Inducing labour: comparison of pharmacological and mechanical approaches

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Citation for published version (APA):

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Chapter one

General introduction
Induction of labour and the three W’s (who, when and with what?)

Induction of labour is probably the most used obstetrical intervention, first described by the ancient Greek physician Hippocrates. The purpose of induction of labour as compared to continuation is to end the pregnancy through vaginal delivery, in situations where pregnancy termination is expected to reduce risks to the mother or her baby. In the decision to induce labour or not, one has to find the right balance between benefits and possible harms in comparison to continuation of pregnancy. The two most important factors in that decision are the mother and her baby.

In some situations, delivery before the due date is needed when the condition of the mother, the baby, or both, is severely compromised. Induction of labour increases the risks for neonatal and long-term developmental complications, but could be justified if continuing pregnancy could jeopardize the baby through infection, asphyxia or intra uterine fetal demise (IUFD), depending on the clinical situation. Similarly, from the maternal perspective, continuation of pregnancy could harm the mother in case of severe hypertension, infection or other pregnancy related complications.

Consequentially, induction of labour is an intervention that should only be performed when the benefits of ending pregnancy outweigh the risks of induction of labour, either from the perspective of the mother, the baby or both, or when the expected harm to one of them is less than the expected benefit for the other. Induction of labour rates increased in the United States from 9.6% in 1990 to 23.8% in 2010. The Netherlands experienced a comparable rise from 15% in 2008 to 21.8% in 2013.

Who and when to induce?
Common indications for induction of labour are hypertensive disorders, post-term pregnancy, prelabour rupture of membranes, diabetes, suspected intrauterine growth restriction, macrosomia, cholestasis in pregnancy and elective reasons. These indications can be subdivided in three categories: indications where only the mother is at increased risk, indications where only the fetus is at increased risk, and mixed indications where both mother and fetus are at risk. For example, hypertensive disorders impose a risk for the mother, but growth restriction or gestational diabetes can jeopardise the baby. A large for gestational age baby can cause cephalopelvic disproportion requiring a caesarean section, which harms the mother, or it might cause shoulder dystocia, possibly harming the fetus. Preeclampsia complicated by intrauterine growth restriction and prelabour rupture of membranes are also situations where mother and fetus both are at risk.

Pre-existing hypertension
Around 1.5% of all pregnant women have pre-existing hypertension, defined as hypertension occurring before the 20th week of gestation. Women with pre-existing hypertension have an increased risk for preeclampsia, acute renal failure, pulmonary oedema and even death. Children of women with pre-existing hypertension have a higher risk of intra uterine growth restriction, neonatal intensive care unit admission and perinatal death. One cohort study including 171,669 women with pre-existing hypertension compared risks for IUFD, neonatal mortality or serious neonatal morbidity (such as neonatal seizures, severe respiratory morbidity or 5-minute Apgar score ≤3). This study demonstrated that in pre-existing hypertension delivery between 38 and 39 weeks appears to provide the optimal time frame.
Pregnancy induced hypertension and preeclampsia

Pregnancy induced hypertension is defined as an elevated blood pressure after 20 weeks of gestation in the absence of proteinuria. Preeclampsia is defined as the combination of pregnancy induced hypertension and proteinuria (more than 0.3 grams over 24 hours)\(^{18}\). Preeclampsia complicates 3-5% of all pregnancies\(^{19}\). Maternal risks arising from preeclampsia are eclampsia, acute kidney injury, clotting disorders, cerebral haemorrhage, hepatic failure, and pulmonary edema\(^{20}\). Neonatal risks include intra uterine growth restriction, placental abruption, and fetal demise\(^{20}\). The HYPITAT study showed that in women with mild term preeclampsia or pregnancy induced hypertension, induction of labour significantly reduced adverse maternal outcomes (including eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease or placental abruption, and maternal death) compared to expectant management (relative risk (RR) 0.71, 95% confidence interval (CI) 0.59-0.86), without jeopardizing neonatal outcomes\(^2\). In late preterm pregnancies (between 34-37 weeks) with hypertensive disorders the reduction of adverse maternal outcomes was not statistically significant (RR 0.36, 95%CI 0.12-1.1), whereas there was significantly more neonatal respiratory distress syndrome in the induction group (RR 3.3, 95%CI 1.4-8.2)\(^3\). Therefore, expectant management until the clinical situation deteriorates or until 37 weeks of gestation is recommended.

Postdate (>41 weeks) and postterm (>42 weeks) pregnancies

In postterm pregnancies, the risk for IUFD starts to increase from 42 weeks onwards, although the absolute risk of IUFD or neonatal death is low\(^{21}\). There is still insufficient evidence regarding possible evaluated neonatal risks between 41 and 42 weeks of gestation. Currently a large randomised controlled trial (INDEX study) is investigating the risks for IUFD and neonatal morbidity between 41 and 42 weeks of gestation\(^{22}\). In current Dutch practice it is common to give postdate women the option to choose for induction of labour, and postterm induction of labour is advised.

Intra uterine growth restriction (IUGR)

IUGR is associated with an increased risk of IUFD and neonatal morbidity, especially for growth bellow the 5\(^{th}\) percentile. It occurs frequently in pregnancies complicated by hypertension or preeclampsia, but can also occur isolated. Growth restriction implies a pathological limitation of the potential growth, likely caused by dysfunction of the placenta. As the diagnosis can only be suspected based on the assessment of fundal height or with ultrasound, suspected IUGR is defined as an estimated fetal weight below the 10th percentile, fetal abdominal circumference below the 10th percentile, flattening of the growth curve in the third trimester or the presence of more than one of these factors\(^8\).

The Disproportionate Intrauterine Growth Intervention (DIGITAT) study was a randomised trial of comparing induction of labour and expectant management of 660 women with suspected IUGR fetuses at or near term (i.e. 36–40 weeks). The DIGITAT study found no statistically significant differences in adverse outcomes, comparing induction of labour with expectant monitoring in women with suspected IUGR. However, a higher rate of neonatal admissions in the induction of labour group was found, as well as a higher rate of neonates with a birth weight below the 3\(^{rd}\) percentile in the expectant management group (30.6% versus 12.5%). Epidemiological data of 1,294,547 women with a growth restricted baby indicate that the perinatal mortality rate is the lowest at 38 to 39 weeks. Thus, for growth restricted babies, delivery and life outside the uterus appears to be safer after 38–39 weeks of gestation\(^{8,23}\). Furthermore, 2 year follow-up data
confirm these results\textsuperscript{24}. Therefore the recommendation would be to induce labour at 38 weeks in case of suspected intra-uterine growth restriction.

\textbf{Gestational Diabetes}

Diabetes complicates around 2.6\% of all pregnancies. Diabetes can be classified as type 1, type 2 and gestational diabetes, with the latter comprising 90\% of all diabetes cases in pregnancy\textsuperscript{25-27}. Diabetes will become increasingly present due to the rising rate of obesity. Pregnancy complicated by diabetes imposes several maternal risks, such as an increased risk of preeclampsia, and possible worsening of diabetic retinopathy or nephropathy. Major concerns for the fetus in a diabetic pregnancy involve congenital malformations, IUFD in the third trimester and macrosomia-related birth trauma\textsuperscript{25-27}. Furthermore, neonatal respiratory distress syndrome is more common in neonates born prior to 39 weeks from diabetic pregnancies compared to neonates from non-diabetic pregnancies. For women whose diabetes is medically managed by insulin or oral medicine, induction is recommended from 38 to 39 weeks of gestation, as induction would lower the change of macrosomia and IUFD, without increasing the risk of caesarean section (RR 0.81; 95\% CI 0.52–1.26)\textsuperscript{27}. Timing of delivery in non-insulin depended diabetes is not well investigated. The current opinion from the American College of Obstetrics and Gynaecologists suggest expectant management up to 40 weeks of gestation\textsuperscript{29}.

\textbf{Suspected macrosomia}

Macrosomia is defined as an estimated weight of at least 4000 g or a weight for gestational age >90th percentile, though multiple definitions are applied\textsuperscript{30}. When macrosomia is suspected, fear for a problematic delivery, in particular the risks of obstructed labour and shoulder dystocia, may prompt physicians to propose induction of labour. Cheng et al. found that women with babies having a birth weight of at least 4000 g undergoing induction of labour at 39 weeks had a lower rate of caesarean delivery compared to women delivering at later gestational ages\textsuperscript{31}. However, this study included birth weight instead of estimated weight. It is well known, however, that there is a significant discrepancy between the measured estimated weight and the actual birth weight\textsuperscript{32,33}. Boulvain et al. performed a multicentre randomised controlled trial among 822 women who were pregnant of babies whose estimated weight exceeded the 95\textsuperscript{th} percentile. They randomised between induction of labour at 37 to 38+6 weeks of gestation (maximum 3 days after diagnosis) or expectant management and demonstrated that induction of labour for suspected macrosomia is associated with a reduced risk of shoulder dystocia and associated morbidity (RR 0.32, 95\%CI 0.15-0.71)\textsuperscript{34}. There was no difference in caesarean section rate between the induction and expectant management group. Therefore, induction of labour between 37 and 39 weeks is recommended.

\textbf{Prelabour rupture of the membranes}

Induction of labour after prelabour rupture of the membranes at term is well accepted globally. It is important to distinguish between women who are carrier of group B streptococcus (GBS) and those who are not. Prolonged rupture of membranes >18 hours is a significant risk factor for early onset neonatal GBS sepsis with an OR of 13.7 (95\%CI 4.8-39.5), justifying immediate induction of labour in GBS positive women\textsuperscript{5,35}. If a women does not carry GBS, expectant management is a safe option until 48 hours after the moment of membrane rupture\textsuperscript{36}.

For preterm prelabour rupture of membranes an expectant management until 37 weeks of gestation is the safest option. A randomised controlled trial at late preterm premature rupture of membranes (34–37 weeks) demonstrated no advantage in terms of the incidence of neonatal sepsis
cholestasis with and without intrahepatic cholestasis of pregnancy in California. Another retrospective cohort study included 1,604,386 singleton pregnancies of women between 34 and 40 weeks of gestation with and without intrahepatic cholestasis of pregnancy. They found that higher levels of bile acids were correlated with spontaneous preterm birth, meconium stained liquor and perinatal death. However, concerns over IUFD and the difficulty to predict IUFD in the presence of obstetric cholestasis account for the policy of many obstetricians to electively induce labour. One retrospective study performed in the Netherlands between 2005 and 2012 included 215 women with cholestasis of pregnancy and divided them in three groups by the serum bile acids level. They found that higher levels of bile acid were associated with other complications such as IUFD, although there is little evidence. However, a retrospective cohort study included 1,604,386 singleton pregnancies of women between 34 and 40 weeks of gestation with and without intrahepatic cholestasis of pregnancy. They found that higher levels of bile acids were correlated with spontaneous preterm birth, meconium stained liquor and perinatal death. However, this study did not differentiate between spontaneous start of labour and induction of labour. Therefore, there is still insufficient data to support the exact timing when induction of labour should take place. Medical treatment such as ursodeoxycholic acid and S-adenosylmethionine can be started to reduce the symptoms of pruritus, but there is still insufficient evidence to determine whether this reduces the occurrence of IUFD.

Elective reasons
Elective reasons include maternal age, psychosocial factors, history of intrauterine death and logistical problems (history of rapid labour, distance to hospital). Psychosocial reasons for induction of labour at term are perhaps the most contentious. Induction of labour on request remains debatable mainly because of the increased risks for surgical assisted delivery (vaginal operative delivery or caesarean section). However, these risks may be minimised with careful counselling, careful management of labour and expectant management when the induction methods fail. Furthermore, there is controversy on whether induction of labour increases the risk of complicated labour requiring caesarean section. Observational data on this matter are unreliable, as women who go in spontaneous labour, compared to women with an indication for induction, are less sick and are therefore at lower risk for caesarean delivery. Systematic review and meta-analysis have indicated that induction of labour at term is actually associated with a small decreased risk of caesarean delivery.

How to induce labour (with what)?
After establishing an indication to induce labour, and planning a date for induction, the next question is how to induce labour. In this matter it is of importance to distinguish between women with a ripe and unripe cervix. When the cervix is `ripe, or favourable’, the membranes can be artificially ruptured followed by oxytocin administration if needed. When the cervix is `unripe, or unfavourable’, and amniotomy is not possible, it is important to ripen the cervix first. The ripeness of the cervix is usually expressed with the Bishop score. The Bishop score was developed in 1964 as a predictor of success for an elective induction in multiparous woman. The
initial scoring system used five determinants (dilatation, effacement, station, position, and consistency) that attributed a value of 0 to 2-3 points each (for a maximum score of 13)\textsuperscript{44}. In 1966, Burnett modified the scoring system (which is still in use and still known as the Bishop score) so that each variable was assigned a maximum value of 2 points (for a maximum score of 10) (figure 1)\textsuperscript{45}. Usually, a cut-off value of 6 is used, meaning that when a Bishop score >6 is present, defined as a favourable or ripe cervix, membranes can be ruptured, while in women with a lower Bishop score first cervical ripeness has to be improved. The premise behind this is that with an unripe cervix, there are not enough oxytocin receptors on the uterine muscle cells, resulting in an insufficient response to amniotomy and the start of oxytocin, and increasing the risk of labour dystocia, failed induction and consequentially the risk for a delivery through a caesarean section\textsuperscript{43,46}. Considering all women undergoing induction of labour in 2013 in the Netherlands, around 60% had a ripe cervix and 40% had an unripe cervix\textsuperscript{12}.

A favourable pre-induction Bishop score of > 6 is predictive of a successful vaginal delivery. Initial studies were limited to multiparous women, but the score was found also to be suitable for nulliparous women\textsuperscript{47}. Taken together, before rupturing membranes and starting oxytocin, it is important to ripen the cervix. There are several different methods for cervical ripening, that can be categorized in mechanical (Foley catheter) and pharmacological (prostaglandins) methods.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Position of cervix</strong></td>
<td>Posterior</td>
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<tr>
<td><strong>Station of the fetal head</strong></td>
<td>Hodge 1</td>
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<tr>
<td><strong>Consistency of cervix</strong></td>
<td>Firm</td>
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<tr>
<td><strong>Cervical dilatation</strong></td>
<td>Closed</td>
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<tr>
<td><strong>Effacement of cervix</strong></td>
<td>0-30%</td>
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*Figure 1. Bishop’s scoring system for cervical ripeness.*

**Physiological course of cervical changes during pregnancy**
To understand the possible working mechanism of different methods for cervical ripening, it is prerequisite to understand the physiological course of cervical changes during pregnancy. The function of the cervix during pregnancy is to maintain enough strength to keep the fetus in utero and protect it from external micro-organisms. Once the baby has developed, the function of the cervix chances, and suddenly it should allow the baby to be born. Cervical remodelling during pregnancy occurs in 4 specific and unique stages, which can be categorized in softening, ripening, dilatation, and postpartum repair\textsuperscript{48}. Each stage of remodelling is characterized with unique endocrinologic and structural features. The endocrine environment includes epithelial, stromal, immune and endothelial cell function and the structural features include the composition and structure of the extracellular matrix\textsuperscript{48}.

The first stage, softening of the cervix, begins in the first trimester of pregnancy\textsuperscript{48}. The cervix consists primarily of collagen, a fibrous connective tissue that undergoes extensive remodelling throughout
all stages of pregnancy. The cervix has three seamless zones of structured collagen: the innermost and outermost rings of stroma contain collagen fibres aligned in the longitudinal direction, and the middle layer contains collagen fibres aligned in the circumferential direction. The solubility of collagen is higher during the softening phase, correlating with an increase in collagen turnover. This newly synthesized collagen in pregnancy has a lower degree of crosslinking. Cross-link density has been found to correlate with mechanical strength of collagenous tissue. Thereby the cervix changes from closed and firm to a more compliant structure, however, it largely maintains its strength and shape. This process of softening is a relatively slow process occupying several months.

The second phase, ripening, is a more accelerative phase occurring in the weeks or days before active labour. The structure and arrangements of cervical collagen changes drastically in the ripening phase. The collagen fibres of the cervix diminish and separate primarily because of a reduction of hydrophilic glycosaminoglycans and an increase of hyaluronic acid. The altered hyaluronic acid and glycosaminoglycans levels change the osmotic pressure and thereby increase fluid influx and as a result further softening and dilatation of the cervix occurs. Prostaglandins play an important role in this process. Arachidonic acid is a prostaglandin precursor, which is present in all cell membranes. Furthermore, it has been proposed that there is a higher influx of inflammatory cells during the ripening phase. It is known that inflammatory cells produce prostaglandins as well. Prostaglandins alter extracellular grounds substance of the cervix by increasing collagenase, elastase, dermatan sulphate, and hyaluronic acid levels. Thereby, further softening, effacement and dilatation (mostly up to 2 cm of dilatation) occur in the ripening phase of the cervix.

After cervical ripening, the active phase of labour starts, where further dilatation takes place mostly due to direct pressure on the cervix derived from uterine contractions. Lastly, in the fourth phase the repair phase starts immediately after birth and ends with the completion of uterine involution.

Mechanical methods (Foley catheter); working mechanism
The first description of mechanical methods for labour induction date from the time of Hippocrates, who suggested cervical dilatation by inserting tree branches into the vagina and tossing. The use of a balloon catheter as induction method was first described in 1862 by Tarnier, who proposed the insertion of a balloon device through the cervix and placement in the lower segment of the uterus, thus facilitating stretching and further dilatation of the cervix. However, in those days the balloons were filled with up to 500 ml of saline. Common side effects were prolapse of the umbilical cord and alternation of the presenting part of the foetus. It is unclear when the Foley catheter, mostly filled with 30-80 ml of saline, was first used as an induction method, but the first reports of its use appeared in 1967 (figure 2).

How a Foley catheter is capable of achieving cervical ripeness is still not completely understood. The hypothesized mechanism of action is twofold. The first is mechanical, by direct dilatation through pressure on the cervix. Secondly, by releasing endogenous prostaglandins from the cervix.
Pharmacological methods (prostaglandins); working mechanism

The first prostaglandin effects were discovered in 1930 by Kurzoak and Lieb. They found that during artificial insemination, semen injected into the uterus was instantaneously expelled. Goldblatt discovered a powerful vasodilator substance in 1935 with the ability to stimulate uterine muscle activity derived from human semen. Later that year, van Euler named this agent prostaglandin as it was found in seminal fluid from the prostate gland.

Prostaglandin receptors can be found in the cervix as well as in the myometrium. Thereby, prostaglandins not only play an important role in cervical ripening, but also have effect on uterine contractility. The working mechanism of prostaglandins in the female reproductive tract can be distinguished in two major components:

1. Alteration of extracellular grounds substance of cervix by increasing collagenase, elastase, dermatan sulphate, and hyaluronic acid levels, and thereby inducing the ripening process of the cervix.
2. Gap junction formation leading to initiation of uterine contractions. Unlike oxytocin which requires an induction of receptors that does not usually occur until the later part of pregnancy, prostaglandins receptors are always present on uterine cells.

The problem with endogenous prostaglandins for obstetrical use is that they have a half-life of only seconds, and a low oral bioavailability. Between 1970 and 1980 synthetic prostaglandins were
created, with slight structural modifications that led to an increase in anti-secretory potency, an increase in duration of action (longer half-life) and improved bioavailability (figure 3)\textsuperscript{57,59}. Although mechanical methods such as the Foley catheter were the first method of choice for a long time, when synthetic prostaglandins were introduced, they largely took over the market for induction of labour\textsuperscript{51}. The introduction of prostaglandins was partly driven by commercial motives and not supported by strong evidence of equivalent or better safety and effectiveness than the older methods such as the Foley catheter. This is regrettable, especially considering the broad range of different preparations, dosing and administration regimes that were developed. Because of the exogenous administration of prostaglandins, levels can accelerate to a critically high level, which induces possible side effects such as hyperstimulation (6 or more contractions in 10 minutes with fetal heart rate changes). Due to hyperstimulation the placental blood flow reduces, inducing fetal hypoxia and as a result neonatal asphyxia can occur. Another possible consequence of hyperstimulation is uterine fatigue with subsequent postpartum haemorrhage.

\begin{center}
\textbf{Figure 3.} Endogenous prostaglandin E1 (top). Synthetic variant prostaglandin E1, misoprostol (bottom).
\end{center}

\textbf{Different prostaglandin preparations for induction of labour compared}

The most frequently used prostaglandins for cervical ripening are prostaglandin E1 and E2 analogues\textsuperscript{60}. Both analogues have a different structure, and therefore different affinities to prostaglandin receptors\textsuperscript{61}. Prostaglandin E1 analogue misoprostol is a selective E-series prostanoid 2/3 receptor agonist, and Prostaglandin E2 is an agonist to all E-series prostanoid receptors\textsuperscript{62}. Different receptor preferences clarify the fact that prostaglandin preparations have diverse effects\textsuperscript{63}. A recently published network meta-analysis showed that, from all prostaglandins, low dose (<50 microgram) titrated oral misoprostol solution has the lowest probability of caesarean section, whereas vaginal misoprostol (≥50 microgram) has the highest probability of achieving a
vaginal delivery within 24 hours, but also had the highest incidence of uterine hyperstimulation with fetal heart rate changes.64

**Different administration routes of misoprostol**

Misoprostol was initially developed in 1986 for the prevention and treatment of gastrointestinal ulcers and peptic ulcer disease caused by prostaglandin inhibitors such as non-steroidal anti-inflammatory drugs (NSAIDS).57 Studies in late 1980’s and early 1990 noted that oral administration of misoprostol causes uterine contractions. Although misoprostol is not approved by the Food and Drug Administration for induction of labour, it is recommended by the American College of Obstetricians and Gynecologists, The British Royal College of Obstetricians and Gynaecologists, as well as the International Federation of Gynaecology and Obstetrics (FIGO) and the World Health Organization for the use of induction of labour.55-68 Thereby, off-label use for induction of labour is currently daily routine in many countries.

Misoprostol was developed for oral use. In the obstetric use other routes such as vaginally, sublingually, buccal and rectal administration have also been used extensively.69 Over the past decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol.57

Following oral intake, misoprostol is rapidly and extensively metabolized in the liver via the first-pass effect into misoprostol acid, its primary active metabolite. Misoprostol acid is responsible for activity at the cellular level and can be measured in plasma. After oral dosing, plasma levels peak in 20-30 minutes, then quickly decline in 2 hours, at which point they stay at low levels.51 The duration of action is thereby 2 hours and mean time to sustained uterine activity is 90 minutes.

The biologic activity of oral misoprostol is equivalent to vaginal administration when the oral dose is twice the vaginal dose.69

The peak plasma level of misoprostol after vaginal administration is 60-80 minutes, with a plasma half-life of 60 minutes. The duration of action appears to be 4.5 to 5 hours, with detectable drug levels still present after 6 hours.57 Vaginal absorption has been shown to be slower and the peak concentrations lower than that for the other routes. In fact, after 6 hours the serum level of misoprostol after vaginal administration is higher compared to the oral route. Therefore, the effect of misoprostol may be present for more than 6 hours. However, the threshold serum level for clinical action is unknown and probably differs between different women. Furthermore, vaginal absorption of misoprostol is inconsistent. In clinical practice, remnants of tablets are sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to the variation between women in the amount and pH of the vaginal discharge. Variation in the amount of bleeding may also affect the absorption of misoprostol through the vaginal mucosa in a negative way.57

The longer times to peak plasma concentrations, slightly reduced plasma concentrations and longer drug exposure might increase the risk of hyperstimulation in vaginal use of misoprostol compared to oral use.51,69 In addition, chemical properties may be altered if the tablet is exposed to lubrication gel, which could inactivate the misoprostol.51

**Misoprostol versus Foley catheter**

While the principles of induction of labour with either prostaglandins or Foley catheter have long been known, and their efficacy had been established since long, comparative studies have been lacking. Industry has mainly pushed for the evaluation of prostaglandins, driven by commercial

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motives. Jozwiak et al. showed that induction of labour with a Foley catheter is as effective as induction with intravaginal prostaglandin E2 gel, with fewer maternal and neonatal side-effects (PROBAAT trial). The caesarean section rate was comparable. In a meta-analysis of three trials on the subject, the Foley catheter revealed a lower rate of hyperstimulation, resulting in fewer cases of neonatal asphyxia and less postpartum haemorrhage.

Although numerous studies have been conducted to compare Foley catheter to different misoprostol preparations, definite answers have not been given because the studies were underpowered. Most studies focused on time to and mode of delivery. Safety, however, meaning the capacity to prevent asphyxia and postpartum haemorrhage, is not well studied but is considerably more important than a fast delivery. The aim of this thesis was therefore to investigate misoprostol compared to Foley catheter as induction agent in term pregnant women with an unfavourable cervix. One could hypothesize that - compared to Foley catheter misoprostol, either vaginal or oral, results in more uterine contractility due the administration of exogenous prostaglandins in combination with endogenous release, thus increasing the chance of fetal distress and postpartum haemorrhage. Furthermore, in a time of paucity of economic means, financial costs become increasingly important. Especially with an intervention used as frequently as induction of labour, it is important to note economic aspects of an induction method. Another point of interest is the experience with and preference for an induction method by the women themselves. This aspect will become increasingly important in a world where medical decisions are more and more made together with the patient.

**Specific research questions**

- Is the Foley catheter safer than 25 microgram vaginal misoprostol?
- Does the Foley catheter have a comparable safety and effectiveness profile as oral misoprostol?
- Is the Foley catheter for induction of labour cost effective when compared to oral misoprostol?
- What are the women’s experiences with and preferences for different induction of labour methods?
- What is the safest and most effective induction method regarding all different Foley catheter fillings and misoprostol administrations, dosage and routes?
Outline of this thesis

*Chapter one* presents the general introduction outlining the rationale behind the research performed in this thesis.

*Chapter two* describes the results of a randomised controlled trial (PROBAAT-M) and meta-analysis of studies comparing Foley catheter to 25 microgram vaginal misoprostol. This randomised controlled trial was conducted parallel to the previous PROBAAT study performed by Jozwiak et al.

*Chapter three* describes the research protocol set up for the PROBAAT-II study, comparing the Foley catheter to 50 microgram oral misoprostol.

*Chapter four* contains the results of the PROBAAT-II study, a multi-centre randomised controlled trial comparing Foley catheter to 50 microgram oral misoprostol in term pregnant women with an unfavourable cervix.

*Chapter five* represents an economic analysis and cost minimization analysis of Foley catheter compared to oral misoprostol. This study was conducted alongside the PROBAAT-II study and handles different scenarios of ripening at home in an outpatient setting, in the antenatal ward and in the labour room.

*Chapter six* reports on the experiences of women with, and preferences for induction of labour with a Foley catheter or oral misoprostol.

*Chapter seven* is a systematic review and meta-analysis of studies comparing Foley catheter to different dosages and administration routes of misoprostol.

*Chapter eight* contains the summary and general discussion, in which the outcomes of the current thesis and future perspectives on labour induction are conferred.
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