bolism in vitro, others (Ghilchik *et al.*, 1970) have shown that trimethoprim has an immunosuppressive effect in vivo in mice.

In some earlier trials with combinations of trimethoprim and sulphonamides other than sulphamethoxazole, minor haematological changes were noted (Bushby, 1970), but these were considered not to represent a real therapeutic hazard. Tests showed that the changes were not due to interference with folic acid metabolism and they were ascribed to the sulphonamides. Our results also fail to demonstrate abnormalities of folic acid metabolism but they show that sulphamethoxazole can interfere with cell division whereas sulphadiazine does not do this even at concentrations 400 times greater.

We thank Miss B. Bradley for technical help. We also thank the Herbert E. Dunhill Trust for support.

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Induction of Abortion by Extra-amniotic Administration of Prostaglandins E₂ and F_{2α}

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British Medical Journal, 1972, 3, 146-149

Summary

The use of prostaglandins E₂ and F_{2α}, administered by extra-amniotic instillation, for the induction of abortion was studied in 94 patients in the first and second trimesters of pregnancy. Abortion was successfully induced in 87% of patients within 36 hours and in 94% within 48 hours. The mean abortion time was 22.4 hours. In 60% of patients abortion was complete.

Though the differences were not statistically significant, on average multigravid patients aborted more quickly than primigravidae, while the mean abortion time in PGE₂-treated patients was less than in those receiving PGF_{2α}.

No serious complications occurred. Some side effects were observed. Occasional vomiting was the commonest symptom but the incidence of side effects was lower than with alternative routes of administration. A leucocytosis was often noted but there were no significant instances of infection.

The method has proved a safe and effective means of terminating pregnancies in the second trimester.

Introduction

There is now considerable evidence concerning the significant oxytocic properties of the prostaglandins. Independent studies have shown the potential value of prostaglandins of the E and F_α series (PGE₂ and PGF_{2α}) both as parturigenic agents (Embrey, 1969, 1970a; Beazley *et al.*, 1970; Karim *et al.*, 1970; Roth-Brandel and Adams, 1970) and as abortifacients (Embrey 1970b; Karim and Filshie, 1970a, 1970b).

These studies were restricted initially to the intravenous route of administration but the prolonged intravenous infusions necessary for induction of abortion commonly caused severe side effects—notably diarrhoea and vomiting (especially with

PGF_{2α}) and venous erythema (especially with PGE₂). Attempts to shorten the infusion time by using larger doses were disappointing and resulted only in an intolerable level of side effects (Hillier and Embrey, 1972).

Other routes of administration have, therefore, been explored, and we (Embrey and Hillier, 1971) described an intrauterine (extra-amniotic) technique. The present paper reports an extended trial of the method.

Patients and Methods

One hundred and twenty patients referred for therapeutic abortion were studied. Twenty-six had received some additional form of therapy—for example, intra-amniotic glucose, saline, or intravenous oxytocin—and though their response to treatment and side effects were no different, they have been excluded, leaving for analysis 94 patients who received prostaglandin alone until abortion occurred or up to 36 hours. After 36 hours the case was considered a treatment failure and intravenous oxytocin administered.

Without anaesthesia a Foley catheter, 14-16 French gauge, was introduced through the cervix with the aid of a speculum (and, if necessary, a single-tooth vulsellum), so that the inflatable balloon lay just within the internal os. The balloon volume varied with gestational age from about 20 ml at 8 weeks to 30 ml at 12 weeks and 40 ml at 16 weeks and over.

The extra-amniotic catheter and a small-bore "manometer" connecting tube were filled with saline containing ampicillin (1 mg/ml) and connected to a three-way tap. A syringe inserted into the three-way tap was used for making the prostaglandin injections, and the same tap, if required, was connected to a pressure transducer and Devices two-channel recorder to register intrauterine pressure changes.

Prostaglandin Administration.—Prostaglandin E₂ (PGE₂) or prostaglandin F_{2α} (PGF_{2α}) was used. PGF_{2α} was supplied in a sterile trometamol solution and was diluted to give a 250-μg/ml solution in sterile water or isotonic saline. PGE₂ supplied as a powder was dissolved in 0.5 to 1 ml of absolute alcohol and made up to 100 μg/ml with distilled water or isotonic saline. The latter was then sterilized by cold ultrafiltration and an aliquot taken for culture. On proof of sterility the solution was used within 48 hours. An initial test dose of 50 μg of PGE₂ or 250 μg of PGF_{2α} was given into the extra-amniotic space, taking into account the dead-space volume of the Foley catheter and connector (approximately 4.5 ml). If no adverse effects occurred a

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fully effective dose of 200 µg of PGE₂ or 750 µg of PGF₂α was given. This dose was repeated at intervals of either one or two hours.

Patient Supervision and Laboratory Data.—Blood pressure and pulse were measured two-hourly and temperature and respiration four-hourly. Close observation was maintained throughout the procedure and side effects were carefully recorded. At least three blood samples were taken from each patient, the first before treatment, the second during the strong contractile phase, and the third 12-24 hours after abortion. Analyses of haemoglobin, packed cell volume, white blood count and differential count, platelets, blood urea nitrogen, and serum total bilirubin, alkaline phosphatase, and aspartate aminotransferase were carried out. All urine specimens were examined for albumin, sugar, and acetone. Each patient had a follow-up examination at six weeks.

Results

In this group of 94 patients, 82 pregnancies (87%) were successfully terminated in 36 hours and the mean abortion time was 22.4 hours, with a wide range of 4 to 82 hours (Table I). Seventy per cent. of patients aborted within 24 hours, while 94% aborted within 48 hours.

There were only 11 patients in the first trimester of pregnancy and their average abortion time (21.8 hours) did not differ significantly from the 83 patients in the second trimester (22.5 hours) (Table I).

The results in primigravidae and multigravidae are graphically illustrated in Figs. 1 and 2 respectively, which show for PGE₂ and PGF₂α the percentage of patients aborting per unit of time. Table II shows that in primigravidae termination of pregnancy (within 36 hours) was successful in 86% of cases, while the mean abortion time was 24.6 hours. In comparison, the success rate in multigravidae was 90% and the mean abortion time 19.9 hours. This difference was not statistically significant (Student's *t* test and χ^2 : *P* > 0.05).

TABLE I—Success Rate in First and Second Trimester Patients

	No.	Success* (%)	Mean Abortion Time	Range
1st trimester ..	11	10 (91)	21.8	7.5-66
2nd trimester ..	83	72 (87)	22.5	4-82
Total ..	84	82 (87)	22.4	

* Success within 36 hours.

FIG. 1—Percentage of primigravid patients aborting per six-hour unit of time.

FIG. 2—Percentage of multigravid patients aborting per six-hour unit of time.

Analysis of results obtained separately with PGE₂ and PGF₂α are shown in Tables III and IV. Sixty-one of the 94 patients received PGF₂α (Table III); 41 (67%) aborted within 24 hours and 53 (87%) within 36 hours. The mean total dose (in all cases) was 11,800 µg and the mean abortion time 24.1 hours. Thirty-three patients received PGE₂ (Table IV); 27 (82%) aborted within 24 hours and 29 (88%) within 36 hours. The mean total dose in all patients receiving PGE₂ was 2,300 µg and the mean abortion time 19.5 hours. The mean abortion time was less and the success rate generally higher in multigravidae than primigravidae for both PGE₂ and PGF₂α though the differences were not statistically significant.

Correlation of mean abortion time with parity is shown in Table V. Multigravidae (para 2-4) had an average abortion time

TABLE II—Success Rate in Primigravidae and Multigravidae

	No.	Success* (%)	Mean Abortion Time	Range
Primigravidae ..	45	38 (86)	24.6	8.75-66
Multigravidae ..	49	44 (90)	19.9	4-82
Total ..	94	82 (87)	22.4	

* Success within 36 hours.

TABLE III—Abortion Times of PGF₂α-treated Patients

	No.	Abortion within 24 Hours (%)	Abortion within 36 Hours (%)	Mean Abortion Time	Range
Primigravidae ..	32	21 (66)	27 (84)	25.5	8.75-66
Multigravidae ..	29	20 (69)	26 (90)	22.3	8-68
Total ..	61	41 (67)	53 (87)	24.1	

TABLE IV—Abortion Times of PGE₂-treated Patients

	No.	Abortion within 24 Hours (%)	Abortion within 36 Hours (%)	Mean Abortion Time	Range
Primigravidae ..	13	10 (77)	11 (85)	22.5	10-46
Multigravidae ..	20	17 (85)	18 (90)	17.5	4-82
Total ..	33	27 (82)	29 (88)	19.5	

TABLE V—Effect of Number of Previous Pregnancies on Abortion Time

Number	Gravida	Mean Abortion Time (Hours)
45	1	24.6*
13	2	22.5
14	3	15.8*
12	4	20.1
6	5	13.6
4	>5	37

* Students *t* test shows significant difference (*P* = 0.05).

less than primigravidae and, in the small numbers studied, the abortion time for one group of patients (para 3) was significantly less than that for primigravidae.

DOSE-EFFICACY RELATIONSHIP

Table VI compares the effect of instilling prostaglandins at one-hourly and two-hourly intervals. No significant differences were noted in the mean abortion times or in the abortion success rates, either in primigravidae or in multigravidae. Nor was any difference observed when patients treated with PGE₂ and PGF₂α were considered separately.

TABLE VI—Effect of One-hourly or Two-hourly Instillation of Prostaglandins on Abortion Time

	No.	Instillation	Abortion Time (Hours)	
			Mean*	Range
Primigravidae ..	26	Every hour	24.8	10-66
Primigravidae ..	19	Every 2 hours	24.3	8.75-61
Multigravidae ..	26	Every hour	17.8	4-47.25
Multigravidae ..	23	Every 2 hours	24	8-82

* Differences in means not significant $P = 0.05$ (Students t test).

SIDE EFFECTS

Twenty-five of the 94 patients experienced vomiting and an additional four had nausea. The number of episodes of vomiting ranged from 1 to 16, the latter in one case over a 48-hour period; the average number for the 25 patients who vomited was 2.4 and for all patients 0.2. There was no difference between PGE₂ and PGF₂α treatment in the incidence of vomiting; thus 9 of the 33 patients (27.3%) receiving PGE₂ vomited and 16 of the 61 (26%) receiving PGF₂α. This incidence was not affected by the frequency of administration of prostaglandin. Diarrhoea occurred in two patients and was limited to one episode in each, occurring after the initial instillation.

Forty patients had a pulse rate raised by 10 or more beats per minute. In one an increase of 30 beats per minute occurred and the average increase was 17. An increase in blood pressure was noted in 22 patients. This was never greater than 20 mm Hg systolic or diastolic pressure and the average for the 22 patients was 13 mm Hg. No difference was observed in the incidence or degree of cardiovascular effects between PGE₂ and PGF₂α.

Changes in total white and differential cell counts were noted during treatment. In 30 patients pretreatment values of the white cell count gave a mean of 9,400/mm³ (range 6,300-15,300); just before abortion this rose to 12,200 (range 7,000-17,700) and after abortion to 11,500 (range 6,000-20,900). The mean percentage of neutrophils was 68.4 (range 54-84) before treatment, 78.9 (range 57-91) just before abortion, and 75.6 (range 51-85) after abortion. The mean percentage of lymphocytes was 24.4 (range 10-37) before treatment, 16.1 (range 3-22) just before abortion, and 19.3 (range 11-28) after abortion. The rise in total white cell count, the rise in neutrophils, and the decrease in lymphocytes in both pre-abortion and post-abortion samples were significant when compared with pretreatment levels ($P = 0.05$). There was little change in other measurements, but in 11% of patients acetonuria was noted.

In one patient a $\frac{3}{4}$ -in (1.8-cm) laceration of the cervix was evident after abortion and before evacuation.

The average hospital stay was 3.6 days and the treatment-discharge period 3.4 days.

Blood loss was estimated clinically at abortion and was less than 300 ml in 85 patients and 300-500 ml in nine. Blood transfusions were not required. A haemoglobin level of less than 10 g/100 ml was seen in six patients after abortion. The average pretreatment level of haemoglobin in 80 patients was 12.4 g while after abortion it was 11.9 g/100 ml.

Pyrexia of more than 1°C was observed at abortion in five patients. In two patients a temperature rise greater than 1°C was seen after evacuation and in one the temperature reached 38°C.

The completeness of abortion was initially judged on clinical grounds and evacuation of the uterus performed only if expulsion of the uterine contents was thought to be incomplete. In the latter part of the study evacuation was performed in every patient.

A total of 62 evacuations were performed, 56 immediately post-abortion and six in patients readmitted with blood loss. In 32 patients evacuation was not performed. Clinical assessment was modified in the light of the findings at uterine evacuation and any case with histological evidence of chorionic tissue classified as incomplete. On this strict basis 56 abortions were complete and 38 incomplete.

Seven patients were readmitted to hospital. Six had continued blood loss (one following routine evacuation) but subsequent exploration showed retained products in only two. The seventh patient had mild pyrexia and iliac fossa pain. Ampicillin was prescribed. Pelvic inflammation was not confirmed and symptoms rapidly subsided.

Discussion

Termination of pregnancy with prostaglandins can be effected by using the local (extra-amniotic, intra-amniotic, vaginal) or the systemic route of administration, and the relative merits of these methods have to be compared.

The present study has confirmed our preliminary reports (Embrey and Hillier, 1971; Embrey, 1971) of the relative efficacy and safety of the extra-amniotic technique. Our experience is corroborated, too, by that of Wiquist and Bygdeman (1970) and Wiquist *et al.* (1972) though (in a small group of first trimester patients only) Roberts *et al.* (1971) obtained disappointing results.

That the use of a Foley catheter might contribute something to the efficacy of the method cannot be denied. However, the stimulatory effect of such a catheter is uncertain and slow. In two midtrimester patients a Foley catheter (40-ml capacity) was inserted and uterine activity recorded for 18 hours before prostaglandin medication. No appreciable uterine contractility was observed and no cervical dilatation occurred. Similar observations have been made in earlier studies. Furthermore, in a preliminary study (Embrey and Hillier, 1971) abortion was effectively induced with extra-amniotic prostaglandins when a thin polyethylene catheter was used in place of a Foley catheter, with results similar to the present series.

The method compares favourably with systemic administration. Using intravenous PGE₂ (2-5 µg/min) Embrey (1970b) induced abortion in 90% of cases. However, using a high-dose regimen (PGE₂ 2.5-20 µg/min; PGF₂α 25-200 µg/min) we induced abortion in only 50% of patients (Hillier, 1971; Hillier and Embrey, 1972). Karim and Filshie (1970a, 1970b) obtained a high success rate with low-dose administration (5 µg/min PGE₂; 50 µg/min PGF₂α), whereas Wiquist *et al.* (1971a) found a mean dose of 108 µg/min PGF₂α was required to achieve comparable success.

Despite the notable variations in efficacy reported, systemic therapy was regularly accompanied by severe side effects, particularly vomiting and diarrhoea. Karim and Filshie (1970b) reported a 50% incidence of diarrhoea with PGF₂α, while 0.4-0.6 was the average number of episodes of diarrhoea and vomiting per hour with PGF₂α in the series of Wiquist *et al.* (1971a). Our own experience with PGF₂α in a high-dose regimen was similar and toxic symptoms approached an intolerable level (Hillier and Embrey, 1972). Although these side effects are less pronounced with intravenous PGE₂ infusions, a phlebotic reaction in the infusion arm is correspondingly more troublesome (Embrey and Hillier, 1971).

In contrast, side effects are much less a problem with extra-amniotic administration of prostaglandins and its superiority

seems clear. In our study vomiting occurred in 26% of patients, with an average of 2.4 episodes for each. One patient vomited 16 times in a 48-hour treatment period; otherwise vomiting presented no problem. Slight diarrhoea occurred in only two patients.

In four cases a pronounced reaction was observed after the initial fully effective dose of prostaglandin—severe uterine pain and contraction with vomiting (and in one case diarrhoea)—but was not repeated on subsequent instillations. In each instance this occurred when slight bleeding followed the introduction of the catheter, suggesting a degree of intravascular absorption of the drug.

Comparison of the extra-amniotic route with other local routes of administration is hampered by lack of numbers and variation in results from different centres. Karim and Sharma (1971a) inserted lactose tablets impregnated with $\text{PGF}_{2\alpha}$ 50 mg or PGE_2 20 mg into the vagina every two hours in 45 patients. All successfully aborted; only six vomited and one experienced diarrhoea. These results compare favourably with the extra-amniotic route and suggest that prostaglandins administered vaginally act locally on the uterus. Wiqvist *et al.* (1971b), however, stated that the incidence of side effects with this route is as high as with intravenous infusion, suggesting systemic absorption, and in a limited study, using pessaries containing 50 mg of $\text{PGF}_{2\alpha}$ at two-hourly intervals, we found that the frequency of side effects was greater than with extraamniotic administration. A pessary releasing prostaglandins over a longer period of time would probably reduce side effects but may affect efficacy.

For midtrimester pregnancies the intra-amniotic instillation of prostaglandins offers another alternative. Karim and Sharma (1971b) used single injections of 25 mg of $\text{PGF}_{2\alpha}$ or 5 mg of PGE_2 into the amniotic sac and terminated all of 10 pregnancies. Three of the patients vomited. Similar results were reported by Bygdeman *et al.* (1971) and Wiqvist *et al.* (1971b) but vomiting occurred in 43% and diarrhoea in 16% of their patients. The discrepancy in the incidence of side effects could be due to the fact that the latter investigators used $\text{PGF}_{2\alpha}$ and repeated administration, while Karim and Sharma (1971b) used mainly PGE_2 and single instillations. Our initial studies on 12 patients given $\text{PGF}_{2\alpha}$ 15 mg and a second similar instillation if necessary after 24 hours have been less encouraging; only three aborted within 24 hours and only seven within 36 hours. The incidence and magnitude of side effects, notably greater than with extra-amniotic administration, were comparable with those reported by Wiqvist *et al.* (1971b) and four of our patients had severe symptoms immediately after the injection. The use of PGE_2 rather than $\text{PGF}_{2\alpha}$ might reduce these side effects. However, compared with extra-amniotic administration, the potential dangers are greater and the need for repeat instillations, if confirmed, would seem to add to the risk and detract from the value of the method.

Comparison of the respective efficacies of PGE_2 and $\text{PGF}_{2\alpha}$ (Tables III and IV, Figs. 1 and 2) shows that the percentage of patients aborting within 24 hours was higher with PGE_2 treatment than with $\text{PGF}_{2\alpha}$ (82 compared with 67) whereas at 36 hours the figures were essentially similar for both groups. (It should be noted that patients were not assigned randomly to treatment groups.) Because of this trend the mean abortion time with PGE_2 treatment was less than with $\text{PGF}_{2\alpha}$. In this series the differences between treatments were not statistically

significant ($P = 0.05$) when subjected to χ^2 and Student's t analysis; however, the trend may or may not be confirmed statistically in larger series. Figs. 1 and 2 indicate that if the pregnancy was not terminated within 24–30 hours (10–20% of patients) then abortion was likely to be prolonged, suggesting that tachyphylaxis to the action of prostaglandins develops and that they become less effective with continued administration (Embrey and Hillier, 1971). PGE_2 seems to be relatively less effective than $\text{PGF}_{2\alpha}$ within 24–36 hours, possibly indicating that tachyphylaxis to it develops more readily.

It is disappointing, but not entirely surprising, to record that in this study only 56 (60%) of the abortions were complete. The proportion of incomplete/complete abortions bears little relation to the method of induction used; rather it is related, chiefly, to the duration of gestation, and in spontaneous abortion in the midtrimester the placenta is often retained. To some extent, too, it is influenced, in our experience, by the skill of the attendant, who can often avoid retention of the placenta by a well-conducted third stage.

In the early weeks of pregnancy evacuation of the uterus can be effected simply and speedily by surgical means. In the second trimester, however, the dangers of one-stage evacuation (from haemorrhage, trauma, sepsis) are great, while hysterotomy or intra-amniotic injections of hypertonic saline or glucose carry their own risks (Stallworthy *et al.*, 1971). In these circumstances the extra-amniotic instillation of prostaglandins may provide an effective alternative.

We wish to thank the Upjohn Company for financial support and supplies of prostaglandins. We are also grateful to Staff Nurse Mary Tuckwell for her expert patient care.

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