Oral Administration of Prostaglandins for the Induction of Labour

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Summary

Prostaglandins E₂ and F₂α administered by mouth were used to induce labour in 100 patients between 35 and 44 weeks of gestation. The usual effective dose of prostaglandin E₂ was 0.5 and of F₂α 5 mg. These were repeated every two hours until labour was established. Induction was successful in 79 out of 80 women treated with oral prostaglandin E₂ and in 16 out of 20 women treated with F₂α.

Introduction

The use of prostaglandins as oxytocics is well established in this hospital. During the past two years over 500 inductions of labour at term have been carried out with prostaglandin E₂ and F₂α, the drugs being administered by continuous intravenous infusion. After oral administration prostaglandins E₂ and F₂α are absorbed into the circulation and produce a stimulant effect on the pregnant human uterus (Karim, 1971). In this paper we report the results of a study on the induction of labour in 100 women at or near term with prostaglandins E₂ or F₂α administered by mouth.

Materials and Methods

The study was carried out in 100 women between the 35th and the 44th week of pregnancy who were in need of induction of labour. The indications for induction are listed in Table I. A prelabour evaluation of inducibility score was made in each patient as described by Friedman *et al.* (1966) (Table II). Uterine activity was measured in all women by recording changes in the intra-amniotic pressure from an 18 gauge epidural catheter (Portex) introduced into the amniotic cavity per abdomen (Caldeyro Barcia and Alvarez, 1952). Spontaneous uterine activity was recorded for at least 30 minutes before the administration of prostaglandins.

Prostaglandins.—A sterile aqueous solution of prostaglandin E₂ containing 0.1 mg/ml or a suspension of prostaglandin F₂α 1 mg/ml in water was used for the study. Each patient received 0.5 mg prostaglandin E₂ or 5 mg prostaglandin F₂α orally. If within two hours the patient started having regular uterine contractions of 40-50 mm Hg amplitude the same dose was repeated every two hours until she was in the active phase of labour with adequate contractions every two to three minutes and a cervical dilatation of 5-6 cm. At this stage the membranes, if still intact, were artificially ruptured. If the first dose of 0.5 mg prostaglandin E₂ or 5 mg prostaglandin F₂α was ineffective in producing adequate uterine contractions then two hours later 1 mg E₂ or 10 mg F₂α was administered. In some women the dose of prostaglandin E₂ was increased to 1.5 mg.

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Results

PROSTAGLANDIN E₂

Induction of labour with oral administration of prostaglandin E₂ was attempted in 80 women at or near term, being successful in 79. Two of these, however, required subsequent caesarean section for disproportion. Previous studies (Karim, 1971) showed that an oral dose of 0.5 mg E₂ stimulated the pregnant uterus at term to contract adequately, and the effect lasted for two to two and a half hours. This was confirmed in the present study; in most of the women (70) 0.5 mg E₂ produced optimum uterine activity lasting for over two hours. Until the patient was in the active phase of labour with the cervix at least 5 cm dilated it was necessary to repeat the oral dose every two hours to maintain optimum uterine activity. The method of delivery in the 80 women is shown in Table III.

Number of doses and Induction-delivery Intervals.—The induction-delivery interval and hence the number of oral doses of prostaglandin E₂ required varied from patient to patient but was related to the prelabour inducibility factor score. In general the smaller the factor score the longer the induction-delivery interval and the higher the number of doses required to effect delivery (Table IV).

Uterine Activity.—In 40 out of 80 women uterine activity was continuously monitored. The type of uterine activity was similar to that induced with intravenous infusion of prostaglandin E₂ and resembled that of normal spontaneous labour (Fig. 1). The time from oral administration to onset of uterine activity usually varied from 5 to 30 minutes.

Side Effects.—No serious side effects could be attributed to

TABLE I—Indications for Induction of Labour

	Primigravida	Multigravida
Postmaturity	25	46
Premature rupture of membranes	5	4
Pre-eclamptic toxæmia	4	7
Breech presentation	1	3
Trial of labour at term	4	1
Total ..	39	61

TABLE II—Prelabour Status Evaluation Scoring System; Vaginal Examination: Cervix

Factor	Score 0	Score 1	Score 2	Score 3	Factor Score
Dilation	Closed	1-2 cm	3-4 cm	5 cm or more	× 2
Effacement	0-30%	40-50%	60-70%	80% or more	
Station	-3	-2	-1, 0	+1, 2	
Consistency	Firm	Medium	Soft	—	
Position	Posterior	Mid. pos.	Anterior	—	
Total score					

TABLE III—Method of Delivery in 80 Women Induced with Oral Prostaglandin E₂

Method of Delivery	Primigravida	Multigravida
Spontaneous vaginal	25	44
Operative vaginal	3	5
Caesarean section*	2	1

*Two caesarean sections for cephalopelvic disproportion and one for failed induction.

TABLE IV—Effect of Prelabour Factor Score of Inducibility on Induction-Delivery Interval and Number of Oral Prostaglandin E₂ Doses Required to Induce Labour in 80 Women

Prelabour Factor Score	Gravida	No. of Women	Average Induction-Delivery Interval	Average No. of Oral Doses
0-3	Primigravida	20	20 hours (for 19 vaginal deliveries)	7
4-7	Primigravida	9	10 hours (for 9 vaginal deliveries)	4
8-12	Primigravida	1	4 hours	1
0-3	Multigravida	30	12 hours (for 29 vaginal deliveries)	5
4-7	Multigravida	17	8 hours	3
8-12	Multigravida	3	3 hours	1

oral prostaglandin administration. Two patients vomited during the drug treatment. Prostaglandin E₂ did not produce uterine hypertonus nor did it have any effect on the maternal blood pressure or heart rate. The fetal heart was also not affected. The Apgar score five minutes after birth was 8 or more in 77 cases, 5-8 in 2 cases, and under 5 in 1 case.

Patient Acceptability and Comfort.—Though most patients found the drug to be bitter and some likened it to the taste of quinine, medical induction of labour by the oral route was more acceptable to them. In the 40 women in whom uterine activity was not monitored the patients' movements were not restricted and it was not necessary to keep them in bed until the uterine contractions became painful.

Caesarean Section and Failed Induction.—There were three cases of caesarean section. In two, both primigravida, labour was successfully induced with prostaglandin E₂ and the cervix was 4 and 5 cm respectively dilated. There was, however, a previously unrecognized minor degree of cephalopelvic disproportion, and lower segment caesarean section was performed. The third case was a gravida-6 patient. Prostaglandin

FIG. 1—Continuous record of effect of orally administered prostaglandin E₂ on pregnant human uterus at term. Patient aged 18, gravida-1, gestation 42 weeks, induction-delivery interval 10 hours. FIG. 2—Continuous record of effect of orally administered prostaglandin F_{2α} on pregnant human uterus at term. Patient aged 24, gravida-2, gestation 40 weeks, induction-delivery interval nine hours.

E₂ in doses of 0.5-1.5 mg given repeatedly for two days failed to produce adequate uterine contraction. On the third day oxytocin was infused at the rate of up to 8 mU/minute for seven hours, but no progress was made and the baby was delivered by caesarean section.

PROSTAGLANDIN F_{2α}

In 20 women induction of labour with oral administration of prostaglandin F_{2α} was attempted, being successful in 16. The dose used was 5 mg in 15 and 10 mg in five. Uterine activity was monitored in five women and was found to be similar to that induced with prostaglandin E₂ (Fig. 2). The five cases of failed induction were successfully induced with oral prostaglandin E₂. The average induction-delivery interval in the 15 successful cases was 23½ hours.

Discussion

The first study describing the use of a prostaglandin for the induction of labour was reported from this medical school in 1968. Prostaglandin F_{2α} was the drug first used (Karim, 1968; Karim *et al.*, 1968). Since that time we have reported studies using prostaglandins E₂, E₁, F_{1α}, and F_{2α} as oxytocics (Karim, 1969a, 1969b, 1970a, 1970b, Karim *et al.*, 1970). Our findings have been mainly repeated and confirmed by others (Beazley *et al.*, 1970; Embrey, 1970). The clinical impression of most obstetricians who have used prostaglandins in this hospital has been that prostaglandin E₂ is superior to prostaglandin F_{2α} or oxytocin for the induction of labour. Recently these impressions have been confirmed in a double-blind clinical trial of the two prostaglandins and oxytocin used for the induction of labour. A total of 300 patients were involved, and the highest success rate was in the prostaglandin E₂ group followed by the prostaglandin F_{2α} group (Karim *et al.*, 1971).

Women with an inducibility factor score in the 0-3 range represent some of the most difficult cases for induction of labour. The cervix is usually long, thick, closed, and uneffaced. Even in these cases, however, prostaglandin E₂ given either intravenously or by mouth was effective.

Successful induction of labour with prostaglandin E₂ or F_{2α} by oral administration is a major advance on previously reported studies. The advantages of the oral route are many, but convenience to the patient and to the medical and nursing staff is the most important. Though we have continuously monitored uterine activity in about 50% of our women this is not essential. The patients can be free to move about during the early stages of oral prostaglandin treatment.

Intravenous infusion of 10% ethyl alcohol completely abolishes uterine contractions induced with prostaglandin E₂ and F_{2α}. Contractions induced with oxytocin are not affected (Karim and Sharma, 1971). Ethyl alcohol has been used in the past as an analgesic during labour. It is also used to inhibit uterine contractions in cases of threatened abortion or premature labour (Fuchs *et al.*, 1967). No doubt ethyl alcohol infusion could be used to overcome hyperstimulation produced by prostaglandins.

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Candida Endocarditis Treated with 5-Fluorocytosine

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Summary

Three patients with endocarditis due to *Candida* species were treated with 5-fluorocytosine. One had endocarditis imposed on senile aortic sclerosis and survived and two had infections on prosthetic valves and died. In the latter two patients chemotherapy failed to eradicate the infection and was associated with marrow depression and possibly hepatic necrosis.

Introduction

Endocarditis caused by *Candida* species carries a very poor prognosis. Kay *et al.* (1968) reviewed 52 cases, of which 46 were fatal. Twenty-four of the patients had been treated with amphotericin B, but only five of these survived, one after surgical replacement of the valve when amphotericin B therapy had failed. The use of amphotericin B is often limited by thrombophlebitis at the sites of intravenous administration and by such toxic effects as fever, vomiting, and azotaemia (Louria *et al.*, 1962). Recent reports of treatment of candida septicaemia and cryptococcal meningitis with the new antifungal agent 5-fluorocytosine (Tassel and Madoff, 1968; Watkins *et al.*, 1969) encouraged us to use this drug for treatment of three patients with candida endocarditis, two of whom had infected prosthetic valves.

Microbiological Methods

Blood specimens were cultured by routine methods with aerobic and anaerobic pour plates and liquid cultures. In patients with prosthetic valves a pour plate was also prepared with glucose peptone agar; and in patients under treatment with antimicrobial agents a hypertonic liquid medium was inoculated for recovery of forms with impaired cell walls (Rosner, 1966; Watanakunakorn *et al.*, 1968).

Minimum inhibitory concentrations (M.I.C.) and serum

concentrations of 5-fluorocytosine were determined by the methods of Shadomy (1969). Species identification of the *Candida* strains and estimation of serum antibodies were carried out by Dr. I. G. Murray (Murray *et al.*, 1969).

Case 1

A 57-year-old man was admitted to hospital with a suspected diagnosis of subacute bacterial endocarditis three months after aortic valve replacement with a Starr Edwards prosthesis. Blood cultures yielded *C. parapsilosis* and he was given amphotericin B 10 mg daily, rising to 60 mg daily one week later. After two weeks' therapy and a total dose of 590 mg he had become afebrile, but because of progressive azotaemia (blood urea 130 mg/100 ml), multiple venous thromboses, and the patient's unwillingness to continue receiving the drug, it was stopped and 5-fluorocytosine was started in a dose of 8 g daily. He at once felt better, he remained afebrile, and there were no further embolic episodes. Microscopical haematuria continued, but his blood urea returned to normal.

He was sent home, very fit, and returned to work. His 5-fluorocytosine dose was reduced to 4.5 g daily because of gastrointestinal symptoms and laboratory evidence of liver damage (serum aspartate aminotransferase 48 units/100 ml; lactate dehydrogenase 500 units/100 ml; bromsulphthalein retention 28% at 45 minutes). His blood count remained normal (platelets 200,000/mm³, leucocytes 4,700/mm³ five weeks later).

Six weeks after discharge, however, he was readmitted with a purpuric rash, and examination of the peripheral blood showed thrombocytopenia and neutropenia. He developed a left hemiparesis and died three weeks later with irreversible marrow failure.

Necropsy Findings.—A large recent subdural haematoma was present. The heart was enlarged (700 g) and showed on adhesive pericarditis. Microscopically, irregular muscle hypertrophy and diffuse fibrosis were found but there was no evidence of recent muscle necrosis, and though significant atheroma was present there was no vascular occlusion. There was a small aneurysm on the aortic suture line. The Starr Edwards prosthesis in the aorta bore very small vegetations on the ventricular aspect in which fungal elements were seen on microscopy. Culture yielded *C. albicans* resistant to 5-fluorocytosine. There were a few mucosal haemorrhages throughout the alimentary tract. The liver was enlarged and congested with large irregular areas of softening. The blood vessels were normal. Microscopically, patchy liver cell necrosis and some collapse of the reticulin framework (largely periportal and midzonal in the lobule) were found. In addition, the Kupffer cells were strongly positive for iron and the liver cells moderately so. The bone marrow was hypoplastic and no megakaryocytes were seen.

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