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Healthy Foetuses – Misoprostol Insert Induction (HF-MIND): a multicentre Italian study on the misoprostol vaginal insert for induction of labour

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ABSTRACT

Objective. To evaluate the efficacy and safety of the misoprostol vaginal insert in a selected cohort of healthy mothers and foetuses at late-term gestation or with premature rupture of membranes.
Methods. Retrospective data were collected by 12 centres that previously developed and shared the same protocol for the induction of labour with the misoprostol vaginal insert. Pregnant women at late-term gestation or with premature rupture of membranes with an unfavourable cervix were recruited. To be eligible, maternal and foetal well-being was assessed: absence of medical and/or obstetrical maternal complications, normal foetal growth (abdominal circumference > 10 percentile, AFI > 5 cm, absence of notch in uterine arteries Doppler velocimetry), category I foetal heart rate and, in case of PROM, normal white blood cell count and PCR. Subgroup analyses were performed for parity, status of membranes and BMI < 30 / > 30.

SOMMARIO

Obiettivo. Valutare l'efficacia e la sicurezza dell'inserto vaginale di misoprostolo in una coorte selezionata di madri e feti sani oltre termine o con rottura prematura delle membrane.
Metodi. I dati retrospettivi sono stati raccolti da 12 centri che in precedenza avevano sviluppato e condiviso lo stesso protocollo per l'induzione del travaglio con l'inserto vaginale di misoprostolo. Sono state reclutate donne in gravidanza oltre termine o con rottura prematura delle membrane con cervice sfavorevole. Per l'idoneità è stato valutato il benessere materno e fetale: assenza di complicanze mediche e/o ostetriche materne, normale crescita fetale (circonferenza addominale > 10 percentile, AFI > 5 cm, assenza di notch nelle arterie uterine velocimetria Doppler), tracciato cardiotocografico categoria I e, in caso di PROM, normale conta leucocitaria e PCR. Le analisi dei sottogruppi sono state eseguite per parità, stato delle membrane e BMI < 30 / > 30.

Results. The median time-to-delivery was 14:07 hours:minutes (hh:mm; range: 10:37-21:10). A total of 256 (62.6%) women delivered within 24 hours from the insertion of the device. Uterine tachysystole occurred in 59 women (14.4%), and tocolysis was used in only 14 patients (3.4%). High maternal BMI > 30 (OR = 0.92; 95% CI 0.86-0.99; p < 0.03), multiparity (OR = 0.48; 95% CI 0.22-0.96; p < 0.05) and PROM (OR = 0.49; 95% CI 0.26-0.86; p < 0.02) were significantly associated with a lower risk of tachysystole. The Caesarean section rate was 22%, and an emergency Caesarean section was performed in 12 patients (2.9%). Neonatal pH was < 7.00 in 4 newborns (1%), and 8 newborns (2%) were admitted to the NICU. No uterine rupture, maternal or neonatal deaths occurred.
Conclusions. In a selected cohort of healthy mothers and foetuses at late-term or with PROM with unfavourable cervix, the misoprostol vaginal insert proved its efficacy for the induction of labour that achieved an effective reduction in time-to-delivery, a reduction in other augmentation interventions, and a low rate of Caesarean section without increasing obstetrical and foetal complications.

Risultati. Il tempo medio al parto è stato di 14:07 ore:minuti (hh:mm; intervallo: 10:37-21:10). Un totale di 256 (62,6%) donne ha partorito entro 24 ore dall'inserimento del dispositivo. La tachisistolia uterina si è verificata in 59 donne (14,4%) e la tocolisi è stata utilizzata solo in 14 pazienti (3,4%).
BMI materno elevato > 30 (OR = 0,92; 95% CI 0,86-0,99; p < 0,03), multiparità (OR = 0,48; 95% CI 0,22-0,96; p < 0,05) e PROM (OR = 0,49; 95% CI 0,26 -0,86; p < 0,02) erano significativamente associati a un minor rischio di tachisistole. Il tasso di taglio cesareo è stato del 22% e in 12 pazienti (2,9%) è stato eseguito un taglio cesareo d'urgenza. Il pH neonatale era < 7,00 in 4 neonati (1%) e 8 neonati (2%) sono stati ricoverati in terapia intensiva neonatale. Non si sono verificate rotture uterine, decessi materni o neonatali.
Conclusioni. In una coorte selezionata di madri e feti sani oltre termine o con PROM con cervice sfavorevole, l'inserto vaginale di misoprostolo ha dimostrato la sua efficacia per l'induzione del travaglio che ha ottenuto un'efficace riduzione del tempo al parto, una riduzione di altri interventi di potenziamento del travaglio e un basso tasso di taglio cesareo senza aumentare le complicanze ostetriche e fetali.

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Key words
Misoprostol vaginal insert; induction of labour; tachysystole; unfavourable cervix; PROM.

INTRODUCTION

Induction of labour (IOL) is an increasingly common procedure in clinical obstetrics that can sometimes put strain on women, gynaecologists, and obstetric units. On one hand, IOL can cause greater pain and women can experience additional anxiety (1). On the other hand, gynaecologists may find themselves dealing with complications such as uterine hyperstimulation and precipitous delivery or vice versa a failure of the procedure itself.
A recent systematic review showed that a low dose ($< 50\ \mu g$) of titrated oral misoprostol solution had the lowest probability of Caesarean section and was associated with a good efficacy profile, whereas vaginal misoprostol ($\geq 50\ \mu g$) had the highest probability of achieving a vaginal delivery within 24 hours (2).
Subsequently, the same author produced a ranking of both pharmacological and mechanical methods for the IOL, finding that misoprostol and oxytocin with amniotomy were more successful than other agents in achieving vaginal delivery within 24 hours (3). In 2014, Mysodelle, a new vaginal insert containing 200 mcg of misoprostol (MVI), was licensed and approved for IOL. In a pivotal study, in comparison with the dinoprostone vaginal insert (DVI), MVI showed a faster action, shortening the time-to-delivery with a comparable safety profile in terms of the Caesarean section rate and neonatal outcomes (4). However, an increase in uterine tachysystole and subsequent tocolysis was observed. The implications of these adverse effects have been investigated in a post hoc study that revealed that managing cases of uterine tachysystole with foetal heart rate (FHR) abnormalities was more challenging for MVI than for DVI due to the longer half-life of misoprostol (5). However, MVI retrieval due to adverse effects did not increase neonatal intensive care unit (NICU) admissions compared with those for women whose inserts were removed for other reasons.
Recently, the European Medicines Agency advised that MVI can cause uterine tachysystole, which might not respond to tocolytic treatment (6). This fact has placed more emphasis on the use of MVI, leading to the publication of several observational

studies that compared MVI with misoprostol by vaginal or oral routes or with dinoprostone (7-12). All of these studies, however, had the limitation of considering rather small samples of patients (fewer than 200 subjects for a single treatment arm to small cohorts of 50 subjects (13)) with different indications for IOL, including intrauterine growth restriction (IUGR) and preeclampsia.
Regarding efficacy, all but one reported studies showed a reduction in the time-to-delivery and a higher rate of vaginal birth within 24 hours for MVI (11). However, concerns and disagreements on the safety profile of MVI were reported, especially with regard to higher tachysystole rates, Caesarean section rates and neonatal outcomes. These safety concerns were greater in cohorts with a large number of pathological pregnancies (9). We hypothesized that a multicentre study could help to overcome the need for a large cohort: this study is the result of a retrospective analysis of clinical data observed in our 12 centres that developed and shared a single protocol focused on the IOL of healthy mothers and healthy foetuses in order to better understand the safety issues posed by this new device.

MATERIALS AND METHODS

Design of the study

Starting in February 2016, 13 Italian obstetric units discussed, developed and then shared a common clinical management procedure for IOL with MVI for pregnant women who were late-term or had premature rupture of membranes (PROM), with no foetal or maternal risk factors according to the following protocol. On September 2018, these centers agreed to conduct a retrospective analysis starting with data from October 2016 to August 2018. The participant centers are listed in **table I**. The beginning date was chosen to let each center test the clinical feasibility of this protocol. Eight months were considered long enough to incorporate this protocol as one of the clinical skills for each staff member in all centers. This study was reported to the ethical committees as per local regulations.

Patients

Inclusion criteria were pregnant women admitted for IOL at late-term pregnancy (41 + 0 to 41 + 6 (weeks + days) of gestation) or at term with PROM (> 37 + 0 (weeks + days) of gestation), with an unfavourable cervix (assessed by a simplified Bishop score < 4), and the following well-being characteristics: foetal abdominal circumference > 10th percentile, amniotic fluid index > 5 cm, absence of notch in uterine arteries Doppler velocimetry, and category I FHR tracing (14). Exclusion criteria were multiple pregnancies, chromosomal or structural foetal abnormalities, previous caesarean section and any positive medical history or complications of pregnancy as hypertensive disorders and insulin dependent diabetes. Women with PROM with PCR > 1.5 mg/dl or white blood cell count > 15.000/μl were excluded from this study.

Table I. *List of participant centers.*

Participant centers
1. San Pietro Hospital FBF, Rome, Italy
2. Buzzi Children's Hospital, ASST FBF Sacco, University of Milan, Milan, Italy
3. ASST Valle Olona, Gallarate and Busto Hospital, Gallarate and Busto Arsizio, Varese, Italy
4. ASST Spedali Civili, University of Brescia, Brescia, Italy
5. San Raffaele Hospital, Milan, Italy
6. Poliambulanza Foundation, Brescia, Italy
7. San Gerardo Hospital - FMBBM, Monza, Italy
8. ASST- Garda, Desenzano del Garda, Italy
9. Policlinico San Pietro- I.O.B. San Donato Group, Ponte San Pietro, Bergamo, Italy
10. Carlo Poma Hospital, Mantova, Italy
11. ASST Rhodense, Rho Hospital, Rho, Milan, Italy
12. Careggi Hospital, University of Florence, Florence, Italy
13. IRRCS Ca' Granda Foundation, Mangiagalli Hospital, University of Milan, Milan, Italy

Methods

Data were collected in real time for each patient from all centers on the same standard case report form.
Written consent for the induction of labour was obtained from patients before the insertion of MVI. FHR monitoring was performed every 4-6 hours depending on the presence of uterine activity. Indications for MVI removal were as follows: more than 24 hours interval from the insertion, onset of labour or presence of regular symptomatic contractions for > 60 min without cervical dilatation > 3 cm, tachysystole or hypertonus, and changes in FHR tracing (ACOG category II or III). Tachysystole was defined as more than five contractions per 10 min for at least 20 min, and uterine hypertonus was defined as a single contraction lasting at least 2 min

(15). Management of these complications involved, first, conservative manoeuvres and, second, tocolysis with ritodrine or atosiban. To reduce overstimulation, MVI was removed in presence of regular symptomatic contractions for > 60 min. If spontaneous expulsion occurred, the device was not replaced with a new MVI. Oxytocin administration, if required, was permitted 30 min after the removal of the vaginal insert. When the Bishop score was persistently low (< 5) after the use of MVI, an attempt to continue with the induction process was made with prostaglandin E2 or Cook double balloon®, amniotomy and/or oxytocin per local protocol. Induction failure was defined as the absence of regular uterine activity after any attempt with induction methods accepted by the patient.

Data recorded included baseline demographic and obstetric characteristics, labour and delivery data and neonatal outcomes.

The primary efficacy outcomes included the median time-to-delivery from the beginning of induction and intrapartum oxytocin use. The primary safety outcomes included the emergency Caesarean section rate, the incidence of tachysystole and hypertonus, arterial pH < 7 and foetal admission to a NICU.

Statistical analysis

For maternal characteristics and study outcomes, descriptive statistics were used. Time-to-delivery was presented graphically using Kaplan-Meier curves. Using Student's t-test for continuous variables and Fisher's exact test for categorical variables, subgroup analyses were performed for nulliparous *vs* pluriparous women, PROM *vs* intact membranes and BMI < 30 *vs* ≥ 30 at term. Main demographic and obstetric characteristics were evaluated as predictors for tachysystole with a univariate linear regression analysis. Parameters with a significance level of up to p = 0.05 were included in a multivariate regression model. Data analysis was performed with Excel and R 3.5.1 software.

RESULTS

A total of 409 women were included in the analysis. Demographic characteristics and indications for the induction of labour are presented in **table II**, according to parity. The main study outcomes are summarized in **table III**.

Main efficacy outcomes

The median time at insert removal from the beginning of induction was 8:40 hours:minutes (hh:mm; IR 5:55-13:00). The most frequent indication for removal was onset of labour (67.5%), followed by tachysystole or hypertonus (14.4%), exceeding 24 hours (7.3%), FHR monitoring category II or III (6.3%) and spontaneous expulsion (4.4%). Additional induction methods were used in only 8 women (1.9%). Induction failure definitively occurred in 9 women (2.2%).

Vaginal delivery within 24 hours occurred in significantly more multiparous than nulliparous women (74 (74.7%) *versus* 182 (56.9%) p = 0.004). Similarly, time-to-delivery from the beginning of induction was significantly shorter in multiparous women (**figure 1**).

No differences were found in the median time-to-delivery between women with PROM and those with intact membranes or between women with BMI >30 *vs* those with BMI < 30 at term (**figure 2**).

IOL in women with PROM was associated with a higher rate of epidural analgesia (66.0% *vs* 53.8%, respectively, p = 0.02) and oxytocin administration (47.5% *vs* 27.5%, respectively, p = 0.0001) and a lower incidence of tachysystole (9.9% *vs* 17.4%,

Table II. *Demographic characteristics and indication for induction of labour.*

	Total (409)		Nulliparous (310)		Multiparous (99)		p value
Maternal Age (years)*	32.7	± 5.4	32.5	± 5.5	33.4	± 5.3	0.16
BMI*	28.2	± 4.1	28.0	± 3.9	28.7	± 4.5	0.12
Gestational Age (weeks)*	40.5	± 1.2	40.4	± 1.3	40.8	± 0.9	0.008
Late-term gestation°	247	60.4%	182	58.7%	65	65.7%	0.16
PROM°	162	39.6%	128	41.3%	34	34.3%	0.23
Bishop score#	2	(1-3)	2	(0-3)	2	(1-3)	< 0.001

*Data presented as mean ± standard deviation; °data presented as numbers and percentage; #data presented as median and interquartile range; P value obtained for comparison between nulliparous and multiparous by Fisher exact test for categorical variables and Student t tests foro continuous variables.

Table III. *Main study outcomes in the total population and according to parity.*

Labour and delivery	Total (409)		Nulliparous (310)		Multiparous (99)		p value
Oxytocin for labour acceleration*	145	35.5%	119	38.4%	26	26.3%	0.03
Median time to vaginal delivery hh:mm (range)#	14:07 (10:37-21:10)		14:41 (11:01-22:10)		13:12 (9:54-17:48)		0.04
Operative vaginal delivery (vacuum)*	61	14.9%	50	16.1%	11	11.1%	0.26
Caesarean Section*	90	22.0%	77	24.8%	13	13.1%	0.017
Median time from MVI removal to CS#	4:51 (1:49-9:04)		5:02 (1:57-8:36)		4:40 (0:50-9:54)		0.85
Any Tachysystole*	59	14.4%	49	15.8%	10	10.1%	0.19
Tachysystole with FHR involvement*	14	3.4%	13	4.2%	1	1.0%	0.20
Hypertonus*	9	2.2%	9	2.9%	0		0.12
Tocolysis*	14	3.4%	12	3.9%	2	2.0%	0.53
Meconium-stained fluid (3rd degree)*	33	8.1%	24	7.7%	9	9.1%	0.67
Maternal outcomes							
PPH >1000 CC*	17	4.2%	11	3.5%	6	6.1%	0.26
3rd degree perineal tear*	6	1.9%	5	2.1%	1	1.2%	1
Neonatal outcomes							
Neonatal birth weight (kg)°	3.5	± 0.39	3.4	± 0.39	3.6	± 0.37	0.0009
APGAR < 7 at 5 min*	4	1.0%	3	1.0%	1	1.0%	1
pH < 7.0*	4	1.0%	3	1.0%	1	1.0%	1
pH < 7.10*	36	8.8%	24	7.7%	12	12.1%	0.22
ABE < - 12*	16	3.9%	11	3.5%	5	5.1%	0.55
Admission to NICU*	8	2.0%	6	1.9%	2	2.5%	1

*Data presented as numbers and percentage; #data presented as median and interquartile range; °data presented as mean ± standard deviation; p value obtained for comparison between nulliparous and multiparous by Fisher exact test for categorical variables and Student t tests for continuous variables.

respectively, p = 0.04) *vs* IOL in women with intact membranes.

Women with PROM showed a non-significant reduction in the Caesarean section rate in comparison with women with intact membranes (18.5% *vs* 24.3%, respectively, p = 0.18). A non-significant reduction was also observed in women with BMI < 30 regardless of the state of the membranes (20.9% *vs* 24.8%, respectively, p = 0.28).

Main safety outcomes

Uterine tachysystole occurred in 59 women, but tocolysis was performed in only 14 of these patients. The main indication for Caesarean section was an abnormal FHR pattern (58.9%), followed by dystocia-arrest of cervical dilatation (22.2%). An emergency Caesarean section was performed in 12 patients (2.9%), and five of these cases were suspected placental abruptions. All women in which placental abruption occurred belonged to the first recruited half of our sample and most of them (4) experienced episodes of tachysystole or hypertonus.

Maternal characteristics and obstetrical factors were investigated by univariate and multivariate analyses as predictors of tachysystole. Only high maternal BMI > 30 (OR = 0.92; 95% CI 0.86-0.99; p < 0.03), multiparity (OR = 0.48; 95% CI 0.22-0.96; p < 0.05) and PROM (OR = 0.49; 95% CI 0.26-0.86; p < 0.02) were significantly and independently associated with a lower risk of tachysystole.

Maternal and neonatal outcomes are shown in **table III**. No significant differences in these outcomes were detected between PROM and intact membranes or between BMI > 30 and BMI < 30. No uterine rupture, maternal or neonatal deaths occurred in this study.

DISCUSSION

The results of this present study confirm the efficacy of MVI for inducing labour in pregnant women who are late term or who have PROM with an unfavourable cervix without additional maternal or foetal risks.

The median time-to-vaginal delivery in this cohort, even with lower oxytocin use, was better than that in the Expedite trial (21 hours and 40%, respectively) (4). In our study, mean BMI was lower and the prevalence of IOL in PROM was higher than those reported by the Expedite trial; both of these maternal characteristics were associated with favourable induction outcomes and could have contributed to

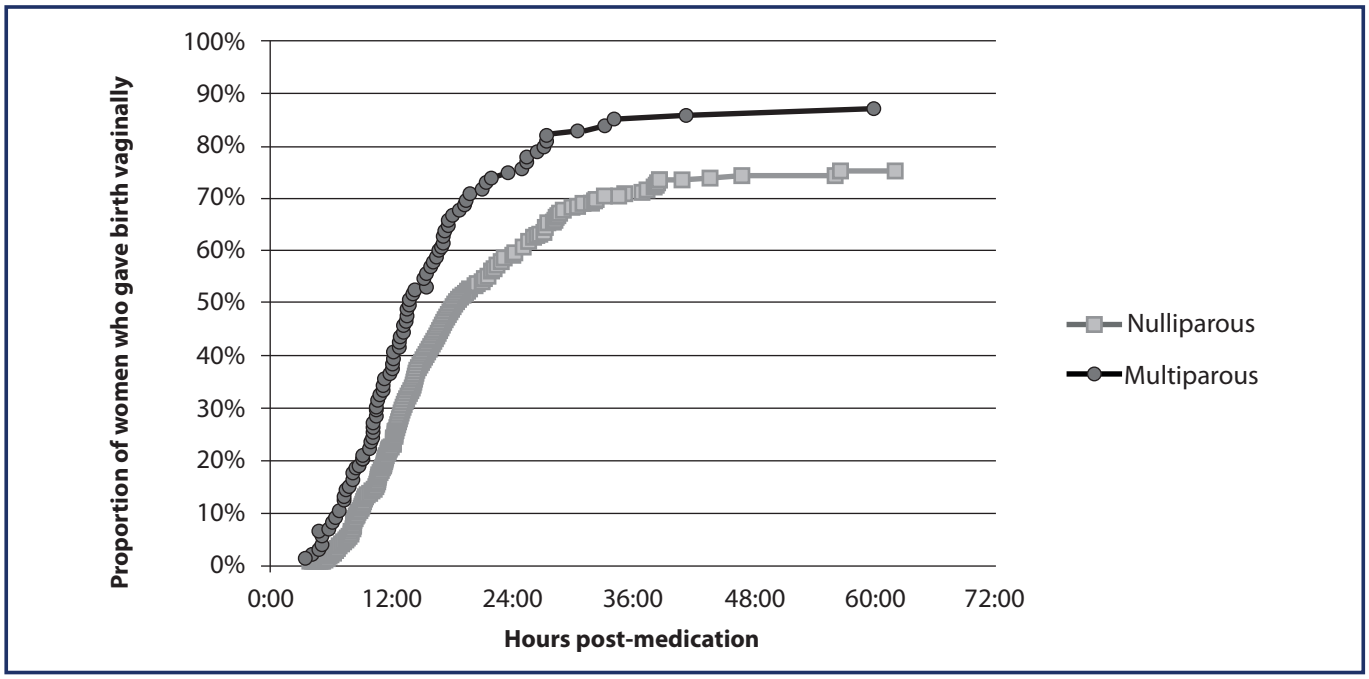

Figure 1. *The Kaplan-Meier plot shows the complete data of the time-to-delivery for nulliparous and multiparous women.*

this outcome (16, 17). Kaplan-Meier plots in **figure 2 a, b** confirmed this trend in our cohort. Recent studies by Marsdal and Mayer, which included women with a mean BMI < 30 and a percentage of PROM > 20%, in agreement with our results, reported a median time to vaginal delivery between 12 and 15 hours (7, 11).

The safety profile observed in our study should be analysed in light of the design of our shared multicentre protocol. We chose to select among patients undergoing IOL those with maternal and foetal well-being, both at late-term gestation or after PROM. These criteria resulted from the analysis of reported cohorts that confirmed a relatively high prevalence of tachysystole (7-13). Healthy foetuses are more likely to overcome these transient episodes of poor oxygenation, thereby reducing the risk of emergency Caesarean section.

The rate of Caesarean sections was in fact lower than that reported in the Expedite trial (22% *vs* 26%, respectively) and in other studies with a smaller number of cases, such as the study by Dobert (4, 9). This latter study included also IUGR and preeclampsia as indications for IOL and reported 47% tachysystole and 39% Caesarean section rates. The Caesarean section rate observed in our cohort was also lower than that reported by Redling (29.7%) in a smaller cohort in which IUGR and gestational diabetes had been excluded (10). An even lower rate of Caesarean sections (11.8%) was recently reported by Marsdal in a sample with 86 pregnant women who underwent IOL, half of whom had a pre-induction with cervical balloon (7). These contradictory results should be interpreted with caution given the small number of patients and different recruitment criteria.

In our cohort, half of Caesarean sections were performed for an abnormal FHR pattern, but only 2.9% occurred as emergency Caesarean sections. However, among the first half of the cases recruited, we observed five Caesarean sections for placental abruption. These data did not emerge in other previous studies and should be emphasized with caution since the association with uterine hyperstimulation. In our cohort, the rate of tachysystole was three times lower than that reported by Wing *et al*. and was still high compared to those obtained with other pharmacological and mechanical induction methods (3, 4). Tocolysis was performed in only 3.4% of patients, while other studies reported higher rates between 16.8% and 38.5% (9, 11).

Excessive uterine activity has been associated with foetal acidosis at birth because of inadequate uterine relaxation time, reduced perfusion pressure and impaired oxygen delivery to the placenta (18). Stewart *et al*. found no differences in infant outcomes when tachysystole occurred during early labour, despite FHR decelerations being associated with an increasing number of contractions (19). However, considering over 50,000 deliveries, Heuser *et al*. found that

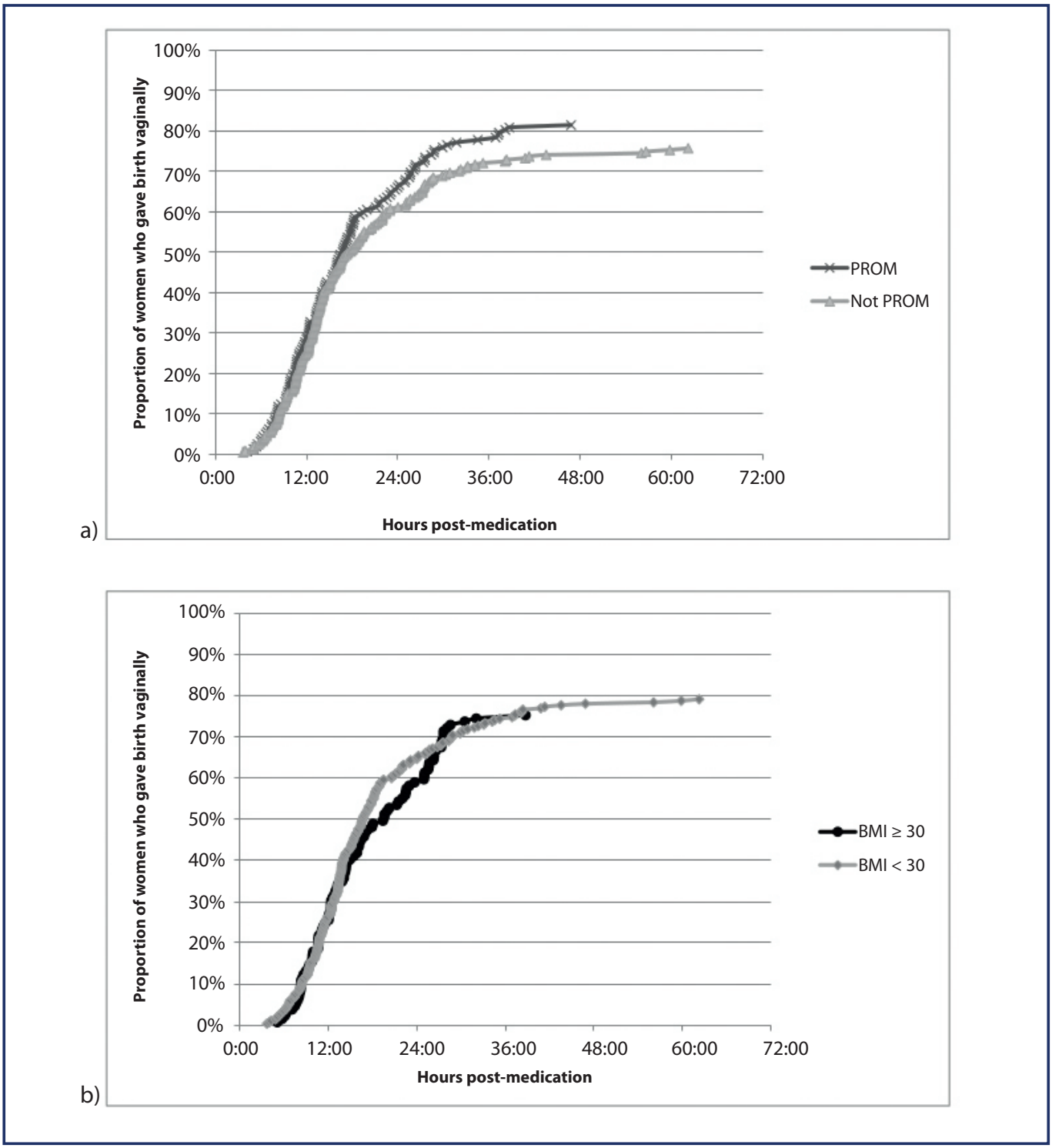

Figure 2. *The Kaplan-Meier plot shows the complete data of the time-to-delivery for two subgroups: women with PROM vs intact membranes (a) and women with BMI > 30 vs BMI < 30 at term (b).*

tachysystole increased the chance of composite neonatal morbidity (20). In that multivariable analysis, significant risk factors associated with tachysystole were the use of oxytocin and misoprostol, epidural analgesia, and hypertension, while multiparity was associated with a decreased risk of tachysystole. No differences in the incidence of placenta abruption were found between women who experienced tachysystole and those who did not.

Bolla *et al*. failed to identify any predictors of tachysystole after MVI administration, while we found a significant risk reduction for high maternal BMI, multiparity and PROM (8). A reason could be that the mean baseline BMI and percentage of PROM

were lower in that study than in our study (mean BMI 22.8 *vs* 27.7, PROM 9.5% *vs* 39.6%, respectively). To understand the direct effect of tachysystole on safety outcomes, we decided both to exclude conditions such as preeclampsia and IUGR and to include only foetuses that met composite criteria for well-being.
This allowed us to observe better foetal outcomes than those of the Expedite study while maintaining a non-negligible percentage of NICU admission of 2% and 4 cases of neonatal pH < 7.0 (1%). However, the percentages of admission to NICU as well as the percentages of Caesarean sections were not significantly different from those observed in a large cohort of IOL with 25 mg of sublingual misoprostol (21).
The validity of the present study is limited to healthy mothers and foetuses. In addition, there is no internal comparison with other induction methods. Evaluating data progressively over time, we noted that most adverse events, including placental abruption, occurred in the first half of recruited patients, which addresses the need for adequate clinical experience.

CONCLUSIONS

In a selected cohort of healthy mothers and foetuses at late-term gestation or with PROM, the MVI could represent an efficient method for the IOL. When this method is applied to patients with these characteristics, the efficacy profiling of MVI regarding the time-to-delivery, the reduction of augmentation interventions, and the low rate of Caesarean section can be exploited without additional risks of obstetrical emergencies or foetal compromise.

CONTRIBUTIONS

All authors contributed to the design of the study and to data collection and discussion of results and commented and improved the manuscript.
Ferrazzi, Brembilla, Urban contributed to data analysis.
Ferrazzi and Brembilla contributed in preparing the draft manuscript.

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CONFLICT OF INTERESTS

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