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**Authors:**

Miller H, Goetzl L, Wing DA, Powers B, and Rugarn O.

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ORIGINAL ARTICLE

## Optimising daytime deliveries when inducing labour using prostaglandin vaginal inserts

Hugh Miller<sup>1</sup>, Laura Goetzl<sup>2</sup>, Deborah A. Wing<sup>3,4</sup>, Barbara Powers<sup>5</sup>, and Olof Rugarn<sup>6</sup>

<sup>1</sup>Watching Over Mothers & Babies Foundation, Tucson, AZ, USA, <sup>2</sup>Department of Obstetrics, Gynecology and Reproductive Sciences, Temple University, Philadelphia, PA, USA, <sup>3</sup>Department of Obstetrics and Gynecology, University of California, Irvine, Orange, CA, USA, <sup>4</sup>Miller Children's and Women's Hospital, Long Beach, CA, USA, <sup>5</sup>Independent Consultant, Phoenixville, PA, USA, and <sup>6</sup>Ferring Pharmaceuticals, Copenhagen, Denmark

### Abstract

**Objective:** To determine induction start time(s) that would maximise daytime deliveries when using prostaglandin vaginal inserts.

**Methods:** Women enrolled into the Phase III trial, EXPEDITE (clinical trial registration: NCT01127581), had labour induced with either a misoprostol or dinoprostone vaginal insert (MVI or DVI). A secondary analysis was conducted to determine the optimal start times for induction by identifying the 12-h period with the highest proportion of deliveries by parity and treatment.

**Results:** Optimal start times for achieving daytime deliveries when using MVI appear to be 19:00 in nulliparae and 23:00 in multiparae. Applying these start times, the median time of onset of active labour would be approximately 08:30 for both parities and the median time of delivery would be the following day at approximately 16:30 for nulliparae and 12:00 (midday) for multiparae. Optimal start times when using DVI appear to be 07:00 for nulliparae and 23:00 for multiparae. Using these start times, the median time of onset of active labour would be the following day at approximately 04:00 and 11:50, and the median time of delivery would be approximately 13:40 and 16:10, respectively.

**Conclusions:** When optimising daytime deliveries, different times to initiate induction of labour may be appropriate depending on parity and the type of retrievable prostaglandin vaginal insert used.

### Introduction

Induction of labour (IOL) is a common obstetric procedure; women have labour induced either for medical reasons, such as pregnancy-related maternal or foetal complications, post-date gestation, or for elective reasons. Women with an unfavourable cervix, particularly nulliparous women, provide a greater challenge if labour needs to be induced because the time to delivery is generally longer and more unpredictable compared with IOL in women with a favourable cervix.

Several studies have suggested that in some healthcare settings, daytime deliveries have better safety outcomes compared with deliveries at night [1–10]. Factors postulated to be associated with increases in neonatal morbidity and

mortality for night time births include reduced staffing levels during night shifts, fatigue of attending medical staff [11–13], and supervision relying to a higher degree on junior staff [14], particularly during night shifts [15] or simply that more higher-risk neonates are born at night [5,15]. In contrast, Caughey et al. demonstrated that there were no significant differences in neonatal morbidity or mortality in an academic teaching hospital [15].

Few studies have investigated the optimal start time for IOL with prostaglandins with a view to optimising daytime deliveries [16]. Moreover, no studies have looked at the optimal start time for IOL with retrievable prostaglandin vaginal delivery systems (vaginal inserts), which are available for IOL or cervical ripening as misoprostol 200 µg vaginal insert (MVI) or dinoprostone vaginal insert (DVI). Presumably, nurse-staffing decisions are most efficient and cost-effective when the time course of labour induction can be reasonably estimated and the predictability of the time from start of IOL to delivery is better understood. The aim of this investigation is to determine a theoretical induction start time when using prostaglandin vaginal inserts which would result in the highest proportion of deliveries between 07:00 and 19:00 (daytime). The analysis is based on data from

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Address for correspondence: Hugh Miller, Watching Over Mothers & Babies Foundation, 5301 E Grant Road, Tucson, AZ 85712, USA. Tel: +1 520-881-9662. Fax: +1 520-529-2736. E-mail: [hmiller1@email.arizona.edu](mailto:hmiller1@email.arizona.edu)



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### Keywords

Daytime deliveries, dinoprostone, induction of labour, misoprostol, retrievable prostaglandin vaginal delivery systems

### History

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nulliparous and parous women at term gestation with an unfavourable cervix who were enrolled in the EXPEDITE (EXogenous Prostaglandin comparing the Efficacy and safety of MVI with the DVI for reducing Time to vaginal delivery in pregnant women at term) trial [17].

## Methods

### Study design

The EXPEDITE trial was a Phase III, randomised, controlled, double-blind study conducted at 35 sites in the United States (clinical trial registration at [www.clinicaltrials.gov](http://www.clinicaltrials.gov); identifier NCT01127581). Women requiring cervical ripening and eligible for IOL using prostaglandins were randomised to receive MVI (Misodel<sup>®</sup>, Ferring Pharmaceuticals Pty Ltd., Pymble, Australia; Mysodelle<sup>®</sup>, Ferring Pharmaceuticals Ltd., West Drayton, United Kingdom; or Myspess<sup>®</sup>, Ferring Pharmaceuticals México, Mexico City, Mexico) or DVI (Cervidil<sup>®</sup>, Forest Pharmaceuticals Inc., St Louis, MO; Propess<sup>®</sup>, Ferring Pharmaceuticals Ltd., West Drayton, United Kingdom). Women were treated with a single vaginal insert for up to 24 h. Intravenous oxytocin was permitted if needed, with a minimum waiting period of 30 min following removal of the vaginal insert, assuming no contraindications. Randomisation was stratified by site and parity to include approximately 60% nulliparous and 40% parous women. The primary publication for the EXPEDITE trial contains a detailed description of the study protocol and study population [17].

### Eligible participants

Pregnant women, aged  $\geq 18$  years were eligible to be included in the trial if they: were  $\geq 36$  weeks gestation with a single-live fetus, required cervical ripening and labour induction (baseline modified Bishop score  $\leq 4$ ); parity  $\leq 3$ ; and had no uterine scar.

### Assessments

As a secondary analysis, times to delivery were summarised by 4-h intervals from the start of the induction (placement of the vaginal insert) with either MVI or DVI for both nulliparous and parous women. The 12-h period (i.e. three consecutive 4-h periods) with the highest proportion of deliveries was identified and used to determine the optimal start times for induction that would then result in the highest chance of having a daytime delivery. Median times to active labour were summarised for both treatment groups by parity. Active labour was defined as progressive cervical dilatation to 4 cm with any frequency of contractions or rhythmic, firm, adequate, quality uterine contractions causing progressive cervical change occurring at a frequency of three or more in 10 min and lasting 45 s or more. This definition of active labour was in line with the American Congress of Obstetricians and Gynecologists (ACOG) guidelines at the time the trial was conducted. The proportion of women who required pre-delivery oxytocin was also described for each treatment group by parity.

### Statistical analysis

A Cox regression analysis was conducted using time of day when IOL began and treatment (either MVI or DVI) as

predictive variables for interval to delivery to test whether the use of hypothetical start times to model expected delivery times were justified. Assuming theoretical IOL start times, the proportions and 95% confidence intervals (CIs) were calculated for all caesarean or vaginal deliveries for a theoretical 12-h daytime period after start of induction for both treatment groups by parity. Unmodified median times to active labour and delivery (any, vaginal or caesarean) were calculated to determine approximate median time of day of these events given the theoretical IOL start times and summarised for both treatment groups by parity.

## Results

### Study population

The primary results of EXPEDITE have been published previously [17]. A total of 678 women received MVI (441 nulliparae; 237 multiparae) and 680 women received DVI (451 nulliparae; 229 multiparae). The median baseline modified Bishop score was 2 for nulliparous and parous women in both treatment groups. The majority of women received epidural anaesthesia (MVI group:  $n = 607$  [89.5%]; DVI group:  $n = 628$  [92.4%]).

### Relationship of actual start of induction of labour and time to delivery

No relationship was identified between the actual IOL start time and interval to delivery for either induction agent justifying the use of hypothetical start times to model expected time to delivery.

### Optimal start times for MVI

A total of 673/678 women (99.3%; 437 nulliparae and 236 multiparae) delivered during the initial induction attempt; vaginal delivery rates were 65.2% (285/437) in nulliparae and 89.8% (212/236) in multiparae. For nulliparae who were induced with MVI, the 12-h interval with the largest proportion of any delivery mode occurred 12–24 h post-insertion; 45.8% (202/441) of all deliveries occurred during this time interval (95% CI: 41.1–50.6; Figure 1A). For multiparae who were induced with MVI, although the 12-h period with the most deliveries was 4–16 h post-insertion with 63.3% of all deliveries, this would have resulted in a recommended start time of 03:00. Given that 03:00 is an impractical start time, we repeated our model with an 8–20 h post-insertion interval for multiparae. This interval resulted in a similar proportion of deliveries (60.8% [144/237]; 95% CI: 54.2–67.0) and would lead to in a more reasonable start time (Figure 1D). These data suggest that 19:00 in nulliparae and 23:00 in multiparae are the optimal start times for achieving daytime deliveries when using MVI.

Applying these start times, the median time of onset of active labour would be the following day at approximately 08:30 for both parities and the median time of delivery would be approximately 16:30 for nulliparae and 12:00 (midday) for multiparae (Table 1). The time-interval distributions for women in the MVI group for vaginal and caesarean deliveries show a similar pattern to the distribution

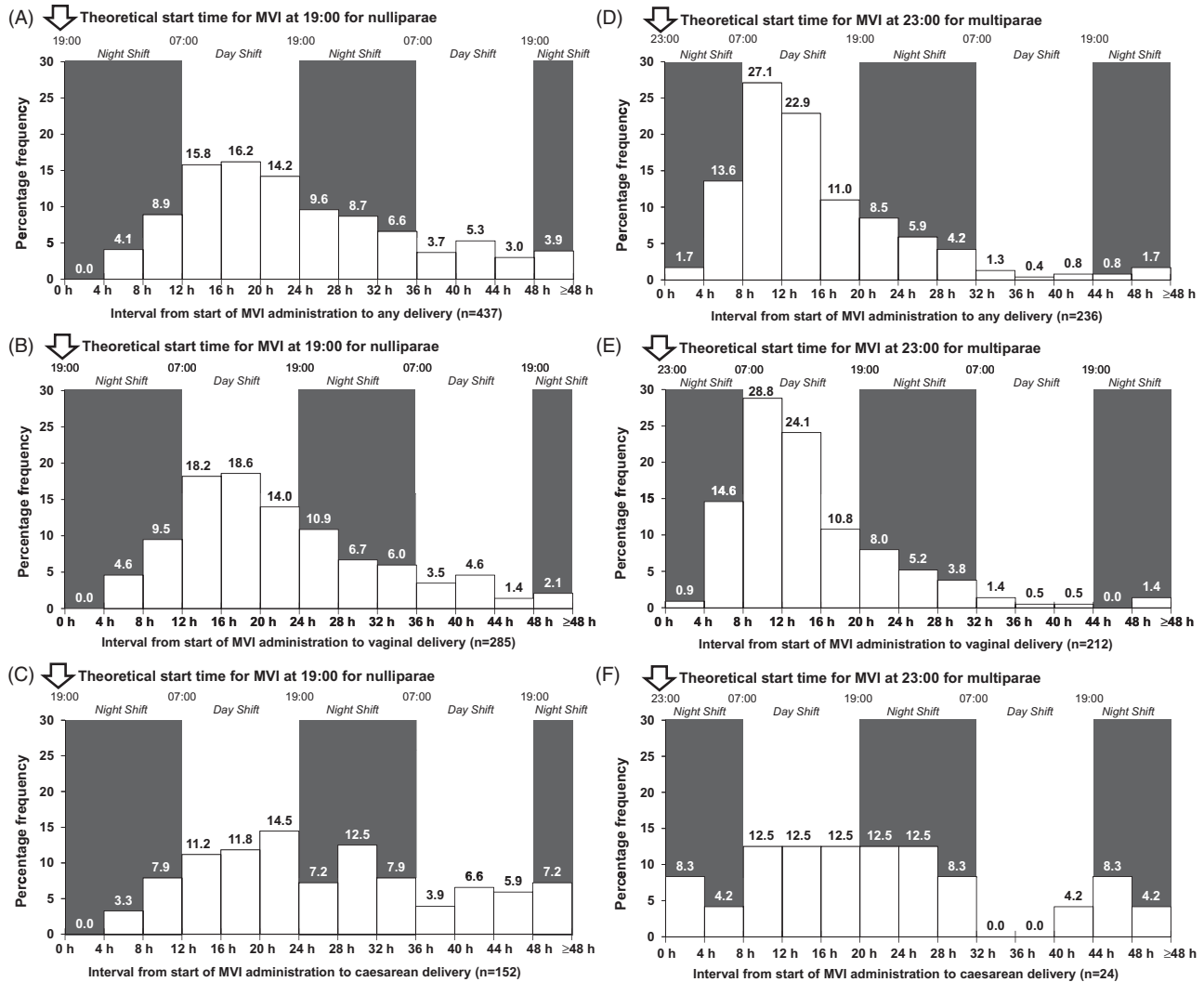


Figure 1. Intervals from MVI insertion to delivery using optimised start times. MVI, misoprostol vaginal insert.

for any delivery, confirming optimal induction start times as 19:00 for nulliparae and 23:00 for multiparae (Figure 1B, C, E and F).

### Optimal start times for DVI

A total of 671/680 (98.7%; 443 nulliparae and 228 multiparae) delivered during the initial induction attempt; vaginal delivery rates were 62.1% (275/443) in nulliparae and 93.0% (212/228) in multiparae. For nulliparae who received DVI, the 12-h interval with the largest proportion of any delivery mode occurred 24–36 h post-insertion; 32.2% (145/451) of all deliveries occurred during this time interval (95% CI: 27.9–36.7; Figure 2A). For multiparae who received DVI, the 12-h interval with the largest proportion of any delivery mode occurred 8–20 h post-insertion; 43.7% (100/229) of all deliveries occurred during this time interval (95% CI: 37.1–50.4; Figure 2D). As such, optimal induction start times for achieving daytime deliveries appear to be 07:00 for nulliparae and 23:00 for multiparae when using DVI. A theoretical start time of 19:00 in multiparae would also result in a similar proportion (40.6%) of deliveries 12–24 h post-insertion, suggesting that a start time between 19:00 and

23:00 would result in a similar number of daytime deliveries in parous women being induced with DVI.

Using these start times for DVI, the median time of onset of active labour would be the following day at approximately 04:00 and 10:50, and the median time of delivery would be approximately 13:40 for nulliparae and 16:10 for multiparae (Table 1). The time-interval distributions for women in the DVI group for vaginal and caesarean deliveries show a similar pattern to the distribution for any delivery, confirming 07:00 and 23:00 as optimal induction start times for nulliparae and multiparae, respectively (Figure 2B, C, E and F).

### Pre-delivery oxytocin use

Pre-delivery oxytocin for labour augmentation and its required monitoring are also important factors when determining staffing needs. Table S1 shows the proportion of women requiring oxytocin for labour augmentation following insert removal for each treatment group by parity.

### Discussion

Our investigation indicates that pre-determined start times for IOL with prostaglandin vaginal inserts may maximise

Table 1. Median time to events.

	MVI N = 678		DVI N = 680	
	Nulliparous n = 441	Parous n = 237	Nulliparous n = 451	Parous n = 229
Time to onset active labour	13 h 27.5 min (n = 400)	9 h 32 min (n = 231)	21 h 6 min (n = 401)	12 h 53 min (n = 225)
Time to any delivery	21 h 32 min (n = 437)	12 h 55.5 min (n = 236)	30 h 41 min (n = 443)	19 h 9 min (n = 228)
Time to vaginal delivery	19 h 46 min (n = 285)	12 h 33.5 min (n = 212)	28 h 37 min (n = 275)	18 h 48.5 min (n = 212)
Time to caesarean delivery	25 h 16 min (n = 152)	20 h 35.5 min (n = 24)	34 h 57 min (n = 168)	27 h 10 min (n = 16)
		Total n = 678		Total n = 680
		12 h 0 min (n = 631)		18 h 2.5 min (n = 626)
		18 h 9 min (n = 673)		27 h 12 min (n = 671)
		16 h 34 min (n = 497)		25 h 4 min (n = 487)
		23 h 51.5 min (n = 176)		34 h 37.5 min (n = 184)

Unmodified median times from start of induction to events during first hospitalisation have been presented. MVI, misoprostol vaginal insert; DVI, dinoprostone vaginal insert.

daytime deliveries. Factors for determining the optimal start time include parity and which agent (MVI or DVI) is being used. Start times of 19:00 and 23:00 optimise daytime deliveries for nulliparae and multiparae who receive MVI, whereas start times of 07:00 and 23:00 optimise daytime deliveries for nulliparae and multiparae who receive DVI; however, a modelled start time of 19:00 also results in a similar number of daytime deliveries as the start time of 23:00 in parous women being induced with DVI, suggesting that any evening induction for parous women would optimise daytime deliveries the following day. As such, to maximise daytime deliveries, it may be appropriate for nulliparous women to receive MVI when admitted during the evening shift whereas it may be more appropriate to induce with DVI when nulliparous women are admitted during the morning. For parous women, it appears that both DVI and MVI should be administered during the evening to maximise daytime deliveries. It should be noted, however, that even when using these optimal IOL start times, at best only around 50% of women would deliver during the first 7:00 am to 7:00 pm (daytime) period after IOL, with the remaining deliveries spread over a period of up to several days. As such, these theoretical start times for either MVI or DVI by parity would likely lead to only a slightly larger proportion of daytime deliveries than those at night, although the proportion of parous women likely to achieve a daytime delivery would be greater than nulliparous women.

Interestingly, the optimal IOL with prostaglandin inserts start times determined in our investigation reflect the circadian rhythm of spontaneous labour, which is more likely to start at night [18–20], with parous women delivering late morning and nulliparous women delivering in early-mid-afternoon [20]. The histograms in Figures 1 and 2 show that MVI-use results in a peak period of deliveries for both nulliparae and multiparae, whereas DVI deliveries are more evenly distributed over time. We postulate that if the optimal times are used for induction with MVI, a higher proportion of women will deliver during the 12-h daytime period compared with women who are induced with DVI. The start times for each type of prostaglandin vaginal insert can be tailored to suit the staffing shift patterns of each individual maternity unit. Some hospitals utilise 8-h shifts, making the 12-h period chosen inappropriate. Nevertheless, understanding the time intervals from start of induction to delivery may help clinicians to determine when best to start induction according to their specific staffing schedules.

Women enrolled in the EXPEDITE study could have the prostaglandin vaginal insert *in situ* for up to 24 h. This is an important consideration when predicting the optimal start time for induction in some regions, including the United States, where DVI is indicated to be removed 12 h after insertion. Furthermore, time from start of induction to the onset of active labour may vary depending on how active labour is defined. During the trial period (between September 2010 and March 2012) [17] the then current ACOG definition was used to define active labour: cervical dilation to 4 cm or when three or more rhythmic and regular uterine contractions occurred within 10 min and lasting 45 s or more. Recently, however, ACOG guidance has changed, with the suggestion

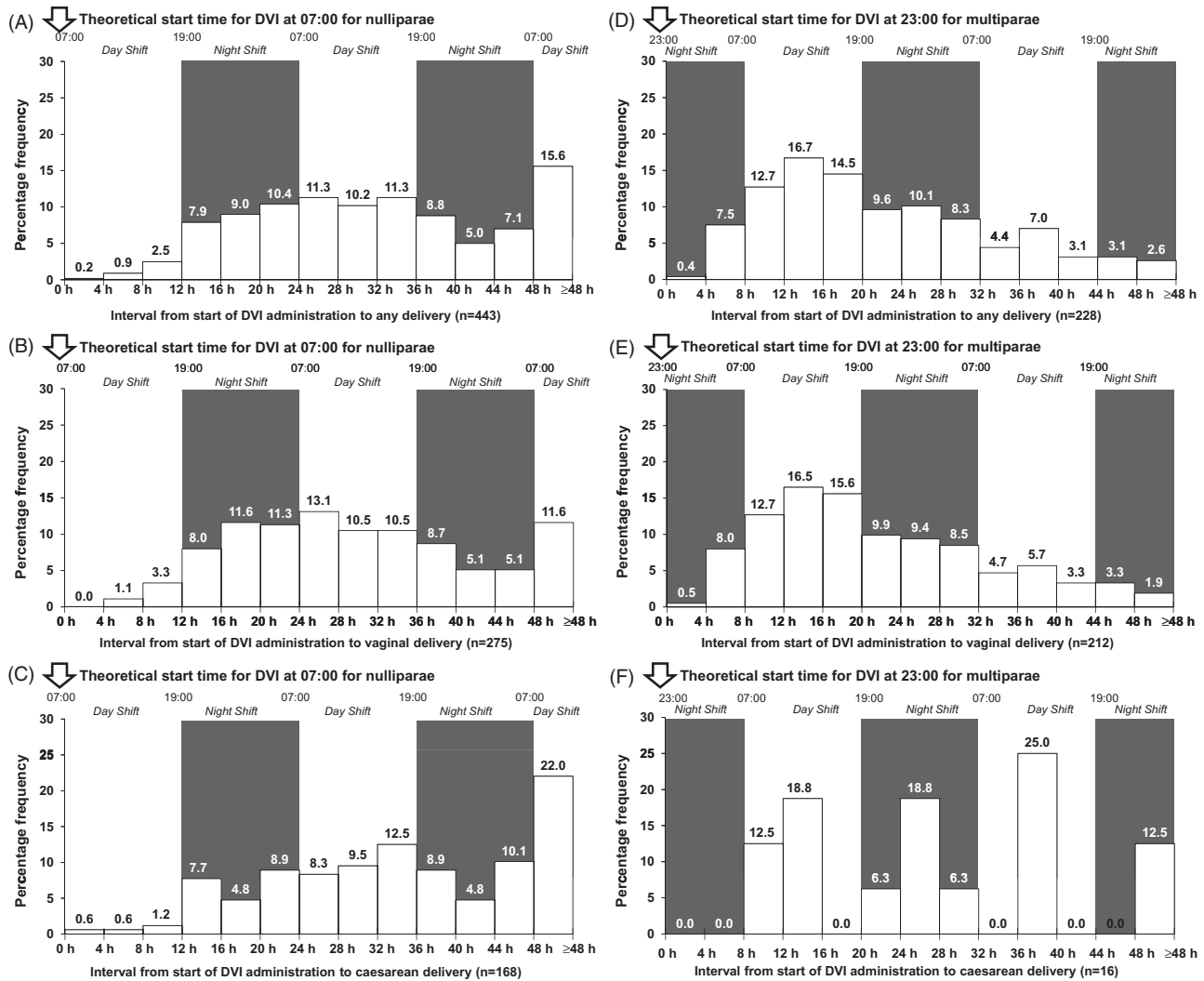


Figure 2. Intervals from DVI insertion to delivery using optimised start times. DVI, dinoprostone vaginal insert.

that cervical dilation of 6 cm should be considered as the start of active phase labour [21].

For women who undergo IOL, daytime deliveries may be advantageous in terms of reducing the risk of neonatal mortality and morbidity [4,5]. Furthermore, other studies indicate better safety outcomes for daytime deliveries in certain clinical settings. For example, neonates admitted to intensive care units when born during the night shift had a higher rate of mortality, morbidity and brain asphyxia compared with those born during dayshifts in four hospitals in Lebanon [6]. Another study with data from 3.36 million births in California, United States identified that early night births (19:00–00:00) had a 12% increase and late night births (01:00–06:00) had a 16% increase in the odds of neonatal deaths in hospitals which provided intermediate, community and regional neonatal intensive care. This increased risk was not shown for hospitals which provide primary care [5]. Another report of 694 888 singleton Swedish births between 1991 and 1997 showed that, after adjusting for potential differences in gestational age, birth weight, breech presentation, malformations, IOL, and year of birth, singletons born at night had a 28% increase in the risk of death during the first week of life [4]. As such, timing the start of IOL to maximise

the number of daytime deliveries may merit consideration. Moreover, by understanding the distribution of induction–delivery intervals, the durations of labour for women enrolled in the EXPEDITE trial and the use of pre-delivery oxytocin for labour augmentation, the duration of labour can more accurately be predicted for women who are induced with either MVI or DVI in clinical practice, thereby enhancing staff-resourcing decisions and planning more efficient use of labour suites.

Current National Institute for Health and Care Excellence (NICE) IOL guidelines [CG70] recommends induction with vaginally administered dinoprostone should be initiated in the morning because of higher maternal satisfaction [22]; however, as stated in the Cochrane review by Bakker et al., only two trials have compared the administration of prostaglandins in the morning versus evening in women with an unfavourable cervix, with few differences between study groups for maternal or neonatal outcomes and with one trial stating that women had a preference for morning inductions [16]. Indeed, published studies investigating morning versus evening start times for pharmacological IOL show a variety of findings, partly because of the range of protocols used for labour induction as well as different criteria for

participation [16,23–26]. These variables make it difficult to make comparisons between the studies or compare them with our current investigation. In addition, our investigation is limited in that the time of vaginal insert administration used to determine the optimal start time was modelled and thus represents theoretical results rather than the actual time used. Further prospective studies with assigned start times for MVI and DVI administration would be required to confirm whether our suggested start times for nulliparae and multiparae would result in a higher incidence of daytime deliveries as well as improved outcomes.

In summary, when outlining the strategy to achieve a higher proportion of daytime deliveries, our results suggest that different times to initiate IOL may be appropriate depending on parity and on the type of retrievable prostaglandin vaginal insert used. Time from administration start to delivery is shorter when using MVI compared with DVI and also shorter for parous women compared with nulliparous women. Pre-delivery oxytocin requirements for labour augmentation are also important when determining staffing needs. This information can be used to optimise resource utilisation around expected active labour and delivery times.

### Declaration of interest

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**Table S1. Pre-delivery oxytocin for labour augmentation during first hospitalisation**

	<b>MVI</b>		<b>DVI</b>	
	<b>N=678</b>		<b>N=680</b>	
	Nulliparous n=441	Parous n=237	Nulliparous n=451	Parous n=229
Women requiring pre-delivery oxytocin, n (%)	231 (52.4)	90 (38.1)	361 (81.5)	136 (59.6)
95% CI for women requiring pre-delivery oxytocin	48.6–58.2	31.9–44.7	77.6–85.0	53.0–66.1
Median time to pre-delivery oxytocin use*	18 h 31 min	13 h 29 min	24 h 35 min	20 h 8 min
Time interval from induction start to oxytocin use,* n (%)				
1 to <3 h	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
3 to <6 h	6 (2.6)	1 (1.1)	4 (1.1)	6 (4.4)
6 to <12 h	33 (14.3)	36 (40.0)	32 (8.9)	26 (19.1)
12 to <18 h	65 (28.1)	29 (32.2)	73 (20.2)	29 (21.3)
18 to <24 h	48 (20.8)	9 (10.0)	54 (15.0)	17 (12.5)
≥24 h	79 (34.2)	15 (16.7)	196 (54.3)	58 (42.6)

MVI, misoprostol vaginal insert; DVI, dinoprostone vaginal insert; CI, confidence interval. \*Oxytocin infusion for labour augmentation was allowed after 30 minutes following removal of the vaginal insert, assuming no contraindications.