following morning. Patients were instructed to return to the hospital if contractions, rupture of membranes, bleeding, or decreased fetal movements occurred. Follow-up assessments were conducted at the hospital the next morning, with five additional doses administered in the outpatient setting if needed.

*Protocol for hospital IOL*

Hospital-based IOL followed a low-dose oral misoprostol protocol using a 200 μg misoprostol (Cytotec®) tablet dissolved in 100 mL of water, with 40 μg doses administered every 2 hours until active labor onset or cervical dilation of ≥3 cm. During 2019-2020 the first two doses were limited to 20 μg. A maximum of 12 doses was allowed, with balloon catheter placement as a secondary induction method if needed. After 2020, a secondary method, such as balloon catheter could also be considered for use after 4-6 doses of misoprostol.

*Outcome variables*

The primary outcome was the rate of vaginal delivery, and the duration of hospital stay before delivery. Secondary outcomes included induction-to-delivery interval, time from 5 cm cervical dilation to birth, total hospital stay duration, total dose of misoprostol, need for additional induction methods, oxytocin augmentation, and safety outcomes including Apgar score <7 at 5 minutes, umbilical cord pH <7.10, NICU admission, cesarean delivery for fetal distress, postpartum hemorrhage ≥1000 mL, obstetric anal sphincter injury and postpartum infection requiring antibiotics.

*Data collection*

Data were retrieved from the delivery register and perinatal records using ICD-10 diagnostic codes specific to outpatient IOL. Information included birth unit, delivery date, IOL setting (inpatient vs. outpatient), maternal age, BMI, parity, Bishop score, and neonatal outcomes. The induction-to-delivery interval was calculated from the first misoprostol dose to delivery. Outpatient participants reported the times of medication administration and returned any unused tablets to the hospital staff.

*Statistical analysis*

All data were analyzed using IBM SPSS Statistics for MAC (version 27). Categorical outcomes were assessed using Pearson's chi-square test, while continuous data were analyzed using Student's t-test if data was normally distributed or Mann-Whitney U tests if data was non-normally distributed. The Shapiro-Wilk test determined data normality. Relative risks with 95% confidence intervals were calculated for cesarean delivery, with statistical significance set at $p < 0.05$.

*Ethical considerations*

The study was approved by the Swedish Ethical Review Authority on March 28, 2022 (file record: 2022–01331-02). Due to the retrospective nature of the study, informed consent was not required and therefore waived.

# Study IV

*Study design*

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Skåne University Hospital in Malmö, comparing patients referred for IOL during two distinct time periods: January 1 to December 31, 2020, and January 1, 2022, to December 31, 2023. The year 2021 was excluded due to the implementation of new guidelines during that period, allowing adequate time for staff training and adjustment to the new protocol without compromising data consistency.

*Study population*

The study included primiparous women carrying a live, singleton fetus in a cephalic position, at or beyond 41 completed weeks of gestation, with intact membranes and having misoprostol as the primary IOL method. Data were collected from electronic medical records and included maternal demographic characteristics, obstetric history, indication for induction, method of induction, and delivery outcomes. All data were de-identified to maintain patient confidentiality.

*Interventions*

Two distinct protocols were compared:

•*2020 Protocol*: Oral misoprostol was administered for 24 hours. A 200-µg tablet of misoprostol was dissolved in 100 mL of water to create a 2 µg/mL solution. Women received 20 mL (40 µg) of the solution every two hours, up to a maximum of 12 doses.

•*2022-2023 Protocol*: Sequential administration of oral misoprostol followed by intracervical balloon catheter insertion. Women received 20 mL (40 µg) of the oral misoprostol solution described above every two hours. If the cervix was unfavorable after 4-6 doses, a cervical balloon catheter was inserted and filled with 60 mL of NaCl solution. Women then received 25 mL (50 µg) of oral misoprostol every four hours, up to a maximum number of 4 doses. The catheter was kept in place for a maximum of 18 hours, with amniotomy performed within one hour of catheter expulsion.

*Outcome variables*

The primary outcome was the time from induction to vaginal delivery. Secondary outcomes included mode of delivery (vaginal, instrumental, or cesarean section), vaginal delivery within 24 and 48 hours, postpartum hemorrhage (blood loss >1000 mL), Apgar score <7 at 5 minutes, umbilical artery pH <7.10, and the rate of 3rd or 4th degree perineal tears.

*Data collection*

Data were collected from the electronic medical records, including demographic details (age, BMI, and gestational age), obstetric history, Bishop score at admission, method of induction, and delivery outcomes. The bishop score was determined upon arrival at the delivery ward. The cervix was classified as unfavorable if the Bishop score was ≤5. Data were anonymized and transferred to a spreadsheet for further analysis.

*Statistical analysis*

Data analysis was performed using SPSS software (version 29 for Apple OS X). Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, depending on distribution. Categorical variables were summarized using frequencies and percentages. The induction-to-delivery interval and other continuous outcomes were compared between the two protocols using the Student's t-test or Mann-Whitney U test, as appropriate. Categorical outcomes were compared using chi-square or Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

*Ethical considerations*

The study was approved by the regional ethics committee in Lund (2018/549), and an amendment by the Swedish Ethical Review Authority (2022-01331-02). Due to the retrospective nature of the study, informed consent was not required and therefore waived.

# Summary of findings

## Study I

This study aimed to evaluate the relative bioavailability of two formulations of misoprostol: Angusta (25 µg) and Cytotec (200 µg), administered via oral and sublingual routes. The study included 72 women admitted for induction of labor at term. No significant differences in demographic characteristics were found between the study groups. The study could not confirm bioequivalence between the two formulations, as the 90% confidence intervals for bioavailability exceeded the accepted range of 80–125%. For Angusta tablets, sublingual administration resulted in a 20–30% higher bioavailability compared to oral administration. Similar results were observed with Cytotec tablets given sublingually, where comparison to the oral route also demonstrated increased bioavailability. Additionally, the time to reach maximum plasma concentration ($T_{max}$) was shorter with oral misoprostol solution compared to misoprostol tablets. The maximum plasma concentration ($C_{max}$) was higher with the sublingual route compared to the oral route for both formulations.

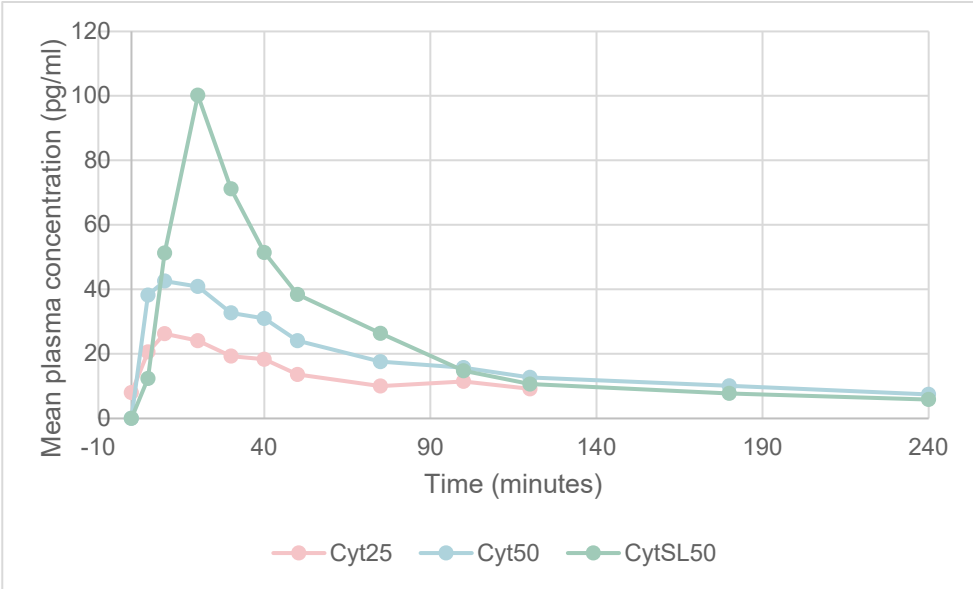


**Figure 2.** Mean plasma concentration-time profiles of misoprostol acid after one dose of misoprostol solution (Cytotec) administered through oral route and misoprostol cut tablet through sublingual route. Cyt25 – oral misoprostol solution 25 µg, Cyt50 – oral misoprostol solution 50 µg, CytSL50 – sublingual misoprostol cut tablet 50 µg.

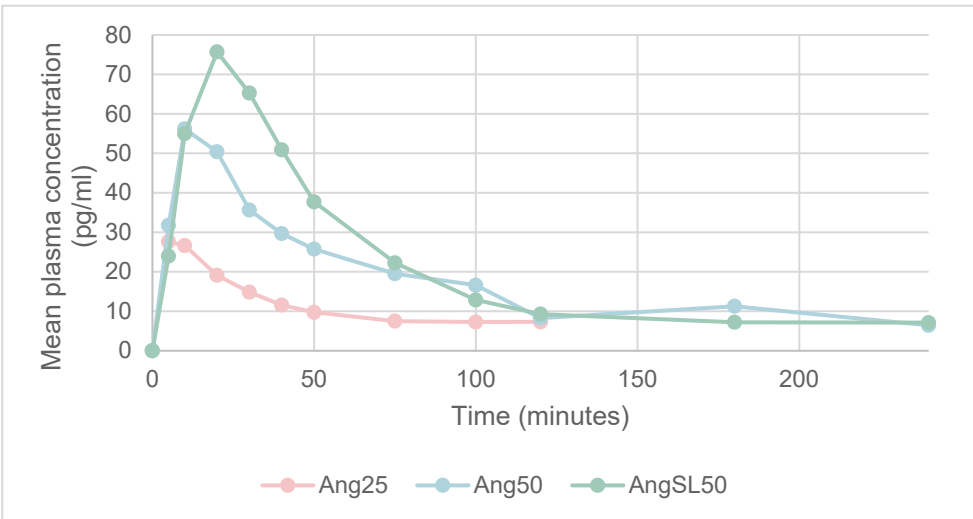


**Figure 3.** Mean plasma concentration-time profiles of misoprostol acid after one dose of misoprostol tablet (Angusta) in oral and sublingual routes. Ang25 – oral misoprostol tablet 25 µg, Ang50 – oral misoprostol tablet 50 µg, AngSL50 – sublingual misoprostol tablet 50 µg

## Study II

This retrospective cohort study compared the outcomes of 2,404 women who underwent labor induction using either sublingual (n=974) or oral misoprostol (n=1,430). Among primiparous women, the cesarean delivery rate was significantly higher in the sublingual group compared to the oral group (28.6% vs. 20.5%, $p < 0.001$). Conversely, in multiparous women, the cesarean delivery rates did not show a significant difference between the sublingual and oral groups (7.5% vs. 4.9%, $p = 0.055$). The time to vaginal delivery was shorter with sublingual administration for both primiparous and multiparous women, with primiparous women delivering in 16.7 hours compared to 21.7 hours in the oral group ($p < 0.001$) and multiparous women delivering in 9.9 hours compared to 13.3 hours ($p < 0.001$). The success rate of achieving vaginal delivery within 24 hours was higher in the sublingual group for both parity groups. Neonatal outcomes, including Apgar scores less than 7 at 5 minutes, did not differ significantly between the two routes for primiparous women. However, in multiparous women, a statistically significant difference in arterial cord pH <7.10 was observed between the sublingual and oral groups, though the number of recorded events was low, suggesting that this finding should be interpreted with caution.

**Table 1.** Primary and secondary outcomes in study II.

| | Primipara | | | Multipara | | |
|---|---|---|---|---|---|---|
| | **Oral solution n=776** | **Sublingual n = 559** | **p-value** | **Oral solution n = 654** | **Sublingual n = 415** | **p-value** |
| **Mode of delivery** | | | p=0.000 | | | p=0.055 |
| Vaginal | 510 (65.7) | 316 (56.5) | | 608 (93) | 377 (90.8) | |
| Instrumental | 107 (13.8) | 83 (14.8) | | 14 (2.1) | 7 (1.7) | |
| Cesarean section | 159 (20.5) | 160 (28.6) | | 32 (4.9) | 31 (7.5) | |
| Time from induction to vaginal delivery (hours) | 21.7 (11.3) | 16.7 (10.3) | p<0.001 | 13.3 (11.9) | 9.9 (7.8) | p=0.000 |
| Vaginal delivery <24h | 390 (63.2) | 310 (77.7) | p<0.001 | 524 (84.2) | 358 (93.2) | p=0.000 |
| PPH >1000ml | 91 (11.7) | 48 (8.6) | 0.064 | 44 (6.7) | 28 (6.7) | p=0.982 |
| Apgar score <7 at 5' | 11 (1.4) | 13 (2.3) | 0.218 | 7(1.1) | 8 (1.9) | p=0.243 |
| aPH <7.10 (%)* | 39 (7.2) | 14 (5.8) | 0.473 | 18 (4.1) | 14 (9.1) | p=0.02 |

Values are numbers (%) except for time from induction to vaginal delivery presented as median (interquartile range). PPH, postpartum haemorrhage.

*Percentages of pH < 7.10 among neonates with obtained umbilical cord blood samples. Primipara 542 samples in the oral group vs 241 in the subligual group. Multipara 439 samples in the oral group vs 154 in the sublingula group.

## Study III

This study included 564 women who underwent labor induction with oral misoprostol, either as outpatients (n=282) or inpatients (n=282). The primary outcomes were the rate of vaginal delivery, and the duration of hospital stay. The study found no significant difference in the rate of vaginal delivery between the outpatient and inpatient groups (84.8% vs. 86.2%; $p = 0.5$). However, the median time from hospital admission to delivery was significantly shorter for the outpatient group compared to the inpatient group (12.8 hours vs. 20.7 hours; $p < 0.001$). Additionally, the total hospital stay was reduced by one day in the outpatient group, with a median stay of 2 days versus 3 days in the inpatient group ($p < 0.001$). The inpatient group required more secondary induction methods, with 33.3% needing additional interventions compared to 25.5% in the outpatient group ($p = 0.042$). Oxytocin augmentation was more commonly used in the outpatient group (65% vs. 52%; $p = 0.003$). Safety outcomes, including NICU admissions (5.3% in the outpatient group vs. 3.5% in the inpatient group; $p = 0.31$) and postpartum hemorrhage (11.3% in the outpatient group vs. 12.1% in the inpatient group; $p = 0.77$), showed no significant differences between the groups.

**Table 2.** Primary and secondary outcomes of study III

| | Misoprostol outpatient n=282 | Misoprostol inpatient n=282 | p-value |
|---|---|---|---|
| **Primary outcomes** | | | |
| Vaginal delivery | 238 (84.4) | 243 (86.2) | 0.552 |
| Duration from hospital admission to delivery (hours), median (IQR) | 12.8 (14.4) | 20.7 (17.1) | <0.001 |
| **Secondary outcomes** | | | |
| Caesarean delivery for fetal distress | 15 (5.3) | 16 (5.7) | 0.55 |
| Caesarean delivery for dystocia, failed induction or maternal exhaustion | 26 (9.2) | 21 (7.4) | 0.63 |
| Instrumental delivery for fetal distress | 17 (6.0) | 19 (6.7) | 0.64 |
| Instrumental delivery for dystocia or maternal exhaustion | 11 (3.9) | 17 (6.0) | 0.45 |
| Additional methods of induction | 72 (25.5) | 94 (33.3) | 0.042 |
| Amniotomy | 157 (55.7) | 149 (52.8) | 0.49 |
| Need for oxytocin infusion | 184 (65.2) | 149 (52.8) | 0.003 |
| Total hospital stay (days) median (IQR) | 2 (2) | 3 (2) | <0.001 |
| Total dose misoprostol (µg), mean rank (IQR) | 253.3(175) | 297(120) | <0.001 |
| Induction start to birth (hours), median (IQR) | 30.4 (19.2) | 20.7 (17.1) | <0.001 |
| Apgar score <7 at 5 minutes | 3 (1.1) | 3 (1.1) | 0.99 |
| Arterial umbilical cord pH below 7.10[a] | 8 (4.8) | 8 (4.8) | 0.99 |
| Admission to NICU | 15 (5.3) | 10 (3.5) | 0.32 |
| Postpartum hemorrhage >1000ml[b] | 31 (11.3) | 34 (12.1) | 0.77 |
| Postpartum infection | 6 (2.1) | 5 (1.8) | 0.76 |
| Rate of 3rd or 4th degree perineal tear | 9 (3.2) | 13 (5.3) | 0.41 |

Values are number (%) unless stated otherwise
[a]Total number with analysis of cord artery pH: 166 outpatients and 167 inpatients.
[b]Total number with documented blood loss: 275 outpatients and 275 inpatients.

## Study IV

This retrospective cohort study compared the outcomes of 664 nulliparous women with prolonged pregnancies (≥41 weeks) and an unfavorable cervix who underwent labor induction with either oral misoprostol alone (n=268) or during a period where a sequential regimen of oral misoprostol followed by an intracervical balloon catheter could be used (n=396). The study found that the median induction-to-delivery interval was significantly shorter in the sequential group compared to the misoprostol-only group (21.8 hours vs 23.0 hours, p=0.003). There were no significant differences between the groups in terms of CS rate between the two groups (19.9% vs. 21.3%, p=0.68). No significant differences with regards to the rates of vaginal delivery within 24 hours (49.2% vs. 45.5%, p=0.40) and within 48 hours were found (79.0% vs. 76.1%, p=0.11). In terms of maternal and neonatal safety outcomes, there were no significant differences in the rates of postpartum hemorrhage >1000 ml (12.1% vs. 9.7%, p=0.33), severe perineal lacerations (3.0% vs. 3.7%; p=0.62), or Apgar scores <7 at 5 minutes (1.3% vs. 1.1%, p=0.87). Additionally, there was no significant difference in the incidence of neonatal umbilical cord artery pH <7.10.

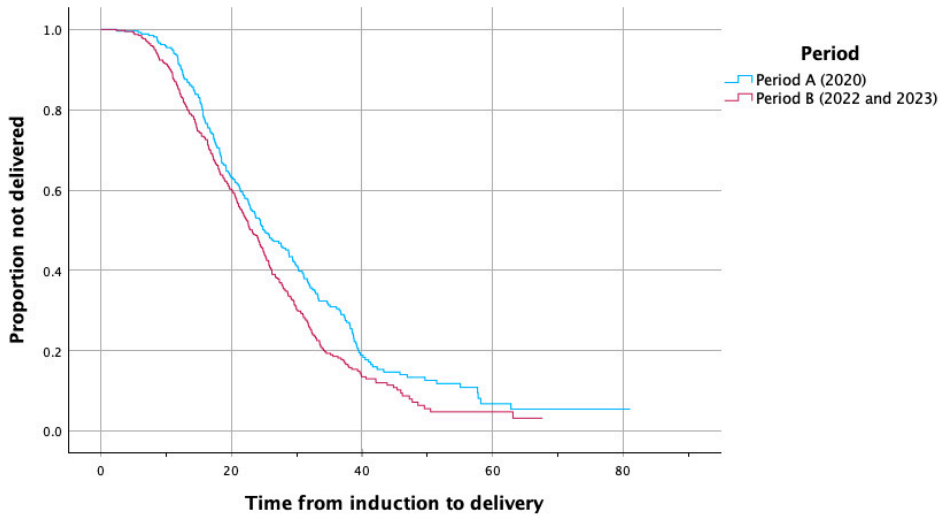


**Figure 4.** Kaplan-Meier curve showing the proportion of women not yet delivered by time from induction to vaginal delivery in hours in period A (2020) vs period B (2022 and 2023).

# General discussion

## Interpretation of Results

The results of this thesis offer a nuanced perspective on the pharmacokinetics and clinical outcomes associated with various misoprostol formulations and induction protocols. These findings not only align with existing theoretical frameworks in pharmacokinetics and obstetrics but also extend the understanding of misoprostol's effectiveness and safety in labor induction.

Firstly, the study comparing the bioavailability of Angusta and Cytotec formulations confirmed the theoretical expectation that sublingual administration enhances bioavailability, resulting in higher peak plasma concentrations compared to oral administration. This finding supports the pharmacokinetic model suggesting that sublingual administration allows for more direct absorption, bypassing first-pass hepatic metabolism, leading to higher bioavailability compared to the same dose given orally. These results are in line with earlier pharmacokinetic studies where misoprostol administered through different routes were compared in women undergoing termination of pregnancy in earlier gestational weeks (82). Interestingly, the oral solution demonstrated a higher AUC and $C_{max}$ compared to oral tablets or solutions of misoprostol. This highlights the potential importance of formulation differences in clinical decision-making, especially when rapid and predictable drug absorption is required. The findings also suggest that sublingual administration could be an option for achieving higher systemic levels of misoprostol, influencing both dosing decisions and the choice of administration routes in labor induction. However, the properties of sublingual administration could with the oral route be mitigated with a compensatory increase in the dosage given or the frequency of dosing. The oral route could therefore be a better alternative in protocols of IOL where titration of misoprostol is a factor of importance.

In the comparative analysis of sublingual versus oral misoprostol, the finding that sublingual administration led to a higher rate of vaginal delivery within 24 hours and a shorter time to delivery could show to a potential efficacy of sublingual routes in accelerating labor. However, the observed increase in cesarean delivery rates among primiparous women indicates a trade-off between faster induction and the potential for operative interventions. This challenges the assumption that quicker induction methods are universally beneficial, underscoring the need for individualized approaches based on factors such as patient parity and clinical

situation. A recent meta-analysis concluded that sublingual misoprostol has a higher rate of vaginal delivery within 24 hours and a shorter induction to delivery interval compared to vaginal misoprostol. The analysis also found that the vaginal route was superior to the oral route regarding these outcomes. No significant differences in the CS rate was found between the routes (87). The shorter interval-to-delivery and vaginal delivery within 24 hours are comparable to our results from study II. The non-significant difference in lower CS rate contrasts with our results, where a higher CS rate was found with the sublingual route. Several smaller studies have compared sublingual to oral misoprostol. Siwatch et al. found no differences in CS rate comparing 25 ug of misoprostol administered orally versus sublingually (144). Datta et al. showed that sublingual misoprostol was associated with a greater change in Bishop score with no significant differences in CS rate compared to the oral route (145). Malik et al. conducted a RCT involving 100 women with PROM, comparing 100ug of misoprostol given orally to 50ug given sublingually. The authors found that sublingual misoprostol was associated with a higher rate of vaginal delivery within 12 hours compared to the oral route. They also found higher CS rate with the sublingual route although the difference was not statistically significant (146). This aligns with the results from study II where we found a shorter induction to delivery interval, yet a higher CS rate compared to the oral route.

The evidence available regarding the direct comparison of sublingual versus oral misoprostol is not sufficient to draw firm conclusions regarding rare adverse outcomes. However, the results from study II adds to the growing evidence.

The evaluation of outpatient versus inpatient induction protocols shed new light on the feasibility of outpatient care for labor induction in low-risk women. The similar vaginal delivery rates between both groups, with reduced time from hospital admission to delivery and shorter hospital stays in the outpatient group in study III, suggest that outpatient induction can be an effective alternative, particularly for low-risk pregnancies. These findings are similar to several meta-analyses available, showing that for low-risk pregnancies, shorter admission to delivery times without compromising CS rates, maternal- or neonatal outcomes are found (110, 111, 147-150). Studies also showing to the overall higher patient satisfaction with outpatient IOL further supports the broader adoption of outpatient induction protocols as an important strategy to optimize healthcare resource utilization without compromising patient safety in the context of mitigating the rising induction rate worldwide (114, 115)

Finally, study IV explored the adoption of a protocol where the sequential use of oral misoprostol followed by an intracervical balloon catheter demonstrated increased efficacy in shortening the induction-to-delivery interval without increasing adverse outcomes. This result reinforces the reasoning for combining pharmacological and mechanical methods to optimize cervical ripening and labor progression, particularly in cases of unfavorable cervixes. The shorter time from induction to delivery and no significant differences in CS rate or neonatal outcomes

found in this study is supported by several other studies (124, 125, 128, 151). The success of this method suggests it could be a valuable strategy for improving induction efficiency in specific patient populations.

Taken together, these findings contribute to the existing body of knowledge by emphasizing the importance of balancing pharmacokinetic properties and clinical outcomes when designing labor induction protocols. The results offer deeper insights into how misoprostol formulations and induction strategies can be tailored and utilized to optimize both efficacy and safety in obstetric practice.

# Implications for the field

The findings from this thesis have potential implications for both clinical practice and theoretical understanding in the field of obstetrics, particularly concerning the optimization of labor induction protocols using misoprostol.

While sublingual misoprostol demonstrates higher systemic levels, the oral route offers distinct advantages that warrants consideration. Although study I showed that oral misoprostol has lower bioavailability, the similar $T_{max}$ and half-life of the oral misoprostol suggest that with a more frequent or adjusted dosing, its effect can closely resemble that of sublingual administration, thereby mitigating the possibility of one route being more efficient than the other. Moreover, the lower CS rate found in study II make it a safer option over the sublingual route, especially for primiparous women, where avoiding that first CS is vital.

The rising rates of IOL puts a strain on existing resources in delivery wards globally. Therefore, the support for outpatient induction protocols, particularly in terms of reducing hospital stay without compromising safety or effectiveness, could influence changes in practice guidelines and serve as an additional tool. Widespread adoption of outpatient induction, particularly with oral misoprostol in low-risk pregnancies, could alleviate the pressure on hospital resources while maintaining high levels of patient safety and satisfaction.

The success of the sequential induction method combining oral misoprostol with a Foley catheter also highlights a practical strategy for managing difficult inductions, particularly in women with an unfavorable cervix. This approach could be integrated into clinical guidelines as a strategy to improve induction outcomes in cases where traditional methods may be less effective. By shortening the induction-to-delivery interval without increasing adverse outcomes, this sequential method offers a way to enhance both the efficiency and effectiveness of labor induction.

# Limitations

While the findings of this thesis contribute valuable insights into the optimization of labor induction protocols using misoprostol in different methods and settings, several limitations must be acknowledged that may affect the interpretation and generalizability of the results.

*Study design*

Most of the studies conducted were retrospective cohort studies, which inherently limit the ability to establish causality. Retrospective studies are prone to biases, including selection bias and information bias, as they rely on existing medical records that may not capture all relevant variables or may include incomplete data. The absence of randomization further complicates controlling for confounding variables, which could have influenced the observed outcomes.

*Sample size and population*

Although the studies included relatively large sample sizes, particularly in the comparative analysis of sublingual versus oral misoprostol, the findings may not be generalizable to all populations. The focus on specific groups, such as nulliparous women and those at term, may limit the applicability of the results to other populations, including multiparous women, women with preterm pregnancies, or those with specific comorbidities or various indications for IOL. Additionally, the small sample size in the pharmacokinetic study on misoprostol formulations may affect the robustness and generalizability of the findings. Studies II-IV were not large enough to detect true differences in rare outcomes.

*Data quality and measurement*

The reliance on electronic medical records introduces potential issues with data quality. Inconsistent documentation practices, incomplete records, and missing data could affect the accuracy of the findings. For example, the limited number of recorded events for certain outcomes, such as neonatal arterial pH, may restrict the ability to draw definitive conclusions.

*External validity*

The studies were conducted in specific clinical settings, which may limit the generalizability of the findings to other healthcare environments. The results of the

outpatient versus inpatient induction study, for instance, may not apply universally to healthcare systems with differing resources, patient populations, or practices. The single-center nature of certain studies further constrains the generalizability of the findings to broader contexts.

*Unmeasured confounding*

Despite efforts to control for confounding variables, the possibility of unmeasured factors influencing outcomes remains. Patient characteristics such as underlying health conditions or obstetric history, which were not fully accounted for, may have impacted the results. Changes in staff and protocols over the period of the thesis could also have influenced the results.

*Variability in protocols*

Differences in induction protocols across studies, including dosing schedules and administration routes, could introduce variability that complicates direct comparisons. The lack of standardized protocols may affect the consistency and broader applicability of the findings.

In summary, while this thesis provides valuable insights into misoprostol-based labor induction, these limitations highlight the need for cautious interpretation of its' findings and suggest areas for further research to validate and expand upon these findings.

# Future perspectives

Building on the findings and limitations of this thesis, several directions for future research are recommended to further optimize labor induction protocols using misoprostol.

*Prospective, randomized controlled trials*

Future research should focus on conducting prospective, randomized controlled trials to address the inherent limitations of retrospective studies. RCTs would provide a higher level of evidence by reducing biases and allowing for more definitive conclusions on the efficacy and safety of different misoprostol formulations and routes of administration.

*Expansion of study populations*

Most obstetric research refer to smaller patient populations or sizes, combining both parity groups when comparing certain outcomes. Future studies should aim to include a broader range of populations to enhance the generalizability of findings. Research exploring the effects of misoprostol in multiparous women, women with preterm pregnancies, and those with comorbidities or specific indications for IOL is needed. A woman requiring IOL for PROM or IUGR might need a different and careful approach compared to a woman with preeclampsia where a faster IOL process might be more beneficial in that situation. Additionally, studies in diverse geographic and healthcare settings would help determine the applicability of findings across various populations.

*Standardization of protocols*

IOL protocols display large variability across countries but even across delivery clinics within that country. When using different protocols there is an inherent difficulty to compare outcomes and assess what measures improve outcomes across these different protocols. There is a need for research focused on standardizing misoprostol induction protocols. Studies could compare the effectiveness of standardized dosing schedules, administration routes, and sequential methods across populations and various indications. Establishing such protocols could help reduce variability in practice and improve outcome consistency and make comparisons in outcomes between studies and protocols easier.

*Longitudinal studies on maternal and neonatal outcomes*

As clinicians in obstetric care, we emphasize primarily on short term outcomes, such as CS or maternal bleeding. What impact does our methods and protocols have on our women and their children in the long run? Future research could include longitudinal studies that follow mothers and neonates over time to assess both immediate and long-term outcomes. These studies could explore postpartum recovery, breastfeeding success, maternal satisfaction, and neonatal development, offering a comprehensive view of the impact of misoprostol-based induction methods.

*Exploratory studies on pharmacokinetics*

Deeper research into the pharmacokinetics of misoprostol, particularly across different formulations and routes of administration, could significantly enhance our understanding of its clinical applications. Further research into repeated dosing and its effects on drug accumulation, as well as determining when a steady state is reached in term pregnant women, would also be highly valuable. Additionally, studies examining how misoprostol's target organs, particularly the uterus and cervix, respond to measurable serum concentrations over time could offer important insights.

Such research could play an important role in refining dosing strategies to improve efficacy while minimizing adverse effects. By gaining a deeper understanding of misoprostol's pharmacokinetics, future protocols for labor induction could be tailored to specific patient populations, optimizing outcomes in both routine and high-risk cases.

*Patient-centered research*

Given the importance of patient satisfaction and experience in obstetric care, future studies should also incorporate patient-reported outcomes and preferences. Research that delves into women's experiences with different induction methods, including their pain perceptions, overall satisfaction, and birth experiences, would provide insights for the development of more patient-centered induction protocols. Such patient-centered research could also inform strategies that enhance patient comfort and support informed decision-making during the labor induction process.

In summary, future research should aim to address the limitations highlighted in this thesis while expanding the scope of investigation into misoprostol-based labor induction. By exploring new dimensions - ranging from pharmacokinetics to patient-centered outcomes - future studies will be instrumental in refining clinical guidelines, improving patient outcomes, and advancing the field of obstetrics!

# Conclusions

The analysis of Angusta and Cytotec formulations could not confirm bioequivalence between the two formulations. Sublingual administration leads to higher bioavailability and a greater maximum plasma concentration compared to the oral route.

The comparison of oral and sublingual misoprostol revealed that the oral route was associated with a lower cesarean delivery rate, especially in primiparous women. Conversely, sublingual administration resulted in a higher rate of vaginal deliveries within 24 hours and a shorter induction-to-delivery time, highlighting the trade-off between speed of induction and the likelihood of cesarean delivery.

Outpatient induction with oral misoprostol was found to reduce the time from hospital admission to delivery and overall hospital stay without compromising delivery outcomes or safety, supporting it as a viable option for low-risk pregnancies.

The sequential use of oral misoprostol followed by a intracervical balloon catheter significantly shortened the induction-to-delivery interval without increasing adverse outcomes, making it an effective approach for women with an unfavorable cervix.

# Methodological considerations

*Study designs and approaches*

The four studies incorporated a range of methodological designs to explore the use of misoprostol for labor induction, each contributing uniquely to the overall understanding of this clinical intervention. While most of the studies were retrospective cohort studies, one was a randomized, open-label comparative bioavailability study. These designs reflect the complexities and practical considerations in obstetric research but also introduce inherent strengths and weaknesses.

*Study I*, as a randomized open-label study, focused on the pharmacokinetics of misoprostol, comparing the bioavailability of two formulations across the oral and sublingual route. The controlled environment and rigorous analysis allowed for precise pharmacokinetic measurements, which are essential for optimizing dosing strategies. However, the study's open-label nature, combined with its relatively small sample size, may limit the generalizability of its findings and introduce potential biases. One potential limitation is that the pharmacokinetics were studied after a single dose, rather than after repeated doses. In clinical practice, multiple doses of misoprostol are often required during IOL to achieve the desired effect. Investigating the pharmacokinetics after repeated dosing, including where steady-state concentrations occur, could provide further insights into how misoprostol behaves throughout the induction process.

In contrast, *Studies II, III*, and *IV* employed retrospective cohort designs, drawing from large datasets based on real-world clinical practice. These designs enabled the examination of outcomes across a broader population, enhancing the external validity of the findings. However, the retrospective nature of these studies also introduced inherent limitations, such as the lack of control over data collection, and raised concerns about selection bias and confounding factors. The non-randomized design further complicates the interpretation of results, making it difficult to establish a direct causal relationship between the interventions and outcomes.

*Population and sample size considerations*

The population and sample sizes across the studies varied significantly. Study I, with its smaller, controlled sample of 72 participants, is typical for pharmacokinetic research but limits the general applicability of the findings. In contrast, the

retrospective cohort studies -Studies II, III, and IV - encompassed much larger sample sizes, ranging from several hundred to over 2400 participants. These larger cohorts provided sufficient power to detect differences between intervention groups, thus improving the reliability of the results.

However, population variability in the retrospective studies presented challenges. For instance, Study II included a large, diverse population, but the absence of randomization may have introduced confounding factors that could have influenced the outcomes. Similarly, while Study III matched outpatient and inpatient groups based on key variables, differences in protocols and the absence of a power analysis could raise questions about the robustness of its findings. Study IV, which focused on a specific group - primiparous women with post-term pregnancies and unfavorable cervices - minimized confounding by narrowing the population scope. However, its single-center design may limit the generalizability of the findings beyond that specific setting and patient selection.

*Induction protocols and outcome measures*

The studies explored various misoprostol induction protocols, including oral, sublingual, and sequential methods. Study I provided detailed insights into the pharmacokinetics of misoprostol, essential for optimizing dosing regimens. Studies II and III compared different administration routes and settings (sublingual vs. oral, outpatient vs. inpatient), while Study IV evaluated the sequential use of misoprostol with a balloon catheter.

While the diversity of protocols reflects the ongoing effort to identify the most effective induction method, it also complicates direct comparisons between the studies. Outcome measures varied accordingly, from pharmacokinetic parameters in Study I to clinical outcomes like cesarean delivery rates, time to delivery, and neonatal outcomes in the other studies. Although these outcomes are clinically relevant, the variation in how they were measured across studies presents challenges when attempting to compare the results.

*Strengths and weaknesses in the methodological approaches*

Several strengths can be identified across the studies. For example, the retrospective cohort studies benefited from the use of real-world data, which enhances external validity. In addition, the controlled conditions in Study I provided valuable pharmacokinetic data, while the large sample sizes in Studies II and IV improved the reliability of the findings. Moreover, the focus on well-defined patient groups in Study IV helped to minimize confounding factors.

Nevertheless, the weaknesses are also evident. The retrospective design of most studies limits control over confounding variables, and the non-randomized nature of these studies introduces potential biases. Additionally, the open-label design of Study I, though offering precision in pharmacokinetic data, may have led to observer

bias. Study IV's single-center focus further reduces the generalizability of its findings. Furthermore, the lack of power analysis in Study III may have introduced additional limitations in interpreting the results. In study II and IV we have compared two protocols across different time periods, which introduces a potential bias. External factors out of our control, such as change in staff or adjustments to other routines could have influenced the results. In summary, studies II-IV with their inherent different protocols did not have sample sizes large enough to detect rare outcomes and adverse events, including mortality.

*Alternative methods considered*

Across the studies, alternative methodologies such as RCTs and prospective cohort studies were considered but not implemented, primarily due to logistical and resource constraints. RCTs would have provided higher internal validity by minimizing bias through randomization, but they are challenging to conduct in obstetric settings. Many obstetrics units already operate with limited resources, and the diversion of staff and funding away from clinical care to support research activities could potentially strain already limited capacities. RCTs usually require dedicated research staff and in some cases long term follow-up to monitor outcomes - all of which demand significant resources and financial investment. Logistical challenges also make RCTs difficult to implement in obstetrics. Recruitment can be challenging because many women may be reluctant to participate in a trial that could place them or the baby at a perceived or actual risk. There might also be little time and room for randomization or waiting for research protocols to be followed without delaying essential care. Prospective cohort studies could offer more controlled data collection, reducing recall bias and improving the consistency of the findings. However, these studies come with their own set of limitations, including the difficulty of controlling for all potential confounders.

# Populärvetenskaplig sammanfattning

Igångsättning av förlossning, även kallad induktion av förlossning är en av de vanligast förekommande obstetriska interventionerna på förlossningskliniker idag. Incidensen av induktioner har ökat markant senaste åren globalt, och i vissa länder induceras nästan var tredje förlossning. Riskerna med induktioner kan innefatta bland annat en ökad förekomst av långdragna förlossningar, instrumentell förlossning samt en ökad risk för kejsarsnitt. Idag använder man både mekaniska och farmakologiska metoder för att sätta i gång en förlossning. Den vanligaste använda mekaniska metoden är ballongkateter, vilket ämnar att på mekanisk väg främja frisättning av det kroppsegna hormonet prostaglandin. Detta hormon verkar genom att stimulera värkar men även genom att mjukgöra och vidga livmodertappen så att förlossningen kan starta. De vanligaste farmakologiska metoderna innefattar att man tillför en syntetisk prostaglandinanalog via olika administrationsvägar och beredningar. De två vanligaste använda prostaglandinanalogerna är misoprostol (prostaglandin E1) samt Dinoproston (prostaglandin E2). Det är inte fullt utforskat vilken metod som är den bästa. Det är heller ej fastställt vilken administrationsväg som är mest effektiv och säkrast vad gäller induktioner. Den kraftigt ökande andelen av induktioner leder även till att många förlossningsklinikers vårdplatser tas upp av patienter som behöver induktion vilket ökar belastningen på personal och upptar resurser som möjligtvis hade kunnat användas på ett mer effektivt sätt.

I detta avhandlingsarbete, som består av fyra delarbeten, studeras induktion av förlossning med misoprostol där jämförelse mellan administrationssätt, start av igångsättning i hemmet eller på sjukhus samt olika metoder utförs. Det övergripande syftet med avhandlingen är att bidra med ökad klinisk kunskap inom induktioner och att främja och stödja framtida klinisk forskning inom induktioner för att förbättra förlossningsutfall.

***I det första delarbetet*** studerades två olika misoprostolberedningar via två administrationsvägar, oralt via munnen samt sublingualt under tungan. Det primära syftet var att jämföra om dessa två beredningar kunde bedömas vara likvärdiga varandra. Vidare jämfördes andra farmakokinetiska parametrar som utfallsmått, som maximal plasmakoncentration, tid till max plasmakoncentration samt halveringstid. I denna randomiserade studie inkluderades totalt 72 fullgångna kvinnor som var planerade för att få förlossningen inducerad. Blodprover togs vid specifika tidpunkter och analyserades. Studien kunde inte visa att de två misoprostolberedningarna var statistiskt sett fullt likvärdiga vad gäller

biotillgänglighet. Studien kunde dock visa att misoprostol administrerat via den sublinguala vägen uppvisade 20–30% ökad biotillgänglighet av läkemedel jämfört med när läkemedlet gavs oralt. Tiden som det tog att nå maximal plasmakoncentration var kortare med den orala misoprostol lösningen jämfört med misoprostol tabletter. Den maximala koncentrationen av läkemedel var högre via den sublinguala administrationsvägen jämfört med den orala för båda beredningarna. Anledningen till att beredningarna ej säkert kunde påvisas likvärdiga kan bero på de relativt låga doserna som patienterna gavs över en kort tid samt att de gravida kvinnorna ej var fastande i samband med induktionen.

***I delarbete II*** utfördes en retrospektiv studie som jämförde induktion av förlossning med sublingualt administrerad misoprostoltablett jämfört med en oralt administrerad misoprostol lösning. Totalt inkluderades under en 5-årsperiod 2,404 kvinnor fördelat på 974 kvinnor i den sublinguala gruppen samt 1,430 i den orala gruppen. Studien visade att frekvensen för kejsarsnitt hos förstföderskor var signifikant högre i den sublinguala gruppen jämfört med den orala gruppen men för omföderskor kunde inte detta statistiskt säkerställas. Risken för kejsarsnitt var försatt förhöjd i den sublinguala gruppen även vid justering för vissa faktorer, såsom ålder, BMI samt cervix mognadsgrad. Tiden från induktion till vaginal förlossning var signifikant kortare hos kvinnor i den sublinguala gruppen, både för förstföderskor samt omföderskor. Frekvensen av vaginal förlossning inom 24 timmar var högre i den sublinguala gruppen jämfört med den orala, både för förstföderskor samt omföderskor. Studien visar att oral misoprostol är mer säkert men inte fullt lika effektiv som sublingualt administrerad misoprostol.

***I delarbete III*** inkluderades 564 kvinnor som genomgick induktion av förlossning, antingen som poliklinisk induktion med start i hemmet (282 kvinnor) eller sjukhusinduktion (282 kvinnor). Det primära utfallet var andelen vaginala förlossningar samt vårdtid från inläggning till förlossning. Studien fann inga statistiskt säkerställda skillnader mellan de två grupperna vad gäller förlossningssätt där 84,4% av de polikliniska induktionerna samt 86,2% av sjukhusinduktionerna födde vaginalt. Tiden i antal timmar från inläggning till förlossning var kortare för de som genomgick poliklinisk induktion jämfört med sjukhusinduktion. Totala vårdtiden i antal dagar var kortare för de som genomgick poliklinisk induktion. Sjukhusinduktionerna behövde i regel fler metoder för att komma i aktiv förlossning. Värkstimulerande dropp användes i mer utsträckning i den polikliniska gruppen. Inga statistisk säkerställda skillnader vad gäller maternella eller neonatala utfall kunde påvisas mellan de två grupperna. Sammanfattningsvis visar denna studie lovande resultat vad gäller polikliniska induktioner som ett alternativ för att sätta i gång graviditeter som bedöms vara låg-risk.

***I delarbete IV*** utfördes en retrospektiv studie som jämförde utfallen hos 664 förstföderskor med graviditeter som har gått över tiden där de antingen får förlossningen igångsatt via misoprostol som enskild metod eller misoprostol med tillägg av en ballongkateter (sekventiell metod) efter 4-6 doser. Primära utfallet var

tiden från igångsättning till vaginal förlossning. Studien fann att tiden från induktion till vaginal förlossning var signifikant kortare med den sekventiella metoden jämfört med misoprostol ensamt. Inga skillnader vad gäller förlossningssätt eller andel vaginala förlossningar inom 24 timmar eller 48 timmar kunde påvisas mellan de två metoderna. Studien fann heller inga skillnader mellan metoderna vad gäller förlossningsbristningar, andel postpartumblödningar eller neonatala utfall.

Sammanfattningsvis visar resultaten från dessa studier att det behövs både standardiserade induktionsmetoder och protokoll som kan göra utfallen mer förutsägbara samtidigt som metoderna behöver i vissa fall individualiseras för att förbättra utfallen. Därför behövs hänsyn tas till vilken administrationsväg som används vid igångsättning med misoprostol. Polikliniska induktioner samt sekventiella metoder är ytterligare verktyg som kommer att behöva användas och optimeras framöver som ett led att förbättra utfall för både mamma och barn.

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**INDUCTION OF LABOR** is among the most frequently performed obstetric procedures worldwide, utilizing diverse methods across various settings. Despite this, no single method stands out as universally superior. Is there truly a 'one-size-fits-all' solution for labor induction, or must we tailor our approach to meet the unique needs of each woman?

This thesis seeks to address these questions by examining the effectiveness of different induction protocols and settings in a tertiary hospital in southern Sweden.

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