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ORIGINAL RESEARCH ARTICLE

Methods of induction of labor in women with obesity: A secondary analysis of two multicenter randomized controlled trials

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Abstract

Introduction: Obesity is an increasing public health concern worldwide and can lead to more complications in pregnancy and childbirth. Women with obesity more often require induction of labor for various indications. The aim of this study is to assess which method of induction of labor is safest and most effective in women with obesity.

Material and methods: This is a secondary analysis of two randomized controlled trials about induction of labor. Women with a term singleton pregnancy in cephalic presentation, an unfavorable cervix, intact membranes and without a previous cesarean section were randomly allocated to cervical priming with a Foley catheter or vaginal prostaglandin-E2-gel (PROBAAT-I) or a Foley catheter or oral misoprostol (PROBAAT-II). The inclusion and exclusion criteria for the studies were identical. Induction methods were compared in women with obesity (body mass index ≥30.0). Main outcomes were cesarean section and postpartum hemorrhage (blood loss >1000 mL).

Results: A total of 2664 women, were included in the trials, 517 of whom were obese: 254 women with obesity received a Foley catheter, 176 oral misoprostol and 87 prostaglandin E2 (PGE2). A cesarean section was performed in 29.1% of women allocated to Foley vs 22.2% in the misoprostol and 23.0% in the PGE2 groups. Comparisons between groups revealed no statistically significant differences: the relative risk [RR] was 1.31 (95% confidence interval [CI] 0.94–1.84) in the Foley vs misoprostol group and 1.27 (95% CI 0.83–1.95) in the Foley vs PGE2 group. The rates of postpartum hemorrhage were comparable (10.6%, 11.4% and 6.9%, respectively; $P = 0.512$). In women with obesity, more often a switch to another method occurred in the Foley

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; OR, odds ratio; PGE2, prostaglandin E2; RCT, randomized controlled trial; RR, relative risk.

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group, (20.1% vs 6.3% in misoprostol vs 1.1% in the PGE2 group; $P < 0.001$). The risk of a failed Foley placement was higher in women with obesity than in women without obesity (8.3% vs 3.2%; adjusted odds ratio 3.12, 95% CI 1.65–5.90).

Conclusions: In women with obesity we found a nonsignificant trend towards an increased rate of cesarean sections in the group induced with a Foley catheter compared to oral misoprostol; however, the study lacked power for this subgroup analysis. The finding of a higher risk of failed placement of a Foley catheter in women with obesity can be used in shared decision making.

KEYWORDS
cervical ripening, Foley catheter, labor, induced, obesity, PGE1, PGE2 misoprostol, prostaglandins

1 | INTRODUCTION

Obesity, defined as a body mass index (BMI) ≥30.0 kg/m^2, is an increasing public health concern worldwide.[1] Among women of reproductive age: in the Netherlands in 1981, 17.5% of women aged between 30 and 40 were overweight (BMI ≥25.0) and 2.8% were obese (BMI ≥30.0). In 2022, 43.0% were overweight and 15.6% obese.[2]

Obesity increases the risk of pregnancy-related complications, such as hypertensive disorders of pregnancy, gestational diabetes and post-term pregnancy.[3–5] Women with obesity have an increased risk of a cesarean section, both for spontaneous labor and when labor is induced, and postpartum hemorrhage. Neonates of women with obesity are more likely to be large for gestational age.[4–11] However, a recent meta-analysis by Krogh et al. compared induction of labor with expectant management among women with obesity and found a lower risk of cesarean section in the case of induction of labor compared with expectant management (19.7% vs 24.5%, relative risk [RR] 0.71, 95% confidence interval [CI] 0.63–0.81).[12]

Women with obesity have a higher risk of requiring induction of labor due to the increased pregnancy-related complications. A large retrospective cohort study conducted in the UK between 2004 and 2008 included women with singleton post-term pregnancies. It showed a higher BMI was associated with an increased risk of postdate pregnancy and an increased induction of labor rate. A total of 43.6% of women with morbid obesity (BMI >40) required induction ($n = 603$) compared with 34.4% of women with obesity (BMI 30–35) ($n = 3061$), 30.5% of overweight women (BMI 25–30) ($n = 2051$) and 26.2% of women with a normal weight (BMI 20–25) ($n = 9530$).[13]

In the last decade the induction of labor rate in Dutch pregnant women has increased significantly, from 16.2% in 2009 to 27.5% in 2021.[14] In approximately half of the inductions of labor, cervical priming is necessary.[15] Priming can be performed either mechanically (with a single or double balloon cervical ripening catheter) or pharmacologically (oral or vaginal prostaglandins).[16] It is unknown whether the need of cervical priming as part of induction of labor is different between women with and without obesity.

Key message

In women with obesity, induction of labor with a Foley catheter is slightly less favorable compared to oral misoprostol or prostaglandin gel in regards to method failure. There was no significant difference in mode of delivery, although an increase in cesarean section rate with the use of a Foley catheter cannot be ruled out.

Little is known in the literature about the safest and most effective method of cervical priming in women with obesity. Since both obesity and induction of labor rates are rising, it is important to assess the safest and most effective method of cervical priming as part of induction of labor in women with obesity. The aim of this study is to assess safety and effectiveness of methods of cervical priming (a Foley catheter, oral misoprostol and vaginal prostaglandin E2 [PGE2]) in induction of labor in women with obesity.

2 | MATERIAL AND METHODS

2.1 | Study design

This is a post-hoc analysis of two Dutch multicenter randomized controlled trials: the PROBAAT-I and PROBAAT-II. The trials were conducted in 12 and 29 Dutch hospitals in 2009–2010 and 2012–2013, respectively. In PROBAAT-I, women were randomized to receive treatment with either a 30-mL Foley catheter or vaginal prostaglandin E2 (PGE2) gel. In PROBAAT-II, women were allocated treatment with a 30-mL Foley catheter group or 25 μg oral misoprostol. More detailed information on trial protocols can be found in earlier publications.[17,18]

2.2 | Inclusion and exclusion criteria

Both PROBAAT trials included pregnant women scheduled for induction of labor at a gestational age of ≥37 weeks, a vital singleton pregnancy in cephalic presentation with intact membranes and an unfavorable cervix (defined as a Bishop Score <6). Exclusion criteria were a history of a cesarean section, age below 18 years, placenta previa, lethal fetal congenital anomalies or hypersensitivity to one of the products used; lethal fetal anomalies or hypersensitivity was not further defined.

Maternal height and weight were registered during first trimester, either self-reported or measured by a healthcare worker, and were used to calculate the pre-pregnancy BMI used throughout this paper. For this paper, a subgroup of women with obesity was created to perform secondary analyses. Obesity was defined as a BMI ≥30.0 according to the World Health Organization.[19]

2.3 | Outcome measures

Primary outcomes were rates of cesarean section and postpartum hemorrhage defined as a postpartum blood loss >1000 mL. We regarded cesarean section as an effectiveness outcome and hemorrhage rates as safety. Maternal secondary outcomes were change of induction method (method other than randomization arm), induction to vaginal birth interval, use of synthetic oxytocin, use of epidural analgesia and maternal death. Neonatal secondary outcomes were Apgar score <7 after 5 minutes, pH of the umbilical artery ≤7.05, admission to the neonatal intensive care unit and neonatal death.

Elective induction of labor was defined as induction before a gestational age of 41 weeks without medical indication but scheduled for convenience or at a women's own wish/request.

First stage of labor was defined as the phase of labor in which labor had started and the cervix dilated. Second stage of labor was defined as the phase between complete cervical dilation and delivery of the neonate.

2.4 | Statistical analyses

For this post-hoc analysis, datasets of the PROBAAT-I and PROBAAT-II trial were merged. The data of women allocated to the Foley group of PROBAAT-I and II were combined, since design, inclusion and exclusion criteria were identical except for the (other) treatment arms. Data was primarily analyzed on an intention-to-treat basis (in accordance with the original PROBAAT trials) and a per-protocol analysis was performed for the primary outcomes. For the subgroup analysis, the dataset was split: women with a BMI ≥30.0 were eligible.

Numerical variables were summarized as means with standard deviations if the distribution was normal and analyzed with a one-way analysis of variance (ANOVA). When distributions were skewed, they were summarized as medians with interquartile ranges and analyzed with a Kruskal–Wallis test. The χ^2 test was used to compare categorical variables. A *P*-value of <0.05 was considered to indicate statistical significance.

The whole dataset was used (including women without obesity) to assess the presence of a statistical interaction between BMI and randomization arm.

The association between BMI or obesity and study outcomes was studied by calculating odds ratios (OR) with corresponding 95% CI using logistic regression analysis. To study the presence of a statistical interaction between BMI and randomization arm on the study outcomes cesarean section and postpartum hemorrhage, the following steps were taken: first, missing BMI values were imputed using multiple imputation. Secondly, the interaction between BMI and each study outcome was assessed in two separate analyses. In the first analysis, BMI was dichotomized using a cut-off value of 30.0 kg/m^2.[16] In a second analysis, BMI was used as a continuous variable after log-transformation to create a parametric distribution. For both the dichotomized and continuous (log)BMI values, the presence of a statistical interaction between study outcomes and BMI was studied using multivariable logistic regression analysis. Interaction terms for BMI and treatment modality were adjusted for trial cohort effect (PROBAAT-I vs PROBAAT-II). No other confounders were taken into account, as women were randomized to their treatment modality.

Statistical analyses were performed in both R-Studio version 4.0.3.1.32 (imputation package MICE) (RStudio: Integrated Development for R, PBC; Boston, MA, USA) and SPSS version 25.0 (IBM Corp.; Armonk, NY, USA).

3 | RESULTS

In the original trials, a total of 819 and 1845 eligible women were randomized in the PROBAAT-1 or PROBAAT-II trials, respectively. Of these 2664 women, a total of 517 women (19.4%) were obese with a BMI ≥30.0. Of the women with obesity, 254 were allocated to cervical priming with a Foley catheter, 176 to oral misoprostol and 87 to vaginal PGE2 (see Figure 1).

The variable BMI was missing in 258 (9.7%) of the women and the missing values were equally distributed between the treatment groups. In the Foley group, BMI was missing in 121 women (9.1%), in the misoprostol group in 103 women (11.1%) and in the PGE2 group in 34 women (8.3%).

Baseline characteristics of the women with obesity in both trials are presented in Table 1. Gestational age, parity and BMI were evenly distributed between the three treatment groups.

Indication for induction was not equally distributed for fetal growth restriction (Foley catheter 3.1% vs misoprostol 6.1% vs PGE2 0%; $P=0.033$). However, these numbers did not differ in bivariate analyses between Foley and oral misoprostol or Foley catheter and PGE2. Also, "elective" as the indication for induction of labor was not equally distributed (24.8% vs 32.4% vs 9.2%; $P<0.001$) but differed in the bivariate analysis only between Foley catheter and PGE2. Other indications were similar.

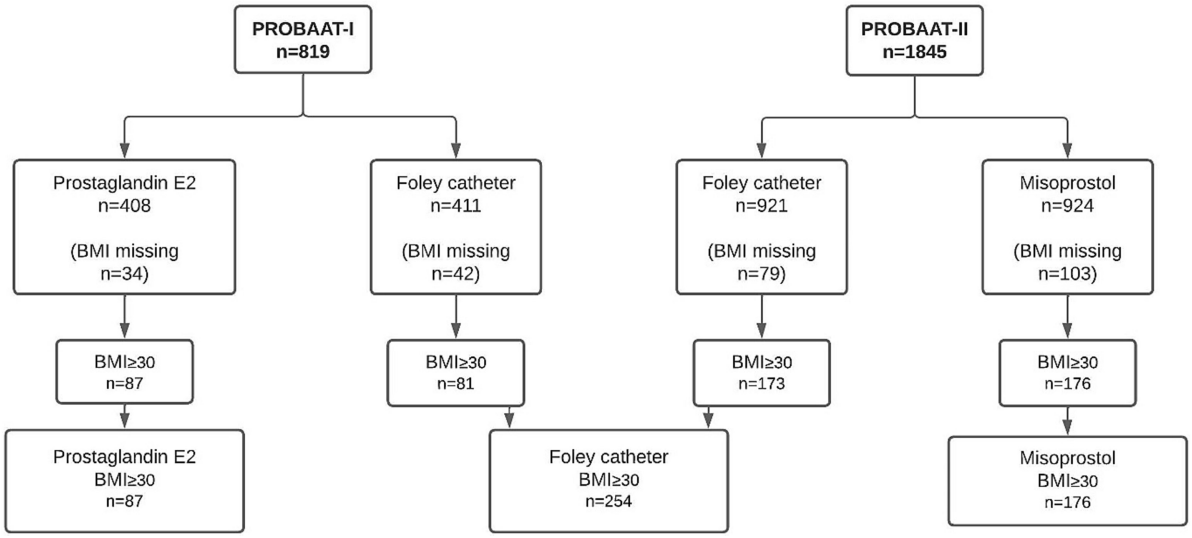

FIGURE 1 Allocation to treatment arms.

Overall, women with obesity had higher odds of a cesarean section compared with women without obesity (25.7% vs 18.2%, OR 1.56, 95% CI 1.24–1.96, *P*-value <0.001).

3.1 | Primary outcomes

The maternal outcomes are presented in Table 2. In the intention-to-treat analysis, the cesarean section rate was not significantly different in women with obesity allocated to Foley catheter (29.1%) compared the group allocated to oral misoprostol (22.2%; relative risk [RR] 1.31, 95% CI 0.94–1.84). Compared with PGE2 (23%), no difference was found either (RR 1.54, 95% CI 0.66–3.61). In the Foley group, more cesarean sections were performed for failure to progress in the first stage of labor compared with the PGE2 group (16.5% vs 6.9%, RR 2.40, 95% CI 1.06–5.44). In the misoprostol group, the failure to progress rate in the first stage of labor was 11.9% (Foley vs misoprostol RR 1.39, 95% CI 0.85–2.26).

Also, in the per-protocol analysis, both cesarean section rates and postpartum hemorrhage rates were not significantly different, although there was also a trend towards a higher rate of cesarean section in the Foley group (57/201, 28.4%) compared with oral misoprostol (32/160, 20.0%; RR 1.41, 95% CI 0.97–2.07; *P*=0.067). No difference was found for Foley vs PGE2 (19/85, 22.4%; RR 1.26, 95% CI 0.81–2.00; *P*=0.293.

In the intention-to-treat analysis, postpartum hemorrhage occurred in 27 women with obesity (10.6%) assigned to a Foley catheter; in 20 women (11.4%) of the misoprostol group and in six women (6.9%) of the PGE2 group. These findings were non-significant (*P*=0.512). Obesity itself was not statistically associated with postpartum hemorrhage rates compared with women without obesity, OR 1.25, 95% CI 0.90–1.74). In the per-protocol analysis, for the outcome of postpartum hemorrhage there were no significant differences (Foley 9.5% vs misoprostol 11.3%, RR 0.84, 95% CI 0.46–1.55; *P*=0.576. Foley 9.5% vs PGE2 7.1%, RR 1.33, 95% CI 0.55–3.24; *P*=0.512).

As we included 254 women in the Foley group and 176 in the oral misoprostol group, our study could be underpowered to detect a clinically relevant difference in the rate of cesarean section between the groups. For example, given the 29.1% cesarean rate found in the Foley group of women with obesity, a sample size of 563 women in both groups would be required to detect a 25% reduction (to 21.83%) in cesarean section with oral misoprostol (power 80%, alpha 5%).

3.2 | Secondary outcomes

For the comparisons between the induction of labor methods, women with obesity allocated to a Foley catheter had a longer duration from start of induction to a vaginal birth compared with the women allocated to PGE2. Also, a Foley catheter increased the use of oxytocin (86.6%) compared with both PGE2 (66.5%; RR 1.30, 95% CI 1.11–1.52) and misoprostol (75%; RR 1.15, 95% CI 1.05–1.27). A vaginally assisted birth occurred less often in women with obesity allocated to a Foley catheter (*n*=19, 7.5%) than oral misoprostol (*n*=24, 13.6%; RR 0.54, 95% CI 0.31–0.97), but compared with PGE2 (*n*=11, 12.6%), no statistical difference was found (RR 0.59 (95% CI 0.29–1.19).

The use of epidural analgesia was not significantly different between the groups (see Table 3). No maternal deaths occurred in this subgroup. For the neonatal outcomes, no differences were found between induction methods. There were two neonatal deaths reported in the Foley group, one due to multiple congenital abnormalities (diagnosed after delivery) and the other to severe asphyxia.

In the group with obesity there was a change of induction method (registered as protocol violation) 51 times (20.1%) in the Foley catheter group, significantly more often compared with the misoprostol

TABLE 1 Baseline characteristics of the women with obesity in the PROBAAT-I and II trials.

	Foley catheter, *n* = 254 *n* (%)	Misoprostol, *n* = 176 *n* (%)	PGE2, *n* = 87 *n* (%)	*P*-value
Gestational age (weeks+days), median [IQR]	39+4 [38+2 to 41+1]	39+1 [38+2 to 41+0]	39+5 [38+2 to 41+1]	0.457[1]
Parity				
Nulliparous	149 (58.7)	105 (59.7)	50 (57.5)	0.942
Body mass index, median [IQR]	33.3 [31.2-36.6]	33.1 [31.2–36.1]	34.3 [31.6–37.9]	0.241[1]
Ethnic origin				
White	254 (73.2)	131 (74.4)	65 (74.7)	0.093
Non-white	53 (20.9)	39 (16.5)	21 (24.1)	
Unknown	15 (5.9)	16 (9.1)	1 (1.1)	
Maternal age, mean (± SD)	31 (±5.3)	32 (±5.1)	32 (±4.8)	0.612[2]
Indication for induction				
Fetal growth restriction	8 (3.1)	11 (6.1)[3]	0[3]	0.033
Oligohydramnios	8 (3.1)	9 (5.1)	1 (1.1)	0.236
Hypertensive disorder	92 (36.2)	51 (29.0)	13 (42.5)	0.076
Post-term (≥41+0 weeks)	69 (27.2)	44 (25.0)	24 (27.6)	0.855
Insulin-dependent diabetes	25 (9.8)	24 (13.6)	12 (13.8)	0.399
Cholestasis	3 (1.2)	5 (2.8)	0	0.172
Decreased fetal movements	16 (6.3)	16 (9.1)	3 (3.4)	0.211
Elective	63 (24.8)[3]	57 (32.4)[3]	8 (9.2)[3]	<0.001
Other	18 (7.1)	10 (5.7)	12 (13.8)	0.059
Bishop Score				
0–2	122/198 (61.6)	83/141 (58.9)	54/87 (59.4)	0.846
3–5	76/198 (38.4)	58/141 (41.1)	33/87 (37.9)	0.846
Birthweight, mean (± SD)	3484 (±507)	3487 (±489)	3473 (±440)	0.729

[1]Kruskal–Wallis test.

[2]One-way ANOVA.

[3]Statistically significant difference in bivariate analysis using χ^2 test or Fisher's exact test as appropriate.

group (*n* = 11, 6.3%) and the PGE2 group (*n* = 1, 1.1%; *P* < 0.001). In 21 of the 51 changes (41.2%) in the Foley catheter group, the reason for the change was a failed placement. Among women who received a Foley catheter in the group without obesity, there was a change of induction method in 10.0% (96/957), 31 times (32.3%) because of failed placement of the Foley catheter (*P*-value < 0.001). Overall, in the group with obesity there was a failure placement of the Foley catheter in 8.3% (51/254) compared with 3.2% in the group without obesity (31/957; adjusted odds ratio [aOR] 3.12, 95% CI 1.65–5.90).

3.3 | Interaction analysis

The interaction analysis was performed on the whole dataset after multiple imputation of the missing BMI values. No statistically significant treatment effects were observed for the risk of cesarean section or postpartum hemorrhage, or the presence of statistical interaction between randomization arm and obesity.

Studying BMI as a continuous log-transformed variable yielded similar results, with a statistically significant increased estimated risk of cesarean section for (log)BMI but not for postpartum hemorrhage, without differences in cesarean section or postpartum hemorrhage risk between treatment modalities and the absence of statistical interaction between (log)BMI and randomization arm (Table S1).

4 | DISCUSSION

In our secondary analysis of two combined randomized controlled trials, we found no statistical differences in cesarean section or postpartum hemorrhage rate between a Foley catheter, oral misoprostol and vaginal PGE2 in women with a BMI ≥30.0. In one in five women with obesity (20.1%) allocated to a Foley catheter the induction method was changed, in 41% because of failed placement of the Foley catheter. No differences were found in neonatal outcomes.

Although no significant difference in cesarean section rate between a Foley catheter and oral misoprostol was found, we did observe a trend towards an increased rate of cesarean sections in women with obesity allocated to a Foley catheter (29.1%) compared with misoprostol (22.2%). This difference was more pronounced in

TABLE 2 Obstetric outcomes of different methods of cervical priming in women with obesity.

	Foley catheter, *n* = 254 *n* (%)	Misoprostol, *n* = 176 *n* (%)	PGE2, *n* = 87 *n* (%)	*P*-value	Foley vs misoprostol RR (95% CI; *P*-value)	Foley vs PGE2 RR (95% CI; *P*-value)
Mode of birth						
Spontaneous	161 (63.4)	113 (64.2)	56 (64.4)	0.979	0.99 (0.85–1.14; 0.862)	0.99 (0.82–1.18; 0.869)
Vaginal, assisted	19 (7.5)	24 (13.6)	11 (12.6)	0.093	0.54 (0.31–0.97; 0.036)	0.59 (0.29–1.19; 0.142)
Cesarean section	74 (29.1)	39 (22.2)	20 (23.0)	0.217	1.31 (0.94–1.84; 0.106)	1.27 (0.83–1.95; 0.268)
Indication vaginal assisted						
Failure to progress	8 (3.1)	10 (5.7)	3 (3.4)	0.404	0.55 (0.22–1.38; 0.197)	0.91 (0.25–3.37; 0.892)
Fetal distress	11 (4.3)	16 (9.1)	8 (9.2)	0.095	0.47 (0.22–1.00; 0.045)	0.47 (0.19–1.13; 0.88)
Other	1 (0.4)	0	0	0.595	n/a	n/a
Indication for cesarean section						
Failure to progress	48 (18.9)	24 (13.6)	9 (10.3)	0.110	1.39 (0.88–2.18; 0.151)	1.82 (0.94–3.57; 0.065)
First stage	42 (16.5)	21 (11.9)	6 (6.9)	0.059	1.39 (0.85–2.26; 0.184)	2.40 (1.06–5.44; 0.026)
Second stage	6 (2.4)	3 (1.7)	3 (3.4)	0.676	1.39 (0.35–5.47; 0.639)	0.69 (0.18–2.68; 0.585)
Fetal distress	24 (9.4)	14 (8.0)	11 (12.6)	0.474	1.18 (0.63–2.23; 0.591)	0.75 (0.38–1.46; 0.397)
Other	2 (0.0)	1 (0.6)	0	0.706	1.39 (0.13–15.17; 0.788)	n/a
Postpartum hemorrhage	27 (10.6)	20 (11.4)	6 (6.9)	0.512	0.94 (0.54–1.61; 0.811)	1.54 (0.66–3.61; 0.309)
Time from start induction to vaginal birth in hours, median [IQR]	29 [17–40]	29 [18–50]	21 [12–37]	0.044[1]	n/a	n/a
Vaginal birth <24 h	63/180 (35.0)	48/137 (35.0)	37/67 (55.2)	0.008	1.00 (0.74–1.35; 0.995)	0.63 (0.47–0.85; 0.004)
Vaginal birth <48 h	141/180 (78.3)	100/137 (73.0)	57/67 (85.1)	0.144	1.07 (0.95–1.22; 0.270)	0.92 (0.81–1.04; 0.238)
Oxytocin (%)	220 (86.6)	132 (75.0)	58 (66.5)	<0.001	1.15 (1.05–1.27; 0.002)	1.30 (1.11–1.52; <0.001)
Epidural (%)	118 (46.5)	81 (46.0)	31 (35.6)	0.189	1.01 (0.82–1.24; 0.929	1.30 (0.96–1.78; 0.079)
Maternal death	0	0	0	n/a	n/a	n/a

n/a = not applicable.

[1]Kruskal–Wallis test.

the per-protocol analysis (Foley 28.4% vs misoprostol 20.0%), which suggests a Foley catheter may be less effective in this subgroup of women with obesity.

To our knowledge, this is the first article with data from randomized trials comparing three methods of cervical priming in women with obesity. BMI was a missing value in 9.7% of women; however, for the interaction analysis we used multiple imputation for the missing data to study the interaction between BMI and priming method and adjusted for cohort effect. We used (log)BMI to create a parametric distribution and BMI was analyzed both as a dichotomous (cut-off point 30.0) as well as a continuous variable to study interaction.

The numbers included in the subgroup analysis were not based on a power calculation and, according to our power analysis, this study might have been underpowered. Although the inclusion criteria of the two randomized controlled trials (RCTs) used were identical, two cohorts from different time periods were merged for our analysis. One could argue that in the time between the two original cohorts, medical options and protocols could have improved, possibly contributing to different outcomes in the RCT conducted later. At the time of the PROBAAT-II trial, there was more experience and general use of mechanical induction with a Foley catheter compared with the time of the PROBAAT-I.[20]

In this secondary (subgroup) analysis, there are some differences in baseline characteristics, mainly in the indication for induction of labor. This was probably caused by a change in management, being less reluctant to perform elective induction of labor. In an earlier publication by our study group presenting a secondary (subgroup) analysis of the PROBAAT-I and PROBAAT-II trials in women with birthweight <10th percentile, we found no significant difference in mode of birth between a Foley catheter, misoprostol or PGE2, although there was a difference in adverse neonatal outcomes in favor of a Foley catheter. For women with obesity, neonatal outcomes did not differ between the three groups.[21]

In studies comparing different induction methods in women with obesity the overall cesarean section rates were high (26% up to 51.3%) and the results between methods of priming were diverse.[22–27] An RCT by Viteri et al. compared a transcervical Foley plus vaginal misoprostol to vaginal misoprostol alone in nulliparous women with obesity and found no difference in cesarean section

TABLE 3 Neonatal outcomes.

	Foley catheter, $n=254$ n (%)	Misoprostol, $n=176$ n (%)	PGE2, $n=87$ n (%)	P-value	Foley vs misoprostol RR (95% CI; P-value)	Foley vs PGE2 RR (95% CI; P-value)
Apgar <7 after 5 minutes	7 (2.8)	4 (2.3)	1 (1.1)	0.688	1.21 (0.36–4.10; 0.750)	2.41 (0.30–19.29; 0.391)
pH in umbilical artery ≤7.05	6/184 (3.3)	3/134 (2.2)	1/67 (1.5)	0.701	1.45 (0.37–5.72; 0.857)	2.18 (0.27–17.82; 0.452)
NICU admission	8 (3.1)	5 (2.8)	1 (1.1)	0.606	1.11 (0.37–3.33; 0.854)	2.74 (0.35–21.60: 0.315)
Neonatal death	2 (0.8)	0	0	0.354	n/a	n/a

n/a = not applicable.

rates (Foley and PGE1 vs PGE1 alone: 45.1% vs 43.1%, RR 1.03, 95% CI 0.75–1.42; $P=0.84$).[26] The cesarean section rates were much higher, with more than half of the cesareans (59/104) were due to failed induction or failure to progress. In the study protocol by Viteri et al. the balloon was removed after 12 hours, after which further management was decided by the labor team; this was a much shorter time compared with 48 hours in the PROBAAT-trials and could perhaps have explained a quicker conclusion of a failed induction.

Suidan et al.,[24] in a retrospective cohort of 564 women, compared induction of labor of women with obesity (BMI ≥30.0) with misoprostol (oral or vaginal administered) with dinoprostone; they concluded that misoprostol leads to a higher rate of successful cervical ripening and lower rates of cesarean section (39.1% vs 51.3%, respectively. OR 0.61, 95% CI 0.44–0.85). No difference was found between misoprostol administered orally or vaginally. Most cesarean sections were performed due to failed ripening (105/253); however, those authors did not describe the duration of priming before this decision was made.[24]

Grange et al.,[25] in a prospective and retrospective cohort study ($n=92$), compared induction of labor of women with obesity with a double-balloon catheter vs vaginal dinoprostone and concluded the double-balloon catheter to be more efficient than vaginal dinoprostone after 24 hours of priming in terms of a favorable cervix; the cesarean section rate was high but not significantly different (39.1% in both groups). Sarumi et al.[27] compared dinoprostone (vaginal), misoprostol (oral and vaginal) and cervical catheters (both single and double balloon catheters) among nulliparous women with obesity and overweight nulliparous women and found a lower, although nonsignificant cesarean section rate in dinoprostone (dinoprostone 22.9%, misoprostol 33.3% and single/double balloon catheter 32.0%; $P=0.342$); the odds ratios were not described.

We found that one of five women with obesity allocated to a Foley catheter had a change of induction method, of which in 41% was because of failed placement of the Foley catheter. This number was two times higher than in women without obesity, who had a change of induction method of 10.0% (32% because of failed placement). After adjusting for study, parity and Bishop Score, we found a threefold higher chance of failed placement in the group with obesity than in the group without obesity (aOR 3.12, 95% CI 1.65–5.90). Two trials previously described failure of Foley catheter placement as a secondary outcome. An RCT by Anabusi et al.[22] ($n=181$) compared mechanical induction with a double vs single balloon catheter among women with vs without obesity and described "difficulty of placement" (it was not specified whether this was failure of placement) as an outcome and found no significant difference of any balloon (both double and single) between women with vs without obesity (80.9% vs 76.8%; $P=0.55$). A cohort study by Beckwith et al.[23] ($n=1502$) compared priming of women with vs without obesity with vaginal misoprostol 25 μg every 4 hours vs Foley catheter plus Pitocin®. Protocol deviation was low but similar in the groups with vs without obesity, both 11%.

Both PROBAAT trials used a Foley catheter filled with 30 mL. A meta-analysis by Schoen et al.[28] showed that a Foley catheter filled with 60 or 80 mL compared to 30 mL, reduced time to delivery by approximately 2 hours; cesarean section rates did not differ. However, there was no subgrouping according to BMI and therefore we could not state whether this would have influenced our results.

Both PROBAAT trials used a (single balloon) Foley catheter as a method of mechanical priming. An RCT by Solt et al.[29] showed that a double balloon was associated with decreased time to delivery in both nulli- and multiparous women and lower cesarean rates in nulliparous women compared with the single balloon catheter. However, the cesarean rate of 46.5% in nulliparous women is not comparable to our study, therefore we cannot state whether use of a double balloon catheter might have had the same effect on our results.

5 | CONCLUSION

Although no significant differences in cesarean section rate or postpartum hemorrhage between induction methods were found in women with obesity, the preferred method of priming might lean less towards a Foley catheter, as we found an increased risk of change of method and failed placement of the Foley catheter, which would make oral misoprostol possibly more patient-friendly. Hemorrhage rates were comparable but the cesarean section rate was relatively high in the group of women allocated to a Foley catheter compared with oral misoprostol; however, the differences were not statistically significant. This study was not powered for this subgroup analysis (subgroup i.e. women with obesity).

Since there is little consensus in literature on which method of induction of labor is the safest and most effective in women with obesity, we would suggest a well-powered RCT to investigate this for the growing group of pregnant women with obesity to minimize complications and the rate of cesarean section. This is especially important as obesity is already a risk factor for perinatal complications and delivery via cesarean section. Until then, we recommend incorporating the increased risk of a failed placement in the shared decision-making process for women with obesity.

AUTHOR CONTRIBUTIONS

DC, KB, RdH, CV and MdB designed and set up this secondary analysis. DC and SM drafted the first version of the manuscript, MdV and JK performed the statistical analyses. DC, MdV, KB, MtE, RdH, MJ, BWM, CV and MdB are members of the PROBAAT-study group. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Ben Willem Mol reports consultancy for ObsEva, Merck KGaA and Guerbet. The other authors have stated explicitly that they have no conflicts of interest in connection with this article.

ETHICS STATEMENT

PROBAAT-I was approved by the ethics committee of the Academic Medical Center, Amsterdam, on January 30, 2009 (NTR 1646, NL:25271.018.08). PROBAAT-II was approved by the ethics committee of the Academic Medical Center, Amsterdam, on July 7, 2012 (NTR3466, EUCTR2011-000026-30-NL). No further approval was required for this study due to its nature.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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