Received: 16 March 2024 | Revised: 30 October 2024 | Accepted: 27 November 2024

DOI: 10.1111/aogs.15034

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH

Comparison of balloon catheter, oral misoprostol, or combination of both for cervical ripening in late-term and post-term nulliparous women: A Finnish randomized controlled multicenter pilot trial

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Abstract

Introduction: Nulliparous women beyond term have high rates of induction failure. The aim of this study was to compare delivery outcomes for balloon catheter, misoprostol, and combination of both in nulliparous late- and post-term women with unfavorable cervices. We intended to explore whether the combination strategy has lower cesarean section rate and is as safe as either method alone.

Material and Methods: The randomized multicenter pilot trial was carried out in the five university hospitals and the largest secondary care hospital of Finland March 1, 2018–March 31, 2022. A total of 273 nulliparous women with viable singleton fetus in cephalic presentation, intact amniotic membranes, and an unfavorable cervix at 41 + 0 gestational weeks were included. The study protocol was registered in the ISCTN registry (ISRCTN83219789). The women were randomized into cervical ripening by balloon catheter, oral misoprostol 50 μg every 4 h, or the combination use of both. The primary outcomes of the study were the rates of cesarean section and composite of adverse neonatal outcomes (5-min Apgar score <7, umbilical artery pH ≤7.05, or NICU admission).

Results: Ninety-seven women (35.5%) were allocated in the balloon catheter arm, 94 (34.4%) in the oral misoprostol arm, and 82 (30.0%) in the combination treatment arm. The rates of cesarean section (balloon catheter 23.7%, $n = 23/97$, vs. oral misoprostol 24.5%, $n = 23/94$, vs. combination 17.1%, $n = 14/82$) or composite adverse neonatal outcome (7.2% vs. 7.4% vs. 7.3%, respectively) were not statistically significantly different between the groups. The median (interquartile range) induction to delivery interval was the shortest in the combination treatment, 21.7 (15.1–33.2) h compared to balloon catheter 31.7 (21.9–44.5) h; $p < 0.01$ or oral

Abbreviations: BC, balloon catheter; CS, cesarean section; IOL, induction of labor; IQR, Interquartile range; NICU, Neonatal Intensive Care Unit; SD, standard deviation.

misoprostol 37.0 (26.7–60.3) h; $p < 0.01$. The proportion of women with induction to delivery interval ≤24 h was significantly higher in the combination arm compared to balloon catheter (54.4% vs. 31.1%; $p < 0.01$) or oral misoprostol (54.4% vs. 21.1%; $p < 0.001$).

Conclusions: Our findings confirm the effectiveness of combining balloon catheter and oral misoprostol for cervical ripening, showing shorter induction to delivery interval and comparable rates of cesarean section and neonatal outcomes compared to either method alone. These results advocate for a shift toward adopting combination strategy in the induction of nulliparous late- and post-term women.

KEYWORDS
balloon catheter, cervical ripening, induction of labor, late- and post-term pregnancy, misoprostol, nulliparous women, unfavorable cervix

1 | INTRODUCTION

The proportion of induced labors, currently approximately 30% in developed countries, is rising with the increasing number of women of advanced maternal age, obesity, and pregnancy complications, such as gestational diabetes and hypertensive issues.[1–5] The rate of induction of labor (IOL) has doubled in the past 20 years also in Finland, currently being 35%.[6] Both balloon catheters (BC) and prostaglandins are available for cervical ripening prior to rupturing of the membranes and administration of intravenous oxytocin.[7] BC mechanically dilates the cervix and lower uterine segment, stimulates the secretion of endogenous prostaglandins, and activates the neuroendocrine Ferguson reflex leading to oxytocin secretion, while exogenous prostaglandins stimulate contractions and cervical maturing.[7,8] Combining both methods for simultaneous pharmacological and mechanical cervical ripening may create a synergistic or additive effect that could promote induction success. Previous studies have demonstrated that combination methods lead to shorter duration of induction compared to misoprostol alone, as well as higher rate of vaginal delivery and lower rates of adverse neonatal outcomes.[9] However, at the time of planning this study, only limited data on the use of combination strategy existed. Furthermore, we are not aware of any study focusing only on late- and post-term nulliparous women.

The effectiveness and success of induction techniques greatly affect the mode of delivery, the duration of hospital stay, maternal childbirth experience, and healthcare costs.[10,11] Oral administration of low-dose misoprostol is as effective as vaginal administration for IOL but carries a lower risk of hyperstimulation and fetal heart rate changes.[12] Oral and vaginal misoprostol administration routes have different plasma peak concentration and metabolism patterns,[13,14] and the currently existing reviews and meta-analyses include both administration routes, as well as a varying number and strength of doses.[9,15,16] Often, studies exploring the advantages of combining misoprostol with use of BC have used vaginal misoprostol,[17,18] while limited reports focusing on the use of oral misoprostol in combination with BC exist.[19–21] Furthermore, the authors are not aware of any other study comparing all three options, BC, oral misoprostol, or combination of both in a randomized setting.

Key message

Combination use of concurrent balloon catheter and oral misoprostol in nulliparous late- and post-term women with unfavorable cervices resulted in shorter induction to delivery interval and comparable rates of cesarean section and neonatal outcomes compared to either method alone.

The aim of this pilot study was to evaluate the efficacy and neonatal safety in the combined use of BC and oral misoprostol compared to either method alone by comparing the delivery outcomes such as rates of cesarean section (CS) and adverse neonatal outcome in nulliparous women with unfavorable cervices at or beyond 41 weeks of gestation. We intended to explore whether the combination strategy has a lower CS rate and is as safe as either method alone. As post-date nulliparous women are known to have higher rates of induction failure leading to CS, delivery complications, and poor childbirth experience compared with parous women, the importance of the most optimal labor induction method in this vulnerable subgroup of parturients is evident.[10,22]

2 | MATERIAL AND METHODS

This randomized multicenter pilot trial comparing the method of cervical ripening in late-term and post-term nulliparous women was carried out between March 1, 2018 and March 31, 2022 in the five university hospitals of Finland (Helsinki, Tampere, Turku, Oulu and Kuopio University Hospitals) and the largest secondary care hospital of Finland (Central Finland Central Hospital). The Ethics

committee (HUS Regional Committee on Medical Research Ethics) of the Hospital district of Helsinki and Uusimaa (HUS/1978/2016, March 16, 2017) and the institutional review boards of all participating hospitals approved the study. The study protocol was registered in the ISCTN registry (ISRCTN83219789). The trial was carried out in accordance with the Declaration of Helsinki, and with all relevant guidelines and regulations.

Nulliparous women of ≥18 years of age with a viable singleton pregnancy at or beyond 41+0 weeks of gestation with intact amniotic membranes, an unfavorable cervix (Bishop score <6), fetus in cephalic presentation, and pregnancy dating confirmed by crown-rump-length measurement during the first trimester ultrasound screening at gestational weeks 11+0–13+6 were included in the study. The exclusion criteria included fetal anomaly, pregnancy complication requiring intervention, fetal ultrasound weight estimation >4500 g or less than 10 percentiles or −1.5 standard deviations (SD) from the average fetal growth, uterine scar, low-lying placenta, suspicion of any active maternal vaginal bacterial or viral infection or chorioamnionitis, and maternal human immunodeficiency virus, hepatitis B or C.

Information on the study was available in Finnish from the primary care givers, in the hospital antenatal clinics, and on the study website during the study period. Women interested in the study contacted the research group online or were referred to the hospital by their primary care giver. All participants had their first screening visit at 41+0 gestational weeks including clinical and obstetric ultrasound examination, cardiotocography, and pre-eclampsia screening by urine sample and blood pressure measurement. The obstetric ultrasound examination included assessment of fetal weight estimation, biophysical profile, amniotic fluid index, placental location, and Doppler of the umbilical artery blood flow. All participants received oral and written information and signed an informed written consent.

The study consisted of two parts, and the first part of randomization to either IOL at gestational week 41+0 or expectant management until gestational week 41+5–42+1 has previously been reported.[23] The second part of randomization included the method of cervical ripening for all participants who underwent IOL at gestational week 41+0–42+1. Randomization was performed by the authors at the start of IOL following clinical examination, confirmation of inclusion and exclusion criteria, and obtaining an informed consent. Randomization was carried out using a custom-made online tool with a computer software program that generated a random allocation sequence with randomly selected block sizes of 5, 10, and 20, and with equal randomization ratios of 1:1:1. No stratification according to centers was used. The women were allocated into three treatment arms; BC, oral misoprostol, or combination of BC and oral misoprostol concurrently. Figure 1 presents the formation of the study population. For this second part of the study, no separate sample size calculation or power analysis was performed prior to study as this was a pilot trial with the cohort size determined by including all eligible labor inductions of the first part of the study.

The induction method intervention was carried out by the authors and the treating staff of the participating hospitals according to the study protocol. Due to the nature of the study, blinding was not possible. The background and delivery outcome data were collected from the patient charts by the investigators in each center. The data sheets were then pseudonymized and delivered to the Helsinki research team who combined and analyzed the data. Data collection was not blinded due to data protection and institutional policies. The investigators of the participating centers could only access their own data, excluding the members of the Helsinki research team who had access to all pseudonymized data and performed the analyses.

The women allocated to the BC arm received a single 75 mL balloon retained for a maximum of 24 h. After expulsion or removal of

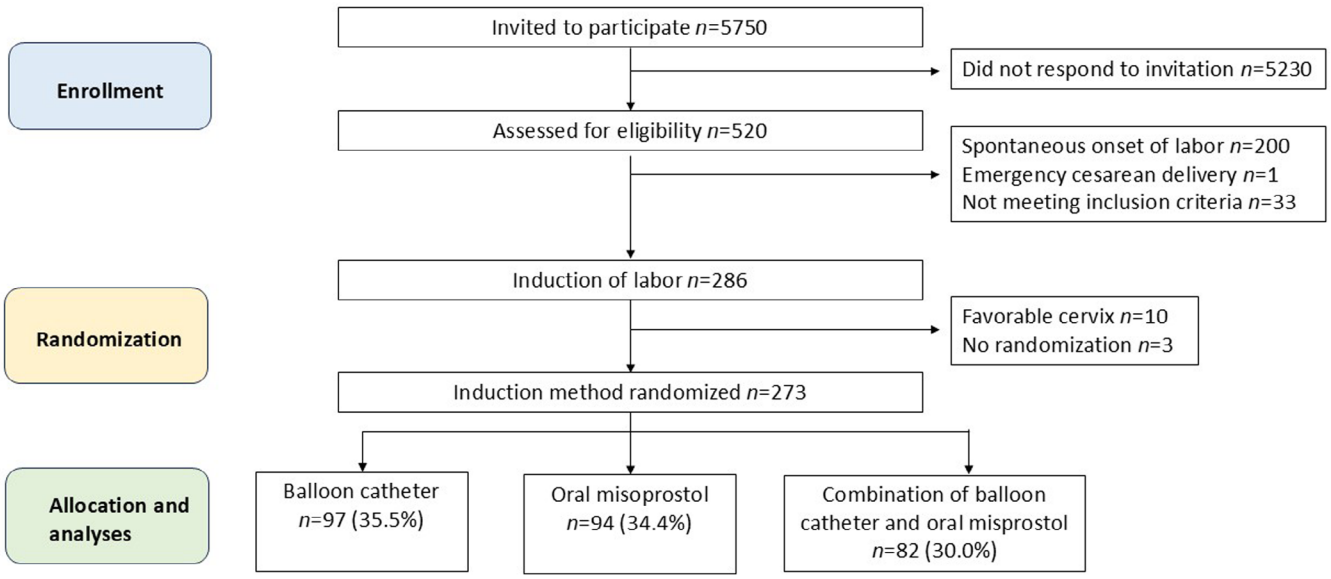

FIGURE 1 Flowchart of the study population ($n=273$).

the balloon, if the cervix was favorable with Bishop score ≥6, amniotomy was performed and intravenous oxytocin infusion was started according to the local protocol. If the cervix remained unfavorable following expulsion or removal of the BC, a new BC was placed every 24 h until a maximum of 72 h of BC ripening. The women allocated to the misoprostol arm received 50 μg orally every 4 h maximally 6 times a day until the onset of regular contractions or reaching Bishop score ≥6, after which amniotomy was performed. If contractions deemed inadequate intravenous oxytocin infusion was initiated in accordance with the local protocol but not earlier than 4 h following the last administration of misoprostol. The women allocated to the concurrent use of BC and misoprostol ("the combination arm") received a single 75 mL balloon retained for a maximum of 24 h and 50 μg of misoprostol orally every 4 h maximally 6 times a day until the onset of regular contractions or reaching Bishop score ≥6, after which IOL was continued as described above. If the cervix remained unfavorable following expulsion of the BC, a new BC was placed while oral administration of misoprostol was continued. If the cervix remained unfavorable after 72 h of the BC, misoprostol, or combination treatment, induction was considered failed and either continued according to the local protocol or CS was performed.

The primary outcomes of the study were the rates of CS and a composite of adverse neonatal outcome defined as 5-min Apgar score <7, umbilical artery pH ≤7.05, or neonatal intensive care (NICU) admission. The secondary outcomes included hemorrhage ≥1000 mL (defined as weighed cumulative blood loss ≥1000 mL within 24 h after the delivery including the intrapartum blood loss), manual removal of a retained placenta, anal sphincter injury, induction to onset of active labor interval (defined as the start of IOL to cervical dilation ≥6 cm and regular contractions), induction-to-delivery interval, and intrapartum or postpartum infection (defined as two or more of the following criteria: maternal fever ≥38°C, fetal tachycardia, purulent discharge, uterine tenderness, white cell count ≥20).

Continuous cardiotocography was routinely used during labor. Oxytocin was administered for labor induction with the starting dose of 2.5 mIU/min (15 mL/h) and increased by 1.7 mIU/min (10 mL/h) increments every 20–30 min until the maximum of 20 mIU/min (120 mL/h) or until contractions were deemed adequate with 3–5 contractions occurring within 10-min period. When contractions were deemed adequate and active labor was reached, oxytocin was paused, and administration was later restarted for augmentation of labor if necessary. Oxytocin augmentation during labor was routinely administered if contractions were deemed inadequate or labor progress was slower than expected. Failed induction was diagnosed after 12–18 h of oxytocin administration with ruptured membranes, and cervical dilation <6 cm with no progress.[24] Labor arrest was defined at cervical dilation of ≥6 cm, ruptured membranes, and no progress despite of 4 h or more of adequate contractions.[24]

The results are presented as numbers (*n*) with percentages (%), means with SD, or medians with interquartile ranges (IQR). For comparison of categorical variables, Chi-squared test and Fisher's exact test were used when appropriate. For continuous variables, we used *t*-test when the data followed normal distribution (age, body mass index, gestational age, Bishop score, and birthweight) and Mann–Whitney *U*-test when it did not (induction to active labor interval, induction to delivery interval, duration of labor). For controlling type I errors, We used hierarchical testing starting the statistical analyses with the primary outcomes, followed by the prespecified secondary outcomes described above (postpartum hemorrhage ≥1000 mL, uterine tachysystole, intrapartum infection, maternal postpartum infection, neonatal infection, grade III–IV perineal tear, manual removal of retained placenta, and birthweight ≥4000 g) in the order they are presented in Table 3. We also conducted a supplementary analysis (data not shown) using the Benjamini–Hochberg procedure to adjust for the false discovery rate within groups of our predefined secondary outcomes, but this adjustment did not affect the significance of our results. The effect of site was assessed by comparing the frequency of primary outcomes (CSs and neonatal composite outcomes) across the centers. We used the Chi-squared test of independence to determine whether observed distributions differed from what would be expected by random variation, indicating a statistically significant difference. Kaplan–Meier survival curve analysis was used for visualization of the induction to onset of active labor interval and the induction to delivery interval. *p*-value <0.05 was considered statistically significant. The data were analyzed as intention to treat according to the randomized group. Statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, NY, USA).

2.1 | Patient and public involvement statement

Before initiating the trial, input from pregnant women and members of the public, including expectant mothers' support groups, were sought to ensure that the study addressed relevant concerns regarding labor induction. Their insights helped in planning the study as well as disseminating research information. Throughout the trial, participants had opportunities to provide feedback on their experiences, follow a blog, and discuss with the investigators on the study website. Furthermore, upon completion of the trial, results will be disseminated to relevant patient advocacy groups and the wider public through community forums, educational materials, and online platforms. By involving patients and the public, this trial aimed to ensure that the findings are relevant, accessible, and meaningful to those directly affected by labor induction decisions, ultimately improving maternal and neonatal health outcomes.

3 | RESULTS

The final study population included 273 women, of which 97 (35.5%) were allocated in the BC arm, 94 (34.4%) in the misoprostol arm, and 82 (30.0%) in the combination arm (Figure 1). One woman who was allocated in the BC arm received misoprostol instead and was analyzed based on intention to treat in the BC arm. However, in the

per-protocol analyses with the woman analyzed in the misoprostol arm, no significant change in the results were seen (data not shown). The mean (SD) age of the women was 28.7 (5.1) years, the mean body mass index was 25.7 (4.8) kg/m^2, and the mean gestational age was 41.5 (0.4) weeks. There were no statistically significant differences in the maternal characteristics between the arms (Table 1), but ultrasonographic fetal weight estimation was more often ≥4000 g in the combination arm ($n=20/82$, 24.4%) compared to the BC or misoprostol arms. Altogether 33 women (12.1%) had a pre-existing medical condition, such as asthma, hypothyroidism, migraine, irritable bowel syndrome, or depression, with no statistical difference between the arms.

Table 2 presents the primary delivery outcomes. The total CS rate in the study population was 22.0% ($n=60/273$). The rates of CS (the BC arm 23.7%, $n=23/97$ vs. the misoprostol arm 24.5%, $n=23/94$ vs. the combination arm 17.1% $n=14/82$) were not statistically significantly different between the groups, although there was a trend toward a higher proportion of spontaneous vaginal deliveries in the combination arm (Table 2). The total rate of composite adverse neonatal outcome in the study population was 5.5% ($n=15/273$). The proportions of composite adverse neonatal outcomes (3.1% in the BC arm vs. 6.4% in the misoprostol arm vs. 7.3% in the combination arm) did not statistically significantly differ between the arms (Table 2). The total NICU admission rate was 3.3% ($n=9$), with no statistically significant differences between the arms (Table 2). In assessing the effect of site, the CS rates were not statistically significantly different between the centers (data not shown; $p=0.10$) but composite adverse neonatal outcome was significantly higher in Oulu, 16.7%, compared to the rates of 0%–8.3% in the other centers (data not shown; $p=0.02$).

The duration of median (IQR) BC retainment was shorter in the combination arm compared to the BC arm, 7.5 (5.1–12.3) h versus 11.5 (6.9–21.5) h; $p=0.003$. The median (IQR) doses of misoprostol were 3.9 (2-5) in the misoprostol arm and 1.6 (1-2) in the combination arm; $p<0.001$. Oxytocin was more often needed for labor induction in the BC arm compared to the other two methods (Table 3). There were no statistically significant differences in the rates of vacuum assisted operative vaginal delivery, grade III–IV perineal tear, manual removal of retained placenta, postpartum hemorrhage ≥1000 mL, uterine tachysystole, intrapartum infection, or maternal postpartum infection (Table 3). The birthweight and the rates of neonatal infection were also similar between the arms (Table 3).

The median (IQR) time from labor induction to the onset of active labor was the shortest 10.4 (6.0–23.6) h in the combination arm compared to 24.5 (10.7–29.2) h in the BC arm ($p<0.01$) and to 24.1 (11.7–45.9) h in the misoprostol arm ($p<0.01$), (Figure 2 and Table 4). The induction to delivery interval in vaginal deliveries was the shortest 21.7 (15.1–33.2) h in the combination arm with the median difference of 10.0 h compared to the BC arm (31.7 h, IQR 21.9–44.5 h; $p<0.01$) and with the median difference of 15.3 h compared to the misoprostol arm (37.0 h, IQR 26.7–60.3 h; $p<0.01$), (Figure 3 and Table 4). The proportion of women with induction to delivery interval ≤24 h resulting in vaginal delivery was significantly higher in

TABLE 1 Characteristics of the study population ($n=273$).

	Balloon catheter $n=97$		Oral misoprostol $n=94$		Combination treatment $n=82$	
Trial site	***n***	**%**	***n***	**%**	***n***	**%**
Helsinki University Hospital	29	29.9	29	30.9	20	24.4
Tampere University Hospital	9	9.3	16	17.0	5	6.1
Kuopio University Hospital	17	17.5	18	19.1	13	15.9
Oulu University Hospital	9	9.3	11	11.7	16	19.5
Turku University Hospital	11	11.3	8	8.5	4	4.9
Central Finland Central Hospital	22	22.7	12	12.8	24	29.3
Gestational weeks at induction (mean, SD)	41.2	0.30	41.2	0.3	41.2	0.40
Maternal age ≥35 years	10	10.3	10	10.6	14	17.1
BMI ≥30 kg/m^2	20	20.6	19	20.2	11	13.4
Group B Streptococcus colonization[a]	21	21.6	20	21.3	15	18.3
Gestational diabetes	9	9.3	14	14.9	9	11.0
Bishop score (mean, SD)	3.7	1.1	3.0	1.4	3.7	1.3

Note: The data are presented by intention-to-treat. No statistically significant differences in the characteristics between the groups existed.

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]Missing values: balloon catheter $n=19$, Misoprostol $n=12$, combination $n=17$.

TABLE 2 The primary delivery outcomes ($n=273$).

	Balloon catheter $n=97$		Misoprostol $n=94$		Combination treatment $n=82$				
	n	%	*n*	%	*n*	%	*p*-value[a]	*p*-value[b]	*p*-value[c]
Cesarean delivery	23	23.7	23	24.5	14	17.1	0.90	0.28	0.23
Fetal distress	6	6.2	6	6.4	3	3.7	1.00	1.00	1.00
Failed induction	10	10.3	9	9.6	4	4.9	0.77	0.49	0.72
Labor arrest	6	6.2	8	8.5	6	7.3	0.52	0.29	0.62
Other[d]	1	2.1	0		1	1.2			
Spontaneous vaginal delivery	55	56.7	56	59.6	56	68.3	0.69	0.11	0.23
Operative vaginal delivery (vacuum)	19	19.6	15	16.0	12	14.6	0.52	0.25	0.60
Composite adverse neonatal outcome[e]	3	3.1	6	6.4	6	7.3	0.29	0.20	0.81
5-min Apgar score ≤7	0		4	4.3	3	3.7	0.06	0.09	1.00
Umbilical cord artery blood pH ≤7.05	1	1.0	3	3.2	1	1.2	0.62	1.00	0.63
NICU admission	2	2.1	3	3.2	4	4.9	0.68	0.42	0.71

Abbreviations: BC, balloon catheter; NICU, Neonatal Intensive Care Unit.

[a]BC compared to misoprostol.

[b]BC compared to combination treatment.

[c]Misoprostol compared to combination treatment.

[d]In the balloon catheter group; large intravaginal hematoma $n=1$, in the combination treatment group; umbilical cord prolapse $n=1$.

[e]Composite adverse neonatal outcome was defined as one or more of the following: 5-min Apgar score <7, umbilical artery pH ≤7.05 or NICU admission.

TABLE 3 Other delivery outcomes ($n=273$).

	Balloon catheter $n=97$		Misoprostol $n=94$		Combination treatment $n=82$				
	n	%	*n*	%	*n*	%	*p*-value[a]	*p*-value[b]	*p*-value[c]
Post-partum hemorrhage ≥1000 mL	11	11.3	9	9.6	10	12.2	0.69	0.86	0.58
Uterine tachysystole	7	7.2	7	7.4	7	8.5	0.95	0.74	0.79
Intrapartum infection	5	5.2	2	2.1	4	4.9	0.45	1.00	0.42
Maternal post-partum infection	1	1.0	0	0.0	1	1.2	1.00	1.00	0.47
Neonatal infection	1	1.0	0		2	2.4	1.00	0.35	0.19
Grade III–IV perineal tear	3	3.1	3	3.2	6	7.2	1.00	0.31	0.31
Manual removal of retained placenta	3	3.1	2	2.1	2	2.4	1.00	1.00	1.00
Birthweight (mean, SD)	3672	352.0	3709	377.0	3734	400	0.82	0.11	0.20
Birthweight ≥4000 g	16	16.5	17	18.1	23	28	0.77	0.06	0.12
Oxytocin use for labor induction	24	24.7	7	7.4	13	15.9	<0.01	0.14	0.08
Duration of BC retainment (Median, IQR)	11.5	6.9–21.5			7.5	5.1–12.3		0.003	
Doses of misoprostol (median, IQR)			3.9	2–5	1.6	1–2			<0.01

Abbreviations: BC, balloon catheter; IQR, Interquartile range; SD, standard deviation.

[a]BC compared to misoprostol.

[b]BC compared to combination treatment.

[c]Misoprostol compared to combination treatment.

the combination arm compared to the BC or oral misoprostol arms (54.4%, $n=37/97$ vs. 31.1%, $n=23/94$ vs. 21.1% $n=15/82$; $p<0.01$, respectively) (Table 4). The durations of labor were similar in the three arms (Table 4).

4 | DISCUSSION

In this multi-center randomized pilot trial, combination of BC and misoprostol for cervical ripening in late- and post-term nulliparous

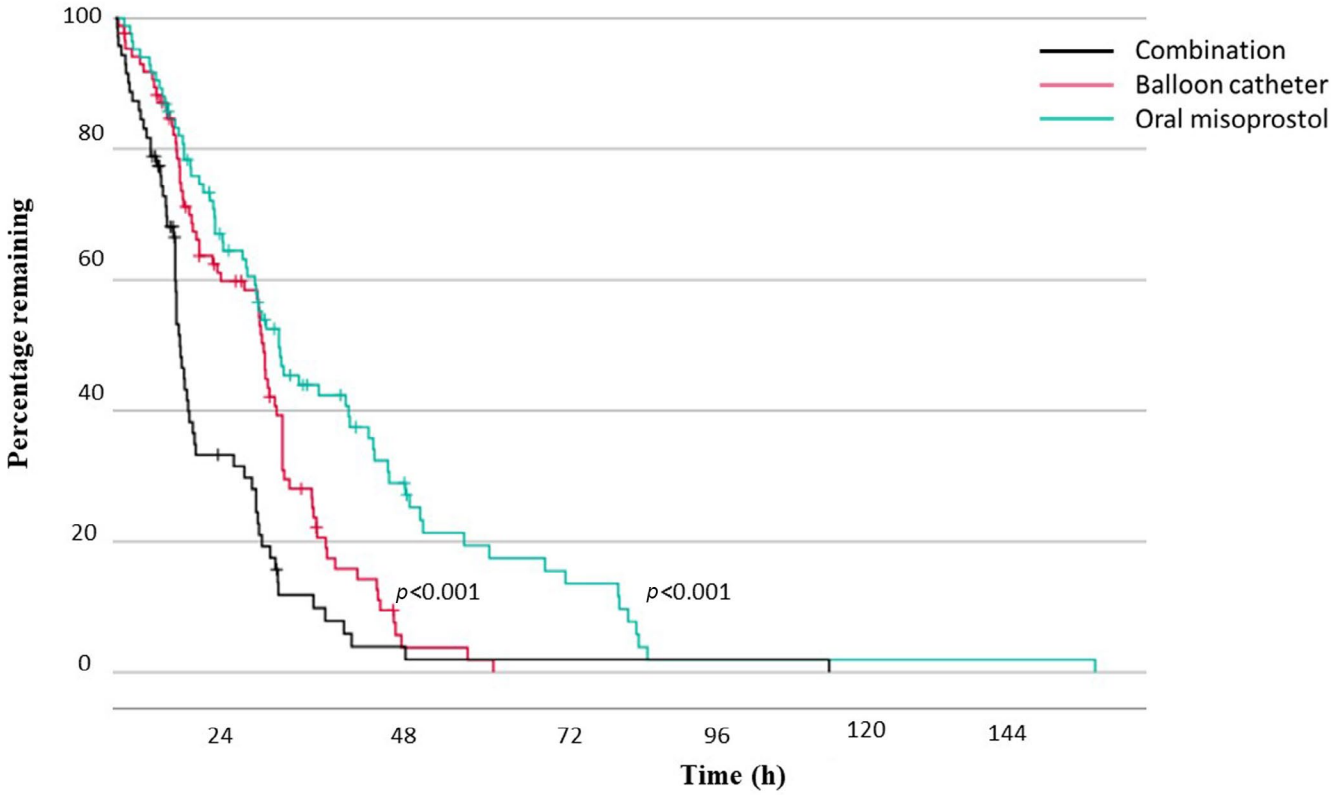

FIGURE 2 The induction to the active labor interval. The interval between the beginning of labor induction and the onset of labor defined as cervical dilation ≥6 cm with regular contractions, was the shortest in the combination treatment arm compared to the balloon catheter and oral misoprostol arms.

TABLE 4 The durations of labor induction and labor (hours) in vaginal deliveries ($n = 213$).

	Balloon catheter $n = 74$		Misoprostol $n = 71$		Combination treatment $n = 68$				
	Median	IQR	Median	IQR	Median	IQR	*p*-value[a]	*p*-value[b]	*p*-value[c]
Induction to active labor interval	24.5	10.7–29.2	24.1	11.7–45.9	10.4	6.0–23.6	0.15	<0.01	<0.01
Induction to delivery interval	31.7	21.9–44.5	37.0	26.7–60.3	21.7	15.1–33.2	0.04	<0.01	<0.01
Induction to delivery ≤24 h (*n*, %)	23	31.1	15	21.1	37	54.4	0.31	<0.01	<0.01
Duration of labor	10.3	7.3–13.6	12.0	7.2–15.9	9.8	6.6–16.9	0.16	0.85	0.43
I Stage of labor	9.4	6.8–12.7	11.4	7.0–15.5	9.3	6.0–15.9	0.13	0.89	0.36
II Stage of labor	0.5	0.3–0.9	0.5	0.3–0.8	0.5	0.3–1.0	0.96	0.16	0.51

Abbreviation: IQR, interquartile range.

[a]BC compared to misoprostol.

[b]BC compared to combination treatment.

[c]Misoprostol compared to combination treatment.

women resulted in no significant difference in the rates of CS or adverse neonatal outcome compared to either method alone, but the duration of labor induction was significantly shorter.

Our findings of shorter induction to delivery interval agree with the two previously published reviews and meta-analyses on 15 and 11 RCTs comparing the combination of misoprostol and BC to misoprostol alone for IOL.[9,15] In both reviews, the combination treatment was associated with a shorter induction to delivery interval with the mean difference of 2 h[15] and 3.7 h.[9] Although an exploratory outcome which should be interpreted with caution, the mean difference in the induction to delivery interval was even greater in our study, 15.1 h shorter in the combination arm compared to misoprostol alone, and 10.0 h shorter compared to BC alone. The induction-to-delivery interval in our study was longer in both the combination and misoprostol arms compared to the reviews[9,15] and to the recent RCT by Anjali et al.,[20] but the median time from induction to

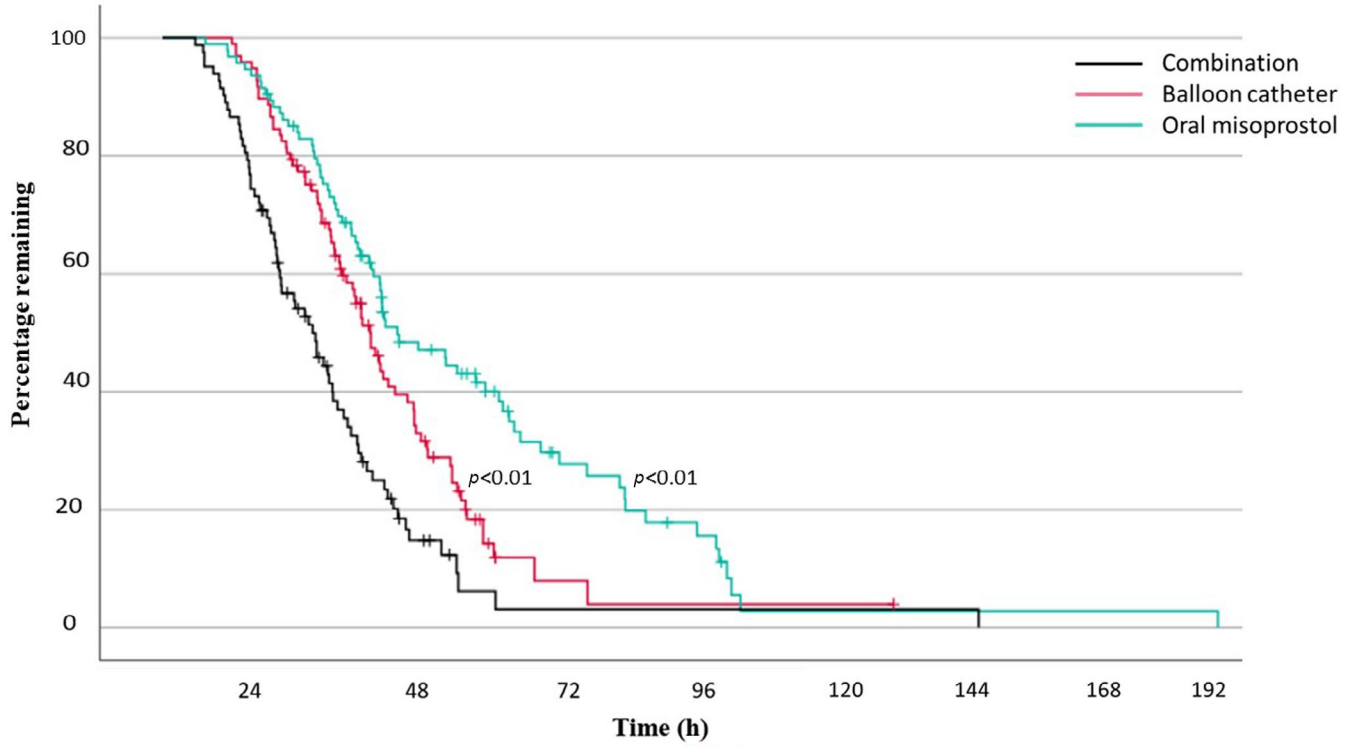

FIGURE 3 Induction to delivery interval. The induction to delivery interval in vaginal deliveries was the shortest in the combination treatment arm compared to the balloon catheter and oral misoprostol arms.

active labor in our study was similar to Anjali's study.[20] However, we only included vaginal deliveries in the induction to delivery interval, while Anjali's study also included cesarean deliveries. We may also have allowed slower progress of active labor, but in our study all the women were nulliparous requiring longer time for their first labor, while more than 40% were multiparous in Anjali's study. The proportion of women delivering within 24 h from the start of induction in our study was 1.7-fold in the combination arm compared to the BC arm and 2.6-fold compared to the misoprostol arm. On the contrary, another recent RCT comparing the combination of BC and oral 100 μg misoprostol to oral 100 μg misoprostol alone with two doses 4 h apart in altogether 2227 women found no difference in the induction to delivery interval.[21] However, this study used only 30 mL balloon inflation, although it is known that higher balloon volumes result in more efficient cervical ripening.[25] Furthermore, the dosage of misoprostol differed from the current recommendation of more frequently repeated smaller doses of oral misoprostol.[11,12] Shortening the duration of induction, considering the increasing number of patients who undergo labor induction, is associated with decreased healthcare costs and use of resources.[26] Using an effective, safe and fast combination strategy may also increase maternal satisfaction on labor induction and childbirth experience.[10,27]

Some studies have shown promising results in reducing the frequency of CS using a combination of methods,[17,28] while most studies found no difference in rates of CS or were underpowered to detect it.[18–21,29] Also in our pilot study, no statistically significant difference in the rates of CS between the groups was found, although there was a trend toward a higher rate of spontaneous vaginal delivery in the combination arm. Although this did not reach statistical significance, the observed disparity of 11% in the rates of spontaneous vaginal delivery between the groups of single and combination methods could, if statistically confirmed, be considered substantial in the clinical setting, especially considering the increasing rates of IOL. The rate of spontaneous vaginal delivery in our study was lower than in previous RCTs comparing labor induction at 41 + 0 gestational weeks and 42 + 0 gestational weeks.[30,31] However, those studies included multiparous women, women with spontaneous onset of labor and women with favorable cervices, whereas our study included only nulliparous post-term women with unfavorable cervices undergoing labor induction, who are known to be at the highest risk for operative delivery following IOL. The 16.8% rate of vacuum-assisted delivery in the study population was in line with the 17% rate of operative vaginal delivery among nulliparous women in Finland.[6]

The recent RCT by Anjali et al. with similar setting as ours found a higher rate of maternal postpartum hemorrhage in the combination group (7% compared to 4% in the misoprostol group),[20] while other studies have reported no difference in the maternal outcomes.[9,15,18,19] Also in our study, although underpowered, no statistically or clinically important differences in the maternal complications were seen.

No statistically significant difference in the rates of adverse neonatal outcomes were seen between the arms, although our pilot study was underpowered to detect these small but potentially

clinically important differences. It is well established that post-term pregnancy is an independent risk factor for neonatal morbidity even in low-risk pregnancies, and the rate of adverse neonatal outcome in our study was similar to those reported by the previous studies.[22,32,33] In the recent reviews, the combination of BC and misoprostol has been associated with a lower risk of NICU admission and fewer cases of uterine hyperstimulation compared with misoprostol only.[9,15] In our study, the rates of composite outcome and NICU admission were higher in the combination arm compared to the misoprostol arm but controversially, fetal asphyxia and low 5-min Apgar score were more frequent in the misoprostol arm than in the combination arm. Notably, at one site, the rate of NICU admission for suspected infection was significantly higher compared to other sites. However, most of those neonates were shortly discharged without a diagnosed infection. Three neonates in the combination arm were admitted to NICU at this site, perhaps partly explaining the discrepancy in the composite outcome for the combination arm. This may also reflect the low threshold in admitting neonates for suspected infection in induced labor.

The national multicenter pilot RCT setting was the major strength of the study, as was the high protocol compliance. Also, the inclusion criteria of only late- and post-term nulliparous women with unfavorable cervices permitted no confounders of previous vaginal or cesarean deliveries for the outcomes. The size and volume of the BC and the regimen of misoprostol used were standardized in all centers. However, there may have been local differences in labor management in each institution, such as the latest possible day of labor induction, the duration and dosage of oxytocin, and the number of cervical examinations. The data being collected from electronic health record systems allowed detailed and reliable data use for the study.

The main limitation of the study was the study design with the lack of a clear hypothesis including a sample size calculation leaving the study underpowered to detect differences in the rates of CS and composite neonatal outcome. For the first part of the study, already published, the target sample size was 400 women according to the power calculation based on the CS rate, which unfortunately was not met.[23] For this second pilot part of the study, no separate power analysis was performed as the sample size was defined by including all the labor inductions from the first part of the study.[23] A post hoc power analysis was conducted using Fisher's exact test for proportions to evaluate the achieved statistical power of comparing the CS rates. In both comparisons, the achieved power is low (0.17 and 0.19), indicating that the study is underpowered to detect a statistically significant difference between the two groups with the current sample size. Furthermore, the secondary outcome findings should be interpreted cautiously due to the exploratory nature of these analyses and the potential risk for type 1 errors in reporting multiple outcomes. Our study also had some limitations related to nonblinding, which may have influenced patient management. However, blinding was not possible with the current design. The authors are also aware that 25 μg low dose oral misoprostol tablets are currently preferred over 50 μg since adverse effects more often occur at higher doses. Despite no significant adverse events in this study, the 25 μg dosage would have been the optimal misoprostol method of choice compared to the 50 μg dosage used in the study. Unfortunately, at the time of planning the study in 2016–2017, the low-dose 25 μg misoprostol tablets were not yet available in Finland. Another limitation is the lack of standardized criteria for NICU admission included in the composite adverse outcome. Instead, each center and professional used their own criteria. Despite this, the rates of composite adverse outcomes did not differ significantly between the methods. We also regret not collecting the data on smoking, educational level, socioeconomic parameters, and duration of hospital stay.

In a future study, a larger sample size would be needed. For example, a sample size of 1548 participants would be needed to test for non-inferiority for safety in terms of adverse neonatal outcome and to evaluate superiority for efficacy. If there is a true difference of 2% (95% vs. 93%) favoring traditional induction methods, 1548 participants would be required to ensure, with 80% confidence, that the upper limit of a one-sided 95% confidence interval excludes a difference favoring the standard methods by more than 5%. This sample size would also provide adequate power to detect superiority in the mode of delivery. Given the current 7% difference in CS rates between the methods, 518 women per group would be needed to detect this difference in CS rates at a 5% significance level with 80% power.

5 | CONCLUSION

The results of our pilot RCT support the evidence on the efficacy of combined use of BC and misoprostol for cervical ripening, as the time from induction to delivery was significantly shorter in the combination treatment arm. The combination method showed no statistically significant difference in the rates of CS or adverse neonatal outcome compared to either method alone, although the study was unpowered to detect these. These findings, coupled with the recent studies suggesting a paradigm shift toward combination strategy, underscore the combination strategy deserving a greater degree of implementation in routine cervical ripening practices.

AUTHOR CONTRIBUTIONS

The study's inception was coordinated by L.R., H.K., K.P., A.T., and S.H. Planning and execution of the study protocol were undertaken by all the authors; L.R., H.K., K.P., A.T., S.H., K.V., M.-R.O., M.V., J.U., K.T., K.R., and K.M. Data analysis was performed by L.R., and the initial draft of the manuscript was led by H.K. with support from L.R. and K.P. Subsequent revisions of the manuscript involved input from all the authors resulting in a united approval of the final version.

ACKNOWLEDGMENTS

Our heartfelt thanks to the research nurses and midwives, Joy Kanerva-Pulkkinen, Anne Vesterinen, and Eija Kortelainen, for their crucial contributions to the study arrangements. Additionally, we express our appreciation to all the doctors and midwives who participated in the recruitment process and provided care for the participants. We would like to extend our warmest thanks to biostatistician Paula Reiterä from Helsinki University for her invaluable contribution and insightful advice.

CONFLICT OF INTEREST STATEMENT

The authors explicitly state no potential conflicts of interest exist.

ETHICS STATEMENT

The Ethics Committee of the Hospital District of Helsinki and Uusimaa (March 16, 2017: HUS/1978/2016) and all the institutional review boards of the other participating hospitals approved the study. The study protocol was registered in the ISCTN registry (October 10, 2017: trial registration number SRCTN83219789 with date of initial participant enrollment March 4, 2018 and the date of the last patient enrollment March 30, 2022). All participants received oral and written information on the study and signed a written informed consent. The trial was carried out in accordance with the Declaration of Helsinki, and with all relevant guidelines and regulations.

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How to cite this article: Kruit H, Place K, Väyrynen K, et al. Comparison of balloon catheter, oral misoprostol, or combination of both for cervical ripening in late-term and post-term nulliparous women: A Finnish randomized controlled multicenter pilot trial. *Acta Obstet Gynecol Scand*. 2024;00:1-11. doi:10.1111/aogs.15034