Intravaginal prostaglandin-E2 for cervical priming and induction of labour

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البروستاغلاندين E2 داخل المهبل لتحريض المخاض وتهيئة عنق الرحم

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الخلاصة: أُجريت دراسة استباقية تتناول سلامة ونجاعة وحصيلة المخاض في 436 امرأة أُجري لهن تحريض للمخاض بالبروستاغلاندين E2 داخل المهبل. وقد اختيرت النسوة ذوات الأحمال المفردة الأجنَّة، (هنّ 235 خَرُوساً (بكرية) و20 وَلُوداً (متعدِّدة الولادة) ممَّن أعناقُ أرحامهن غير ملائمة سريرياً، مع وجود استطباب لتحريض المخاض. وقد كانت الفترة الوسطية من بدء العمل بهذه الدراسة وحتى الولادة أقصر بدرجة يُعْتَدُّ بها إحصائياً لدى الوَلوُدات منها لدى الخَرُوسات (البكريات)، إذْ بلغت لدى الوَلُودات 13.5 ساعة (± 1.8) مقابل 15.5 ساعة (±2.4) لدى الخَرُوسات. ولم تتجاوز الحاجة للوصول إلى عنق رحم يمكن سريرياً إجراء بَضْع السَّلَى من خلاله، قرصَيْن من البروستاغلاندين E2 من عيار 3 مغ. وقد بلغت الحاجة الإجمالية للأوكسي توسين لزيادة المخاض 42٪، وهو أكثر بمقدار يُعتدُّ به إحصائياً لدى البكريات (47٪) ممَّا لدى الوَلوُدات (35٪)، في حين لم يشاهد أيُّ اختلاف يُعْتَدُّ به إحصائياً بين المجموعتَيْن، بالنسبة للمضاعفات أثناء المخاض أو ضرورة إجراء العملية القيصرية أو الوفيات حوالي الولادة.

ABSTRACT A prospective study examined the safety, efficacy and labour outcome in 436 women undergoing labour induction using intravaginal prostaglandin E2. Women with singleton pregnancies (235 nulliparas and 201 multiparas) were recruited if they had a clinically unfavourable cervix, and indications for induction. The mean (standard deviation) interval from initiation to delivery was statistically significantly shorter in multiparas than nulliparas: 13.5 hours (SD 1.8) versus 15.5 hours (SD 2.4). No more than 2 × 3 mg tablets were needed to achieve a clinically feasible cervix for amniotomy. The overall need for oxytocin augmentation of labour was 42%, significantly higher in nulliparas (47%) than multiparas (35%). Intrapartum complications, caesarean section and perinatal deaths showed no statistically significant differences between the groups.

Administration intravaginale de prostaglandine E2 pour la maturation du col utérin et le déclenchement du travail

RÉSUMÉ Une étude prospective a évalué la tolérance, l'efficacité et l'issue du travail chez 436 femmes (235 nullipares et 201 multipares) après déclenchement du travail par administration intravaginale de prostaglandine E2. Les critères de recrutement étaient les suivants : grossesse simple, risque avéré d'inertie du col utérin et indications pour un déclenchement du travail. L'intervalle de temps moyen (E.T. : écart type) entre l'instauration de la méthode et l'accouchement s'est révélé plus bref chez les multipares que chez les nullipares : 13,5 heures (E.T. : 1,8) *versus* 15,5 heures (E.T. : 2,4). Pas plus de 2 comprimés dosés à 3 mg n'ont été nécessaires pour obtenir un col cliniquement accessible à l'amniotomie. La fréquence globale du recours à la stimulation du travail par administration d'ocytocine a été de 42 %, s'avérant significativement plus élevée chez les nullipares (47 %) que chez les multipares (35 %). Les complications *intrapartum*, les césariennes et les morts périnatales n'ont laissé apparaître aucune différence statistiquement significative entre les groupes.

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Introduction

Labour induction has become commonplace in modern obstetrics and is indicated in medical, obstetric and fetal conditions in which prolongation of pregnancy would jeopardize maternal and fetal well-being and in which there are no contraindications to the use of labour induction methods. The process of cervical ripening is believed to be controlled by certain hormones, in particular prostaglandin E2 (PGE2), that play a role in triggering uterine contractile activity [*1*]. The use of prostaglandins for cervical ripening and induction of labour administered by any route has been reported to improve the rate of vaginal delivery, and decrease the rate of caesarean section and instrument deliveries [*2,3*].

Because pregnancies indicated for induction are at higher risk of perinatal morbidity and mortality, this creates a stressful environment for women and physicians alike. A pregnancy requiring induction of labour is a decision dilemma between facing the problems of an unfavourable cervix at induction and those of increased perinatal complications if it is decided to let the pregnancy continue. PGE2 has been shown to be safe and efficacious in promoting preinduction cervical ripening and in initiating labour [*4,5*].

Induction of labour is a common procedure in our unit. The total number of deliveries conducted in our hospital during the study period (12 months) was 5069. The caesarean section rate was 16.4%, while the rate of assisted vaginal deliveries was 1.9%. The total number of inductions of labour was 1059 (20.9%) and 436 were induced using vaginal PGE2. This study assessed the efficacy, safety and outcome of vaginal PGE2 pessary for the ripening of the cervix and induction of labour in this group of women, comparing multiparas and nulliparas.

Methods

This prospective study took place between September 2003 and August 2004 at Prince Rashed Ben Al-Hassan Military Hospital, Irbid, Jordan. A total of 436 pregnant women were recruited for the study who had a clinically unfavourable cervix and indications for labour induction. Patients were considered eligible if they had a singleton pregnancy, vertex presentation, intact membranes, and Bishop score ≤ 5. Women with ruptured membranes, contraindications for vaginal birth, previous caesarean section and unexplained antepartum haemorrhage were excluded.

Upon admission for induction, the estimated date of confinement was reviewed based on reliable menstrual history obtained at early antenatal booking when early gestation was calculated from the last menstrual period. This was confirmed by sonograms from the 1st and 2nd trimester, before 20 weeks gestational age. Full physical and pelvic examination was performed for all the women together with a nonstress test and sonogram (to evaluate amniotic fluid). Intravenous access was obtained and baseline laboratory tests were done. A dinoprostone 3-mg vaginal pessary was inserted in the posterior vaginal fornix. This was repeated after 6 hours if the signs of labour were not detected.

Amniotomy was performed within 1–2 hours of the diagnosis of labour (or as soon as clinically feasible), unless membranes spontaneously ruptured. Labour progress was monitored by pelvic examination every 2 hours. Labour abnormalities were defined by Friedman's criteria [*6*]. In this case, oxytocin augmentation was started (with Syntocinon) and administered in the manner outlined by Seitchik and Castillo [*7*]. This was stopped in cases of uterine hyperstimulation or changes suggestive of fetal hypoxia. Continuous fetal heart rate

monitoring during labour was performed in each parturient. Fetal distress was defined as the occurrence of fetal heart rate abnormalities that require the attending physician to complete the delivery either by assisted vaginal or abdominal delivery. The presence of meconium was noted either at the time of amniotomy or subsequently during labour. Every infant was given immediate suctioning of the oropharynx at the time of delivery.

Statistical analysis

Student *t*-test was used for continuous data, while for categorical data, the Fisher exact test or chi-squared test was used where appropriate. Significance was considered as $P < 0.05$.

Results

Of the 436 women induced with PGE2, 235 were nulliparas and 201 multiparas. Maternal age ranged between 17 and 36 years for nulliparas and 23 and 45 years for multiparas. Gestational age ranged between 29 and 42 weeks for nullipara and 30 and 42 weeks for multiparas.

Table 1 presents the indications for induction. Postdates, pre-eclampsia, diabetes and presumed macrosomia were the most frequent indications in both groups. These were significantly higher ($P = 0.001$), whereas suspected intrauterine growth restriction, oligohydramnios and non-reassuring cardiotocography were not significant.

Table 2 shows the outcomes of labour and delivery. Overall 42% of the women needed oxytocin for augmentation of labour. The need for labour augmentation was significantly higher in nulliparas (47%) compared with multiparas (35%) ($P = 0.001$). The interval from the initiation of oxytocin to delivery was statistically significantly shorter in multiparas (mean 13.5 hours, SD 1.8 hours) compared with nulliparas (mean 15.5 hours, SD 2.4 hours). Of the nulliparas 67% delivered within 16

Table 1 **Indications for induction among women with pregnancies induced with prostaglandin E2**

Indication for induction	Nulliparas (*n* = 235)		Multiparas (*n* = 201)		*P*-value
	No.	%	No.	%	
Postdates	127	54	96	48	0.001
Pre-eclampsia	53	23	32	16	0.001
Diabetes	14	6	26	13	0.001
Suspected IUGR	16	7	10	5	0.113
Presumed macrosomia	7	3	12	6	0.001
Previous IUFD	0	0	14	7	0.000
Oligohydramnios	5	2	3	1	0.353
Non-reassuring CTG	13	6	8	4	0.192
Total	235	100	201	100	

IUGR = intrauterine growth restriction; IUFD = intrauterine fetal death; CTG = cardiotocography.
n = *total number of women.*

Table 2 **Labour and delivery outcome for the women with pregnancies induced with prostaglandin E2**

Labour and delivery outcome	Nulliparas (*n* = 235)		Multiparas (*n* = 201)		*P*-value
	No.	%	No.	%	
Oxytocin needed	111	47	71	35	0.001
Induction to delivery interval (hours)					
< 16	158	67	147	73	0.001
16–24	59	25	42	21	0.021
> 24	18	8	12	6	0.226
Mean (SD)	15.5 (2.4)		13.5 (1.8)		0.000
Intrapartum complications					
Fetal distress	17	7	11	6	0.198
Pyrexia	4	2	4	2	0.577
Failure to progress	10	4	11	6	0.131
Haemorrhage	8	3	6	3	0.512
Chorioamnionitis	3	1	2	1	0.482
Transfusion	3	1	1	< 1	0.101
Shoulder dystocia	2	< 1	2	1	0.704
Delivery types					
Spontaneous vaginal	184	78	160	80	0.442
Forceps	8	3	3	1	0.001
Vacuum	12	5	8	4	0.138
Caesarean section:	31	13	30	15	0.144
Fetal distress	13	6	12	6	0.677
Abruptio placenta	5	2	3	1	0.353
Cord prolapse	3	1	4	2	0.131
Dilatation arrest	6	3	4	2	0.406
Descent arrest	4	2	7	4	0.007

n = *total number of women; SD = standard deviation.*

hours after oxytocin compared with 73% of multiparas ($P = 0.001$).

For women in both groups (93%) who delivered within 24 hours of starting induction no more than 2 × 3 mg PGE2 vaginal tablets were needed to achieve a clinically feasible cervix for amniotomy. Women who took more than 24 hours from induction to delivery needed 4 × 3 mg PGE2 tablets. There was no statistical significant difference between the proportion of multiparas and nulliparas who took > 24 hours from induction to delivery. Intrapartum complications showed no statistical significant differences between the groups. Forceps delivery showed a statistically significant difference in nulliparas (3%) compared with multiparas (1%) ($P = 0.001$). Vaginal delivery was achieved in 86% of the whole study group. There was no statistically significant difference in the caesarean section rate between the groups, but descent arrest as a cause of caesarean delivery was sig-

nificantly more common among multiparas (3.5%) than nulliparas (2%) ($P = 0.007$).

Table 3 presents the fetal outcomes of the study groups. There were no statistically significant differences in the rate of perinatal deaths between the groups. The main causes of death were: respiratory distress, birth asphyxia and congenital anomaly. These causes could not be attributed to the use of intravaginal prostaglandin E2.

Five-minute Apgar score < 6 ($P = 0.008$), meconium presence at delivery ($P = 0.001$) and admission to neonatal intensive care unit ($P = 0.001$) were all significantly higher in nulliparas than in multiparas. Birth weight was significantly higher among multiparas than nulliparas ($P < 0.0001$).

Discussion

This study demonstrates that the use of intravaginal PGE2 for cervical ripening as well as labour induction in nulliparas and multiparas is safe and effective. This was demonstrated by the high delivery rate before 24 hours (93%), and the low need of oxytocin for labour augmentation (42%). Also there were no serious maternal or neonatal side-effects attributable to the use of PGE2.

The percentage of multiparas who delivered within 16 hours after initiation of PGE2 (73%) was significantly higher than nulliparas (67%). The overall vaginal delivery rate of 86% in our study is comparable with that previously reported by Hassan [*8*]. This finding would eliminate the option of elective caesarean delivery in women who require delivery regardless of the Bishop score. This study revealed a short induction-to-delivery interval of 93% within 24 hours (the great majority delivered in less than 16 hours). This would indicate a short first stage of labour from an increased uterine activity. This is in agreement with the findings of Egarter et al. [*9*].

The use of oxytocin for labour augmentation was low in our study (used in 47% of primiparas and 35% of multiparas). This is in contrast to the report of Casey et al. [*10*] who used vaginal prostaglandins even in the presence of a ripe cervix and oxytocin was used in 75% of primiparas and 40% of multiparas in their study group. The use of PGE2 for induction of labour appeared to be effective in achieving cervical ripening, initiation of labour and optimal type of delivery; this corresponds to that reported by D'Aniello et al. [*11*].

Table 3 **Fetal/neonatal outcomes for the women with pregnancies induced with prostaglandin E2**

Outcome	Nulliparas (*n* = 235)		Multiparas (*n* = 201)		*P*-value
	No.	%	No.	%	
Mean (SD) birth weight (g)	3250 (415)		3503 (575)		< 0.0001
5 min Apgar score < 6	23	10	13	7	0.008
Meconium present	63	27	32	16	0.001
Admitted to NICU	13	6	6	3	0.001
Perinatal death	4	2	3	1	0.693

NICU = neonatal intensive care unit.
n = *total number of women; SD = standard deviation.*

Intrapartum complications showed no statistically significant differences between the groups. Although the most dangerous complication of induction of labour by PGE2 is rupture of the uterus, this was seen most commonly where there is a previous lower segment scar. There were no cases of rupture of the uterus in our patients. This corresponds to other reports by MacKenzie et al. [*12*] and Al-Bar et al. [*13*] which recorded no rupture of uterine scar following PGE2 induction, and disagrees with Ramsey et al. [*14*] and Raskin et al. [*15*] who reported uterine rupture in women receiving PGE2 for labour induction. Furthermore, the results of the current study revealed no statistically significant differences in perinatal mortality between the groups. So there were no apparently serious maternal or fetal complications. This corresponds with the findings of Ben-Haroush et al. [*16*].

This study agrees with other reports [*13,17,18*] regarding the use and safety of PGE2 vaginal tablets for labour induction, which showed a significant improvement in cervical favourability within 24 hours resulting in an increase in successful vaginal delivery rates in 24 hours and no increase in operative delivery rates.

In the view of these findings, cervical priming as well as labour induction using intravaginal PGE2 is safe and effective and produces no harm attributable to the method.

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Emergency Preparedness and Humanitarian Action

1st Regional Training of Trainers on Logistics Supply System

A total of 25 pharmacists, logisticians, supply officers, warehouse managers, emergency coordinators and IT experts were trained from 23 to 26 April 2007 in Amman, Jordan in the "Logistics Supply System", WHO/UN software which enhances efficiency and transparency of management of humanitarian supplies.

Participants came from the Islamic Republic of Iran, Iraq, Jordan, Lebanon, Sudan, Syria, and the West Bank and Gaza and from different organizations: the United Nations Relief and Works Agency for Palestine Refugees in the Near East, the World Food Programme, the Ministry of Health and WHO.

The training is part of a larger programme aiming to implement the system in several countries in the Region and to ensure it is always used immediately after a natural disaster or crisis occurs for the management of incoming donations.