Parker, J. (1969). Ph.D. thesis (London).
 Parker, J., Ellis, F. G., Cameron, J. S., and Ogg, C. S. (1970). *Proceedings of the European Dialysis and Transplant Association*, 7, 331.
 Parker, J. R., and Mowbray, J. F. (1971). *Transplantation*, 11, 201.
 Rapoport, A., and Husdan, H. (1968). *Canadian Medical Association Journal*, 99, 149.
 Russel, P. S., and Monaco, A. P. (1964). *New England Journal of Medicine*, 271, 502.
 Salaman, J. R. (1970). *British Medical Journal*, 2, 517.

Salerni, B., et al. (1970). In *Proceedings of 5th Congress of European Society for Experimental Surgery*, p. 108.
 Sampson, D. (1969). *Lancet*, 2, 976.
 Smiddy, F. G., Burwell, R. G., and Parsons, F. M. (1961). *Nature*, 190, 732.
 Smith, M. G. M., et al. (1969). *British Medical Journal*, 4, 275.
 Storb, U., and Weiser, R. S. (1966). *Journal of the Reticuloendothelial Society*, 4, 51.
 Tennenbaum, J. I., St. Pierre, R. L., and Cerilli, G. J. (1968). *Transplantation*, 6, 986.

Prostaglandin E₂ Compared with Oxytocin for the Induction of Labour

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British Medical Journal, 1971, 3, 276-279

Summary

A comparison has been made between the effectiveness of infusing prostaglandin E₂ with Syntocinon for the induction of labour in the presence of intact membranes. Rapid titration schedules were used to induce an early uterine response. All 15 subjects receiving prostaglandin E₂ achieved cervical dilatation, whereas this occurred in only 9 out of 15 patients receiving Syntocinon.

Introduction

The intravenous infusion of oxytocin is now widely accepted as an effective and safe method of inducing labour even when administered on a rapid titration basis. Recently it has been reported that the infusion of prostaglandin E₂ is also effective in inducing labour (Beazley *et al.*, 1970; Embrey, 1970; Karim *et al.*, 1970). Karim *et al.* (1970) succeeded in inducing labour in each of 50 patients by using a continuous infusion of 0.5 µg/min. Embrey (1970), who used doses of 0.5-6.0 µg/min, had two failures in a series of 25 inductions. In some women oxytocin administration may fail to induce labour, especially when the membranes remain intact. This fact prompted us to compare the effectiveness of prostaglandin E₂ with that of the synthetic oxytocin, Syntocinon, in inducing labour.

Patients and Methods

The patients who participated in this study required induction at or near term for various reasons. They were selected at random into two groups according to whether their case record ended in an odd or an even number, one group receiving oxytocin and the other prostaglandin E₂. Those with a multiple pregnancy, an abnormal presentation, suspected cephalopelvic disproportion or a height under 5 ft 1 in (155 cm), or a previous operation on the cervix were excluded. The agents were admini-

stered by a slow infusion pump (Scientifica and Cook) on a titration basis according to the schedules described below in the presence of intact membranes.

The infusion rates were adjusted so that contractions occurred optimally every two to three minutes and lasted 40-50 seconds, and the infusion was maintained until delivery in each instance. Uterine contractions and fetal heart recordings were monitored continuously throughout labour with a Hewlett Packard cardiotocograph. Baseline recordings were obtained for at least 15 minutes before the start of infusion. During the induction of labour the membranes were ruptured artificially only in those cases of suspected fetal distress, as determined by fetal heart variations of more than 30 minutes' duration. In these subjects fetal blood samples were taken and they were subsequently eliminated from the final analysis. This was made on 30 patients, 15 in each group.

The essential criterion chosen to indicate successful induction was dilatation of the cervix. Since both primigravid and multigravid patients were studied it was decided to regard an increase in dilatation over that present before the onset of infusion as evidence of success rather than cervical dilatation of a certain arbitrary degree. Failure was considered to have occurred if there was no change over a 12-hour period. In this event the infusion was stopped, the patient was allowed to rest for the night, and other plans were made to effect delivery the next day. If progress had occurred infusions were kept running until delivery, maintaining contractions at the optimum rate and duration. Vaginal examinations were performed every four hours by one observer in each case. The degree of cervical dilatation was noted on each occasion though consideration was not given to changes in the length of the cervical canal.

Before the infusion was started each subject had an epidural catheter inserted. Bupivacaine 0.5% was later given at intervals as required, ensuring a standard method of analgesia and facilitating accurate recording of contractions and fetal heart rate by the external cardiotocograph. The times of alteration in the infusion rate were recorded, ensuring knowledge of the total quantity of each agent used. The times of onset of spontaneous membrane rupture and full dilatation were noted, as was the presence of any maternal cardiovascular or gastrointestinal side effects. Fetal well-being was assessed by Apgar scores taken at one and five minutes. At the conclusion of the study an attempt was made to correlate the Apgar score and the occurrence of type 2 decelerations in fetal heart rate recorded on the cardiotocograph with the agent used.

TITRATION SCHEDULES

Oxytocin.—The regimen used was that described by Turnbull and Anderson (1968). The infusion was started at 1 mU/min, the rate being doubled every 10 minutes until contractions

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started and then doubled every 20 minutes until contractions were optimum as recorded on the tocograph. The 15-speed infusion pump delivered a maximum concentration of 128 mU/min, which is approximately equivalent to 30 units of oxytocin made up in 500 ml and run at 30 drops/min.

Prostaglandin E₂.—The infusion rate of prostaglandin E₂ was increased more cautiously than that of oxytocin owing to the different biological activity of the former substance and so as to minimize possible uterine hypertonus. The stock solution of prostaglandin E₂, which was prepared in ethanol and stored at -20° C, contained 1 mg/ml. Aliquots of 1 ml were made up to 100 ml with normal saline (10 µg/ml) and the solution was used within 48 hours of preparation. It was kept in a refrigerator at 4° C when not in use. Subsequently the activity of prostaglandin E₂ made up in saline and kept at this temperature for one month was found to compare favourably with that of the stock solution. The infusion rate was started at 0.5 µg/min for 30 minutes, then increased every 15 minutes until optimum uterine activity occurred through the following dose range: 0.75, 1.0, 1.5, 2.0, 3.0, to a maximum concentration of 4.0 µg/min.

Results

The results of the administration of intravenous oxytocin and prostaglandin E₂ are shown in Tables I and II respectively.

It is seen from Table I that 9 (60%) of the 15 patients receiving oxytocin had evidence of cervical dilatation within 12 hours. The mean induction-full dilatation interval was 8 hours 23 minutes. Of those that failed Case 3 had tense membranes at the conclusion of the infusion and then delivered rapidly after their rupture, and Cases 6, 18, and 28 had optimum uterine activity as recorded on the tocograph with low concentrations of oxytocin. Case 12 had short episodes when the frequency of

contractions was not optimum even with the maximum concentration of 128 mU/min, and Case 29 had contractions of optimum frequency but rather low amplitude with the same dose. All except one of the failures (Case 29) required regular analgesia for discomfort. There was no correlation between parity and response, for two out of the five primigravid patients and four out of 10 multigravid patients failed. By using this titration regimen an early uterine response was produced in all instances, and contractions occurring with a frequency of once every three minutes first occurred within 30-60 minutes in all but two patients. Cases 6 and 29 took 90 minutes to achieve this frequency. Of the successes Cases, 8, 9, and 26 had little or no changes in cervical dilatation for six to eight hours. Fetal heart decelerations suggestive of fetal distress were recorded in two patients, but only one infant had an Apgar score of 5 or less at one minute. All were normal at five minutes.

It is seen from Table II that dilatation of the cervix was produced in all 15 patients receiving prostaglandin E₂. The mean induction-full dilatation interval was 9 hours 55 minutes. Despite this success rate, however, Cases 7, 19, 23, 24, and 25 had little or no change in cervical dilatation for many hours before spontaneous rupture of the membranes, despite optimum uterine activity. Case 11 had no dilatation for eight hours and then subsequent rapid progress to full dilatation occurred with the membranes intact. Type 2 decelerations in fetal heart recordings were noted in a greater number of subjects, and two infants had an Apgar score of less than 5 at one minute. In retrospect fetal blood sampling should have been performed in Case 11. The low Apgar score at five minutes was associated with a low pH of a cord blood sample, but in other instances there was no obvious correlation between fetal heart decelerations and pH values of fetal scalp or cord blood.

One further patient, not considered in this analysis because artificial rupture of the membranes was subsequently performed,

TABLE I—Details of Cases Induced with Oxytocin

Case No.	Age	Gravida	Maturity (Weeks)	Indication	Cervical Dilatation in 12 hr (+/-)	Spontaneous Membrane Rupture		Induction-Full Dilatation Interval (hr. min)	Maximal Infusion Rate (mU/min)	Total Dose to Full Dilatation (Units)	Delivery	Apgar Score		Type 2 Deceleration in Fetal Heart Rate (+/-)	Comment
						Time since Onset of Infusion (hr. min)	State of Cervix (cm)					1 min	5 min		
1	21	2	39	Poor obstetric history	+	9.10	9	9.45	128	28.1	Normal	5	8	+	No dilatation of cervix in 12 hr. Membranes tense then ruptured, fully dilated in 1½ hr. Analgesia × 4. Good contractions. Analgesia × 3.
2	20	1	40	Pre-eclampsia	+	8.05	5	9.35	32	13.4	Forceps	6	10	+	
3	25	2	41	Postmaturity	-				64	30.4				-	
6	26	2	41	Postmaturity	-				16	6.1				-	Little change in cervical dilatation for over 6 hr before spontaneous rupture of membranes. Rapid progress after cervical dilatation for 8 hr, when cervix was 3 cm dilated. Rapid progress after Short intervals when uterine activity not optimum, even on 128 mU/min. Analgesia × 3.
8	28	4	40	Social	+	6.41	3	7.40	48	14.0	Normal	7	10	-	
9	34	1	40	Hypertension	+	9.30	10	9.30	16	8.2	Forceps	9	10	-	
12	23	2	38	Hypertension	-				128	7.9				-	Good contractions. Analgesia × 2.
14	19	2	42	Postmaturity	+	6.10	7	7.10	128	44.0	Forceps	8	10	-	
18	24	1	42	Postmaturity	-				8	3.8				-	
20	22	3	41	Postmaturity	+	7.45	10	7.45	64	19.8	Normal	9	10	-	Slow cervical dilatation from 1.5 to 3 cm in first 8 hr. Good contractions. Analgesia × 4. Low amplitude contractions with 128 mU/min. No analgesia required.
22	23	2	40	Suspected dysmaturity	+	4.00	10	4.00	64	11.9	Forceps	10	10	-	
26	21	1	41	Postmaturity	+	11.50	10	11.50	8	5.3	Forceps	6	10	-	
28	19	2	42	Postmaturity	-				16	5.7				-	
29	25	1	39	Pre-eclampsia	-				128	83.7				-	
30	40	2	39	Prediabetes	+	6.44	7	8.19	64	30.6	Forceps	9	10	-	

TABLE II—Details of Cases Induced with Prostaglandin E₂

Case No.	Age	Gravida	Maturity (Weeks)	Indication	Cervical Dilatation in 12 hr (+/-)	Spontaneous Membrane Rupture		Induction-Full Dilatation Interval (hr. min)	Maximal Infusion Rate (µg min)	Total Dose to Full Dilatation µg	Delivery	Apgar Score		Type 2 Deceleration in Fetal Heart Rate (+/-)	Comment
						Time since Onset of Infusion (hr. min)	State of Cervix (cm)					1 min	5 min		
4	24	3	41	Postmaturity	+	6.17	10	6.17	3.0	871	Normal	9	10	-	Marked type 2 dips for 30 min before full dilatation F.B.S. pH 7.32 after membranes ruptured spontaneously. Slow progress in cervical dilatation from 1 to 3 cm over 9 hr before this. Meconium + F.B.S. pH 7.28 after membranes ruptured spontaneously. C.B.S. pH 7.31
5	24	2	41	Suspected dysmaturity	+	7.45	5	9.10	4.0	1776	Forceps	2	10	+	
7	28	1	41	Postmaturity	+	9.15	3	13.30	4.0	1923	Forceps	8	10	+	
10	30	1	42	Postmaturity	+	4.20	3	13.00	1.0	689	Forceps	9	10	+	No change in cervical dilatation for 8 hr, then rapid progress from 3 cm to full dilatation in 3 hr. C.B.S. pH 7.19
11	28	3	41	Postmaturity	+	11.20	10	11.20	2.0	1228	Forceps	3	4	+	
13	26	3	39	Poor obstetric history	+	4.55	10	4.55	2.0	504	Forceps	7	10	-	
15	26	1	41	Postmaturity	+	4.00	3	7.40	4.0	860	Forceps	10	10	+	C.B.S. pH 7.28
16	35	2	42	Postmaturity	+	5.15	6	7.45	4.0	1314	Forceps	8	10	-	
17	19	2	41	Postmaturity	+	15.05	7	15.25	2.0	1198	Normal	9	10	-	
19	25	4	42	Postmaturity	+	8.00	3	12.00	2.0	750	Normal	10	10	+	Little cervical dilatation in first 8 hr from 1.5 to 3 cm before spontaneous membrane rupture. Subsequent F.B.S. for persistent type 2 dips, pH 7.22, 7.27. C.B.S. pH 7.28
21	21	1	41	Postmaturity	+	5.35	8	6.45	4.0	849	Forceps	9	10	-	
23	26	1	41	Postmaturity	+	8.50	3	12.00	4.0	1390	Forceps	9	10	-	
24	41	2	38	Pre-eclampsia	+	7.20	3	9.20	4.0	948	Forceps	9	10	-	Little cervical dilatation in first 7½ hr from 1.5 to 3 cm before spontaneous membrane rupture. Rapid progress after No change in cervical dilatation for 7½ hr before spontaneous membrane rupture
25	26	2	38	Poor obstetric history	+	7.45	2	11.00	3.0	1774	Normal	10	10	-	
27	19	1	39	Hypertension	+	8.50	10	8.50	1.5	971	Normal	9	10	-	

F.B.S. = Fetal blood sample. C.B.S. = Cord blood sample.

also had evidence of fetal distress during and after discontinuance of prostaglandin E₂ therapy. Induction at term had been performed for dysmaturity and previous threatened abortion at 27 weeks. During labour a small revealed accidental haemorrhage occurred and fetal heart decelerations suggestive of distress became apparent. The infusion was stopped, the membranes were ruptured, but unfortunately fetal blood sampling was omitted. The fetal heart stopped in the second stage, five hours after discontinuing the infusion, and a stillborn dysmature infant weighing 5 lb 3 oz (2,350 g) was delivered. The placenta was severely infarcted and a small retroplacental clot was present.

About half of the subjects receiving prostaglandin E₂ vomited during the course of labour and many experienced soreness and erythema along the course of the venous drainage from the infusion site. There were no instances of cardiovascular disturbance. By using the titration regimen described above an early uterine response occurred within 60 minutes, but direct comparison could not be made between the two groups about when the onset of effective contractions had started. The tocograph tracings showed that oxytocin produced an early uterine response with regular contractions of similar amplitude. However, it generally took prostaglandin E₂ longer to induce a similar pattern of contractions, the initial uterine response being contractions of varying amplitude and frequency suggesting an initial "irritable" state.

We are unable to exclude for certain whether any significant

degree of uterine hypertonus occurred in this study, for an external tocograph rather than an intrauterine recording device was used. Nevertheless, in three subjects there were episodes when the tracing was deflected by a contraction from the baseline for more than five minutes, within 90 minutes of the start of the infusion, but there was no significant effect on the fetal heart rate at the time. Two (Cases 10 and 11) were receiving 0.5 and 1.0 µg of prostaglandin E₂/min respectively, and the other (Case 6) 16 mU of oxytocin/min. In the former the deflections did not recur despite the continuation of therapy at the same infusion rate, though fetal heart recordings later became abnormal, and definite fetal distress was present in one. In the subject receiving oxytocin the finding did not recur, though the infusion was temporarily reduced.

Discussion

In the only other study reported comparing the effectiveness of prostaglandin E₂ with oxytocin in the induction of labour, Beazley and Gillespie (1971) found no essential difference between the two agents. According to their criteria of success 73% of each group achieved a dilatation of 6 cm or more within 12 hours of the start of infusion. The difference in response found in the study reported here when subjected to statistical analysis shows a significant difference between the two groups ($\chi^2 = 7.5$, $P < 0.01$). Nevertheless, the impression

that prostaglandin E₂ is more effective in inducing labour must be considered with caution, for though the patients were selected at random the groups were not identically matched.

The differences found in these studies may be partly explained by essential differences in the plan of each investigation and the exact protocol undertaken. Beazley and Gillespie (1971) started the infusion of prostaglandin E₂ at 0.21 µg/min and oxytocin at 2.1 mU/min. These rates were doubled every hour until contractions were effective and then usually maintained at a fixed rate. In addition some patients' membranes were ruptured artificially when labour was established. Our approach was basically different in that rapid titration regimens were used to induce an early onset of regular contractions in each group, as we considered it was impossible to know that the stimulatory effect of doubling the infusion rates of prostaglandin E₂ was quantitatively equivalent to doing the same with oxytocin. It is therefore not surprising that the results were different.

By using the titration regimens an initial uterine response occurred at a comparable time with both substances, though regular contractions of similar amplitude generally occurred earlier with oxytocin. Despite this fact prostaglandin E₂ was more effective in dilating the cervix, and it is our impression that this substance had a greater stimulatory effect on the uterus than oxytocin in the dose range used. One feature tending to confirm this impression was the finding that while prostaglandin E₂ invariably resulted in spontaneous rupture of the membranes, this occurred before dilatation of the cervix had reached 6 cm in eight out of 15 patients. With oxytocin this was so in only two out of the nine successes. With both agents basically two types of response were elicited. One resembled normal labour in that progressive cervical dilatation occurred with time, while in the other little or no change in dilatation resulted for many hours, usually until the onset of spontaneous membrane rupture. About one-third of the successes in each group were in this latter category.

With regard to the practicality of using oxytocin to induce labour in the presence of intact membranes, we feel that a greater success rate could probably be achieved if the infusion rate were increased above that required to induce contractions which appear "optimum" on an external tocograph. In effect oxytocin titration would be against cervical dilatation rather than contractions. The limitation of such a policy is a possibility of causing uterine hypertonus, though Francis *et al.* (1970) did not demonstrate this in their series of 130 inductions with

oxytocin infusions in doses ranging from 2 to 128 mU/min. We feel, however, that there are possible dangers of pursuing a similar policy of increasing the dose of prostaglandins above that required to induce optimum contractions. Besides maternal disturbance caused by possible vomiting and soreness of the arm it is our impression that fetal distress may be provoked, for contractions of excessive frequency or strength may result or uterine hypertonus may occur, as recently reported by Roberts and Turnbull (1971).

In this study the necessity for performing fetal blood sampling to establish the significance of fetal heart variations was noticeably different in the two groups, though a pH of <7.20 was found in only one instance. It is possible that these findings could have been minimized had the infusion rates been reduced after spontaneous rupture of the membranes. This occurred at an early stage of cervical dilatation in five out of the six subjects suspected of having fetal distress. Besides the alteration in uterine activity known to follow membrane rupture, it is possible that prostaglandins have an augmented effect on the uterus itself through vaginal absorption of prostaglandins known to be present in liquor during labour (Karim and Devlin, 1967).

Since prostaglandin E₂ has a profound stimulatory effect on the uterus we feel that a detailed study of the effects of different dose levels on the metabolic and biochemical status of the fetus should be evaluated before their widespread introduction into clinical obstetric practice.

We wish to thank Professor Peter Curzen for his helpful advice, the nursing staff for their co-operation, the Board of Governors of the Westminster Hospital for a research grant, and Hewlett Packard Ltd. for the loan of monitoring equipment.

References

- Beazley, J. M., Dewhurst, C. J., and Gillespie, A. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 193.
- Beazley, J. M., and Gillespie, A. (1971). *Lancet*, 1, 152.
- Embrey, M. P. (1970). *British Medical Journal*, 2, 256.
- Francis, J. G., Turnbull, A. C., and Thomas, F. F. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 594.
- Karim, S. M. M., and Devlin, J. (1967). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 74, 230.
- Karim, S. M. M., Hillier, K., Trussell, R. R., Patel, R. C., and Tamusange, S. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 200.
- Roberts, G., and Turnbull, A. C. (1971). *British Medical Journal*, 1, 702.
- Turnbull, A. C., and Anderson, A. B. M. (1968). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 75, 24.

Vesico-ureteric Reflux after Renal Transplantation

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British Medical Journal, 1971, 3, 279-281

Summary

The uretero-vesical junction has been examined by micturating cystography in 20 patients after renal transplantation. Intravenous pyelograms were used to investigate the upper urinary tract in 13 of the patients.

Persistent urinary infection did not occur in patients without vesico-ureteric reflux. However, both those with reflux of their own and the transplant ureters had persistent infection. When reflux affected the tunnelled transplanted ureter there was no infection, but two patients without a tunnel implant had a persistent urinary infection.

Introduction

Murray and Harrison (1963) first described the use of a tunnel method of ureteric implantation in patients receiving renal transplants. Calne (1967) also advocates the use of this method, though others (Starzl *et al.*, 1964) use more complex techniques.

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