Possibly the real lesson to be learned is that because a pulmonary secondary has appeared it does not mean that the clinicians must remain passive on the assumption that further trouble is bound to develop. Boldness, as Tudor Edwards showed more than 20 years ago, has its rewards.

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Induction of Labour with Prostaglandins E₁ and E₂

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British Medical Journal, 1970, **2** 256–258

Summary: The use of intravenous infusions of prostaglandin E (E₁ or E₂) for the induction of labour was studied in 25 patients at or near term. Labour was successfully induced in 23 patients. The pattern of uterine motility produced resembled that of normal labour. No hypertonus was recorded nor were there any undesirable side-effects.

Introduction

The prostaglandins, first recognized for their effects on the contractility of uterine and other smooth muscle, are now known to comprise a group of chemically related long-chain hydroxy fatty acids. Each is derived from the basic (but not itself active) prostanoic acid, consisting of a 5-carbon (cyclopentane) ring with two hydrocarbon chains attached to neighbouring carbon atoms. Depending on the configuration of the 5-carbon ring, each belongs to one of four groups (F_a, E, A, or B), while for each group a suffix numeral (1, 2, or 3) describes the degree of unsaturation of the side chain (see formula below).

The prostaglandins are widely distributed in mammalian

tissues and are believed to be responsible for an extensive range of biological activity (Bergström *et al.*, 1968; Pickles, 1969). Hitherto, on the basis of laboratory experiment—concentrated on non-pregnant myometrium—it was generally believed that prostaglandins belonging to the F_a series stimulated while E prostaglandins inhibited uterine myometrium (Bygdeman and Eliasson, 1963; Pickles and Hall, 1963; Bygdeman, 1964; Pickles *et al.*, 1965). Recently, however, it was shown that in the human uterus in pregnancy the E prostaglandins possess even more striking stimulatory properties than those of the F_a series. The uterotonic effects observed in vitro (Embrey and Morrison, 1968) were soon corroborated in a preliminary study of the pregnant uterus in situ (Embrey, 1969). That study showed, moreover, that the intravenous infusion of only small amounts of prostaglandins—especially E prostaglandins—was often followed by the successful induction of labour.

The present study explores further the potential value of the E prostaglandins (E₁ and E₂) in the induction of labour.

Patients and Method

Studies were undertaken in 25 women at or near term (36–42 weeks) who were recommended for induction of labour. The indications for interruption of pregnancy were: post-maturity 7, pre-eclampsia 7, hypertension 3, unstable lie 3, breech 1, hydramnios 1, diabetes 1, anencephaly 1, and intrauterine death 1. Immediately before the study a careful assessment of the obstetric findings was made, noting particularly the station of the presenting part and the state of the cervix. The membranes were already ruptured in four patients.

Pure prostaglandins (E₁ and E₂) in solution in normal saline (2 µg./ml.) were administered by continuous intravenous infusion. The prostaglandins were first dissolved in a small volume of ethanol and diluted with sodium carbonate 0.2 mg./ml. to provide a stock solution of 100 µg./ml. The solution was sterilized by filtration and kept frozen when not in use. The stock solution was further diluted with normal saline before use. Uterine contractility was recorded either internally by means of a small intrauterine balloon or in some cases by external means with the Oxford tocograph. Spontaneous contractility was observed for at least 30 minutes before beginning the infusion, and throughout the study

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observations of fetal heart, maternal pulse, and blood pressure were made every quarter-hour.

In the early cases (Nos. 1-9) the infusion rate varied considerably. Usually, in an effort to judge dose responses, it was progressively advanced in the range 0.5-6 $\mu\text{g./min.}$ and in one case to 8 $\mu\text{g./min.}$ Because of limitation of supplies of prostaglandins the infusion was necessarily of short duration. Thereafter (Cases 10-25) the infusion rate varied between 0.5 and 2 $\mu\text{g./min.}$ —being advanced as necessary in the steps 0.5, 1, and 2 $\mu\text{g./min.}$ —and the aim was to continue the infusion until labour was established. Details of infusion times and total amounts of prostaglandin used are shown in the Table.

Results

Stimulation of the frequency and amplitude of contractions was observed in all cases after a latent interval of 15 to 30 minutes. As the infusion continued there was a progressive augmentation of uterine activity, the tocographic pattern of contractility resembling that seen in normal labour. In the patient with the highest infusion rate of 8 $\mu\text{g./min.}$ (Case 3) there was a transient increase of tone, which quickly disappeared when the infusion was slowed. No hypertonus was seen in any of the other studies. Sample records in Case 17 are shown in Fig. 1.

Induction of labour was successful in 23 out of 25 cases. The infusion time varied from half an hour to 10½ hours and the total amount of prostaglandin administered was 140 to 600 $\mu\text{g.}$ In two patients (Cases 11 and 15) contractions slowly diminished after a first infusion was stopped and the patients "went out of labour." In each instance the infusion had been stopped before cervical dilatation reached 3 cm. A second infusion was begun the following day, being continued till labour was firmly established. In two patients induction of labour with E prostaglandins was not successful. One (Case 9), at 38 weeks with an unripe cervix, had an infusion of 300 $\mu\text{g.}$ over one hour. The dosage was probably inadequate, but further material was not available. Labour began spontaneously 48 hours later. The other patient (Case 13), with pre-eclampsia at 39 weeks, failed to go into labour after

FIG. 1.—Intravenous infusion of prostaglandin E₂ for induction of labour. Case 17. Sample records beginning 0, 1, 2½, and 3½ hours after infusion.

infusion of 270 $\mu\text{g.}$ over two and a quarter hours. The next day it was felt that further delay was inadvisable, so the membranes were ruptured, labour beginning four hours later.

Of the 23 successful cases, 15 had a spontaneous vaginal delivery after a short labour. One patient was delivered with forceps because of fetal distress in the second stage of labour, while 5 others received caudal analgesia during labour and were subsequently delivered with forceps. There was one assisted breech delivery. Caesarean section was performed in one instance (Case 2). The patient was a primigravida two

Induction of Labour by E. Prostaglandins

Case No.	PG	Para	Grav.	Maturity	Mem-branes*	Cervix†		Dosage			Stimulatory Effect		Induction of Labour	Induction of Labour Interval (Hours)	Induction Delivery Interval (Hours)	Delivery	Result
						Before Infusion	After Infusion (cm.)	Rate (Max.) ($\mu\text{g./min.}$)	Time (Hours)	Total Dose ($\mu\text{g.}$)	Amplitude and Frequency	Tone					
1	E ₁	0	0	40	U	F	6	2-6	½	140	++	○	Successful	1	2	N.D.	SB
2	E ₂	0	0	42	U	U	3	2-6	½	160	++	○	Successful	7	12	L.S.C.S.	A
3	E ₂	1	0	42	U	I	4	4-8	½	260	++	+	Successful	1½	3½	N.D.	A
4	E ₂	1	0	41	U	I	5	4-6	½	280	++	○	Successful	5	10½	Forceps	A
5	E ₂	0	0	37	U	U	3	4-6	½	260	++	○	Successful	12	40½	Caudal forceps	A
6	E ₂	0	0	42	R	I	6	2-6	½	260	++	○	Successful	3	7	Caudal forceps	A
7	E ₂	0	0	40	U	U	4	2-4	1	250	++	○	Successful	3½	27½	Caudal forceps	A
8	E ₂	3	0	40	U	U	3	2-4	1½	300	++	○	Successful	3	8½	N.D.	A
9	E ₂	1	2	38	U	U	U	2-6	1	300	++	○	Failed	48	51½	Caudal forceps	A
10	E ₂	1	0	40	U	I	4	2	2½	330	++	○	Successful	2½	10½	N.D.	A
11	E ₂	0	0	39	U	U	3	2	2½	510	++	○	Successful	21	35	N.D.	A
12	E ₂	1	0	41	R	I	7	2	2½	300	++	○	Successful	5	11½	N.D.	A
13	E ₂	0	0	39	U	U	U	2	2½	270	++	○	Failed	24	33	N.D.	A
14	E ₂	1	1	42	U	I	4	1	4½	280	++	○	Successful	4½	8½	N.D.	A
15	E ₂	4	0	40	U	F	3	1	1½	300	++	○	Successful	24	29	Caudal forceps	A
16	E ₁	1	0	39	R	U	5	2	4	400	++	○	Successful	4	8	N.D.	A
17	E ₂	0	0	41	U	I	7	2	4½	540	++	○	Successful	4½	9	N.D.	A
18	E ₂	1	0	40	U	I	8	1	7½	440	++	○	Successful	7½	11½	N.D.	A
19	E ₂	1	0	40	U	I	8	1	6½	380	++	○	Successful	6½	12½	Breech del.	A
20	E ₂	7	0	40	U	I	4	1	8	450	++	○	Successful	8	20	N.D.	A
21	E ₁	1	0	40	U	U	4	1	10½	600	++	○	Successful	10½	13½	N.D.	A
22	E ₂	0	0	40	U	I	5	1	4½	270	++	○	Successful	4½	20½	Caudal forceps	A
23	E ₂	1	0	38	U	U	8	2	3½	420	++	○	Successful	3½	4½	N.D.	A
24	E ₂	2	0	40	U	F	4	1	3½	210	++	○	Successful	3½	5½	N.D.	A
25	E ₂	1	0	38	R	I	5	1	3½	225	++	○	Successful	3½	7½	N.D.	A

*Membranes: U = Unruptured, R = Ruptured.

†Cervix: F = Favourable, U = Unfavourable, I = Intermediate.

N.D. = Normal delivery. L.S.C.S. = Caesarean section. A = Alive. SB = Stillbirth.

weeks past term with a "high head" and slightly contracted pelvis. Labour was induced successfully with prostaglandin E₂. After five hours of strong labour the head remained high, there was sudden fetal distress, and lower-segment caesarean section was performed. In the first patient studied intrauterine death of the fetus had occurred four days before induction of labour. In all other cases the baby was born alive and spontaneous respiration was soon established. There were no complications of the third stage of labour in the series.

Discussion

So far the effects of prostaglandins on human pregnant myometrium *in vivo* have been explored only to a limited extent. The present study corroborates the earlier observation that E prostaglandins have significant oxytocic properties and indicates that their intravenous infusion—in the dosage 0.5–2 µg./min., using total amounts varying from 100 to 600 µg.—can be used as an effective method of inducing labour, without apparently undesirable results to mother or baby.

Though in a small series of patients given E prostaglandins at 4–8 µg./min. Bygdeman *et al.* (1968) reported that hypertonus "frequently occurred" there was no hypertonus in the present study with infusions up to 6 µg./min. Nor were there any undesirable toxic effects, though at a much higher infusion rate (0.2–0.7 µg./kg./min.) subjective symptoms, tachycardia, and hypotension have been reported (Bergström *et al.*, 1959).

The prostaglandins of the F_a group appear to be much less potent in their oxytocic effects than the E prostaglandins. Used in a similar dose range (0.5–4 µg./min.) in a personal study, induction of labour has been successful so far in only four out of nine cases and it is becoming evident that much larger amounts of prostaglandin F_{2a} (about 5 to 10 times the amount of prostaglandin E necessary) have to be administered for success. The dose found necessary by Karim *et al.* (1969) for the successful induction of labour by F_{2a} supports this view. Apart from their uterine effects the prostaglandins

are now believed to be responsible for a perplexing variety of biological activities, but as recent reviews emphasize, their precise physiological functions are far from being fully understood.

The role of the prostaglandins in parturition, if any, is as yet only a matter of conjecture. Nevertheless, evidence is accumulating to suggest their implication. Prostaglandins have been identified in amniotic fluid (Karim and Devlin, 1967) and in blood during labour (Karim, 1968) and they have been shown to initiate uterine activity closely resembling that in normal labour (Embrey, 1969; Karim *et al.*, 1969). The demonstration now that E prostaglandins can be effective—and possibly therapeutically useful—agents for the induction of labour is further circumstantial evidence of a possible physiological role in normal labour.

I wish to thank Professor J. A. Stallworthy for advice and encouragement, and gratefully acknowledge gifts of prostaglandins from Dr. J. Pike, of the Upjohn Co., and Dr. D. A. van Dorf, of the Unilever Research Laboratory.

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Induction of Abortion by Prostaglandins E₁ and E₂

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British Medical Journal, 1970, **2**, 258–260

Summary: Intravenous infusions of prostaglandin E (E₁ or E₂) were used for termination of pregnancy in 11 patients. Induction of abortion was successful in nine instances and in eight the abortion was complete. No undesirable side-effects were recorded.

Introduction

A new group of closely related hydroxy fatty acids known as the prostaglandins have now been chemically identified and shown to have significant effects on the contractility of uterine and other smooth muscle (Bergström *et al.*, 1968; Pickles, 1969). While earlier laboratory studies suggested their role was inhibitory, it has recently been shown (Embrey and Morrison, 1968; Embrey, 1969) that in regard to the human pregnant uterus the E prostaglandins have significant stimulatory properties—even more pronounced than those of the F_a series. In a separate study (Embrey, 1970) the oxytocic pro-

perties of E prostaglandins in late pregnancy and their potential value in the induction of labour were examined. The present paper deals with the effects of prostaglandins E₁ and E₂ in early and mid-trimester pregnancy and their possible therapeutic role in the termination of pregnancy.

Patients and Method

Eleven patients recommended for termination of pregnancy were studied. The age of gestation varied from 9 to 28 weeks. Uterine contractility was monitored in all cases either internally by means of a small intrauterine balloon or intra-amniotic catheter, or externally with the Oxford tocograph. The prostaglandin, dissolved in a small volume of ethanol, was first diluted with sodium carbonate 0.2 mg./ml. to provide a stock solution of 100 µg./ml. The solution was sterilized by filtration and kept frozen when not in use. Before use the stock solution was further diluted with normal saline to make a 2 µg./ml. solution. Recording of uterine contractility was begun 30 minutes before the infusion was started. The patient was kept under close observation

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