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Two dosing regimens for preinduction cervical priming with intravaginal dinoprostone pessary: a randomised clinical trial

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Objective To compare the efficacy within 24 hours of a three-times-a-day intensive dosing regimen with a standard once daily dosing regimen using dinoprostone vaginal pessary in preinduction cervical priming.

Design Randomised controlled trial.

Setting Department of Obstetrics and Gynaecology, Singapore General Hospital.

Participants One hundred singleton term primigravidae with cephalic presentation with unfavourable cervical scores (Bishop score ≤ 5) requiring induction of labour.

Methods Eligible women were randomly assigned the standard regimen (3000 μg dinoprostone [Prostin, Upjohn, Crawley, UK] once daily) or an intensive regimen (3000 μg dinoprostone given sequentially three times daily four hours apart) for cervical priming until successful priming (Bishop score of ≥ 6) or the onset of active labour occurred.

Main outcome measures Number of women whose cervices were ripened successfully or who entered active labour within 24 hours of starting cervical priming, priming to induction interval, and priming to delivery interval.

Results Forty-nine women were assigned to the standard regimen and 51 to the intensive regimen. The median number (range) of dinoprostone pessaries used was two (one to seven) in the standard regimen and three (one to nine) in the intensive regimen. Forty-two women (82·4%) who underwent the intensive regimen achieved successful cervical ripening or active labour within 24 hours, compared with 21 assigned to standard regimen (OR 6·2, 95% CI 2·3–17·4). This difference was statistically significant. The median intervals from priming to induction, and from priming to delivery, were also statistically significantly shorter in women treated with the intensive regimen. Thirty-five women (68·63%) assigned the intensive regimen experienced pain, compared with 21 (42·86%) in the standard regimen (OR 2·92, 95% CI 1·19–7·21), with two and one women in the respective regimens requiring opiate analgesics. Five women with oligohydramnios had transient cardiotocographic abnormalities during priming with the intensive regimen, none of which required immediate intervention, and the babies were born in good condition. There were no cases of uterine hypertonus and the outcomes of labour were similar for women from both regimens.

Conclusions Preinduction cervical priming with the intensive dosing regimen improves the chances of successful ripening within 24 hours for primigravidae with unfavourable cervical scores at full term singleton pregnancies, and shortens the interval from priming to induction, and priming to delivery. This regimen may be more cost effective by shortening the period of hospital stay. The overall incidence of adverse reactions to the mother and fetus during priming was low. However, close fetal surveillance must be maintained, particularly in pregnancies complicated with oligohydramnios.

INTRODUCTION

Induction of labour at full term of pregnancy is performed for a wide range of indications in 5%–30% of women in modern obstetric practice[1]. This procedure sometimes leads to protracted and exhausting labour, and a high caesarean section rate in excess of 30%[1]. Prostaglandins in the form of a viscous gel, wax pessary or slow release pessary administered vaginally or endocervically have been shown to be an effective and safe method of ripening of the cervix for induction of labour[2]. In our local practice a prostaglandin E_2 pessary

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(dinoprostone) inserted vaginally is the method used. Most studies in the literature report the efficacy of prostaglandins compared with alternative methods of cervical priming. Studies reporting different regimens use the prostaglandin gel preparations rather than the vaginal pessary[3,4]. Presently there are no studies to determine the optimal frequency using the dinoprostone vaginal pessary, and there is no standard regimen of a prostaglandin application between different obstetric centres.

The standard dosing regimen in our centre involves the insertion of a 3 mg dinoprostone (Prostin, Upjohn, Crawley, UK) vaginal pessary into the posterior vaginal fornix. Cardiotocographic (CTG) monitoring is performed before, immediately and six hours after inserting the dinoprostone. A vaginal examination is performed the next day if the woman has not gone into labour. If the cervix remains unfavourable a second pessary is inserted. The procedure is repeated the following day if the vaginal examination reveals that the cervix remains unripe. We observed that only 40% of primigravidae would have their unfavourable cervices ripened successfully within 24 hours. Indeed, it takes up to five days before some women go into labour. This not only negates the primary intention to deliver the women soon but also inflicts an adverse psychological effect on the women, many of whom become exhausted by the time they go into established labour. Women were especially dissatisfied if the induction failed and a caesarean section resulted.

Campbell[5] found that reducing the time interval between insertion of pessaries could increase the efficacy of induction of labour. He reported a success rate of 55% in a mixed population comprising both primigravidae and multigravidae. Based on pharmacokinetic considerations, it is possible to administer the prostaglandin pessary at four hourly intervals three times a day[6]. We are therefore encouraged to investigate whether a more intensive dinoprostone pessary regimen will shorten the interval for cervical ripening in primigravid women. Our null hypothesis is that the intensive regimen with a 4 hourly dinoprostone pessary three times a day will have the same proportion of success as the standard one pessary a day regimen in achieving successful cervical ripening within 24 hours in primigravidae.

METHODS

Primigravidae with singleton pregnancies in cephalic presentation at 37 completed weeks or beyond and who were admitted for ripening of the cervix with dinoprostone 3 mg vaginal pessary for induction of labour were eligible for inclusion into the study. All women gave informed consent to the trial, which was approved by the local hospital ethics committee. All the women had Bishop scores of ≤ 5 out of a possible 10. Exclusion criteria included a history of hypersensitivity reactions to prostaglandins, maternal heart disease, active asthma, unstable lie, ruptured membranes, uncontrolled pregnancy induced hypertension, previous surgery on the uterus (e.g. myomectomy, uteroplasty and any contraindications to vaginal delivery) and any co-existing gastroenterological conditions such as peptic ulcer or active hepatitis.

Instructions on two different dosing regimens were prepared. Regimen A comprised the traditional administration of dinoprostone pessary once a day until the cervix was favourable for amniotomy. Regimen B involved the administration of vaginal pessaries three times a day at four hourly intervals until the cervical score was favourable. These instructions were kept in sealed envelopes in two batches. Each batch of 50 envelopes comprised equal numbers of both regimen assignments. The envelopes were mixed. After a woman had given her informed consent, she was randomised to her assigned regimen by the antenatal ward sister by drawing one of the envelopes. A new batch of envelopes was used only when all the envelopes in the first batch had been drawn. Owing to the different dosing frequencies in the two regimens, the assessors and participants were not blinded.

Clinical monitoring and measurements

The study form recorded the following measurements: Bishop's scores before and after insertion of the pessary and at the time of induction of labour by amniotomy; outcome of priming, spontaneous labour, spontaneous rupture of membranes, record of CTG findings before and after insertion of the pessary; presence of uterine hypertonus, nausea, vomiting and diarrhoea, pain and analgesia requirement; cervical priming to amniotomy interval; nature of the amniotic fluid; duration of labour; total dosage of oxytocin required for labour augmentation; outcome of labour; and Apgar scores of the baby at 1 and 5 minutes of life.

Maternal vital signs (e.g. blood pressure, pulse rate, respiratory rate and temperature) were obtained before insertion of the pessary. Electronic fetal heart rate monitoring was performed for 20 minutes before insertion. Clinical examination of each woman was performed. The cervical condition was assessed using the Bishop score. A 3 mg prostaglandin E_2 pessary was then inserted into the posterior vaginal fornix and the woman was requested to rest in bed for two hours. Each episode of nausea, vomiting and diarrhoea was recorded following the application of dinoprostone pessary for 24 hours. For patients on regimen A, the procedure was repeated the following day.

For patients on regimen B, the procedure was repeated at four hourly intervals up to a maximum of

three pessaries per day. At any time the woman experienced regular uterine contractions at a frequency of one every 5–10 minutes, or on reporting of leaking of amniotic fluid she was examined clinically and the cervix assessed to detect the onset of labour.

As far as possible, the same obstetrician evaluated the cervix prior to the next pessary insertion and after completion of the ripening process. To ensure consistent scoring, all participating assessors had their technique and accuracy of assigning Bishop scores evaluated by the primary investigators.

Success was defined as a post-cervical priming Bishop score of at least ≥ 6 out of 10 or the onset of labour. Upon successful ripening, the woman was transferred to labour ward for management of labour by forewater amniotomy and intravenous oxytocin infusion. Failure was defined as an interruption of the priming process for any reason before a Bishop score of 6.

Labour management

Intrapartum management followed an active management protocol, together with continuous electronic fetal heart rate monitoring. Indications for assisted delivery and emergency lower caesarean section were in accordance with standard obstetric criteria.

Maternal gastrointestinal reactions were treated with intravenous hydration. Allergic reactions were initially managed with an attempt to retrieve the pessary. Cutaneous reactions were treated expectantly while more serious manifestations, such as bronchospasm and hypotension, were managed with bronchodilator nebuliser and intravenous fluids, respectively. Uterine hypertonic contractions (defined as a series of single contractions lasting two minutes or more) or a contraction frequency of five or more in 10 minutes, were contained with intravenous salbutamol infusion.

Statistical methods

We believed that improving the successful cervical ripening rate from the rate of 40% observed in our local practice using the traditional one pessary a day regimen, to 80% in primigravidae with unfavourable cervical scores would be clinically significant and desirable. Calculations indicated that a sample size of 41 women in each arm would have a 95% power to demonstrate this difference at a significance level of 5%. It was necessary therefore to recruit 100 women into this study.

The results were analysed based on intention-to-treat. Maternal age was expressed as mean (SD) and the difference in the means between the two arms was tested for significance by the unpaired t test. Data on gestational age, pre-priming Bishop score, priming to induction interval and priming to delivery interval were expressed in median (range), and the data were analysed statistically by Mann-Whitney U tests. Categorical data were compared by χ^2 or Fisher's exact test when the frequency number is less than five. The level of statistical significance was set at $P = 0{\cdot}05$.

RESULTS

One hundred women were recruited with 49 patients in regimen A and 51 patients in regimen B. The two groups were comparable in all measured demographic variables, including mean maternal age, median gestational age, initial Bishop scores and indications for induction of labour (Table 1).

Primary outcome

Of the 51 women who were treated with the intensive four hourly dinoprostone regimen, the cervices of 42 (82·3%) were ripened successfully to a Bishop score of ≥ 6 or went into active labour within 24 hours of commencing the treatment (Table 2). In contrast, only 21 women (42·9%) in the standard one pessary regimen did so (OR 6·2%, 95% CI 2·3–17·4). The difference is statistically significant. The median (range) number of dinoprostone pessaries used was two (one to seven) in the standard regimen and three (one to nine) in the intensive regimen.

Secondary outcomes

The median (range) interval between inserting the first pessary to induction of labour was also significantly shorter in the intensive regimen compared with the standard regimen (Table 2). Similarly, significant shortened

Table 1. Characteristics of the women studied. Values are given as mean (SD), median, or n [%]. GDM = gestational diabetes; IUGR = intrauterine growth restriction.

	Standard regimen (n = 49)	Intensive regimen (n = 51)
Maternal age (years)	29·3 (3·3)	29·2 (5·4)
Gestational age (weeks)	39·5	39·1
Initial Bishop score	2	2
Indications for induction of labour		
Postdates	22 [45]	20 [39]
Oligohydramnios	11 [22]	14 [27]
Postdates and oligohydramnios	6 [12]	5 [10]
GDM	2 [4]	1 [2]
Decreased fetal movements	2 [4]	2 [4]
IUGR	1 [2]	1 [2]
Pre-eclampsia	2 [4]	6 [12]
Social	3 [6]	2 [4]

There was no statistically significant difference between regimens in the measures.

Table 2. Outcome of dinoprostone ripening. Values are given as *n* (%) or median [range].

	Standard regimen ($n = 49$)	Intensive regimen ($n = 51$)	*P*
Primary outcome			
No. success within 24 h of priming	21 (43)	42 (82)	0·0001*
Secondary outcomes			
1st dinoprostone application-to-induction interval (h)	26 [4–238]	13·5 [4–190]	0·004
1st dinoprostone application-to-delivery interval (h)	33·5 [9–250]	23 [10–205]	0·008

*OR 6·2 (95% CI 2·3–17·4).

median interval between the first pessary inserted to delivery in the intensive regimen compared with the standard regimen (Table 2) was observed.

Cervical priming failed in six women in the standard regimen and in one woman in the intensive regimen. The odds ratio for failed ripening was 0·14 (95% CI 0·014–1·38) in the intensive regimen.

The number of women requiring augmentation with oxytocin is similar (32 in the standard regimen and 39 in the intensive regimen) and the median total dose of oxytocin used was similar for the two regimens (3·9 units and 3·5 units, respectively).

Of the women in the standard regimen treatment group, 21 (42·9%) reported pain during cervical priming, of whom two required narcotic analgesics; this compares with 35 women (68·6%) in the intensive regimen who reported pain, only one of whom required analgesia. Four women in the intensive treatment group developed nausea and vomiting compared with none of the women on the standard regimen. These symptoms were easily managed with the usual anti-emetics. There were no cases of uterine hypertonus in either group of women (Table 3).

Transient abnormal electronic fetal heart rate patterns were encountered during cervical priming, five from the intensive treatment and one from the standard regimen. These occurred in women in whom oligohydramnios was the indication for induction of labour. The changes were not ominous and none required expedited delivery or caesarean section, and the newborn babies were in good condition on delivery (Table 3).

The outcome of labour and mode of delivery are summarised in Table 4. There are no significant differences in these indices between the two regimens of dinoprostone usage.

DISCUSSION

Vaginal prostaglandin application is an effective and widely accepted method for ripening of the cervix as a prelude to induction of labour[7,8]. Compared with placebo, both the induction-to-delivery interval and incidence of casesarean section for failed induction are improved with the usage of prostaglandins[9–12]. However, a common problem encountered during cervical ripening in our local practice is the uncertain outcome and prolonged duration needed to achieve successful cervical ripening using the standard regimen with daily vaginal application of one dinoprostone pessary a day. Several studies have demonstrated a better outcome with multiple dosing regimens with prostaglandin gel[3–5,13]. There has been no published data on the experience with different dosing regimens with slow release pessaries for ripening of the cervix.

This prospective randomised controlled study suggests that dinoprostone administered at a dosing frequency of three times a day demonstrated a significantly higher rate of success within 24 hours (84% *versus* 42%) compared with the standard once daily regimen. The odds ratio was 6·2 (95% CI 2·3–17·4). The time intervals, from commencement of cervical priming to induction of labour, and from commencement of cervical priming to eventual delivery, were also significantly shorter for women in the intensive regimen. We believe these results agree with findings of researchers who used prostaglandin gel[3,4,13,14]. As the median number of pessaries used were not significantly different in either dosing regimens, we believe that the intensive dosing regimen will also improve the cost effectiveness of

Table 3. Maternal and fetal morbidity. Values are given as *n* (%). CTG = cardiotography; MSL = meconium stained liquor.

	Standard regimen ($n = 49$)	Intensive regimen ($n = 51$)
Maternal morbidity		
Hypertonus	0 (0)	0 (0)
Nausea and vomiting	0 (0)	4 (8)
Pain*	21 (43)	35 (69)
Fetal morbidity		
Transient abnormal CTG	1 (2)	5 (10)
MSL	3 (6)	3 (6)
Apgar < 6 at 1 min	2 (4)	4 (8)
Intrapertum fetal distress	2 (4)	5 (10)
Abruptio placentae	0 (0)	1 (2)

*OR 2·92 (95% CI 1·19–7·21).

Table 4. Labour outcomes. Values are given as *n* (%). NVD = normal vaginal delivery; LSCS = lower segment caesarean section.

	Standard regimen ($n = 49$)	Intensive regimen ($n = 51$)	OR (95% CI)
Labour > 12 h	11 (22)	14 (27)	1·31 (0·48–3·58)
NVD	20 (41)	24 (47)	1·29 (0·54–3·07)
Instrumental vaginal delivery	15 (30)	16 (31)	1·03 (0·41–2·63)
LSCS	14 (29)	11 (22)	0·69 (0·25–1·87)

Data did not reach statistical significance.

induction of labour by shortening hospital stays, in agreement with the study of Mackenzie *et al.*[15] who found financial advantages with a two dose prostaglandin regimen compared with a single dose regimen.

There were four women in the intensive regimen compared with none in the once daily regimen who developed nausea and vomiting. These numbers were small and the symptoms were satisfactorily controlled with standard anti-emetics. The odds ratio for pain arising during the cervical priming with the intensive regimen was 2·92 (95% CI 1·19–7·21).

An important observation of this study was that there were no cases of uterine hypertonus during the priming phase in either group of nulliparous women. However, antepartum CTG abnormalities were seen in five women on the intensive regimen and in one woman on the standard regimen. All these women had a low amniotic fluid index noted at the time of cervical priming. This contrasted with the observations of Larson *et al.*[16] where oligohydramnios was not associated with an increased incidence of CTG abnormalities. It is reassuring to note that all these changes were mild and transient in nature; no interventions were necessary for the infants born in good condition. No emergency caesarean section was required during the cervical priming phase. Intrapartum complications, such as meconium stained amniotic fluid, fetal distress and depressed Apgar scores at birth were equally distributed between both regimens of pessary administration. Nevertheless, this emphasises the importance of vigilant fetal surveillance during the period of cervical ripening and refutes the suggestion that preinduction ripening of the cervix may be safely performed on an outpatient basis[17].

It is interesting to note that the intensive dosing regimen does not alter the main obstetric outcomes in terms of the incidence of prolonged labour exceeding 12 hours, oxytocin usage, assisted delivery and caesarean section rates when compared with the once daily regimen. This agrees with Mackenzie *et al.*[15], that a two dose prostaglandin E_2 gel regimen did not cause any discernible difference in oxytocin augmentation, rate of intrapartum interventions, mode of delivery and fetal or neonatal outcomes compared with a one dose regimen. Likewise, Campbell[5] found no significant reduction in the duration of labour between women induced with prostaglandin and those with placebo, despite a significant increase in the favourability of the cervix in the prostaglandin group. This is not surprising since these features are not dependent on prostaglandin function.

We conclude that dinoprostone (Prostin) pessaries given sequentially three times a day improves the chances of successful preinduction cervical ripening within 24 hours for full term singleton primigravidae with unfavourable cervical scores. Other advantages associated with this dosing regimen include reduced priming to induction and priming to delivery intervals which may prove more acceptable to women. Maternal gastrointestinal symptoms observed are mild. Fetal surveillance must be vigilant in women treated with the intensive dosing regimen, particularly in those with low amniotic fluid indices, intrauterine growth restriction and pre-eclampsia.

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