high success rate of Karim as we had two failures in 10 cases. Moreover, all but one of our patients were parous, whereas two-thirds of Karim's group were primigravidae. It may be that persistence with the drug for a longer time would have ultimately brought success, and Karim described a case in which prostaglandin E₂ was given in repeated doses of 0.5 to 1.5 mg over a period of two days.

We do not feel that it is justifiable to persist with any single method of induction for more than six to eight hours, and if labour has not been established within that time then alternative methods of induction should be sought. However, with further experience of these drugs it is probable that more effective dose schedules will be evolved without loss of safety to mother or infant. Neither drug seemed to have an adverse effect on mother or infant, but with F₂α vomiting and diarrhoea occurred in most cases and this might prove to be a limiting factor in the number of doses administered.

It was also noted that the small number of patients who failed to respond to prostaglandin and were subsequently treated with intravenous infusion of Syntocinon proceeded rapidly to delivery. This supports the theory, at present under investigation, that there may be a synergistic action between these drugs.

In conclusion, there is no doubt that prostaglandins E₂ and F₂α, given by mouth, are often effective in inducing labour. Extensive trials are now in progress and it remains to be seen

what role they will ultimately assume in the search for the ideal induction agent, which must be safe, effective, and convenient to use.

We are indebted to Dr. Margaret Lawson, who gave unstintingly of her time and energy to monitor these patients during labour. We also thank Mrs. Davidson and her staff in the labour suite of the Queen Mother's Hospital, and Mr. Sheerlaw, the hospital pharmacist, and his staff, who prepared the drugs for oral administration. Our thanks are also due to our consultant colleagues for permission to include patients under their care in the trial and to Messrs. Upjohn Ltd., who supplied the prostaglandins.

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Amniotomy and Oral Prostaglandin E₂ Titration for Induction of Labour

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Summary

The efficacy of oral prostaglandin E₂ used on a titration basis in association with amniotomy for the induction of labour was investigated in a series of 50 patients. Induction was successful in 29 out of 32 primigravid and 17 out of 18 multigravid patients. The mean induction-delivery intervals in successful cases were 10½ and 6 hours respectively. There were no significant effects on the fetuses.

Introduction

The induction of labour by the intravenous infusion of prostaglandins is now well documented (Karim *et al.*, 1968; 1970; Beazley *et al.*, 1970; Embrey, 1970; Karim, 1970). Other studies have compared the effectiveness of using prostaglandin E₂ with oxytocin administered by this route (Beazley and Gillespie, 1971; Craft *et al.*, 1971; Karim, 1971).

Karim and Sharma (1971) reported the induction of labour with oral prostaglandins. This was successful in 79 out of 80 patients treated with prostaglandin E₂ and in 16 out of 20 patients treated with F₂α. There were no serious side effects. Amniotomy was not performed at the outset in this study.

Since current obstetric practice is tending to favour an active approach to induction consisting of membrane rupture and simultaneous oxytocic stimulation, a study was undertaken into

the efficacy of oral prostaglandins used on a titration basis in association with amniotomy. Initially prostaglandin F₂α capsules were used but because of gastrointestinal side effects and limited success experienced with this formulation it was discontinued. This paper reports the results of using prostaglandin E₂ orally in association with amniotomy in a series of 50 patients requiring induction.

Patients and Methods

The patients, who were unselected, were induced at or near term for a variety of reasons. Their inclusion in this study was based solely on their willingness to act in a volunteer capacity and not on other factors known to affect the outcome of induction—for example, favourability of the cervix, descent of the presenting part, maturity, etc. Of the total, 32 patients were primigravid and 18 multigravid. The presentation was cephalic in each instance, including three cases of multiple pregnancy.

A standard method of induction was undertaken by me in each subject. After premedication with intravenous diazepam 10 mg forewater rupture was performed. At the same time a prelabour score (Bishop, 1964), indicating an inducibility rating, was assessed by noting the state of the factors recorded in Table I. No factor was given extra weighting in the calculation of this score. Simultaneously oral prostaglandin E₂ was begun according to the titration schedule described below.

The progress of labour was assessed by noting the strength and frequency of uterine contractions, alteration in the state of the cervix, and descent of the presenting part. Vaginal examinations were performed every four hours as a routine, and at intervals between to confirm full dilatation if suspected, usually by the same observer. Initially uterine contractions and fetal heart recordings were monitored continuously throughout

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labour with an external cardiotocograph, but after evaluation of the first 25 cases it was found unnecessary, these criteria being recorded in the usual manner by the midwives at 15-minute intervals.

Facilities were available for performing fetal blood sampling if fetal distress was suspected. To standardize the method of analgesia an epidural catheter was inserted in each patient either immediately preceding or shortly after amniotomy. Initially

TABLE 1—Pre-labour Inducibility Rating (Bishop, 1964). (To Calculate Score Encircle Appropriate Number)

	cm	0	1-2	3-4	5-6
Dilatation	0	1	2	3	
%	0-30	40-50	60-70	80+	
Effacement	0	1	2	3	
	-3	-2	-1, 0	+1, +2	
Station	0	1	2	3	
	Firm	Medium	Soft		
Consistency	0	1	2		
	Posterior	Mid	Anterior		
Position	0	1	2		

2 ml of bupivacaine 0.5% was given as a test dose, and subsequently "top-ups" of 5-10 ml were given as required.

Failure of induction was thought to have occurred if (1) labour was not progressing satisfactorily after 24 hours and/or (2) the severity of side effects limited the possibility of giving further prostaglandin. In either event prostaglandin therapy was discontinued and intravenous oxytocin started within 30 minutes, being administered by a slow infusion pump on a titration basis starting at 1 mU/min and doubling the dose every 15-30 minutes until optimum uterine activity was present.

The following details were recorded in each patient: (1) the induction to first epidural "top-up" interval, (2) the induction to full dilatation interval, (3) the induction to delivery interval, (4) the maximum and total doses administered, and (5) the incidence of side effects.

After delivery fetal well-being was assessed by Apgar scores undertaken at one and five minutes.

PROSTAGLANDIN E₂ TITRATION

An aqueous solution of prostaglandin E₂ containing 0.1 mg/ml was prepared immediately before induction by diluting the contents of an ampoule containing 10 mg of prostaglandin E₂ dissolved in N, N-dimethylacetamide with 99 ml of sterile water,

TABLE II—Details of 32 Primigravida Patients

Case No.	Age	Maturity (weeks)	Indication	Inducibility Rating	Induction to Epidural "Top-up" Interval			Induction to Full Dilatation Interval	Induction to Delivery Interval	Maximum Oral Dose (mg)	Total Dose (mg)	Delivery	Apgar Score		Comments
					Hours	Minutes							1 min	5 min	
1 ..	29	39	Pre-eclampsia	7	1-13	8-18	8-45	1-0	4-0	4-0	Forceps	9	10		Vomiting × 3. Diarrhoea × 3
5 ..	23	41	Postmaturity	7	1-11	5-54	6-29	0-5	1-5	1-5	Normal	9	9		
7 ..	21	40	Pre-eclampsia	9	0-51	4-06	4-48	0-5	1-0	1-0	Forceps	9	10		
8* ..	24	43	Postmaturity	2	5-33	35-33	35-51	1-5	12-5	12-5	Forceps	8	10		Vomiting × 4. PGE ₂ stopped at 24 hr because little cervical dilatation and poor uterine activity. Success with intravenous oxytocin
11 ..	25	39	Hypertension	7	1-22	6-27	8-37	0-5	2-0	2-0	Forceps	9	10		
12 ..	26	41	Postmaturity	6	0-50	7-20	8-37	1-0	3-5	3-5	Forceps	9	10		
13 ..	27	40	Social	7	1-45	14-00	15-05	1-0	5-0	5-0	Forceps	8	10		Vomiting × 3
14 ..	29	39	Previous threatened abortion	4	2-35	7-55	8-52	1-0	4-0	4-0	Normal	7	9		
15 ..	28	41	Postmaturity	4	1-11	13-14	13-51	1-5	5-5	5-5	Forceps	8	10		Diarrhoea × 5. No vomiting. Meconium-stained liquor at A.R.M.
16 ..	19	40	Pre-eclampsia	3	3-32	15-52	16-21	1-5	9-0	9-0	Forceps	2	6		After 12 hr cervix changed only from 1.5 to 3 cm. Faulty resuscitation
18 ..	23	38	Pre-eclampsia	6	1-17	8-15	8-38	0-5	2-5	2-5	Forceps	8	10		
19 ..	26	40	Pre-eclampsia	6	2-55	10-25	11-04	1-0	5-0	5-0	Forceps	9	10		
20 ..	29	41	Postmaturity	6	3-20	6-35	7-00	1-0	4-0	4-0	Forceps	7	10		Vomiting × 1
23* ..	22	38	Pre-eclampsia	3	4-37	26-02	26-34	3-0	23-0	23-0	Forceps	7	9		Diarrhoea × 3. No vomiting. PGE ₂ stopped at 24 hr when cervix 6 cm and uterine activity poor. Success with intravenous oxytocin
24 ..	22	33	Fulminating pre-eclampsia	10	0-16	1-39	1-41	0-5	1-0	1-0	Forceps	8	10		
25* ..	39	40	Elderly primigravida	3	4-05	—	27-40	2-0	17-5	17-5	Caesarean section	5	8		Vomiting × 2. PGE ₂ stopped at 24 hr when cervix 4 cm. Subsequent good uterine activity with intravenous oxytocin. Caesarean section because of slow dilatation in an elderly primigravida
26 ..	27	40	Pre-eclampsia	6	4-15	9-00	9-14	1-5	4-5	4-5	Forceps	8	10		
29 ..	17	41	Postmaturity	6	0-50	24-00	26-13	1-0	8-0	8-0	Forceps	7	8		Vomiting × 8. Diarrhoea × 8. Side effects limited increase in dose although uterine activity not optimal
31 ..	24	41	Postmaturity	10	2-15	4-15	5-02	0-5	1-5	1-5	Normal	9	10		
32 ..	19	40	Social	5	1-18	7-00	8-10	1-0	2-5	2-5	Forceps	8	10		Vomiting × 2. Meconium-stained liquor at A.R.M.
34 ..	24	40	Social	6	1-34	6-10	7-02	0-5	2-0	2-0	Forceps	8	10		Slight loose stools at full dilatation
35 ..	18	39	Twin pregnancy pre-eclampsia	8	1-05	5-30	5-55	0-5	2-0	2-0	Forceps	7, 7	10, 10		Postpartum haemorrhage 2,000 ml. Blood transfusion
36 ..	20	41	Postmaturity	3	3-10	10-42	11-50	0-5	3-0	3-0	Forceps	7	9		Meconium-stained liquor at A.R.M.
37 ..	21	42	Postmaturity	7	3-00	8-28	9-38	1-0	4-0	4-0	Normal	9	10		
39 ..	30	41	Postmaturity	2	6-55	20-15	21-41	2-5	18-5	18-5	Forceps	8	10		Vomiting × 1. No change in cervical dilatation for 12 hr
40 ..	20	40	Social	6	2-05	5-25	5-45	0-5	2-0	2-0	Normal	9	10		
41 ..	26	42	Postmaturity	6	3-15	6-56	8-35	1-0	3-0	3-0	Normal	9	10		
46 ..	23	41	Postmaturity	7	2-00	5-50	6-19	1-0	2-5	2-5	Normal	9	10		
47 ..	19	39	Hypertension	3	5-32	22-42	22-53	1-5	15-5	15-5	Forceps	9	10		Vomiting × 1
48 ..	28	41	Postmaturity	7	2-40	4-55	6-20	0-5	1-5	1-5	Forceps	9	10		
49 ..	28	41	Postmaturity	9	3-00	7-18	8-42	0-5	2-0	2-0	Forceps	8	9		Meconium-stained liquor at A.R.M.
50 ..	24	41	Postmaturity	4	3-25	20-45	22-25	1-0	6-5	6-5	Normal	9	10		Little change in cervix from 1.5 to 3.5 cm dilatation in first 12 hr. Occipitoposterior. Head not engaged at induction. Height 4 ft 11 in (150 cm)

*Failed induction.

using a glass syringe. Fresh solutions were made up each day and kept in a refrigerator at 4°C when not in use.

In order to stimulate an early onset of optimum uterine activity with contractions occurring every two to three minutes and lasting 40 to 50 seconds, prostaglandin E₂ was given on a titration basis. The initial dose given at the time of amniotomy was 0.5 mg. It was given as a draught in about 50 ml of water. This dose was repeated at one hour if optimum activity was not present. Subsequent doses were given at two-hourly intervals because it had previously been shown that this drug given by this route has a stimulant effect on the uterus for two to two-and-a-half hours (Karim and Sharma, 1971). Doses were increased if necessary by 0.5 mg until optimum uterine activity was present and then maintained at this level until full dilatation. Occasionally the dose had to be reduced because of maternal side effects. The maximum dose varied from 0.5 to 3 mg.

Results

The results in primigravid and multigravid patients are given in Tables II and III respectively. Table II shows that induction was successful in 29 out of 32 patients. The mean induction to full dilatation interval in the successes was 9 hours 38 minutes and the mean induction to delivery interval 10 hours 32 minutes. The mean total dose given was 4.4 mg. The relation of the inducibility score to the induction to delivery interval is given in Table IV.

Each of the failures had a score of 3 or less, representing some of the most difficult obstetric cases to induce. In Case 8 prostaglandin E₂ was discontinued after 24 hours when the cervix was only 3 cm dilated and uterine contractions were infrequent—that is, one every seven minutes—despite previous optimal activity. Episodes of vomiting prevented increasing the dose above 1.5 mg every two hours. Even with intravenous oxytocin titration (maximum dose 32 mU/min) full dilatation did not occur for another 11 hours despite an early optimal uterine response.

Case 23 presented a similar picture in that therapy was stopped at 24 hours when the cervix was 6 cm and contractions had reduced to one every eight minutes despite doses of 2.5–3 mg every two hours. Full dilatation occurred 1 hour 40 minutes after starting oxytocin titration (maximum dose 32 mU/min).

TABLE IV—Relation of Inducibility Rating (Bishop, 1964) to Induction to Delivery Interval in All Cases

Inducibility Score	Primigravidae (hr min)	Multigravidae (hr min)
	Mean ± S.E. of Mean	Mean ± S.E. of Mean
0–3..	23.16 ± 2.58 (n = 5)	12.14 ± 6.30 (n = 3)
4–7..	10.20 ± 1.12 (n = 20)	6.12 ± 0.58 (n = 13)
8+..	5.14 ± 1.07 (n = 7)	4.58 ± 0.18 (n = 2)

In Case 25 contractions were never really optimal, an increase in dose above 2 mg being restricted by vomiting. At 24 hours the cervix was 4 cm dilated. There had been little change during the preceding 14 hours. The head was not engaged and was occipito-posterior in position. Subsequent good uterine activity followed intravenous oxytocin (8 mU/min) but after a further three-and-a-half hours, although the cervix achieved some further dilatation, the head did not descend and a caesarean section was undertaken in this elderly primigravida. A 9 lb 6 oz (4,250 g) infant was delivered. Pelvimetry was normal.

The results in multigravid patients are given in Table III. Induction was successful in 17 out of 18 subjects. The mean induction to full dilatation interval was 5 hours 36 minutes and the mean induction to delivery interval 6 hours 1 minute. The mean total dose given was 2.2 mg. Table IV shows the relation of the inducibility rating to the induction to delivery interval. In only one patient (Case 9) was induction thought to have failed. Prostaglandin therapy was discontinued after 19 hours because of slow progress and repeated vomiting. Cervical dilatation had changed from 2 to 5 cm but had remained at the latter for seven hours. Full dilatation occurred after five hours of oxytocin titration, a maximum dose of 32 mU/min being given. The inducibility rating in this patient was low, as with the primigravid failures.

As for side effects there was no evidence of uterine hyper-tonus in those continuously monitored, although only external tocography was used. Similarly there was no significant effect on fetal heart recordings even in the five subjects in whom the liquor was meconium-stained at amniotomy. Fetal blood sampling was not required in any subject. In only one infant was an Apgar score below 5 recorded at one minute, and all were above this figure at five minutes. Gastrointestinal side effects of vomiting and/or diarrhoea occurred in 18 subjects (36%); in

TABLE III—Details of 18 Multigravid Patients

Case No.	Age	Gravida	Maturity (Weeks)	Indication	Inducibility Rating	Induction to Epidural "Top-up" Interval			Maximum Oral Dose (mg)	Total Dose (mg)	Delivery	Apgar Score		Comments	
						Induction to Full Dilatation Interval	Induction to Delivery Interval	Hours				Minutes	1 min		5 min
2	25	2	39	Hypertension	4	1-25	15-50	16-10	1-5	6-5	Normal	8	10	Vomiting × 2. Little change in cervical dilatation for 10 hr. Rapid progress after Vomiting × 1 Vomiting × 6. Diarrhoea × 1. PGE ₂ stopped at 19 hr because of side effects and failure to progress. Success with intravenous oxytocin	
3	32	3	40	Social	5	1-04	3-59	4-08	1-0	2-0	Normal	9	10		
4	20	2	42	Postmaturity	4	1-27	7-06	7-30	0-5	2-0	Normal	8	10		
6	31	2	42	Postmaturity	7	1-35	4-05	4-28	0-5	1-0	Normal	9	10		
9*	32	4	41	Postmaturity	2	1-12	24-40	24-57	1-0	6-0	Forceps	9	10		
10	25	2	38	Pre-eclampsia	4	1-02	5-05	5-25	0-5	1-5	Forceps	8	9	Diarrhoea × 5. No vomiting Slight loose stools at full dilatation	
17	29	2	42	Postmaturity	7	2-35	6-35	7-05	1-0	3-0	Normal	8	10		
21	27	2	40	Social	6	3-21	7-31	8-35	0-5	2-5	Forceps	8	10		
22	33	5	39	Twin pregnancy	10	1-51	3-54	4-40	1-0	2-0	Normal	8, 8	10, 10		
27	24	2	40	Hypertension	5	2-20	5-55	6-02	0-5	2-0	Normal	7	9		
28	28	3	38	Twin pregnancy											
				Pre-eclampsia	3	1-46	3-05	3-31	0-5	1-5	Forceps	9, 9	10, 10	Vomiting × 1. Cervix unchanged for 6 hr. Rapid subsequent dilatation Vomiting × 2 Vomiting × 1. Meconium-stained liquor at A.R.M.	
30	31	3	42	Postmaturity	7	1-30	1-49	2-35	0-5	1-0	Normal	7	10		
33	35	3	40	Weak rhesus antibodies	3	6-23	7-53	8-13	1-0	4-0	Normal	8	9		
38	22	2	40	Hypertension	5	0-48	5-08	5-38	0-5	2-0	Normal	9	9		
42	32	7	41	Postmaturity	7	1-00	2-25	2-45	0-5	1-0	Normal	9	10		
43	24	3	41	Postmaturity	7	2-42	4-02	4-22	0-5	1-5	Normal	8	9		
44	24	2	41	Postmaturity	6	2-48	5-38	5-53	1-0	2-0	Normal	9	10		
45	24	2	38	Hypertension	8	2-13	5-08	5-17	1-0	2-0	Normal	9	10		

*Failed induction.

three diarrhoea occurred alone. Vomiting usually occurred between 20 and 50 minutes after an oral dose. While episodes were infrequent and caused little disturbance in some, in others they were troublesome—for example, in Case 29 repeated vomiting and diarrhoea occurred with 0.5-mg doses, which limited an early increase in dosage despite non-optimal uterine activity. Although in general these side effects were worse in those requiring the larger doses of prostaglandins, there was considerable variation in individual susceptibility.

Discussion

It is not possible to compare these results directly with those of the only other study using oral prostaglandin E_2 , reported by Karim and Sharma (1971), for the protocols followed were different. In the latter induction failed in only 1.2% of patients. In this investigation failure, based on the criteria previously described, occurred in 8% of unselected patients. It seems possible, therefore, since these investigations were undertaken in women of different racial characteristics, that a relation might exist between response to prostaglandin therapy and ethnic group, provided the prostaglandins used have the same activity, for their greater success was achieved without amniotomy at the onset of induction and discontinuation of oral prostaglandins during labour when adequate contractions were present and the cervix was 5-6 cm dilated. In addition, maximum doses of 1.5 mg were used, but doses of this magnitude were ineffective in stimulating optimal activity in some patients in this series, even in association with amniotomy. The larger dosage required was consequently associated with a greater incidence of gastrointestinal side effects, 36% compared with 2.5%, although in many these were not troublesome.

A common finding noted was that of a relation between the prelabour inducibility score and dose of prostaglandin required to induce labour. The score seems to reflect a prostaglandin "index"—that is, the likely sensitivity of the uterus to stimulation by this agent. Generally the lower the score the greater the maximum and total doses required and the greater the length of labour, and vice versa. This was most noticeable in primigravid patients. That a score of 3 or less reflects a relatively insensitive uterus was confirmed by the finding, especially in primigravidae, that the time from surgical induction until analgesia was first required was generally much longer in these patients than in those with more favourable conditions.

Uterine inertia may result in unfavourable cases despite oral prostaglandin titration, as was seen in some of the failures. This may be due in part to non-absorption of some of the drug, secondary to gastrointestinal side effects, or to inertia itself.

Another significant feature noted was the safety of using prostaglandin E_2 titration, so far as the effect on over-stimulation of the uterus and fetal well-being is concerned, even when given in doses in excess of those previously described. This lack of effect led to discontinuation of monitoring and management in a routine manner. That fetal blood sampling was not required in this

series suggests that prostaglandin titration is safer with oral than with intravenous administration, for in a previous study there was a greater need to perform sampling during the latter (Craft *et al.*, 1971).

As regards the mode of delivery, the high incidence of forceps in primigravid patients reflects in part a policy of elective forceps for all hypertensive and pre-eclamptic patients and the use of epidural analgesia and is unrelated to prostaglandin therapy.

The results of this study indicate that oral prostaglandin E_2 titration associated with amniotomy is a safe, convenient, and effective method for the induction of labour in most primigravid and multigravid patients. The short induction-delivery interval, especially in multigravidae, commends this method of induction for routine clinical use. However, in those with unfavourable conditions and an inducibility score of 3 or less the outcome is likely to be less successful, more prolonged, and associated with side effects. In this small group it seems more logical therefore to use intravenous oxytocin titration from the outset, for it is likely that an intravenous infusion will be required to limit ketosis, as was found in this study. This is not to say that oral prostaglandin E_2 is a less effective uterine stimulant than intravenous oxytocin in these cases, but the doses required to induce optimal activity may provoke gastrointestinal side effects of a degree not experienced with oxytocin and limit effective titration and the progress of labour. Although intravenous oxytocin was successful in stimulating uterine activity in those in whom induction had failed, this may have been due in part to an enhanced effect following previous prostaglandin therapy (Gillespie, 1972).

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