Inducing labour: comparison of pharmacological and mechanical approaches

ten Eikelder, Mieke

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Chapter eight

Summary and general discussion
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When prostaglandin preparations were introduced for induction of labour in the 70s and 80s, older methods such as the Foley catheter were rapidly replaced, without confirmation of equal or better safety and effectiveness profiles of the new drugs. In the first PROBAAT study (also called PROBAAT-I), Jozwiak et al showed that the Foley catheter had a better safety profile than prostaglandin E2 preparations.1,2

In this thesis, we investigated the safety and effectiveness profile of the Foley catheter compared to prostaglandin E1 (misoprostol). Here, we summarise the different studies as described in the chapters. Subsequently, we will discuss the findings of the studies described in this thesis from the perspective of safety, effectiveness, women’s preference and costs, including implications for future research. We will then discuss the use of Foley catheter in an outpatient setting and the implementation of the results of this thesis. The chapter will end with a general conclusion on induction of labour using either Foley catheter or oral misoprostol.

Summary

Chapter two describes the results of a randomised controlled trial (PROBAAT-M) and meta-analysis of studies comparing Foley catheter to vaginal misoprostol for induction of labour in term pregnant women. This small randomised controlled trial was conducted parallel to the PROBAAT-I study, in the same period. Women were randomised to either Foley catheter (n=56) or 25 microgram vaginal misoprostol (n=64). We found that caesarean delivery rates were not significantly different (14 women (25%) in the Foley catheter group versus 11 women (17%) in the vaginal misoprostol; RR 1.46, 95% CI 0.72 - 2.94), but more caesarean deliveries were performed for failure to progress in the first stage of labour after induction in the Foley catheter group (8 women (14%) versus 2 women (3%); RR 4.57, 95% CI 1.01- 20.64). When using a Foley catheter, oxytocin augmentation was required more often compared to vaginal misoprostol (82% versus 50%, RR 1.64, 95% CI 1.25- 2.16), p-value <0.001). Maternal and neonatal secondary outcomes, including postpartum haemorrhage and arterial umbilical cord pH <7.10, did not differ significantly between these groups, as expected due to the small size. In our meta-analysis, we found that Foley catheter compared to 4-hourly 25 microgram vaginal misoprostol yields comparable caesarean delivery rates (230 women (30%) versus 187 women (25%), RR 1.24, 95% CI 0.94-1.63), and vaginal instrumental deliveries rates (38 women (13%) versus 57 women (18%), RR 0.64, 95% CI 0.35-1.17), and reduced hyperstimulation with fetal heart rate changes (21 women (3.8%) versus 52 women (9.5%), RR 0.39, 95% CI 0.24-0.61). Based above described outcomes, Foley catheter is superior to vaginal misoprostol for induction of labour at term.

Chapter three describes the research protocol of the PROBAAT-II study, a randomised clinical trial comparing induction of labour with Foley catheter versus 50 microgram oral misoprostol. All women with a term singleton pregnancy in cephalic presentation, intact membranes, unfavourable cervix, and an indication for induction of labour where eligible for inclusion. Women with a history of caesarean section, age <18, lethal congenital malformations and hypersensitivity for any of the products used were excluded. After written informed consent, women were randomised by means of a web-based application. Stratification was applied for previous vaginal birth (nulliparous versus
multiparous) and for centre. The study was staffed by obstetricians, midwives and research staff associated with the Dutch Consortium for Studies in Women’s Health and Reproductivity. Women were either allocated to induction of labour with a 16 of 18F Foley catheter or 50 microgram oral misoprostol tablets. The Foley catheter was placed with a speculum or digitally, and women were examined every 12 hours whether the Foley catheter had not expelled spontaneously. When the Bishop score remained <6; the location of the Foley catheter was evaluated and a new Foley was placed after 24 or 48 hours, depending on the preference of the participating centre. Women allocated to oral misoprostol received a 50 microgram misoprostol capsule every 4 hours, with a maximum of three times a day. In both groups, when there was a Bishop score of >6, membranes were ruptured and if necessary oxytocin augmentation was started. The primary outcome was a composite outcome of neonatal asphyxia (defined as a neonatal arterial umbilical cord pH of ≤7.05 and/or 5 minute Apgar score <7) and/or postpartum haemorrhage (defined as an estimated blood loss of ≥1000ml ascertained over 24 h postpartum). This combined outcome was chosen because both conditions are considered to be a result of hyperstimulation. The trial was designed as a non-inferiority trial, and we calculated our sample size with a power of 80% and a one-sided 0.05 risk of type 1 error. We needed 1,860 women (930 per group) to demonstrate non-inferiority, i.e. that the absolute difference in the composite outcome was less that 5% increase in the misoprostol group compared to the Foley catheter group.

Chapter four presents the results of the PROBAAT-II study. We performed an open-label randomised non-inferiority trial in 29 hospitals in the Netherlands. Women with a term singleton pregnancy in cephalic presentation, an unfavourable cervix, intact membranes, and without a previous caesarean section who were scheduled for induction of labour were randomly allocated to cervical ripening with 50 microgram oral misoprostol once every 4h or to a 30 mL transcervical Foley catheter. Between July 2012 and October 2013, we randomly assigned 932 women to oral misoprostol and 927 women to Foley catheter. The primary outcome was a composite of asphyxia (pH ≤7.05 or 5-min Apgar score <7) or post-partum haemorrhage (≥1000 mL). The composite primary outcome occurred in 113 (12.2%) of 924 participants in the misoprostol group versus 106 (11.5%) of 921 in the Foley catheter group (RR 1.06, 90% CI 0.86–1.31). The proportion of patients who had a caesarean section was comparable (in 155 (16.8%) women receiving oral misoprostol versus 185 (20.1%) women receiving a Foley catheter; RR 0.84, 95% CI 0.69–1.02, p-value 0.067), with fewer caesarean sections performed as a result of failure to progress in the first stage of labour in the oral misoprostol group as compared to Foley catheter group (57 women (6.2%) versus 98 women (10.6%); RR 0.58, 95% CI 0.42–0.79, p-value <0.001). There were more vaginal instrumental deliveries in the misoprostol group than in the Foley catheter group (125 women (13.5%) versus 88 women (9.6%), RR 1.41, 95% CI 1.09–1.83, p-value 0.0076). In conclusion, in women with an unfavourable cervix at term, induction of labour with oral misoprostol and Foley catheter has a similar safety and effectiveness profile.

Chapter five represents an economic analysis of Foley catheter compared to oral misoprostol for induction of labour at term. This study was conducted alongside the PROBAAT-II study. We estimated direct medical costs associated with healthcare utilisation from randomisation until discharge. The robustness of our findings was evaluated in sensitivity analyses. Mean costs per woman in the oral misoprostol group and in the Foley catheter group were €4470 versus €4158, respectively (mean difference €312 (95% confidence interval (CI) -€508 to €1063)). This difference was mainly driven by
longer labour ward occupation in the oral misoprostol group. Multiple sensitivity analyses did not change these conclusions. When cervical ripening for low-risk pregnancies in the Foley catheter group would be carried out in an outpatient setting, with admittance to labour ward at start of active labour, the costs would have been €4470 versus €3489, respectively (mean difference €981 (95% CI €225 to €1817)). Thereby, we conclude that oral misoprostol and Foley catheter generate comparable costs and outpatient induction with a Foley catheter could potentially save €981 per woman.

Chapter six reports on the experiences with and preferences for induction of labour with a Foley catheter or oral misoprostol. This study was performed alongside the PROBAAT-II trial. In 18 of the 29 participating hospitals in the PROBAAT-II trial, women were asked to complete a questionnaire within 24 hours after delivery. We adapted a validated questionnaire about expectancy and experience of labour and asked women whether they would prefer the same method again in a future pregnancy. The questionnaire was completed by 502 (72%) of 695 eligible women; 273 (54%) had been randomly allocated to oral misoprostol and 229 (46%) to Foley catheter. Experience of duration of labour, pain during labour, general satisfaction with labour and feelings of control and fear related to their expectation were comparable in both groups. In the oral misoprostol group, 16 women (6%) would prefer the other method if induction is necessary in future pregnancy, versus 27 women (12%) in the Foley catheter group (RR 0.70, 95%CI 0.55–0.90, P-value 0.02). Multivariate analyses showed that the women preferring the switch to the alternative method in future pregnancies was not influenced by mode of delivery, time from randomization to delivery, the use of analgesics and postpartum admission of mother and/or child. Therefore, we conclude that women’s experiences of labour after induction with oral misoprostol or Foley catheter are comparable. However, women in the Foley catheter group prefer more often to choose a different method for future inductions.

Chapter seven is a systematic review and meta-analysis of studies comparing Foley catheter to different dosages and administration routes of misoprostol. We reviewed the literature and assessed induction methods on their safety and effectiveness profile. Main outcomes for safety were hyperstimulation (>5 contractions/10 min over a minimal period of two times ten minutes with FHR changes (defined as a non-reassuring CTG by treating physician)), meconium stained liquor, caesarean section for non-reassuring FHR, vaginal instrumental delivery for non-reassuring FHR, postpartum haemorrhage, arterial umbilical cord pH <7.05, Apgar score <7, neonatal intensive care admission and neonatal mortality. Main outcomes for effectiveness of induction of labour were total caesarean section rate, caesarean section for failure to progress in the first stage and total vaginal instrumental deliveries. We searched PubMed, Cochrane and Web of Science from January 1st 1980 to February 12th 2016. We included 22 randomised controlled trials comparing Foley catheter with or without misoprostol to misoprostol alone (both vaginal and oral) for induction of labour (5,015 women). Most included studies were underpowered to detect differences in safety outcomes, as the majority was powered for time to delivery or caesarean section. Meta-analysis of these studies does not allow a sufficiently powered comparison of the safety profile of Foley catheter compared to different administration routes and dosages of misoprostol. Comparison of the total group of Foley catheter versus misoprostol (any dose, any administration route) (17 studies, 4,234 women) shows that Foley catheter results in less hyperstimulation compared to misoprostol (37 women (2%) versus
71 women (4%), RR 0.54, 95%CI 0.37-0.79) and fewer caesarean sections for non-reassuring fetal heart rate 81 women (5%) versus 112 women (7%), RR 0.72 95%CI 0.55-0.95), while there were no statistically significant differences in neonatal outcomes. The total amount of women delivering through a caesarean section was 539 (26%) versus 469 (22%) (RR 1.16, 95%CI 1.00-1.34). There were fewer vaginal instrumental deliveries after induction with a Foley catheter compared to misoprostol (139 women (10%) versus 190 women (14%), RR 0.74, 95%CI 0.60-0.91). Foley catheter with misoprostol compared to misoprostol alone (any dose, any administration route) (7 studies, 1073 women) resulted in less hyperstimulation then misoprostol alone (52 women (17%) versus 82 women (23%), RR 0.71, 95%CI 0.52-0.97). Caesarean sections for non-reassuring fetal heart rate were comparable (29 women (7%) versus 41 women (9%), RR 0.79, 95%CI 0.51-1.22). Neonatal outcomes were infrequently reported. The total number of caesarean sections was 176 (34%) versus 187 (34%) (RR 1.01, 95%CI 0.86-1.19). In conclusion, in women with an unripe cervix at term, Foley catheter seems to have a better safety profile than misoprostol (any dose, any administration route) for induction of labour. Larger studies are needed to investigate the safety profile of a Foley catheter compared to separate dosing and administration regimens of misoprostol.
**General Discussion**

The main goal of labour induction is to establish vaginal delivery in a safe manner. When vaginal delivery is not achieved in women with a sound indication for induction, or when significant side effects for mother or baby occur, planned caesarean section is probably a better option. Therefore, studies assessing different methods for induction of labour should provide insight in safety and effectiveness, thus allowing women and their care givers to balance these two.

**Safety**
The major safety concern in induction of labour is hyperstimulation, resulting in asphyxia, interventions for fetal distress (vaginal instrumental delivery, caesarean section), and postpartum haemorrhage. Different methods and dosing regimens and administration routes for induction of labour have different safety and effectiveness profiles.

Induction of labour with Foley catheter compared to 25 microgram vaginal misoprostol reduced hyperstimulation with fetal heart rate changes (chapters two and six). In our comparison of Foley catheter to oral misoprostol, this difference was not statistically significant (chapter four). Foley catheter with concurrent use of misoprostol as compared to misoprostol alone (chapter six), showed fewer cases of hyperstimulation with fetal heart rate changes. Use of a Foley catheter for cervical ripening resulted in fewer caesarean sections for non-reassuring fetal heart rate as compared to induction with misoprostol as a whole (if all dosages, and administration routes were viewed together, chapter six). When induction with the Foley catheter was compared to separate dosing and administration regimes for induction with misoprostol, this difference was not significant (chapter two, four and six). Vaginal instrumental delivery for non-reassuring fetal heart rate did not differ between Foley catheter and misoprostol, however when investigating all vaginal instrumental deliveries, they occur less often when labour is induced with a Foley catheter (chapter two, four and six). Other safety outcomes such as postpartum haemorrhage, umbilical cord pH < 7.05, Apgar score < 7 at 5 minutes, neonatal intensive care unit admission and neonatal mortality were comparable between Foley catheter induction and different misoprostol dosages and administration routes (chapter two, four and six).

Although numbers of pregnant women are high, research on induction of labour, like many other research subjects in obstetrics, is difficult, as relevant outcomes that are studied are relatively rare, and the populations are clinically heterogeneous. This has resulted in publication of numerous smaller studies, with different in- and exclusion criteria, and with limited power to detect differences in relevant safety outcomes. This complicates the generation of definitive answers relevant for clinical practice, especially for safety issues. As a consequence, results on safety need to be interpreted with caution. The absence of a significant difference does not prove that compared methods are equally safe. For example, to detect a clinical relevant difference in arterial umbilical cord pH < 7.05 of 0.5% (from 2.2% to 1.7%), with a power of 80% and an alpha-error of 5%, we would need a randomised controlled trial with more than 12,000 women. While this seems very difficult to realize, we showed that a sample size of around 2,000 women is very feasible. Nevertheless, the majority of induction of labour studies does not reach such sample sizes, as most reports are on less than 1,000 women. Such studies do not allow definite conclusions on safety.
An option to address this issue is to perform a retrospective cohort study, as these are generally less costly than randomised controlled trials, and therefore more likely to include much larger groups of subjects and evaluate rarely occurring safety outcomes. The issue can also be solved by combining randomised controlled trials in meta-analysis, as we did in chapter six. However, even in our meta-analysis the number of women remained low while characteristics of women such as pregnancy duration, Bishop Score, intact or ruptured membranes, and populations studied varied between the studies. Investigation of relatively rare safety outcomes can also be assessed with network meta-analysis, in which data of all studies that investigate either Foley catheter or misoprostol are included. Therewith, also studies that do not directly compare these methods one on one can be used.

Chen and colleagues compared oral misoprostol to vaginal misoprostol in a large systematic review and network meta-analysis. They found vaginal misoprostol (all dosages) to have the highest probability to induce hyperstimulation with fetal heart rate changes and Foley catheter to have the lowest probability. Oral misoprostol (all dosages) had the lowest probability of caesarean section. Another network meta-analysis by Alfirevic et al. compared all induction methods (including oral and vaginal misoprostol, Foley catheter, and prostaglandin E2 preparations) to placebo. From these methods, ≥50 microgram vaginal misoprostol and ≥50 microgram oral misoprostol had the highest probability of uterine hyperstimulation with fetal heart rate changes compared to placebo. Titrated oral misoprostol achieved the lowest probability of caesarean section. Neither of these network meta-analysis included neonatal or maternal mortality and serious morbidity because these were too rare or poorly reported for meaningful analysis. However, from the safety results that are given, these network meta-analysis affirm oral administration of all possible administration routes to be the best available option.

A more novel method of evidence synthesis is Individual Patient Data Meta-Analysis (IPD-MA). This method aims to compare the different interventions evaluated in randomised clinical trials on the level of individual patient data. The advantage of an IPD-MA is that it has the potential to overcome the choice of heterogeneous endpoints and standardisation of inclusion and exclusion criteria across studies. Also, IPD-MA allows a better analysis among subgroups of patients, thus facilitating a more personalized approach to women in whom labour is induced. For example, various induction methods might have different effect in multiparous and nulliparous women, women at different gestational ages and with different indications for induction of labour. Therefore, it would be interesting to perform an IPD-MA on safety outcomes such as hyperstimulation with fetal heart rate changes, vaginal instrumental delivery or caesarean section due to fetal distress and neonatal mortality and morbidity such as low Apgar score, low umbilical cord pH, asphyxia and postpartum haemorrhage.

Systematic reviews, including our systematic review in chapter six, have included studies comparing different dosing regimens and administration routes of misoprostol, and add them up in meta-analyses. Not only the dosage and the route of administration, but also the intervals between different dosages of misoprostol could influence the effects and side-effects when used for induction of labour. As described in the introduction, when used vaginally, ‘low-dose’ regimens with two- to four-hourly administrations may result in a higher cumulative dose over 24 hours than when the comparative oral dose is used. This might be an explanation why orally administrated misoprostol has a comparable safety profile to Foley catheter, whereas vaginal misoprostol seems to be inferior. Furthermore, the plasma peak levels of oral misoprostol are the highest after 20-30 minutes, and
they quickly decline until low levels after 2 hours. Therefore, from a pharmacokinetic point of view, optimal use of misoprostol would be oral administration, in 2 hourly intervals until start of active labour or ≥3 contractions in 10 minutes. To affirm this knowledge in clinical practice, future studies need to be done, with different interval schemes.

In conclusion, in induction of labour, the Foley catheter has a better safety profile than vaginal administration of misoprostol (all dosages), and a comparable safety profile to 50 microgram oral misoprostol. However, for the detection of differences in rare serious adverse events, larger studies are needed. For the combination of Foley catheter with misoprostol compared to Foley catheter alone there are not enough data to draw definite conclusions on safety profile.

**Effectiveness**

The main effectiveness outcome in this thesis was vaginal delivery, which is the main aim of induction of labour. Vaginal delivery can obviously be expressed as its reciprocal, caesarean section. Caesarean section has the advantage that this outcome is straightforward and well documented. However, the choice of caesarean section as an outcome is debatable, as it is an intervention and not a side-effect or complication. Complications or side-effects that lead to a caesarean section in labouring women are mostly non-progressive labour and suspected fetal distress. We believe it to be important to distinguish between these indications, making caesarean section for fetal distress an important safety outcome and a caesarean section for non-progressive labour an important effectiveness outcome. Other outcome measures for effectiveness are changes in Bishop Score, time to delivery and delivery within 24 hours.

In chapters two, four and six we found that induction with Foley catheter or misoprostol is equally effective, as the caesarean section rates were comparable. In chapter four, we found that in the Foley catheter group, more caesarean section for failure to progress occurred compared to the oral misoprostol group. An explanation for this difference could be that the diagnosis failed induction was made to early, with unclear definitions of failed induction in the protocol (chapter three). Furthermore, there is no clear definition of labour arrest/failure to progress in our protocol. Also internationally, there is a discussion on how to determine failure to progress in labour. Zhang and colleagues conclude that in spontaneous labour a two hour threshold for diagnosing labour arrest is too short before six cm, with a 95th percentile of six hours from four to five cm dilatation in nulliparous women6. Furthermore, as Rinehart and colleagues attentively pose, the standards that we commonly use to evaluate adequate progress of labour should not be applied to women in whom labour is induced7. Additionally, the diagnosis of labour arrest should be reserved for women who have actually entered the active phase of labour, as only after a dilatation of six cm is reached during induction, labour progress is similar to women in spontaneous labour, and the active phase or accelerative phase only starts after five cm of dilatation8,9. We therefore believe that with more time and patience we might even be able to reduce the total amount of caesareans performed when inducing with a Foley catheter compared to inducing with misoprostol.

Another effect measure investigated in chapters two and four is time to delivery. Chapter two describes a slower delivery when induced with Foley catheter compared to 25 microgram vaginal misoprostol, with a median time from start induction to birth of 36 hours for the Foley catheter group compared to 25 hours for the 25 microgram vaginal misoprostol group. Chapter four shows us
that within the first 30 hours, induction of labour with oral misoprostol is significantly faster than induction with Foley catheter. However, when a woman did not deliver after 30 hours, the effect reverses, and Foley catheter is faster than oral misoprostol. The mean time to delivery for oral misoprostol is 29 hours, were for Foley catheter it is 30 hours. We need to understand if this difference is actually due to the ripening method or to the protocols used for induction of labour. As the Foley catheter does not induce contractions, most women slept during the night. As a result start of active labour was deferred till the next morning, even if the women had completed the ripening process during the night. In contrast, misoprostol does induce uterine contractions, therefore women in this group were examined more often (Chapter four). As a result, amniotomy was performed earlier (also during the night) than in the Foley catheter group. If this hypothesis is true, Foley catheter may even be faster than oral misoprostol in achieving vaginal birth.

As an example, in the PROBAAT-P study, both women in the Foley catheter group and women in the prostaglandin inserts group were generally examined in the morning, and no difference in time to birth was found in this comparison. However, even more important is the question of the relevance of a fast delivery. The Cochrane collaboration, WHO and NICE established that birth within 24 hours of the start of induction is the ‘clinically most relevant measure of effectiveness for trials investigating methods of labour induction’. As a consequence, most studies on different induction methods use time to delivery or delivery within 24 hours as primary outcome. Furthermore, as discussed in chapter six, many studies use a maximum duration of cervical ripening of 24 hours. If not delivered or in active labour within this time frame, the conclusion of failed induction is drawn, and a caesarean section is performed. We believe this practice to be arguable, as the goal of labour induction is a safe vaginal delivery for mother and child and not a fast delivery.

In the evaluation of induction method effectiveness, the indication for labour induction should be considered as well. For example, in women with severe preeclampsia, fast delivery might be crucial to prevent the occurrence of serious complications such as eclampsia or HELLP syndrome. In that case, an induction method with a high chance of fast delivery is required, accepting possible induction induced safety risks (higher change of instrumental delivery, hyperstimulation and postpartum haemorrhage) as they outweigh the risk of continuing the pregnancy. Instead, when mother and child are in a more stable situation more time until delivery is allowed, thus making uncomplicated induction a higher priority over speed of induction.

Indications in which fast delivery is crucial are severe preeclampsia or severe gestational hypertension (defined as systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5g or higher per 24h), and HELLP syndrome10. As early delivery by induction of labour in these women can help prevent severe pregnancy complications such as eclampsia, intracerebral haemorrhage, liver rupture, haemorrhage from placental abruption and even maternal death11,12. Other indications that justify fast delivery are term pre-labour rupture of membranes with a positive GBS culture, and chorioamnionitis, as with these indications there is a plausible risk for the development of maternal or neonatal sepsis13,14,15,16.

For all the other indications, induction of labour and delivery of the baby lowers the maternal or neonatal morbidity and mortality compared to expectant management, but the risk does not increase significantly from one day to another. In these cases a safe delivery is more important than a fast one and we consider induction of labour up to 4 days to be acceptable. We would suggest the following indications: pre-existing hypertension (defined as hypertension occurring before the 20th week of gestation17), pregnancy induced hypertension and mild pre-eclampsia (with an elevated
blood pressure after 20 weeks of gestation in the absence of proteinuria or with mild proteinuria (between 0.3 and 5 grams over 24 hours\textsuperscript{10}), postdates (>41 weeks) and post term (>42 weeks) pregnancies, diabetes (type 1, type 2 and gestational diabetes, whereas the later one comprises 90\% of all diabetes cases in pregnancy\textsuperscript{18-20}), suspected macrosomia (defined as an estimated weight of at least 4000 g or a weight for gestational age >90th percentile, though multiple definitions are applied\textsuperscript{21}), oligohydramnios, multiple gestation, preterm rupture of membranes (without GBS colonization), cholestasis of pregnancy, maternal age, elective reasons such as psychosocial, history of intrauterine death, logistic indications, and intrauterine growth restriction (defined as 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\textsuperscript{21}). The latter group might have a higher risk to be compromised by uterine contractions. As Foley catheter only facilitates cervical ripening and does not induce contractions, Foley catheter might be a safer option than oral misoprostol especially in this group. To affirm this assumption we would like to perform a secondary analysis on all PROBAAT data combined.

In conclusion, if we leave the idea that women should deliver within 24 hours from the start of induction, and if we distinguish different indications for induction of labour, we could prevent unnecessary caesarean sections for failure to progress and herewith prevent possible maternal and neonatal morbidity.

**Costs**

As mentioned in the introduction, induction of labour is one of the most frequently used obstetrical interventions. Currently in 20-30\% of all pregnant women labour is induced, and this number is still rising\textsuperscript{22}. In view of the financial pressure on the health care budget, costs become more and more important, especially when safety and effectiveness of two induction methods are comparable.

In chapter five, we have assessed the direct medical costs of induction of labour using Foley catheter compared to oral misoprostol. The mean costs of the two different induction methods were comparable and the costs differences predominantly originated from duration of labour ward stay. Women receiving oral misoprostol had non-significant higher costs due to longer labour ward stay. This might be explained by the underlying working mechanism. As oral misoprostol not only ripens the cervix, but also facilitates uterine contractions, women could have been admitted to the labour room in an earlier stage of labour\textsuperscript{23}. In contrast, the Foley catheter only facilitates ripening of the cervix, thereby making it a possible safe option for induction of labour in a ward or even an outpatient setting. In chapter five we assessed the possible cost difference for an outpatient scenario. When cervical ripening in the Foley catheter group would be carried out in an outpatient setting, costs differences could be almost €1,000 per induced woman.

**Women’s preferences**

It is more and more accepted that women are involved in medical decisions and choices regarding their own health, and shared decision making is recognized as a tool to do so. When effectiveness and safety profiles of certain induction methods are comparable, the woman’s point of view is an essential item. We know from previous studies that women who had their labour induced had a less positive birth experience compared to a spontaneous start of labour\textsuperscript{24,25}. Unfortunately, many studies comparing different induction methods do not include women’s preferences in the outcome measures. Until now, there are no validated questionnaires to address this issue.
In chapter 6, we evaluated the experiences with and preferences for induction of labour with a Foley catheter or oral misoprostol. We used questions from a validated questionnaire made by Wijma et al. Experience of the duration of labour, general satisfaction with labour, and feelings of control and fear related to expectation, as well as pain perception were comparable in both groups. More women in the Foley catheter group, compared to oral misoprostol, would prefer an alternative method if induction would be required in a future pregnancy. As multivariate analysis on the subject showed that factors such as mode of delivery, time to delivery, the use of analgesics and admission postpartum had no influence on this outcome, other circumstances should be at hand. Unfortunately we did not include a question on why women would prefer another method for labour induction. One hypothesis is that Foley placement is considered uncomfortable, compared to administration of oral tablets. Jonsson et al, showed that women could experience placement of the Foley catheter past the internal os of the cervix as painful.

For further research implications, it is important to develop validated questionnaires for women’s experiences and preferences for induction of labour, and include them in all research projects comparing different induction methods. Previous reports showed that most relevant domains for women’s overall experience of labour are the availability and quality of (emotional) care received during labour, worries about the baby’s health and safety and the experienced duration until the first contact with the newborn. We would advise to include these elements in a future questionnaire to achieve a better delivery-specific outcome measure.

**Outpatient induction of labour**

As Foley catheter induction does not facilitates contractions during the ripening phase, it may be an useful method for an outpatient setting. The potential for adverse outcome by using an outpatient protocol but monitoring the patient overnight as an inpatient was studied in a large retrospective cohort of 1905 women. The authors found that there were no adverse events such as caesarean for non-reassuring fetal heart tracing, abruption of the placenta, and stillbirth occurring 2 hours after inpatient Foley insertion at 9-11 pm until 6 am. Another small randomised trial compared 61 women with outpatient cervical ripening with a Foley catheter to 50 women with inpatient cervical ripening. All pregnant term women with a singleton in cephalic presentation, a reactive non-stress test, an amniotic fluid index above the fifth percentile and a Bishop score of no more than 5 were included. Excluded were women with a placenta previa, low-lying placenta, undiagnosed vaginal bleeding, preeclampsia, fetal anomalies, intrauterine growth restriction, Rhesus immunisation, fetal demise, rupture of the membranes, maternal heart disease, known latex allergy, active genital herpes infection, poor or no access to a telephone, excessive distance (more than 30 minutes) from the hospital, and/or unreliable transportation. The authors found both methods to be equally safe. Nevertheless, rare adverse maternal and/or fetal events could not be monitored due to small sample sizes in both these studies.

As mentioned in chapter five, an outpatient setting for induction of labour with a Foley catheter could be interesting from an economic point of view. Furthermore, from studies examining women’s preference for inpatient or outpatient settings using prostaglandins, we know that women generally indicate a preference for outpatient ripening. More research is needed to determine the safety of a home induction. A key question to be answered before induction with Foley catheter in an outpatient setting can be applied is whether complications occur after insertion of the balloon but before start of the first stage of labour. If this question is answered reassuring, induction in an
outpatient setting can be safely applied, when there is no reason to monitor the condition of the pregnant woman and baby continuously. Due to an anticipated safe profile of Foley catheter cervical ripening, outpatient cervical ripening with the Foley catheter is already occurring. Many hospitals in the Netherlands and worldwide are already implementing this feature in their labour induction protocols. It is important to monitor this process. We have therefore planned a large prospective cohort study on outpatient induction with Foley catheter, including safety outcome measures and women’s preferences.

**Implementation**

After publication of the PROBAAT results many hospitals in the Netherlands already switched to the use of a Foley catheter as first choice induction method. After publication of the PROBAAT-II results more hospitals pitched up on the use of a Foley catheter. We would recommend the use of a Foley catheter as primary choice for all indications where time to delivery is less urgent, and if not effective or not possible oral misoprostol as second option. For other indications, where the change of severe maternal and/or neonatal morbidity increases by the hour, we would suggest the use of oral misoprostol or even vaginal prostaglandins as primary induction agent, as it leads to a faster delivery. Unfortunately national and international guidelines are still recommending prostaglandins (E2) as first choice.

We would like to plead for rapid revision of these protocols. Both Foley catheter and oral misoprostol have promising features for the use for induction of labour in low-resource settings. Both are inexpensive and easy to store at room temperature. However, in low-resource settings facilities for close fetal and maternal monitoring are not always available and consequentially possible risks such as hyperstimulation cannot not be observed easily. The fact that oxytocin is less often needed after induction with oral misoprostol, makes this probably the preferred method of induction in low-resource settings, since oxytocin requires cooled storage which is often not available. Also, Foley catheter might increase the occurrence of intrauterine infections in countries where the prevalence of such infections is higher. We are currently adjusting the PROBAAT-II studies protocol for use in low-resource settings and planning an adequately powered randomised controlled trial comparing Foley catheter to oral misoprostol in such settings.

**Conclusion**

Foley catheter and oral misoprostol should be considered as first choice for induction of labour with an unripe cervix. Oral misoprostol can be used as 50 microgram tablets 4 hourly or 25 microgram tablets 2 hourly. Both methods have a comparable safety and effectiveness profile, and generate comparable costs.

We would suggest the use of a Foley catheter for all indications where time to delivery is less urgent as first choice, and the use of oral or vaginal misoprostol for all indications where the risk of deterioration of the underlying disease or the fetal condition is worse when pregnancy is continued.
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