Pickles, V. R., and Hall, W. J. (1963). *J. Reprod. Fertil.*, **6**, 315.
Pickles, V. R., Hall, W. J., Best, F. A., and Smith, G. N. (1965). *J. Obstet. Gynaec. Brit. Cwlth*, **72**, 185.
Ramwell, P. W., Shaw, J. E., Douglas, W. W., and Poisner, A. M. (1966). *Nature (Lond.)*, **210**, 273.
Ramwell, P. W., Shaw, J. E., and Kucharski, J. (1965). *Science*, **149**, 1390.
Samuelsson, B. (1963). *J. biol. Chem.*, **238**, 3229.
Samuelsson, B. (1965). *Angew. Chem., int. ed.*, **4**, 410.
Shaw, J. E. (1966). *Fed. Proc.*, **25**, 770.
Smith, P. E. (1932). *Amer. J. Physiol.*, **99**, 345.
Smythe, C. N. (1957). *J. Obstet. Gynaec. Brit. Emp.*, **64**, 59.
Stamm, O., and Monnier, J. (1954). In *Exposition scientifique*, 73, edited by Comité du Congrès international de Gynécologie et d'Obstétrique. Geneva.
Suzor, R., Juret, P., and Poli-Marchetti, P. (1952). *Gynéc. et Obstét.*, **51**, 122.
Williams, E. D., Karim, S. M. M., and Sandler, M. (1968). *Lancet*, **1**, 22.

Response of Pregnant Human Uterus to Prostaglandin-$F_{2\alpha}$-induction of Labour*

S. M. M. KARIM, B.PHARM., M.SC., PH.D.; R. R. TRUSSELL, M.B., CH.M., F.R.C.O.G.
R. C. PATEL, M.B., B.S., M.R.C.O.G.; K. HILLIER, B.SC.

Brit. med. J., 1968, **4**, 621–623

Summary: Labour was successfully induced in 10 women at or near term with prostaglandin $F_{2\alpha}$ infusion. In no case was there an increase in the resting tone of the myometrium, and complete relaxation between contractions was recorded.

Introduction

The identification of four prostaglandins in human amniotic fluid obtained during labour and spontaneous abortion has been reported (Karim, 1966; Karim and Devlin, 1967). Prostaglandin $F_{2\alpha}$ has proved to have a potent uterine-muscle-stimulating action on isolated strips of pregnant human myometrium (Bygdeman, 1964, 1967). Karim (1968) has further shown that prostaglandin $F_{2\alpha}$ appears in the maternal venous blood in variable amount during labour, and that the concentration of this prostaglandin is highest immediately before a uterine contraction.

This work has prompted the suggestion that prostaglandin $F_{2\alpha}$ may play a part in parturition (Karim, 1966, 1968). In order to gain additional evidence for this suggestion, the effect of the intravenous infusion of prostaglandin $F_{2\alpha}$ on the uterine activity of pregnant women at or near term was studied. The investigation was carried out in three parts. (1) A pilot study to investigate the effect of infusion of prostaglandin $F_{2\alpha}$ on the cardiovascular system of five male and one non-pregnant female volunteers was carried out, in view of reports that some prostaglandins have a vasodepressor effect in man (Bergström *et al.*, 1959, 1965; Carlson, 1967). (2) The effect of prostaglandin $F_{2\alpha}$ infusion on the pregnant human uterus in vivo in two women with intrauterine death of the foetus was studied and the foetuses were delivered. (3) Labour was successfully induced in eight women at or near term with prostaglandin $F_{2\alpha}$ infusion. Labour appeared to be normal, and live children were delivered in all cases.

Materials and Methods

Ten women were studied between the 34th and 44th weeks of pregnancy. Uterine activity was measured by recording changes in the amniotic fluid pressure by using an external guard-ring tocodynamometer (Stanley Cox Ltd.) attached to a Honeywell electronic recorder (Smyth, 1957). The tocograph was sited over the upper part of the fundus uteri and held in this position by a strap attached around the patient's waist. The relation of the foetal head to the pelvic brim and the condition of the cervix uteri were recorded before administration of prostaglandin. Spontaneous uterine activity was recorded for at least one hour before the infusion of prostaglandin. Prostaglandin $F_{2\alpha}$ was administered continuously at rates of 0.025–0.05 μg./kg./min. by means of a Palmer infusion pump. The volume of the fluid injected did not exceed 15 ml./hour. Maternal blood pressure and foetal heart rate were measured and recorded every 10 minutes. Progress in labour was assessed by observation of the descent of the foetal head and dilatation of the cervical os.

* Department of Pharmacology and Therapeutics and Obstetrics and Gynaecology, Medical School, Makerere University College, University of East Africa, P.O. Box 7072, Kampala, Uganda.

Results

The results of the first part of the investigation to study the cardiovascular effects of prostaglandin $F_{2\alpha}$ infusion have been separately reported (Karim *et al.*, 1968), and only a brief summary is given here. Within the concentration 0.01–2 μg./kg./min. prostaglandin $F_{2\alpha}$ had no significant effect on the heart rate, systolic and diastolic pressures, respiration rate, or the E.C.G. pattern in the six volunteers studied.

Intrauterine Deaths

Intrauterine death had occurred in two cases (Nos. 1 and 2). One of the babies had died three weeks before induction. The second patient had ruptured her membranes before the induction of labour and the cord had prolapsed. Both were multigravid patients and were not in labour. Infusion of prostaglandin, 0.05 μg./kg./min., initiated uterine contractions after a latent period of 18 and 20 minutes respectively. The contractions were well spaced and showed no tendency to summation. The resting tone returned to normal between contractions. The induction delivery intervals were 10 and 6 hours respectively. Fig. 1 shows the record of uterine activity in Case 1.

Induction of Labour at or near Term

Only one of the series of eight patients was a primigravida (Case 6). She was four weeks post-mature, and a trial of labour was planned for possible minor disproportion. Uterine contractions started 15 minutes after prostaglandin infusion, contractions were good from the outset, and relaxation was excellent. Progress, however, was slow, and in spite of 12 hours of good contractions labour was terminated by caesarean section for disproportion with a mentoposterior presentation. The child weighed 8 lb. 10 oz. (3,910 g.), and showed no evidence of distress either before or after delivery. The remaining

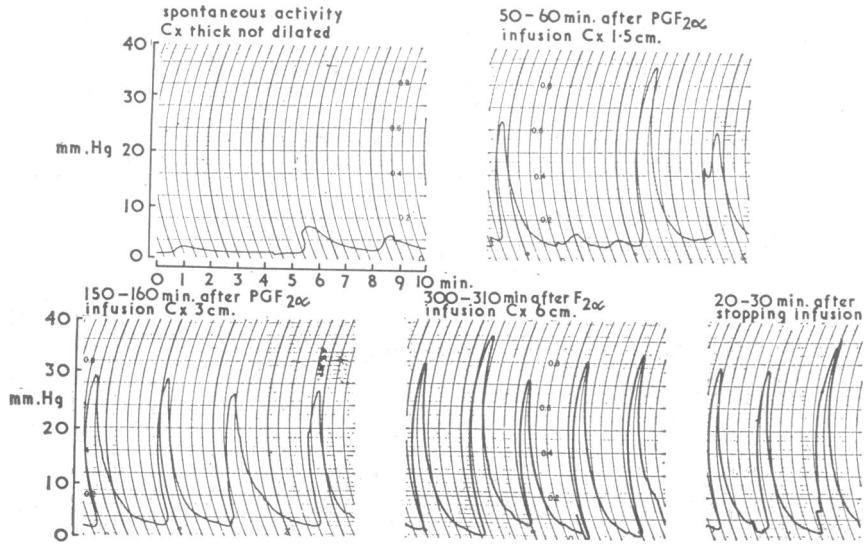

FIG. 1.—Effect of prostaglandin $F_{2\alpha}$ infusion at 0.05 μg./kg./min. on uterine activity of pregnant woman (Case 1) with dead foetus at 36 weeks' gestation. The infusion was stopped after six hours when the cervix had dilated 6 cm. Membranes ruptured four and a half hours after the start of the prostaglandin infusion, and the dead foetus was delivered 10 hours after the infusion was begun. Cx=Cervical dilatation.

seven cases varied from gravida-2 to gravida-11. Induction was carried out for post-maturity in five cases, and for failure to start labour spontaneously 48 hours after the membranes had ruptured in two cases. None was in labour before the infusion of prostaglandin was started. One of these cases had a Shirodka suture in her cervix until the membranes ruptured (Case 5).

In all cases uterine contractions started approximately 20 minutes after the onset of infusion. The average induction/delivery interval was 6 hours 46 minutes. Full details of results are shown in the Table. As with Cases 1 and 2 the pattern of uterine contractility was similar to that of normal labour with complete relaxation between contractions without a tendency to summation. The patients relaxed well between contractions, and did not complain of persistent discomfort or backache. Subjective response to pethidine given intramuscularly was normal and did not appear to modify prostaglandin-induced contractions. Fig. 2 shows a continuous record of uterine activity (Case 3) during the infusion of prostaglandin.

Though several patients had a considerable degree of post-maturity and meconium was present in one (Case 7), careful monitoring of the foetal heart failed to show any irregularity in any of the eight cases studied. Similarly, maternal blood pressure was not affected by prostaglandin infusion. The babies were all born in good condition and gave no anxiety. The third stage was normal and spontaneous in all cases. Post-partum haemorrhage was not seen.

Discussion

This is the first report of the effect of prostaglandin $F_{2\alpha}$ on the intact human uterus. The results of this preliminary investigation have shown that prostaglandin $F_{2\alpha}$ infusion at 0.025–0.05 μg./kg./min. causes the pregnant uterus at or near term to contract in a rhythmic and regular fashion. Many investigations into the effect of various prostaglandins on isolated strips of human pregnant and non-pregnant myometrium have been reported (Bygdeman, 1964, 1967). As with the intact uterus the effect of prostaglandin $F_{2\alpha}$ on isolated strips of uterus is one of stimulation. There is, however, one important difference. On the isolated strips of uterine muscle prostaglandin $F_{2\alpha}$ increases the frequency and amplitude as well as the tone of the muscle, whereas on the intact uterus only increase in the frequency and amplitude was observed in the present study. In no case was there an increase in the resting tone of the myometrium, and complete relaxation between contractions was recorded.

Bygdeman *et al.* (1967) studied the effect of infusing prostaglandin E_1 on the intact myometrium in three mid-pregnant and four term-pregnant women. They reported that, in vivo, prostaglandin E_1 "primarily increased uterine tonus but also increased the amplitude and frequency of contractions" in five out of seven women. In addition to the increase in the tone of the uterus prostaglandin E_1 increased the pulse rate. Bergström *et al.* (1959, 1965) also studied the cardiovascular effects of prostaglandin E_1 infusion in man, and reported that in concentrations a little higher than those used by Bygdeman *et al.* (1967) this prostaglandin increases the heart rate and produces a fall in blood pressure, and that some subjects complained of headache and abdominal cramps. In contrast, prostaglandin $F_{2\alpha}$ up to 2 μg./kg./min., a concentration 40 to 80 times higher than that used successfully in the induction of labour, had no effect on the heart rate, blood pressure, or respiration. None of the subjects complained of any subjective side-effects such as reported for prostaglandin E_1 (Karim *et al.*, 1968). In this respect prostaglandin $F_{2\alpha}$ seems to have a very selective effect on the pregnant myometrium.

The first contraction after starting the infusion of prostaglandin $F_{2\alpha}$ was usually recorded 15 to 20 minutes later. In one woman (Case 9) infusion of prostaglandin was discontinued before labour was established. The uterine activity slowly returned to the preinfusion levels within two or three hours. A latency of 15 minutes and the slow disappearance of the effect for prostaglandin E_1 have been reported by Bygdeman *et al.* (1967). In the remaining nine cases infusion of prosta-

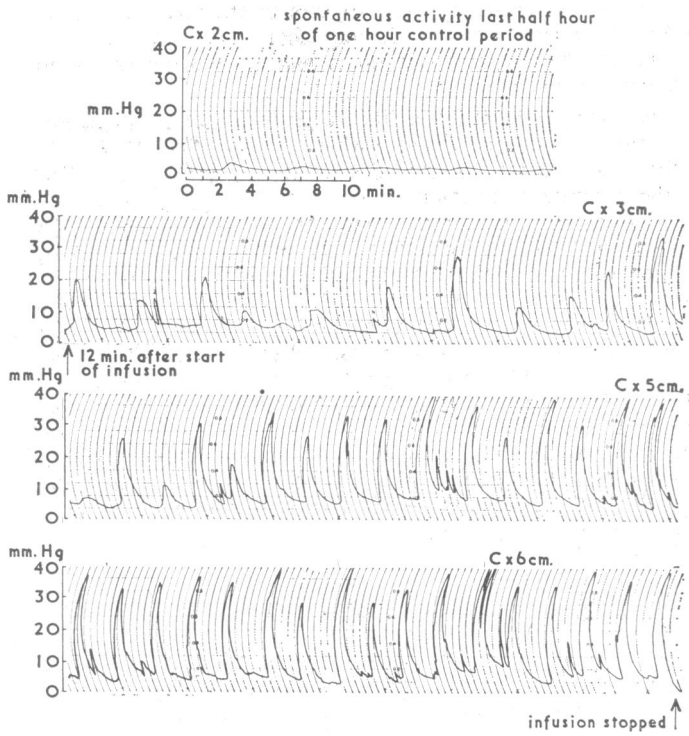

FIG. 2.—Continuous record of the effect of prostaglandin $F_{2\alpha}$ infusion on uterine activity of woman at term (Case 3). The infusion rate for the first 75 minutes was 0.05 μg./kg./min. For the next 60 minutes the infusion rate was 0.025 μg./kg./min. At the end of two and a quarter hours, when the infusion was stopped the cervix had dilated 6 cm. A live baby weighing 8 lb. (3,630 g.) was delivered six and a half hours after starting the prostaglandin infusion.

Results of Infusion of Prostaglandin $F_{2\alpha}$ in Pregnant Women At or Near Term

Case No.	Age	Gravida	Maturity	Indication	Infusion Time in Hours	Cervical Dilatation		Infusion/ Delivery Time	Baby			
						At Start of Infusion	At Finish of Infusion		Weight lb. oz.	Weight g.	Result	Apgar Score
1	22	4	36	I.U.D.	6	Closed	6 cm.	10 hr	5 10	2,550	Stillbirth	—
2	28	6	39	Prolapse of cord + I.U.D.	4	2 cm.	8 cm.	6 hr.	8	3,630	Stillbirth	—
3	28	7	44	Post-maturity	2½	2 cm.	6 cm.	6 hr. 30 min.	8	3,630	Alive	9
4	34	11	43	Post-maturity	3½	2 cm.	8 cm.	4 hr. 55 min.	7	3,175	Alive	10
5	28	9	34	Premature rupture of membranes	2	3 cm.	8 cm.	5 hr. 30 min.	4 10	2,100	Alive	6
6	16	1	44	Post-maturity	3	Closed	5 cm.	12 hr. 30 min.	8 10	3,910	Alive	8
7	31	6	40	Uterine inertia	2½	3 cm.	8 cm.	2 hr. 40 min.	5 13	2,635	Alive	10
8	26	7	43	Post-maturity	1	2 cm.	8 cm.	2 hr.	6 8	2,950	Alive	8
9	21	2	44	Post-maturity	5	Closed	3 cm.	Stopped contracting after 7 hours				9
					1½	2 cm.	6 cm.	7 hr.	7	3,175	Alive	
10	22	2	38	Premature rupture of membranes	3½	2 cm.	6 cm.	8 hr. 20 min.	8 6	3,800	Alive	10

In all cases the rate of infusion did not exceed 0·05 μg/kg./min. In Cases 3 and 10 the rate of infusion was reduced to 0·025 μg./kg/.min. after 1½ hours and 2½ hours respectively. One patient (Case 7) was an Asian; the remaining nine were African Negroes.

glandin $F_{2\alpha}$ was continued until the patient was established in labour as judged by strong regular contractions every two to three minutes and by a cervical dilatation of 5–6 cm.

This preliminary study is too limited for comparison of the results with those of the only other drug available for the induction of labour—namely, oxytocin. A much wider investigation now in progress should enable us to make such a comparison.

The successful induction of labour with prostaglandin $F_{2\alpha}$ and the appearance of this substance in the maternal blood during labour and in close relation to uterine contractions previously reported tend to suggest that it has a physiological function in the process of parturition.

We wish to thank Mr. Raman Khiroya for technical assistance. Our thanks are also due to the medical and nursing staff of the labour ward. The work was supported in part by Makerere University College Council Research Grant No. 410, which is gratefully acknowledged.

Requests for reprints should be addressed to S. M. M. Karim.

REFERENCES

Bergström, S., Carlson, L. A., Ekelund, L.-G., and Orö, L. (1965). *Acta physiol. scand.*, **64**, 332.
Bergström, S., Duner, H., Euler, U. S. von, Pernow, B., and Sjövall, J. (1959). *Acta physiol scand.*, **45**, 145.
Bygdeman, M. (1964). *Acta physiol scand.*, **63**, Suppl. No. 242.
Bygdeman, M. (1967). In *Prostaglandins*, edited by S. Bergström and B. Samuelsson, p. 71. New York.
Bygdeman, M., Kwon, S., and Wiqvist, N. (1967). In *Prostaglandins*, edited by S. Bergström and B. Samuelsson, p. 93. New York.
Carlson, L. A. (1967). In *Prostaglandins*, ed. S. Bergström and B. Samuelsson, p. 123. New York.
Karim, S. M. M. (1966). *J. Obstet. Gynaec. Brit. Cwlth*, **73**, 903.
Karim, S. M. M. (1968). *Brit. med. J.*, **4**, 618.
Karim, S. M. M., and Devlin, Jean (1967). *J. Obstet. Gynaec. Brit. Cwlth*, **74**, 230.
Karim, S. M. M., Somers, K., and Hillier, K. (1968). *Europ. J. Pharmacol.*, accepted for publication.
Smyth, C. N. (1957). *J. Obstet. Gynaec. Brit. Cwlth*, **64**, 59.

Gonorrhoea and the Intrauterine Contraceptive Device

R. STATHAM,* M.B., CH.B.; R. S. MORTON,* M.B.E., F.R.C.P.ED.

Brit. med. J., 1968, **4**, 623–625

Summary: Though pelvic infection in women fitted with an intrauterine device (I.U.C.D.) is reported to be rare, three cases, gonococcal in origin, are presented. These case histories suggest that the presence of an I.U.C.D. increases the severity of gonorrhoea, while removal of the device before antibiotic therapy is probably essential for proper management. The literature and our experience suggest that where pelvic infection and an I.U.C.D. coexist gonorrhoea should be considered a likely diagnosis.

Introduction

Gräfenberg's intrauterine contraceptive device lost favour in the 1920s owing to associated pelvic infection, sometimes fatal. In the last six or seven years new thoughts and materials have brought fresh designs and the I.U.C.D. is again in frequent and increasing use. Its hazards—spontaneous expulsion, pain, bleeding, and particularly pelvic infection—are therefore a matter for investigation.

* Department of Venereology, Royal Hospital, Sheffield.

Lippes (1965), using his I.U.C.D. types A and D, cited infection rates of 0.4 and 0.7 per 100 woman-years respectively. He stated that the few pelvic infections which did occur cleared quickly whether the device was removed or not. A World Health Organization Scientific Group (1966) considered that endometrial curettings, before and after insertion, show little difference in bacterial or cellular content. Such post-insertion changes as did occur were usually slight, subclinical, and reversible. The problem of introducing vaginal or cervical organisms when taking specimens was overcome by Mishell *et al.* (1966). They showed that where an I.U.C.D. had been fitted for a month or more before hysterectomy, transmural samples from such excised uteri were always sterile.

It therefore seems that the modern I.U.C.D. is rarely associated with infection either as a concomitant feature or as a later complication. The following three cases are worthy of note.

Case Reports

Case 1

A married woman aged 21 was prompted to attend hospital by the finding of recently acquired gonorrhoea in her husband, who