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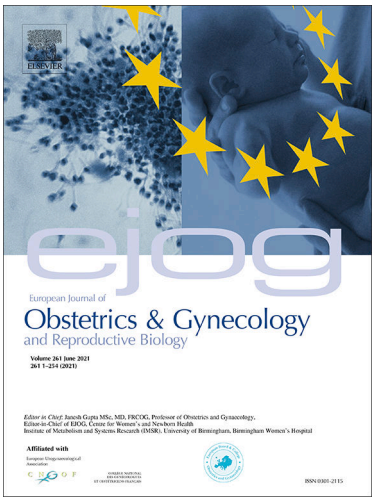

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The influence of various induction methods on adverse outcomes in small for gestational age neonates: A secondary analysis of the PROBAAT 1 and 2 trials

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Short title: induction methods and SGA

Abstract:

Objective: To evaluate the safety aspects of different induction methods in pregnancies with small-for-gestational-age neonates.

Study design: This was a secondary analysis of two previously reported multicenter, randomized controlled trials conducted in the Netherlands. In the original trials, women were randomized to either a 30cc Foley catheter, vaginal prostaglandin E2 (PROBAAT-1) or oral misoprostol (PROBAAT-2). A total of 425 patients with a term, singleton pregnancy in cephalic presentation with an indication for labor induction and a small-for-gestational-age neonate were included in this secondary analysis. Our primary outcome was a composed adverse neonatal outcome of Apgar score <7 after 5 minutes and/or a pH in the umbilical artery <7.05 and/or NICU admission. Secondary outcomes were mode of birth, operative birth for fetal distress and pH <7.10 in the umbilical artery. For these outcome measures, multivariate as well as bivariate analyses were performed.

Results: An adverse neonatal outcome occurred in 4.7% (10/214) induction with a Foley catheter, versus 12.8% (19/149) after misoprostol (RR 0.36; 95% CI 0.17-0.76) and 4.7% (3/64) after Prostaglandin E2 (RR 0.98; 95%CI 0.28-3.51).
For individual components of the composed outcome of adverse events, a difference was found between a Foley catheter and misoprostol for Apgar score <7 at 5 minutes (0.5% versus 3.4; RR 0.14; 95%CI 0.02-1.16) and NICU admission (1.9% versus 6.1%; RR 0.31; 0.10-0.97). No differences were found for mode of birth.

Conclusions: For women who gave birth to a small-for-gestational-age neonate, a Foley catheter is probably a safer induction method compared to oral misoprostol.

Keywords: Induction of labor, cervical ripening, Foley catheter, balloon, PGE2, prostaglandin, PGE1, misoprostol, FGR, SGA

Highlight:

- A foley catheter for induction of labor is probably safer for small-for-gestational age babies compared to oral misoprostol

Acknowledgement

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Disclosure of interests:

BM reports consultancy for ObsEva, Merck KGaA and Guerbet. The other authors declare they have no conflicts of interest.

Contribution to authorship

BM, KB, RH, and MV designed the study. MV analyzed the data and drafted the manuscript. MV, DC, CV, MB, KB, MJ, ME, BM and RH all interpreted the data, critically revised the article, and approved the final version.

Details of ethics approval

The original trials (PROBAAT-1 and 2) were approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Academic Medical Centre, Amsterdam, by the board of directors of each participating hospital, and registered with the Dutch Trial Registry (NTR 1646 and NTR3466).

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1. Introduction

Induction of labor has become a common procedure and numbers have increased steadily over the last two decades. In developed countries up to 30% of all births are induced[1,2]. In case of an unfavorable cervix, induction starts with ripening of the cervix for which a variety of methods can be used. Approaches to cervical ripening can be pharmacologically (Prostaglandin E1 or Prostaglandin E2) or mechanically (Foley catheter). The mechanism of cervical ripening is different between both methods. Where synthetic prostaglandins imitate physiological cervical ripening and increases the sensitivity of the uterine wall to oxytocin, a foley catheter induces labor by direct mechanical pressure and stimulating endogenous release of prostaglandins[3,4].

Until a decade ago, the most preferred method for induction was vaginal applied Prostaglandin E2 (PGE_2)[5,6]. This tendency changed after publications of the PROBAAT-1 and 2 trials, two multicenter randomized controlled trials, evaluating the safety and effectivity of the transcervical placed Foley catheter compared to PGE_2 and oral misoprostol, respectively[7-9]. Although the CS rate between a Foley catheter and PGE^2 did not differ, fewer CS were performed for fetal distress when a Foley catheter was used[8]. When compared to oral misoprostol, non-inferiority was found between both methods regarding a composite outcome of neonatal asphyxia and post partum hemorrhage[9].

A Foley catheter, as well as oral misoprostol are now the recommended methods for induction of labor in the Netherlands[10] A recent Cochrane review on mechanical methods for induction of labor showed a better neonatal safety profile for induction with a foley catheter, with a 50% reduction in severe neonatal adverse events when compared to PGE2[4].

In current clinical practice, a Foley catheter is more often used in pregnancies with an increased risk of fetal distress, which is the case in pregnancies with an estimated fetal weight $<10^{th}$ percentile. Although small-for-gestational-age neonates (SGA; neonates with a birthweight $<10^{th}$ percentile) are at risk of fetal distress when labor is induced compared to non-SGA neonates, studies on the effect of different induction methods on neonatal outcome in these pregnancies are limited[11-13].

The aim of this study is to evaluate the effect of different induction methods on obstetric and perinatal outcomes in pregnancies where an SGA neonate was born.

2. Material and Methods

This is a post hoc exploratory analysis of the PROBAAT-1 and PROBAAT-2 trials. Both studies were multicenter randomized controlled trials for which the full-scale methods and results were published elsewhere[8,9]. In brief, the PROBAAT-1 trial randomized women to induction of labor with a 30cc Foley catheter or vaginal Prostaglandin E2 gel. The PROBAAT-2 trial randomized women to a 30cc Foley catheter or oral misoprostol.

In total, 29 hospitals collaborating in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium 2.0) participated in one or both PROBAAT trials. Both trials were approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Academic Medical Center, Amsterdam and by the board of directors of each participating hospital and registered with the Dutch Trial Registry (NTR 1646 and NTR3466). No further approval was required due to the nature of this study.

Both PROBAAT trials studied pregnant women scheduled for induction of labor beyond 37 weeks of gestation with a vital singleton pregnancy in cephalic presentation, intact membranes, and an unfavorable cervix (Bishop score <6). Women younger than 18 years, with a previous caesarean section, placenta previa, lethal fetal congenital anomalies, or known hypersensitivity for one of the products used for induction were ineligible. For this secondary analysis, we only included women who gave birth to a SGA neonate (birthweight <10th percentile) based on the Hoftiezer curve, further described as SGA-pregnancies[14]. For all pregnancies, the gestational age was determined by first trimester measurement of the crown-rump length.

Details on randomization and interventions in each trial have been described previously[7,8]. In short, after written informed consent, women were randomly allocated to induction of labor with either a Foley catheter or prostaglandin by their attending physician, in a 1:1 ratio, using an online program.

In both studies, women allocated to induction with a Foley catheter had a 16F or 18F Foley catheter introduced through the cervix either digitally or using a vaginal speculum and was filled with 30 mL 0·9% sodium chloride or sterile water. If the Bishop score remained less

than 6 after 24 hours, the location of the Foley catheter was checked. When still in correct position, the Foley catheter was either left in place or replaced with a new one after 24 hours.

Women allocated to prostaglandin E2 (PROBAAT-1) were treated with a starting dose of 1 mg prostaglandin E2 gel, followed by 1 mg after 6 hours, with a maximum of two doses per 24 hours inserted into the posterior vaginal fornix. An initial dose of 2 mg was allowed in nulliparous women, as prescribed by the manufacturer (Pfizer, New York, NY, USA). Women allocated to oral misoprostol (PROBAAT-2) received 50 mcg capsules once every 4 hours with a maximum of three times daily.

In both trials, if the cervix was still unfavorable for amniotomy after 48 hours of treatment, women were generally assigned a day of rest followed by another 48 hours of induction.

The main outcome of the current study was a composed outcome of adverse neonatal events being Apgar score <7 after 5 minutes and/or a pH in the umbilical artery <7.05 and/or NICU admission. Other outcomes were uterine hyperstimulation, meconium-stained amnion fluid, oxytocin use, time from start induction to vaginal birth (hours), mode of birth (spontaneous, assisted vaginal birth or CS), assisted birth for fetal distress, pH <7.10 in the umbilical artery, and birthweight.

Data were analyzed on an intention-to-treat basis. Numerical variables were summarized as means with standard deviations if the distribution was normal and analyzed with a one-way ANOVA. When distributions were skewed, they were summarized as medians with interquartile ranges (IQR) and analyzed with a Kruskal-Wallis-test. The X^2 test was used to compare categorical variables. A *p*-value of <0.05 was considered to indicate statistical significance. If a statistically significant difference was found, a bivariate analyses was performed to locate between which comparisons the difference was present. For the direct comparisons (foley catheter versus misoprostol or Foley catheter versus PGE2) relative risk (RR) and 95% confidence intervals (95%CI) were reported. For the primary outcome of this study, a multivariate logistic regression analysis was performed for study (PROBAAT 1 or 2) and other detected cofounders. Statistical analyses were performed with SPSS version 25.0 (IBM corp, Armonk, NY, USA).

3. Results

During the original trial periods, 819 and 1845 eligible women were randomized in the PROBAAT 1 and PROBAAT 2 trials, respectively. Of these 2664 women, 1332 (411 and 921, respectively) were allocated to induction with a Foley catheter, 408 women to PGE2 and 924 women to oral misoprostol. In the Foley catheter group, 214 (16.0%) women gave birth to an SGA neonate, in the PGE2 group 64 (15.7%) women, and in the misoprostol group 147 (15.9%) women (see Figure 1).

Baseline characteristics of the included women are presented in Table 1. The groups were comparable with respect to age, BMI at booking, ethnicity, parity, and gestational age. The indication fetal growth restriction was not equal distributed between the women allocated to a Foley catheter (79/214; 36.9%), misoprostol (48/147; 32.7%) and PGE2 (13/64; 20.3%; p=0.046). Also, more women in the misoprostol group were induced for decreased fetal movements (18/147; 12.2%), compared to the Foley catheter group (10/214; 4.7%) and the PGE2-group (1/64; 1.6%; p=0.004).

An adverse neonatal outcome occurred less often when a Foley catheter (10/214; 4.7%) or PGE2 (3/64; 4.7%) was used compared to oral misoprostol (19/147; 12.9%; p=0.009; Table 2). In the bivariate analyses, statistical significance was only present in the direct comparison between a Foley catheter and oral misoprostol (RR 0.36; 95%CI 0.17-0.76;). A multivariate analysis, in which there was controlled for study (PROBAAT 1 or 2) and indication for induction of labor did not change the result (adjusted odds ratio (aOR) 0.35; 95%CI 0.14-0.87).

When the individual components of the composed adverse neonatal outcome between a Foley catheter, misoprostol and PGE2 were analyzed, there was a statistical difference found for Apgar score <7 at 5 minutes (1/214; 0.5% versus 5/147; 3.4% versus 0/64; 0%, respectively; p=0.039) as well as NICU admission (4/214; 1.9% versus 9/147; 6.1% versus 0/64; 0%, respectively; p=0.021). In the bivariate analyses, a statistical difference was only present between a Foley catheter compared to oral misoprostol for Apgar score <7 after 5 minutes (RR 0.14; 95%CI 0.02-1.16) as well as NICU admission (RR 0.31; 0.10-0.97). No differences were found for mode of birth between induction with a Foley catheter, oral misoprostol or PGE2 (Table 3). The caesarean section rate was 39/214 (18.2%) versus 28/147 (19.0%) versus 12/64 (18.8%), respectively (p=0.980). Also, no statistical difference was

found for caesarean section for fetal distress (21/214; 9.8% versus 22/147; 15.0% versus 10/64; 15.6%; *p*=0.246) or operative birth for fetal distress (35/214; 16.4% versus 37/147; 25.2% versus 14/64; 21.9%; *p*=0.115). Time from start induction to vaginal birth was longer when a Foley catheter was used compared to misoprostol or PGE2 (29 hours versus 26 hours versus 16 hours; *p*=0.003).

Subgroup analyses for lower birthweight percentiles showed the same differences for an adverse neonatal outcome between a Foley catheter and misoprostol (table 4). In the subgroup birthweight <p5, the numbers being 7/137 (5.1%) versus 13/94 (13.8%), respectively (RR 0.40; 95%CI 0.15-0.9) and for birthweight <p3 , 4/85 (4.7%) versus 10/62 (16.1%), respectively (RR 0.29; 95%CI 0.10-0.89).

4 Discussion

4.1 Main findings

In our subgroup analyses of two multicenter randomized controlled trials, we found that a Foley catheter is probably a safer induction method for SGA neonates compared to misoprostol. The results show a lower rate of a composed outcome of adverse neonatal events. Also, individual components of this outcome, being Apgar score <7 after 5 minutes and NICU admission were lower with the use of Foley catheter compared to misoprostol. Between a foley catheter and PGE2, no difference in adverse neonatal outcomes were observed.

4.2 Strengths and weaknesses

The main strength of our study was the availability of a large, combined database of women with term pregnancies, whose induction method was determined by randomization to either a Foley catheter, oral misoprostol or PGE2. We therefore had access to a substantial subgroup of pregnancies in which an SGA neonate was born (n=425), which makes our study the largest randomized prospective study present. Unfortunately, the group of women who received PGE2 was relatively small and as a result, no valid judgement for PGE2 in comparison the other methods could be made.

The presence of suspected FGR (defined as an EFW <10th percentile in trial protocols) turned out to be a too small of a subgroup and might have been underreported. This led us to the decision to choose birthweight <10th percentile. An explanation for a possible underreporting might be that the effect of induction methods in FGR pregnancies was not the

focus of the original trials. Therefore, it was possible that, if FGR was not the main indication of induction, the presence of an EFW <10th percentile was not registered as such. Also, it is not known if all women had a recent biometry measurement before randomization. This could also explain the discrepancy between cases of suspected FGR (n=183) and SGA (n=425). Also, especially during the PROBAAT-1 trial, little was known on safety and efficiency of mechanical induction, which could have caused a selection bias, meaning clinicians could have withheld study participation for women with pregnancies with severe FGR. We acknowledge that suspected FGR would have made a more ideal subgroup as actual birthweight is not known at forehand. Also, we acknowledge that the definition of suspected FGR in the original trial protocols is outdated. Unfortunately, a subgroup formed on recent standards for the diagnosis of FGR with the data available, was not possible[15]. This makes that our study findings cannot be directly extrapolated for suspected FGR. On the other hand, the main goal of fetal biometry is to estimate the actual weight of the neonate. However, fetal biometry still has a relatively high false negative rate for detection of birthweight below 10th percentile[16]. This implicates that in even more pregnancies an undetected SGA-fetus could be present which raises the question whether induction with a Foley catheter is more preferable in case of an EFW in the lower percentile range.

The fact that we performed a subgroup analysis, and the outcomes of our study were not predefined in our original trail protocol creates a risk of a type 2 error. In general, this means the more analyses you perform, the higher the risk (1in 20) for a false positive result. However, looking at the consistency of our result and statistical significance being even stronger in different subgroups of SGA (<5th percentile and <3rd percentile), we think a type 2 error is unlikely.

4.3 Interpretation in light of what is known

To our knowledge, this is the first study in which a foley catheter was compared to oral misoprostol specific in SGA pregnancies. Studies on the effect of different induction methods in SGA pregnancies are sparse and mainly of low-quality evidence. Our results differ from studies in which a foley catheter is compared to vaginal misoprostol, where no differences in adverse neonatal outcomes were found[12,13].

We found one randomized controlled trial in which different induction methods were compared in SGA pregnancies[12]. Chavacula et al. randomized 100 women diagnosed with FGR in a tertiary center in South India to either 25 µg vaginal misoprostol or a foley catheter.

In this relatively small study, no difference was found in perinatal outcomes such as NICU admission or Apgar score <7 after 5 minutes.

Familiari et al. recently published a systematic review with meta-analyses of randomized and non-randomized studies, which to date is the most comprehensive study regarding safety issues of different induction methods, being vaginal misoprostol, vaginal PGE2 and a Foley catheter, in SGA pregnancies[13]. They included 12 studies, one of them being the RCT of Chavacula et al., two prospective studies and nine retrospective studies. Data from this meta-analyses suggests that induction with a foley catheter might reduce intrapartum adverse events (composed outcome of tachysystole, non- reassuring fetal heartrate, caesarean section and/or operative birth for fetal distress, fever or meconium-stained amniotic fluid), but found no evidence for a difference in adverse neonatal outcomes (composed outcome of NICU admissions, pH <7.20 in the umbilical cord artery or Apgar score <7 after 5 minutes) between a foley catheter, vaginal applied misoprostol and vaginal PGE2. Although data was pooled, the authors state that substantial heterogeneity was present and therefore a direct comparison was not possible.

4.4 Conclusion

In case of labor induction in women with an unfavorable cervix, a foley catheter seems to have a better safety profile for SGA neonates compared to low dose oral misoprostol. For this group, a Foley catheter might reduce NICU admissions and Apgar scores <7 after 5 minutes. No valid judgement could be made in comparison to PGE2

We suggest to incorporate the possibility of a lower rate of adverse neonatal outcomes with the use of a Foley catheter in the shared decision process regarding induction of labor due to suspected FGR.

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Table 1 Baseline characteristics of the study population

	Foley catheter n=214	**Misoprostol n=147**	**PGE_2 n=64**	***p*-value**
Gestational age (weeks + days)	39+6 [38+2-41+1]	39+2 [38+2-41+1]	39+5 [38+1-41+2]	0.600†
Parity				0.727
Nulliparity	161 (75.2%)	108 (73.5%)	45 (70.3%)	
multiparity	53 (24.8%)	39 (26.5%)	19 (29.7%)	
Body Mass Index	23.8[1] [21.3-27.5]	23.9[2] [21.4-27.4]	23.0[3] [21.2-26.2]	0.688†
Ethnic origin				0.073
Caucasian	151 (70.6%)	106 (72.1%)	55 (85.9%)	
Non-Caucasian	51 (23.8%)	30 (20.4%)	9 (14.1%)	
Unknown	12 (5.6%)	11 (7.5%)	0	
Maternal age (years)	30 (±5.1)	31 (±5.1)	30 (±5.4)	0.158‡
Indication for induction				
Fetal growth restriction	79 (36.9%)*	48 (32.7%)	13 (20.3%)*	0.046
Oligohydramnios	27 (12.6%)	13 (8.8%)	8 (12.5%)	0.510
Hypertensive disorder	64 (29.9%)	36 (24.5%)	25 (39.1%)	0.100
Post term (≥41 weeks)	61(28.5%)	44 (29.9%)	17 (26.6%)	0.880
Insulin dependent diabetes	7 (3.3%)	3 (2.0%)	1 (1.6%)	0.658
Cholestasis	0	2 (1.4%)	0	0.150
Decreased fetal movements	10 (4.7%)*	18 (12.2%)*^	1 (1.6%)^	0.004
Elective	25 (11.7%)	13 (8.8%)	4 (6.3%)	0.386
Other	10 (4.7%)	11 (7.5%)	4 (6.3%)	0.532

Bishop Score				
0-2	110/176 (62.5%)	57/105 (54.3%)	38/64 (59.4%)	0.398
3-5	64/176 (36.4%)	47/105 (44.8%)	26/64 (40.6%)	0.374

Values are given as numbers (%), mean (±SD) or median [IQR]. †Kruskal-Wallis-test, ‡ one-way ANOVA
Data missing: [1] 30 (16%) [2] 13 (9%) [3] 8 (9%)
* or ^: statistically significant in bivariate analysis using (X^2 test or Fisher's exact test when appropriate)

420

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Table 2 Perinatal outcomes

	Foley catheter n=214	Misoprostol n=147	PGE_2 n=64	*p*-value	*Foley vs misoprostol RR (95%CI; p-value)*	*Foley vs PGE2 RR(95%CI; p-value)*
Composed adverse neonatal outcome (%)	10 (4.7%)*	19 (12.9 %)*	3 (4.7 %)	0.009	0.36 (0.17-0.76; *0.005*)	0.98 (0.28-3.51; *0.996*)
Apgar <7 after 5 minutes (%)	1 (0.5%)*	5 (3.4%)*	0	0.039	0.14 (0.02-1.16*; 0.043*)	NA
pH in umbilical artery						
pH ≤7.10	18/166 (10.8%)	19/108 (17.6%)	5/56 (8.9%)	0.169	0.62 (0.34-1.12; *0.110*)	1.21 (0.47-3.12; *0.684*)
pH ≤7.05	7/166 (4.2%)	8/108 (7.4%)	3/56 (5.5%)	0.524	0.57 (0.21-1.52; *0.257)*	0.79 (0.21-2.94; *0.722*)
NICU admission (%)	4 (1.9%)*	9 (6.1%)*	0	0.021	0.31 (0.10-0.97; *0.330*)	NA
Birthweight (gram)	2675 [2439-2950]	2652 [2370-2955]	2720 [2435-2965]	0.839†	NA	NA
Birthweight <p5	137 (64.0%)	94 (63.9%)	39 (60.9%)	0.896	1.00 (0.86-1.17; *0.989*)	1.05 (0.84-1.31; *0.654*)
Birthweight <p3	85 (39.7%)	62 (42.2%)	27 (42.2%)	0.913	0.94 (0.73-1.21; *0.641*)	0.94 (0.68-1.31; *0.724*)
Meconium (%)	15 (7.0%)*	15 (10.2%)	12 (18.8%)*	0.022	0.69 (0.35-1.36; *0.280*)	0.37 (0.19-0.76; *0.005*)
Neonatal mortality	0	0	0	NA	NA	NA

Composed adverse neonatal outcome: Apgar <7 after 5 minutes and/or pH in umbilical artery ≤7.05 and/or NICU admission
Values are given as numbers (%) or median [IQR]. NA = not applicable
†Kruskal-Wallis-test
*statistical significant in bivariate analysis using (X^2 test or fisher's exact test when appropriate)

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Table 3 Obstetric outcomes

	Foley catheter n=214	Misoprostol n=147	PGE_2 n=64	*p*-value	*Foley vs misoprostol RR (95%CI; p-value)*	*Foley vs PGE2 RR(95%CI; p-value)*
Time from start induction to vaginal birth (hours)	29 [16-37]^	26 [16-46]#	16 [11-29]^#	0.003†	NA	NA
Uterine hyperstimulation	9 (4.2%)	8 (5.4%)	2 (3.1%)	0.642	0.77 (0.31-1.96; *0.586*)	1.35 (0.30-6.07; *0.697*)
Oxytocin (%)	179 (79.4%)*	87 (59.2%)*	39 (60.9%)	<0.001	1.34 (1.15-1.56; *<0.001*)	1.30 (1.06-1.60; *0.003*)
Epidural (%)	87 (40.7 %)	53 (36.1%)	22 (34.4%)	0.541	1.13 (0.86-1.48; *0.378)*	1.18-0.81-1.72; *0.367*)
Mode of birth						
Spontaneous	154 (72.0%)	102 (69.4%)	45 (70.3%)	0.865	1.04 (0.91-1.19; *0.597*)	1.02 (0.86-1.23; *0.797*)
Vaginal assisted	21 (9.8%)	17 (11.6%)	7 (10.9%)	0.864	0.85 (0.46-1.55; *0.594*)	0.90 (0.40-2.01;*0.793*)
Caesarean section	39 (18.2%)	28 (19.0%)	12 (18.8%)	0.980	0.96 (0.62-1.48; *0.843*)	0.97 (0.54-1.74; *0.924*)
Assisted birth for fetal distress	35 (16.4%)	37 (25.2%)	14 (21.9%)	0.115	0.65 (0.43-0.98; *0.039*)	0.75 (0.43-1.30; *0.309*)
Caesarean section for fetal distress	21 (9.8%) 14 (6.5%)	22 (15.0%) 15 (10.2%)	10 (15.6%) 4 (6.3%)	0.246 0.392	0.66 (0.38-1.15; *1.138)*	0.63 (0.31-1.26; *0.195*)
Vaginal assisted for fetal distress					0.64 (0.3201.28; *0.209*)	1.05 (0.56-3.07; *0.934*)

Values are given as numbers (%) or median [IQR].
†Kruskal-Wallis-test
*statistical significant in bivariate analysis (X^2-test)
^ or # statistically significant in bivariate analysis (Mann-Whitney-U test)

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Table 4 Primary outcome for subgroup birthweight <5th and <3rd percentile

Birthweight <5th percentile		**Foley catheter n=137**	**Misoprostol n=94**	**PGE_2 n=39**	***p*-value**	***Foley vs misoprostol RR (95%CI; p-value)***	***Foley vs PGE2 RR(95%CI; p-value)***
	Composed adverse neonatal outcome (%)	7 (5.1%)*	13 (13.8%)*	2 (5.1%)	0.045	0.40 (0.15-0.89; *0.021*)	1.00 (0.20-5.04; *0.996*)
	Apgar <7 after 5 minutes (%)	0*	4 (4.3%)*	0	0.022	NA	NA
	pH in umbilical artery ≤7.05 (%)	4/108 (3.7%)	3/72 (4.2%)	2/34 (5.9%)	0.859	0.89 (0.21-1.07; *0.875*)	0.63 (0.93-1.12; *0.582*)
	NICU admission (%)	3 (2.2%)*	9 (9.6%)*	0	0.010	0.23 (0.06-0.82; *0.013*)	NA
Birthweight <3rd percentile		**Foley catheter n=85**	**Misoprostol n=62**	**PGE_2 n=27**	***p*-value**	***Foley vs misoprostol RR (95%CI; p-value)***	***Foley vs PGE2 RR(95%CI; p-value)***
	Composed adverse neonatal outcome (%)	4 (4.7%)*	10 (16.1%)*	1 (3.7%)	0.031	0.29 (0.10-0.89; *0.020*)	1.27 (0.15-10.90; *0.826*)
	Apgar <7 after 5 minutes (%)	0	2 (3.2%)	0	0.161	NA	NA
	pH in umbilical artery ≤7.05 (%)	2/70 (2.9%)	2/49 (4.1%)	1/24 (4.2%)	0.920	0.70 (0.10-4.80; *0.715*)	0.69 (0.07-7.23; *0.753*)
	NICU admission (%)	2 (2.4%)*	9 (14.5%)*	0	0.004	0.16 (0.04-0.72; *0.009*)	NA

Composed adverse neonatal outcome: Apgar <7 after 5 minutes and/or pH in umbilical artery ≤7.05 and/or NICU admission
Values are given as numbers (%)
*statistically significant in bivariate analysis (X^2-test)

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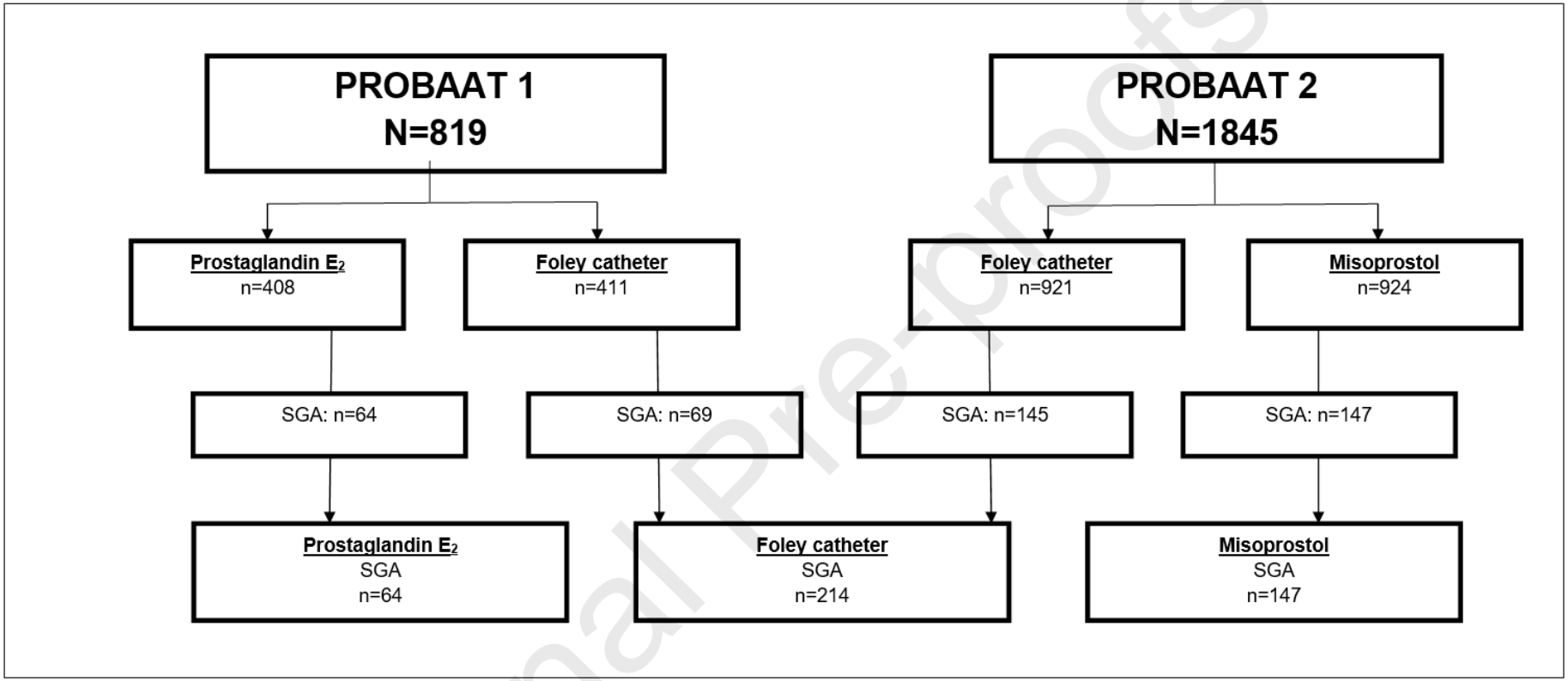
Figure 1 - Flow chart of inclusions



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