Prostaglandin F_2 alpha for induction of labour

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PROSTAGLANDINS ARE a group of active biological compounds found widely distributed in mammalian tissues. They are lipid soluble unsaturated 20-carbon hydroxy acids with a cyclopentane side ring and have been divided into four major groups called the E,F,A and B series.

Recently prostaglandins were subjected to intensive investigations. Bygdeman (1964) demonstrated that the prostaglandin F_2 alpha (PGF_2 alpha) had a potent stimulatory effect on pregnant myometrial strips. Embrey and Morrison (1968) found PGF_2 alpha to have a selective spasmogenic effect on the upper segment of the myometrium and relatively inactive on lower uterine segment strips. At the same time, the identification of PGF_2 alpha in amniotic fluid and in the maternal venous blood during labour were reported (Karim & Devlin, 1967; Karim, 1968). This was followed by the first successful clinical trial of PGF_2 alpha for the induction of labour administered via a continuous intravenous infusion. (Karim et al, 1969a).

In the University Hospital, a study of the use of PGF_2 alpha for the induction of labour was undertaken. The chief aim was to test the efficacy of the drug in our local population and to gain experience in the use of prostaglandins, particularly with regards to its side effects, if any, on the mother or foetus.

Materials and Methods

When this study was commenced, all patients requiring induction of labour were put on the trial, till our sample of PGF_2 alpha was exhausted. Altogether we had 17 cases.

Table I: Results of PGF2alpha infusion for Induction of Labour

Case No.	Age	Parity	Gestational Age	Indication for Induction	Cx at start of Infusion Length (cm.)	Cx at start of Infusion Dilatation (cm.)	Total Dose Infused (ug)	Induction — Uterine activity interval	Induction — delivery interval
1	23	2	Term+2 days	PET	2	3	3500	13 minutes	14 hrs. 43 mins.
2	24	3	Term+10 days	Postmaturity	2	2	4000	5 minutes	24 hrs. (failed)
3	37	6	Term+13 days	Postmaturity	3	1	500	12 minutes	5 hrs. 30 mins.
4	33	6	Term+11 days	Postmaturity	3	2	1000	30 minutes	7 hrs.
5	26	0	Term+14 days	Postmaturity	2	1	1100	10 minutes	9 hrs. 30 mins.
6	27	2	Term−3 days	PET	3	1	1000	15 minutes	7 hrs.
7	32	11	Term+7 days	Postmaturity	2	2	4300	5hrs. 30 mins.	22 hrs. (failed)
8	26	1	Term−7 days	PET	2	3	5000	50 minutes	23 hrs. (failed)
9	22	1	Term+11 days	Postmaturity	1	2	500	15 minutes	6 hrs. 15 mins.
10	27	2	Term+18 days	Postmaturity	1	2	1000	45 minutes	11 hrs. 45 mins.
11	33	2	Term+14 days	Postmaturity	2	1	2000	45 minutes	8 hrs. (failed)
12	20	2	Term+14 days	Postmaturity	2	1	500	40 minutes	5 hrs. 35 mins.
13	24	1	Term+10 days	Postmaturity	1	2	3350	1hr. 40 mins.	20 hrs. 10 mins.
14	19	1	Term+20 days	Postmaturity	2	1	1350	3 hrs.	14 hrs. (failed)
15	29	4	Term−2 days	PET	2	1	500	10 minutes	6 hrs. 5 mins.
16	25	1	Term+12 days	Postmaturity	1	2	1000	1 hr. 20 mins.	9 hrs. 40 mins.
17	30	2	Term−1 day	PET	2	1	4000	50 minutes	22 hrs. 40 mins.

Table II: Details of the Cases of Failures

Case No.	PGF_2 alpha Infusion Rate Minimum ug/min.	Maximum ug/min.	Total Dose	Hours of Infusion	Cx Dilatation achieved (cm.)	Uterine Activity Achieved: Frequency	Duration	Resting Tone	Strength	Subsequent Delivery
2	2	6	1000	24	2	1 in 7	60 secs.	8 cm.	50 cm.	Delivered vaginally with Pitocin Drip in 6 hours
7	2	4	4300	22	4	1 in 6	50 sec.	6 cm.	40 cm.	LSCS for Prolapsed Hand 10 hours later
8	2	4	5000	23	5	Irregular	30-60 sec.	14 cm.	12-80 cm.	Delivered with Pitocin Drip in 3 hours
11	2	2	2000	8	3	1 in 2	45 sec.	13 cm.	80 cm.	Delivered with Pitocin Drip 8 hours later
14	2	2	1350	14	4	1 in 3	60 sec.	15 cm.	70 cm.	Delivered with Pitocin Drip 5 hours later

The patients were first examined by one of us and basal recordings obtained in respect of maternal pulse, blood pressure, respiratory rate, foetal heart rate, cervical length and dilatation and station of the presentating part. Uterine tone and contractions were monitored prior to and during the induction process with a twin-channelled external tocograph.

In all cases, amniotomy was performed prior to the commencement of PGF_2 alpha infusions. Continuous tocographic recordings were made for the first four cases, but it was later felt sufficient to make half-hourly recordings of ten-minute durations each time, complemented by clinical palpations for uterine contractions. All other vital data, such as maternal blood pressure, pulse, foetal heart rate, were taken at half-hourly intervals. Vaginal examination was performed when indicated or at six-hourly intervals to assess progress of labour.

The ampoules of PGF_2 alpha supplied (1,000 ug/ml) were first diluted in 500 ml. of 5% Dextrose to give a concentration of 2 ug/per ml. Infusion of the PGF_2 alpha was then commenced at the rate of 2 ug per minute and gradually stepped up at hourly intervals to 6 ug per minute depending on response.

The third stage of labour in all cases were managed as routinely performed in the unit, comprising intra-muscular injection of syntometrine at crowning of the foetal head and employing controlled cord traction when the uterus was well contracted.

Results

The efficacy of PGF_2 alpha in the induction of labour is shown in Tables I and II. Twelve

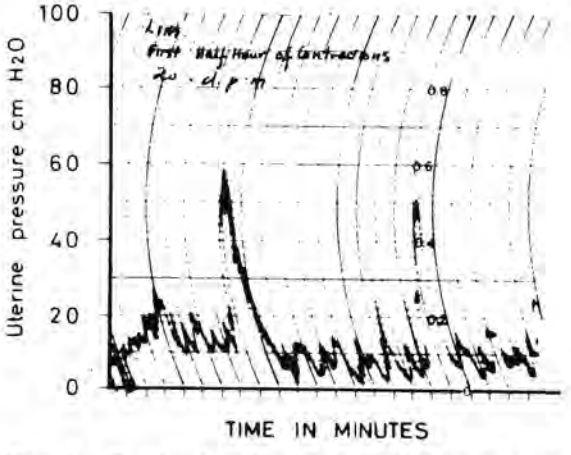

Fig. 1. Typical uterine activity seen within half-hour of infusion

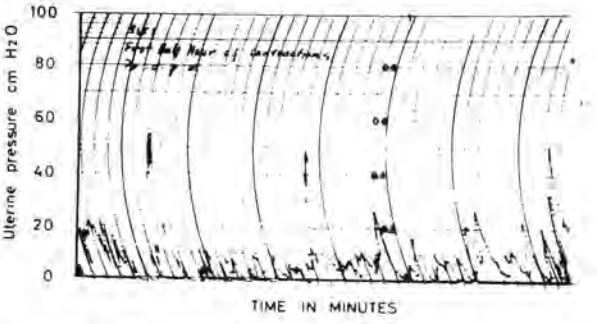

Fig. 2. Another typical recording of early uterine activity.

out of the 17 patients studied were successfully induced, the time taken varied from 5 hours to 24 hours; 9 patients delivering within 12 hours, 1 patient delivering in 15 hours and 2 patients between 20 to 24 hours. All deliveries did not require assistance except for an episiotomy where indicated.

Uterine Activity

Uterine activity was recorded in 8 patients within half an hour of PGF_2 alpha infusion, within one hour in 4 patients, within 2 hours in 2 patients and in $5\frac{1}{2}$ hours in the last patient. Figures 1 and 2 show examples of the type of uterine activity obtained within the first half hour of PGF_2 alpha infusion. There was no correlation between the time taken to initiate uterine contractions and successful induction.

Pattern of uterine contractions

The pattern of uterine contractions, however, differ markedly in the later stage between those who deliver successfully and those who fail. Figure 3 is typical of a case successfully induced, where there was increasing intensity of uterine contractions at regular intervals. In this case, there was also complete uterine relaxation between contraction. Figures 5 and 6 are recordings obtained in a case which failed to deliver under PGF_2 alpha stimulation; in this case it was obvious uterine contractions were ineffectual, occurring at irregular intervals and of varying intensity.

Uterine tone

An increase in uterine tone in-between contractions (Figs, 4, 5 & 6) has been found in 12 of the cases studied. This represents failure of the uterus to relax completely between contractions and the residual pressure recorded varied from 5 to 15 cms of water. During the second stage,

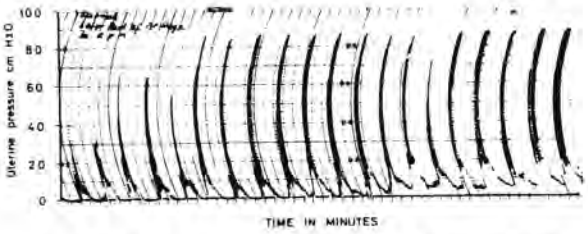

Fig. 3. Regular uterine contractions in a successful case.

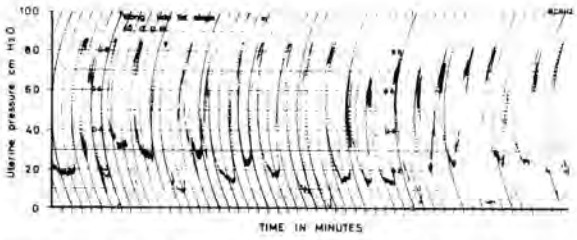

Fig. 4. Regular uterine contractions with raised uterine tone between contractions in a successful case.

uterine tone was maximal at about 20 cms of water. There was no case of summation of uterine tone leading to tetanic contraction observed.

General effects on the Mother and Foetus

The blood pressure, pulse, respiration, micturition and general condition of all the patients monitored remained normal throughout labour. None of the patients had diarrhoea. All babies born had good apgar score of at least 7 and above taken at one and at 5 minutes after delivery. In the post-natal period, they had remained normal. In the 5 patients who desired to breast-feed, there was no failure of lactation encountered. The others had lactation suppressed successfully as required.

Complications

One patient had excessive sweating and complained of hotness (but afebrile) after half an hour of the start of PGF_2 alpha infusion at the rate of 2 ug/minute. This, however, subsided in the following hour when the infusion was persisted and the excessive perspiration did not recur. She was delivered successfully in 14 hours 43 minutes. (Case No. 1)

Another patient began to vomit excessively (six times) when the infusion was continued for 22 hours and a total dose of 5,000 ug was reached, the infusion rate at which time was 6 ug/minute. This case (No. 8) was considered a failure and the PGF_2 alpha infusion stopped as the cervical dilatation was then at 5 cms with poor uterine contractions coming at intervals of about 1 in 4 to 5 minutes, each lasting for about 40 seconds. She, however, delivered vaginally, without complications within the next 6 hours 20 minutes when the infusion was changed over to a syntocinon drip.

There were 2 patients who developed mark phlebitis, at the site of infusion. These occurred after 15 hours and 19 hours of the infusion when total doses of 1100 ug and 2400 ug were infused respectively. No other cases were observed to have developed phlebitis in the puerperium. The phlebitis, however, resolved completely within the next six days with symptomatic treatment.

Post-partum haemorrhage was encountered in two patients. In one case, it occurred three hours after delivery with a blood loss of 600 ml. This was due to uterine relaxation and was effectively treated with intra-muscular injection of syntometrine and a syntocinon drip. No blood transfusion was deemed necessary and the patient recovered and was discharged well on the 5th post-partum day. In another patient, 400 ml. of blood loss occurred 2 hours after delivery also due to uterine relaxation; she was similarly treated, and discharged well.

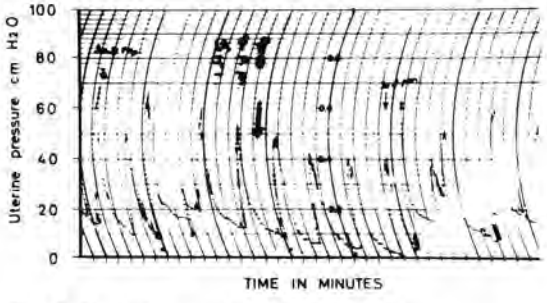

Fig. 5. Irregular contractions with raised uterine tone in an unsuccessful case.

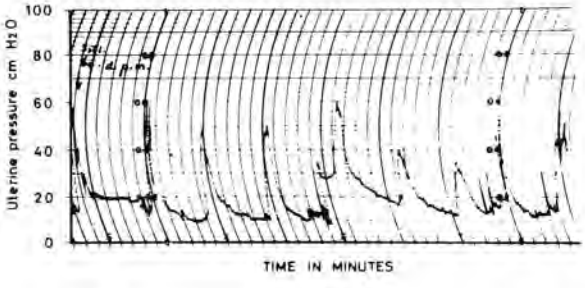

Fig. 6. Same case as in Fig. 5. at a later stage.

Failures

Five patients failed to deliver with the PGF_2 alpha infusion and their details are given in Table II.

In all these patients, uterine activity were found to be erratic, being irregular and weak. Resting tone was also generally high between contractions in the range of 10 to 15 cms of water. Cervical dilatations achieved were less than 5 cms. in all these cases. The duration of the infusion varied from 8 hours to 24 hours. No correlation was found between the failures and gestational age of the pregnancy, parity of the patient and the time taken for the PGF_2 alpha to initiate uterine activity.

It is interesting to note that 4 of these patients were subsequently delivered between 3 hours and 8 hours when the infusion was changed over to syntocinon.

Discussion

Prostaglandin F_2 alpha is effective for the induction of labour at term. The results obtained in our present series of 17 patients, however, did not reflect the high success rate as reported in other clinical trials. Karim (1969) using a continuous intravenous infusion at the rate of 0.05 ug/kg/min. was successful in 33 out of 35 women, who delivered normal babies except when prior foetal death had occurred; Kinoshita et al (1971) were successful in all the 30 women they studied using an infusion rate of PGF_2 alpha ranging from 0.02 - 0.18 ug/kg/min. Lately, Gerald et al (1972) in a comparative study on the efficacy of PGF_2 alpha, PGE_2 and synthetic oxytocin for induction of labour in 100 cases reported an overall success rate of 76 per cent for PGF_2 alpha. They also noted an added advantage of a shortened infusion-delivery interval for PGF_2 alpha.

In all our cases, amniotomy was performed prior to PGF_2 alpha infusion. This is in keeping with the current practice of inducing labour wherein amniotomy is always performed when possible in conjunction with an oxytocin infusion. We felt amniotomy should be performed in our series as it would also facilitate the early recognition of foetal distress by noting meconium staining of liquor and allow foetal-scalp blood sampling to be performed where indicated.

In our study, uterine activity was initiated in a variable period of time varying from 5 mins. to 5 hours 30 mins. No correlation was found between the time taken for the initiation of uterine activity and gestational age of the pregnancy, parity and eventual success of the induction. Embry (1969) using a dose range 2 - 8 ug/min. reported uterine stimulation within 15-30 minutes after the starting of infusion in all his 5 cases. Karim (1969) using a continuous low dose 0.05 ug/kg/min reported that the first uterine contractions were usually recorded within 15-20 minutes after starting the PGF_2 alpha infusion, and this was also the experience of Kinoshita et al (1971) in his series of 30 women. An apparently longer latent interval is found in our series. Whether this could be due to racial and ethnic differences will require to be further explored. This latent interval supports the theory that prostaglandin may be acting on the uterus via a metabolite or by a release of an intermediate substance.

The pattern of uterine contractions in all those who delivered were similar to that occuring in normal labour as obtained in studies by Caldeyro et al (1950).

However, 12 of our cases had increased uterine tone in between contractions, 4 of which occurred in those who failed to deliver with PGF_2 alpha infusion. This high incidence of increased uterine tone is again not found in other clinical trials, where hypertonicity was reported as a rare occurence in occasional cases. Occasional increase in intra-uterine tone is said to occur transiently in normal labour which could be alleviated by altering the position of the patient (Caldeyro-Barcia et al 1960). In our 12 cases, the increase in tone persisted almost throughout the entire course of the induced labour, and this disappeared when the PGF_2 alpha infusion was stopped. This is an unsatisfactory feature as increase in tone between uterine contractions can compromise the well-being of the foetus due to diminished placental perfusion. There was, however, no incidence of any tetanic uterine contractions.

Complications arising from PGF_2 alpha infusions include vomiting, diarrhoea, hyperventilation and severe phlebitis. With the dosage used so far in clinical trials, there has not been any case of tetanic uterine contractions, ruptured uterus, maternal or foetal death. Karim et al (1969b) in their investigation into the safety of PGF_2 alpha infusions at rates of 2 ug/kg/min (40-80 times higher than the dose used for induction of labour) in male and non-pregnant female volunteers reported that there was no significant effect on the heart rate, blood pressure, respiration rate or on the electrocardiogram. Hillier and Embrey (1972) using high doses of PGF_2 alpha (25 ug/min — 200 ug/min) for termination of mid-trimester pregnancy did not find any significant change in blood urea, S.G.O.T., total bilirubin and alkaline phosphatase, but toxic

effects such as vomiting and diarrhoea were common. There appear so far no evidence that PGF_2 alpha affects the blood sugar or creatinine, but these were not studied in our present series.

Chemical phlebitis as seen in our two cases is a serious limiting factor to continual intravenous infusion. The effect manifests itself as an area of erythema and tenderness overlying the infused vein and collateral circulation. The patients complained bitterly about the pain as the infusion was continued and the area affected was variable. However, over a period of six days these resolved completely with symptomatic treatment and no residual thrombosis or venous thickening were observed. This tissue reaction is either an apparent individual sensitivity or perhaps there had been a local extravasation of the infusion. It is not strictly dose related or dependent on the length of time the infusion is carried out. There is increasing evidence that prostaglandins are important agents in the "inflammatory reaction" of tissue trauma and infection. Perhaps local extravasation at the site of infusion is responsible for the phlebitis seen.

Post-partum haemorrhage due to subsequent uterine relaxation was also encountered in two patients. The practice of immediately removing the PGF_2 alpha infusion on delivery could have been contributory.

An interesting feature was noted by us in the 5 cases who failed to deliver. Except for one case who required Caesarean section for dystocia associated with a prolapsed hand, all the other four patients responded readily to syntocinon infusion and delivered normally within 3 to 8 hours. The suggestion is made that PGF_2 alpha could either sensitise or enhance the action of subsequent oxytocin infusion. This pharmacological phenomenon has been recently reported by Gillespie (1972) and the clinical advantage if it could be further explored appears very promising, as it would then allow smaller doses of prostaglandin and/or oxytocin to be used in combination for induction of labour, thereby not only increasing their effectiveness but also perhaps reducing the troublesome side effects of either agent when used alone.

Conclusion

1. A prelimary study of the use of PGF_2 alpha for induction of labour was carried out in 17 cases and there were 5 failures.
2. Minor complications of vomiting, hyperventilation and chemical phlebitis were encountered and there were two cases of post-partum haemorrhage.
3. Our results have shown that though PGF_2 alpha is effective for inducing labour, perhaps greater familiarity with the use of the drug and dosage regime may be required to obtain a success rate comparable to those reported in other clinical trials.
4. The incidental finding of enhancement of uterine response to oxytocin by prior PGF_2 alpha infusion appears to be of promising clinical value.

Acknowledgements

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