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Concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction of nulliparas with an unfavourable cervix: a randomised placebo-controlled trial

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Objective To compare concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction for nulliparas with an unfavourable cervix.

Design A randomised double-blind study.

Setting University Malaya Medical Centre, Malaysia.

Population Nulliparas at term with intact membranes, Bishop score ≤ 6 and admitted for labour induction.

Methods All women received 3 mg dinoprostone pessary for labour induction. Those randomised to the oxytocin arm received oxytocin infusion started at 1 mu/minute and doubled every 30 minutes to a maximum 16 mu/minute. Women assigned to placebo received identical volume of saline infusion. After 6 hours, infusion was stopped and vaginal reassessment performed to guide further management.

Main outcome measures Primary outcome was vaginal delivery within 24 hours.

Results Concurrent oxytocin infusion with dinoprostone pessary did not significantly increase vaginal delivery rate within 24 hours (48.6 versus 35.9%; $P = 0.07$, relative risk [RR] 1.4 [95% CI 1.0–1.9]). It reduced the requirement for repeat dinoprostone (37.1 versus 61.2%; $P = 0.001$, RR 0.61 [95% CI 0.45–0.81]) and improved maternal satisfaction with the birth process (median score of 3 versus 5 on a 10-point visual analogue scale, $P = 0.007$). Caesarean rates were not different (41.9 versus 44.7%, $P = 0.52$).

Conclusions Labour induction with concurrent oxytocin infusion and vaginal dinoprostone could be considered for nulliparas with an unfavourable cervix. Larger studies are needed.

Keywords Dinoprostone, induction of labour, oxytocin, prostaglandin, trial.

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Introduction

Contemporary labour induction rate is about 20% of term pregnancies[1,2] and has been increasing since the early 1990s.[1,2] Induction of labour is associated with a doubling in the caesarean section delivery rate compared with spontaneous labour.[3]

In nulliparas with an unfavourable cervix undergoing labour induction, caesarean delivery rate is reported to be more than 30%.[4] In a recent study on labour induction performed at our centre among nulliparas at term, the overall caesarean section delivery rate was 40.6%.[5] In a Cochrane meta-analysis of prostaglandins use in labour induction,[6] there is only one randomised controlled study of prostaglandin versus placebo of nulliparas with an unfavourable cervix, and this study[7] shows that 78.9% did not deliver vaginally within 24 hours of induction with prostaglandins.

Dinoprostone vaginal tablet or pessary is an effective method of cervical ripening and labour induction.[6] Oxytocin infusion is also effective in cervical ripening and labour induction, but a Cochrane meta-analysis has concluded that 'prostaglandin agents probably overall have more benefits than oxytocin alone'.[8] Dinoprostone pessary is as effective as gel or long-acting preparations and is also cheaper.[6]

There are few studies looking at concurrent oxytocin infusion with prostaglandin administration for cervical ripening and labour induction. We performed a PubMed search in all languages on 6 September 2006 using the terms

'prostaglandins and oxytocin and labor induction and trial' and found 408 entries, but only four entries related to concurrent use of oxytocin infusion with a prostaglandin for labour induction with intact membranes.[9–12] Three of these studies[10–12] have shown shorter induction-to-delivery interval with concurrent infusion of oxytocin with a prostaglandin agent at initiation of labour induction, but the largest of the four trials with 151 women did not demonstrate a significantly shorter induction-to-delivery interval with concurrent oxytocin infusion.[9]

Our study aim was to determine whether a concurrent 6-hour infusion of oxytocin at initiation of labour induction in conjunction with a commercially available 3-mg dinoprostone pessary would be of benefit to a group of nulliparas with an unfavourable cervix.

Methods

A double-blind randomised control study was performed to compare 6 hours of concurrent oxytocin infusion with vaginal dinoprostone 3-mg tablet with placebo saline infusion and vaginal dinoprostone 3-mg tablet at initiation of labour induction at term. The study was approved by the Medical Ethics Committee of University of Malaya Medical Centre, and written consent was obtained from all women. About 5000 women per year deliver at our centre.

Based on an earlier study[12] that showed a 76 versus 56% vaginal delivery rate within 24 hours of commencement of labour induction with the use of concurrent oxytocin infusion and prostaglandin gel versus a sustained-release prostaglandin vaginal insert, taking alpha of 0.05, power of 0.8 and a recruitment ratio of one to one, 97 women were needed in each arm for a suitably powered study with vaginal delivery within 24 hours as a primary outcome. Assuming a 10% drop out, a total of 216 women would need to be recruited.

Primary outcome was vaginal delivery within 24 hours. We collected a number of secondary outcome measures including change in Bishop score over the 6 hours of infusion, analgesic requirement during the 6 hours of infusion, total number of doses of dinoprostone pessary used, visual analogue scale (VAS) pain score after the 6-hour infusion period (using a 10-point score, with 0 representing no pain to 10 representing unbearable pain), meconium-stained liquor, intrapartum epidural analgesia use, oxytocin augmentation, duration of oxytocin augmentation (if needed), vaginal delivery within 12 hours of induction, postpartum haemorrhage of ≥500 ml, maternal blood transfusion, maternal fever, labour induction-to-delivery interval and delivery-to-discharge interval. Neonatal outcomes collected included neonatal admission, Apgar score at 5 minutes, umbilical cord blood pH and neonatal jaundice. As soon as possible after delivery, women were asked to provide a birth process satisfaction score using a 10-point VAS (with 0 representing complete satisfaction to 10 representing total dissatisfaction).

Nulliparous women at term (>36 weeks) with a singleton fetus, intact membranes, cephalic presentation and an unfavourable cervix (defined as a Bishop score ≤ 6)[9,10,12] were recruited after they presented to the induction bay of the delivery suite for scheduled labour induction. Recruitment was carried out by one of the investigators or the staff of the induction bay. Women with an intrauterine fetal death or known gross fetal anomaly were excluded. Recruitment was from August 2005 to July 2006.

Randomisation sequence was generated by an investigator (P.C.T.) not involved in recruitment using a computer random number generator. Three different block sizes of 8, 10 and 12 were used. The sequence of the block size to be used was also similarly determined. The master list for the randomised treatment allocation sequence was kept by the same investigator. The treatment allocation was placed into numbered, sealed, opaque envelopes each of which contained a piece of paper bearing the legend 'Oxytocin infusion' or 'Placebo saline infusion'.

After an eligible woman had consented to participate, the next available randomisation number was assigned to that woman, and the numbered treatment allocation envelope was then given to a study nurse not otherwise involved with the woman's management to be opened in an isolated area of the delivery suite. The nurse then prepared the allocated infusion solution according to written instructions. The prepared solution was then labelled with a pre-prepared sticker bearing the individualised randomisation number, the woman's name and the legend 'Trial Medication—Oxytocin or Saline Placebo'. Treatment allocation was not revealed to study women or providers.

For women assigned to the oxytocin arm, 10 units of oxytocin was added to 500 ml of commercially available 0.9% saline in a translucent plastic container, the container labelled as mentioned above and then shaken to distribute the drug evenly. This preparation contained oxytocin at a concentration of 20 mu/ml. For women assigned to placebo, an identical container of 0.9% saline only was labelled.

Prior to trial entry, a mandatory cardiotocography (CTG) was performed, and all study women had a reassuring CTG according to Royal College of Obstetricians and Gynaecologist, UK, criteria.[13]

Sterile vaginal examination was performed in the usual fashion, and the Bishop score was recorded. The 3-mg dinoprostone pessary was placed digitally as high as possible in the posterior fornix.

As soon as possible after the insertion of the dinoprostone pessary, intravenous infusion was started at a rate of 3 ml/hour (equivalent to 1 mu/minute of oxytocin if assigned to oxytocin), and the infusion rate was double every 30 minutes to a defined maximum of 48 ml/hour

(16 mu/minute of oxytocin)—this infusion rate would normally be achieved after 2 hours unless the uterine contraction frequency was more than five per 10 minutes An electric infusion pump was used in all cases. Trial protocol dictated that the infusion rate would be increased in a geometric manner as planned unless uterine contraction frequency was five or more per 10 minutes in which case infusion rate would be maintained to sustain contraction frequency of four to five per 10 minutes. Infusion was continued for a total of 6 hours. Study women were on continuous electronic fetal monitoring throughout the 6-hour infusion.

In the event of contraction frequency of six or more per 10 minutes over two consecutive 10-minute periods but without fetal heart rate abnormality (tachysystole), infusion rate would be halved every 10 minutes until contraction frequency of five or less per 10 minutes was achieved. In women with uterine hyperactivity (i.e. tachysystole or a prolonged contraction of ≥2 minutes) and fetal heart rate pattern abnormality, the following management sequence was suggested with escalation as dictated by clinical response: 1) stop infusion, 2) perform vaginal examination and attempt to remove dinoprostone pessary if still present, 3) administer terbutaline 0.25 mg subcutaneously for tocolysis and 4) expedite delivery by caesarean section if necessary. Any such occurrence was recorded as an adverse trial event.

Women given vaginal dinoprostone for cervical ripening and labour induction in our hospital were normally only reassessed vaginally after 6 hours to institute further management. We also recorded any indicated vaginal assessment and any analgesia needed during the 6-hour infusion as trial events. Intramuscular pethidine (75 mg) and promethazine (25 mg) were routinely offered as first-line analgesia at this point, with epidural analgesia also available if needed.

Infusion was stopped after 6 hours following which another sterile vaginal assessment was performed and Bishop score recorded. At this assessment, depending on cervical findings, a further dinoprostone can be administered if the cervix remained unfavourable, amniotomy performed or no action taken if contractions are strong and good progress has been made. Following amniotomy or spontaneous rupture of membranes, oxytocin augmentation would be started if labour progress was unsatisfactory as determined by partogram assessment with a 2-hour delay action line. If a second dinoprostone pessary was administered, another vaginal assessment was performed 6 hours later. Once membranes had ruptured or labour had become established, vaginal assessment was performed at least 4 hourly.

We allowed a maximum of two dinoprostone pessaries per day. In the event that cervical status remained unfavourable after two doses of dinoprostone and amniotomy was not possible, women who were well and with a reactive CTG were normally rested overnight.

Up to four doses of dinoprostone pessary over 2–3 days might be used in our hospital in nonurgent labour inductions, provided the women and their babies remained well during the labour induction process. However, some women might opt for a caesarean delivery after two doses of dinoprostone had failed to achieve cervical ripening. Decision to perform a caesarean delivery was made based on our usual obstetric practice, and the indication for caesarean delivery was recorded.

Data were entered into a statistical software package SPSS version 11 (SPSS Inc., Chicago, IL, USA), and GraphPad Instat and QuickCalcs software (GraphPad Software Inc., San Diego, CA, USA) were also used for data analysis. SISA software (Quantitative Skills, Hilveraum, the Netherlands) was used to perform Fisher's exact test with larger than 2×2 data sets. The Kolmogorov–Smirnoff test was used to check for normal distribution. The t test was used to analyse means and distributions, and the Mann–Whitney U test was used to check for consistency in the event that t test was applied to non-normal data or ordinal data. Relative risk (RR) and its 95% confidence interval were calculated using GraphPad Instat. Numbers needed to treat (NNT) and its 95% confidence interval were generated with GraphPad Quickcalc. $P < 0.05$ in any test was considered statistically significant, and all test used two-sided results. Analysis was performed per protocol and on intention-to-treat basis.

Results

Two hundred and twenty-seven nulliparas were approached. Two hundred and twenty agreed to participate and were randomised (Figure 1). However, due to infringements of the inclusion criteria, 12 women (7 randomised to oxytocin and 5 to placebo) were excluded after randomisation and opening of their treatment allocation envelopes. Thus, 105 women allocated oxytocin and 103 women allocated to placebo were available for per-protocol analysis. All women received allocated treatment.

The characteristics of study women are listed in Table 1. There was no significant difference ($P > 0.05$) in any recorded characteristic between women randomised to oxytocin and those randomised to placebo infusion (Table 1). This finding remains consistent even if we had taken into account the 12 women excluded due to infringement of inclusion criteria (intention-to-treat analysis).

The distributions of the VAS pain and birth process satisfaction scores, mean change in Bishop score after 6 hour of infusion, total number of dinoprostone pessary used and the Apgar score at 5 minute were nonparametric when assessed using the Kolmogorov–Smirnoff test.

Primary outcome and secondary outcomes are reported in Table 2. Vaginal delivery within 24 hours of labour

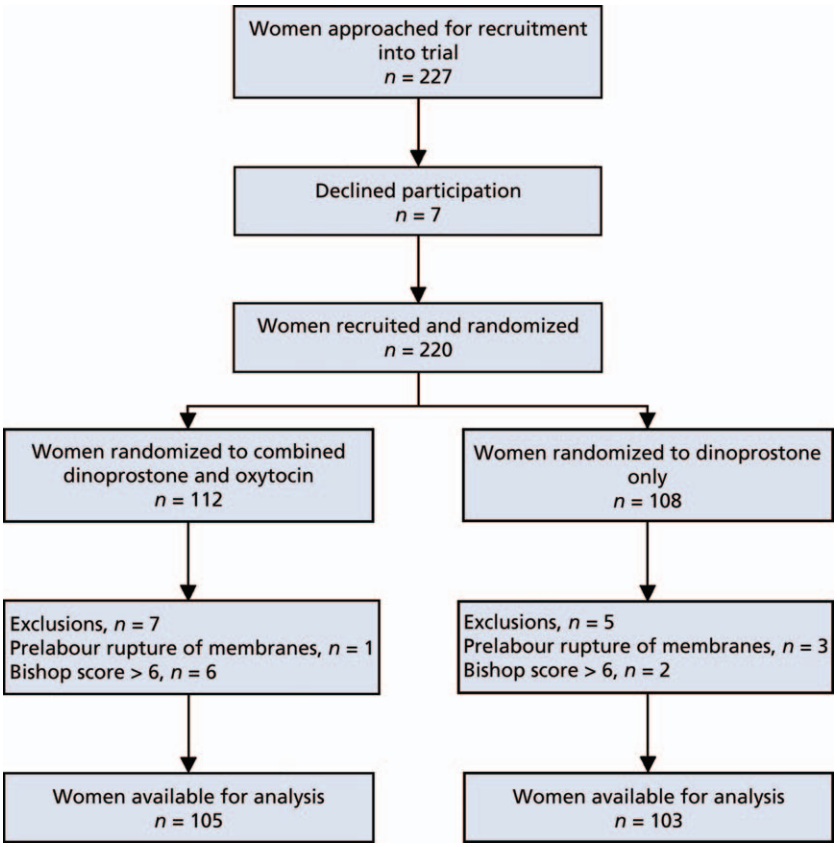

Figure 1. Recruitment flow chart for randomised trial of combined vaginal dinoprostone and oxytocin infusion for 6 hours versus vaginal dinoprostone alone at initiation of labour induction in nulliparas with unfavourable Bishop score.

induction was not significantly increased with concurrent oxytocin infusion (48.6 versus 35.9%, RR 1.4, 95% CI 1.0–1.9; $P = 0.07$), but this was a borderline result. Inclusion of 12 women excluded due to inclusion criteria infringements (intention-to-treat analysis) did not change this finding (50.0 versus 38.0%, RR 1.3, 95% CI 0.97–1.9; $P = 0.08$).

Women allocated to oxytocin infusion were less likely to need a further dinoprostone pessary (NNT = 5, 95% CI 2.7–9.2). There was no significant reduction in the caesarean delivery rate (41.9 versus 44.7%, RR 0.94, 95% CI 0.69–1.28; $P = 0.78$). They expressed better satisfaction with their birth experience (median score of 3 versus 5 on a 10-point VAS, $P = 0.007$). However, they reported worse VAS pain score at end of the 6-hour infusion (median score of 5 versus 4 on a 10-point VAS, $P < 0.001$) and were more likely to receive analgesia during the 6-hour infusion (number needed to harm is 7, 95% CI 3.9–16.3). Intramuscular pethidine and promethazine analgesia were administered as required; no study women needed epidural analgesia during the 6-hour infusion.

There was no significant difference in the occurrence of uterine hyperstimulation syndrome (tachysystole or prolonged contraction with fetal heart rate abnormality) between the two groups—with two women in the oxytocin arm and one in the placebo arm. These women responded rapidly to the reduction or stopping of the trial infusion. No woman needed removal of dinoprostone pessary, terbutaline injection or expedited delivery due to uterine hyperstimulation syndrome. One woman allocated to saline placebo needed an emergency caesarean section during the 6-hour infusion period for fetal heart rate decelerations on CTG but without uterine hyperactivity.

There was no significant difference in meconium-stained liquor. Umbilical cord blood pH was marginally lower (mean 7.26 ± 0.08 SD versus mean 7.28 ± 0.07 SD; $P = 0.044$) in women allocated oxytocin, but the number [%] of babies with umbilical cord arterial blood pH < 7.1 (3 [2.9] versus 8 [7.8], $P = 0.13$) and the number [%] of neonatal admissions to a neonatal unit (6 [5.7] versus 12 [11.7], $P = 0.15$), although not significantly different, were lower in women assigned to oxytocin. Apgar score at 5 minutes and the incidence of neonatal jaundice were not different. There was no perinatal mortality in this study.

Two women, both allocated to oxytocin, had somewhat unusual management of their labour induction, which

Table 1. Characteristics of study women stratified according to treatment allocation to combined dinoprostone and oxytocin or dinoprostone only at initiation of labour induction in nulliparas with unfavourable Bishop score

	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103
Age (years)*	27.9 ± 3.6	27.8 ± 3.9
	28 [5]	27 [5]
Age ≥ 35 years	6 (5.7)	8 (7.8)
Gravidity*	1.3 ± 0.7	1.2 ± 0.5
	1 [0]	1 [0]
Gestational age*	40.0 ± 1.3	40.0 ± 1.2
Gestational age > 40 weeks	52 (49.5)	49 (47.6)
Gestational age determined by		
Dates and confirmed by ultrasound	97 (92.4)	90 (87.4)
Early ultrasound only	8 (7.6)	11 (10.7)
Dates only	0 (0)	2 (1.9)
Ethnicity		
Malay	63 (60.0)	58 (56.3)
Chinese	20 (19.0)	13 (12.6)
Indian	19 (18.1)	27 (26.2)
Others	3 (2.9)	5 (4.9)
Indication for labour induction**		
Prolonged pregnancy ≥ 41 weeks	40 (35.7)	32 (29.6)
Diabetes	41 (36.6)	43 (39.8)
Hypertension	13 (11.6)	14 (13.0)
Nonreassuring fetal status***	14 (12.5)	16 (14.8)
Others	4 (3.6)	3 (2.8)
Height (cm)	156 ± 6	155 ± 6
Height < 150 cm	16 (15.4)	22 (21.4)
Body mass index	30.3 ± 5.2	30.3 ± 4.3
Preinduction Bishop score*	4.2 ± 1.3	4.2 ± 1.3
	4 [1]	4 [1]
Birthweight (kg)	3.15 ± 0.44	3.13 ± 0.41
Delivery blood loss (ml)*	348 ± 163	351 ± 178
	300 [150]	300 [150]

Data are represented as mean ± SD, median [interquartile range] and *n* (%). Analyses were by *t* test for comparison of means and Fisher's exact test for categorical data sets. Mann–Whitney *U* test was used to check consistency with *t* test for nonparametric data. $P > 0.05$ for all variables.
*Nonparametric data.
**Total indications added up to 220 because seven women on the combined treatment arm and five women on the dinoprostone only arm had two indications for induction of labour.
***Nonreassuring fetal status includes oligohydramnios, reduced fetal movements, intrauterine growth restriction, suboptimal CTG and suboptimal umbilical artery Doppler profile.

resulted in significant skewing in the analysis for the mean induction-to-delivery interval. One woman was allowed nine 'rest' days following initial failed induction and another had two rest days. Without correction for the above unusual management, mean ± SD induction-to-delivery time was 26.7 ± 30.2 versus 26.2 ± 14.2 hours ($P = 0.87$) for oxytocin-assigned versus placebo-assigned women, respectively. If rest days given to the two women assigned to oxytocin were disregarded in the induction-to-delivery calculation, the result would be 24.2 ± 16.3 versus 26.2 ± 14.2 hours ($P = 0.36$).

Inclusion of the 12 excluded women into the analysis did not significantly change the finding on any secondary outcomes (data not shown), with one exception: the mean increase in Bishop score after 6 hours of oxytocin infusion (2.4 ± 1.8 versus 1.9 ± 1.7, $P = 0.036$; Table 2), but this finding was no longer significant (2.3 ± 1.7 versus 1.9 ± 1.7, $P = 0.08$) when all randomised women were analysed.

Discussion

Frontloading with oxytocin infusion for 6 hours concurrent with vaginal dinoprostone at the initiation of labour induction compared with vaginal dinoprostone alone was associated with a better birth process satisfaction score even though

Table 2. Outcomes in randomised trial of concurrent intravenous oxytocin infusion for 6 hours with vaginal dinoprostone versus placebo saline infusion and vaginal dinoprostone at the initiation of labour induction in nulliparas with Bishop score ≤ 6

Outcomes	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103	*P* value	RR (95% CI)
Primary outcome				
Vaginal delivery within 24 hours	51 (48.6)	37 (35.9)	0.07	1.4 (1.0–1.9)
VAS for satisfaction with birth process[*,†]	3.2 ± 2.4	4.1 ± 2.4	0.007	
	3 [4]	5 [4]	0.007[‡]	
Outcomes during labour induction				
Mean change in Bishop score (first 6 hours)[†]	2.4 ± 1.8	1.9 ± 1.7	0.036	
	2 [3]	2 [2]	0.041[‡]	
Analgesic requirement (first 6 hours)	26 (24.8)	9 (8.7)	0.003	2.8 (1.4–5.8)
Total doses of vaginal dinoprostone used	1.6 ± 0.8	1.9 ± 0.9	0.01	
	1 [1]	2 [1]	0.03[‡]	
Need for repeat vaginal dinoprostone	39 (37.1)	63 (61.2)	0.001	0.61 (0.45–0.81)
Uterine hyperstimulation[§]	2 (1.9)	1 (1)	1.0	1.96 (0.18–21.3)
Need for vaginal examination (within initial 6 hours)	10 (9.5)	4 (3.9)	0.17	2.45 (0.79–7.57)
Indication for vaginal examination within initial 6 hours			0.17	
Pain	3	1		
Spontaneous rupture of membranes	5	2		
Vaginal delivery	2	0		
Unprovoked fetal heart decelerations	0	1		
VAS for pain at 6 hours[‖,†]	5.5 ± 2.3	4.2 ± 2.3	<0.001	
	5 [3]	4 [4]	<0.001[‡]	
Intrapartum outcomes				
Meconium-stained liquor	16 (15.4)	17 (17.0)	0.85	0.92 (0.49–1.72)
Intrapartum epidural anaesthesia	58 (55.2)	62 (60.2)	0.49	0.92 (0.73–1.16)
Oxytocin augmentation	76 (72.4)	77 (74.8)	0.75	0.97 (0.82–1.14)
Duration of oxytocin augmentation (hours)	8.0 ± 3.7	7.9 ± 4.3	0.90	
Delivery outcomes				
Vaginal delivery within 12 hours	15 (14.3)	9 (8.7)	0.28	1.6 (0.7–3.6)
Mode of delivery				
Caesarean section	44 (41.9)	46 (44.7)	0.52	
Instrumental vaginal	17 (16.2)	11 (10.7)		
Normal vaginal	44 (41.9)	46 (44.7)		
Indications for caesarean delivery				
Failed induction of labour	15 (34.1)	10 (21.8)	0.34	
Failure to progress during labour	13 (29.5)	22 (47.8)		
Nonreassuring fetal status	11 (25.0)	10 (21.7)		
Others	5 (11.4)	4 (8.7)		
Neonatal outcomes				
Admission to neonatal unit	6 (5.7)	12 (11.7)	0.15	0.49 (0.19–1.26)
Indication for neonatal admission			0.33	
Meconium aspiration	0	4		
Neonatal tachypnoea	2	1		
Hypoglycaemia	1	1		
Observation	3	6		
Apgar score at 5 minutes	9.8 ± 0.4	9.8 ± 0.6	0.64	
	10 [0]	10 [0]	0.57[†]	
Apgar score < 7 at 5 minutes[¶]	0 (0)	1 (1)	0.50	
Umbilical cord arterial blood pH	7.26 ± 0.08	7.28 ± 0.07	0.044	
Umbilical cord arterial blood pH < 7.1	3 (2.9)	8 (7.8)	0.13	0.37 (0.10–1.35)
Neonatal jaundice	30 (28.6)	29 (28.2)	1.0	1.01 (0.66–1.56)

(*continued*)

Table 2. (*Continued*)

Outcomes	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103	*P* value	RR (95% CI)
Postdelivery outcomes				
Postpartum haemorrhage ≥ 500 ml	14 (13.3)	15 (14.6)	0.84	0.91 (0.47–1.8)
Blood transfusion¶	2 (1.9)	0 (0)	0.50	
Fever ≥ 38°C#	22 (21.0)	33 (32)	0.084	0.65 (0.41–1.04)
Delivery-to-discharge interval (days)	1.6 ± 1.1	1.5 ± 1.0	0.47	

Data are represented as *n* (%), mean ± SD or median [interquartile range]. Analyses were by *t* test for means and Fisher's exact test for categorical data. Mann–Whitney *U* test was also performed for nonparametric data to check for consistency with the *t* test.
*10-point VAS, with 0 representing complete satisfaction and 10 representing total dissatisfaction with the birth process.
†Nonparametric distribution of data.
‡Mann–Whitney *U* test for nonparametric data.
§Uterine hyperstimulation defined as six or more contractions in 10 minutes with fetal heart rate abnormality.
||10-point VAS, with 0 representing no pain and 10 representing unbearable pain.
¶RR not calculated as one cell has zero as value.
#Any fever of ≥38°C noted from commencement of labour induction to hospital discharge.

vaginal delivery within 24 hours, mean induction-to-delivery interval and overall caesarean delivery rate were not significantly different.

A 6-hour oxytocin infusion regimen was chosen for this study because it fitted well with our induction of labour management plan where a routine reassessment was performed 6 hours after commencement of induction to consider further intervention. It was also felt that 6 hours of oxytocin infusion should be sufficient exposure for an effect.

Maternal satisfaction with the birth process VAS score was significantly correlated with the induction-to-delivery interval (Spearman's rho = 0.43, $P = 0.01$); shorter induction-to-delivery interval correlated with higher satisfaction. We believe that although vaginal delivery within 24 hours was not significantly higher, this was a borderline result, and as corrected mean induction-to-delivery time was also shorter, although not significantly so, these factors might be sufficient to result in women allocated to oxytocin assigning a better VAS birth process satisfaction score.

Our study design was different from that of previous studies[9–12] of concurrent oxytocin with prostaglandin for labour induction in women with an unfavourable cervix in that we planned to administer oxytocin for only 6 hours at initiation of labour induction compared with earlier studies where oxytocin infusion once started usually continued until delivery. We were interested in applying oxytocin in this manner as a previous study from our centre has shown that a single membrane sweep at initiation of formal labour induction in conjunction with either vaginal dinoprostone or amniotomy has beneficial effects,[5] and we were interested to establish whether 'frontloading' with oxytocin at initiation of labour induction would have similar benefits by tipping women into labour more effectively. Labour once established is probably self-sustaining and is thought to involve a self-perpetuating cascade of endogenous release of prostaglandins.[14]

We used a lower maximum dose (up to 16 mu/minute) oxytocin infusion regimen than in previous studies where maximum oxytocin infusion rate permitted ranged from 36[10] to 40[9] mu/minute, and two other studies had no specified upper limit, although infusion rate more than 30 mu/minute was uncommon.[11,12] We had opted for a lower oxytocin dose regimen to minimise risk of uterine hyperstimulation syndrome and also as infusion rate of 16 mu/minute is effective in nearly 90% of women.[15] It is possible that a higher maximum oxytocin dose regimen or a longer infusion period may be more effective in reducing induction-to-delivery time.[10–12] However, one other previous trial that employed a higher maximum oxytocin dose has also not shown a shorter induction-to-delivery time with concurrent oxytocin infusion and vaginal prostaglandin for labour induction, but different prostaglandin agents (slow-release dinoprostone plus oxytocin infusion versus multidose misoprostol) were used in the treatment arms, making it difficult to compare directly with our study.[9]

To the best of our knowledge, our study is unique in determining the effect of frontloading with concurrent oxytocin that used an identical dinoprostone regimen in opposing arms at initiation of labour induction. Three of the four previous randomised studies we have identified that involved concurrent oxytocin and prostaglandin for labour induction used different prostaglandin regimens in the opposing arms.[9,11,12] The fourth study compared early concurrent oxytocin infusion with sustained-release prostaglandin with

late oxytocin infusion after removal of the prostaglandin sustained-release device.[10]

Concurrent low-dose oxytocin infusion for 6 hours with vaginal dinoprostone at initiation of labour appeared to be safe. Although in women assigned to oxytocin the mean umbilical cord blood pH was significantly lower (7.26 versus 7.28), the pH difference of 0.02 was marginal and was probably clinically irrelevant as proportion of cases with severe acidosis pH < 7.1 and the neonatal admission rate although not significantly different actually were less in women allocated to concurrent oxytocin. Also, babies with Apgar score at 5 minutes <7 were rare (occurred in only one baby of a woman assigned to saline infusion). In addition, previous studies that used higher maximum oxytocin doses have not reported uterine hyperstimulation,[9–12,16] supporting further the impression that concurrent oxytocin and vaginal prostaglandin for labour induction in women with an unfavourable cervix is safe.

There was no indication from our study that caesarean delivery rate could be significantly reduced by concurrent oxytocin and dinoprostone in nulliparas with an unfavourable cervix at high risk for caesarean delivery. Our caesarean rate was 41.9 versus 44.7% for concurrent use of oxytocin with dinoprostone versus dinoprostone pessary only, respectively. A powered study on caesarean delivery rate as primary outcome would require 4987 women in each arm using the caesarean rate achieved in this study. Previous trials have achieved similar results with regards to caesarean delivery rate.[9–12]

Our overall caesarean delivery rate of more than 40%, which was rather high, might be due to the high-risk profile in terms of caesarean delivery of our study population, e.g. all study women were nulliparas[4,17] with low Bishop score ≤ 6,[18] all were Asian,[19] 40.4% had labour induction for diabetes in pregnancy,[20] 34.6% for gestational age ≥ 41 weeks,[17] 14.4% for antenatal nonreassuring fetal status[20] and 13% for hypertension[20]—all these characteristics are established independent risk factors for caesarean delivery at induction of labour.

Although treatment allocation was blinded from study women and providers, it was possible that assigned treatment could be deduced by women or their providers as pain was significantly increased and more women needed analgesia during the 6-hour infusion in the concurrent oxytocin group. We did not study frequency or strength of uterine contractions, but concurrent oxytocin and prostaglandin has been reported to produce more frequent and stronger contractions more quickly.[16]

The labour induction regimen in our centre where we were prepared to allow a longer latent phase in women who required prolonged cervical ripening is in keeping with a recent report that a latent phase of 18 hours or even longer is acceptable and does not result in greater risk of blood transfusion, hysterectomy or prolonged hospitalisation.[21] We believe our findings are widely generalisable as vaginal dinoprostone for cervical ripening and labour induction in nulliparas with an unfavourable cervix is common[22] and oxytocin is universally available.

We did not demonstrate a significantly higher labour induction success rate (defined as vaginal delivery within 24 hours) with concurrent oxytocin infusion and dinoprostone pessary but a rate of 48.6 versus 35.9% ($P = 0.07$) with an absolute difference of 12.7%, a borderline significant P value and with the reported increased maternal birth process satisfaction is probably clinically significant. It is possible that our study remained underpowered as we used a beta of 0.2 in our power calculation. Larger studies in this clinically important area are warranted.

Medically indicated induction of labour in nulliparas with an unfavourable cervix remains a considerable clinical challenge associated with a lengthy process and a high caesarean delivery rate.

Conclusion

Concurrent oxytocin infusion with prostaglandin at induction of labour in nulliparas appears to be safe and can improve woman satisfaction with the birth process. However, the optimal maximum infusion rate of oxytocin and its duration of infusion should be subjected to further study. ■

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