Intra/extra-amniotic administration of prostaglandin F_2a in fetal death, missed and therapeutic abortions

E. SALAMALEKIS - D. KASSANOS - D. HASSIAKOS
C. CHRELIAS - G. GHRISTODOULAKOS

Summary: Prostaglandin F_2a was used for termination of pregnancy in two groups of patients. The first included eighteen patients with either missed abortion or intrauterine fetal death, and were treated by intrauterine-extraamniotic infusion of 20 mg prostaglandin F_2a. The treatment was successful in 14 patients (mean induction-abortion interval 6.7 hours). Four patients, where the above method failed to induce labor, were given intravenously prostaglandin F_2a or oxytocin simultaneously or separately; the expulsion time ranged from 12 to 48 hours. The second group included twelve patients who underwent a therapeutic abortion following either a diagnosis of fetal congenital abnormality or because of a maternal indication. The therapeutic abortion was performed using prostaglandin F_2a (25-40 mg) via amniocentesis. The treatment was successful in all patients (mean induction-delivery interval 10.6 hours).

Key words: prostaglandin; intra/extra-amniotic; abortion.

INTRODUCTION

Fetal death in utero may occur at any stage of pregnancy. In the first trimester the termination of pregnancy is effected by cervical dilatation and aspiration or curettage. For many years the termination of second trimester pregnancy either in cases of intrauterine death or in viable fetuses, has been mainly performed by vaginal evacuation of the uterus (Keirse 1982, Kajanoja 1983).

Active intervention in pregnancy presented a series of problems, such as excessive bleeding and the formation of synechiae. Induction of labor was difficult since the mid-trimester uterus was unresponsive to oxytocin. The availability of prostaglandin has offered a new look at this clinical problem.

This retrospective study was undertaken to determine the efficacy, side effects and complications of PGF_2a extraamniotic and intramniotic administration in patients with intrauterine fetal death and therapeutic abortions.

MATERIAL AND METHODS

During the period January 1985 - June 1987, 18 patients with a diagnosis of fetal death confirmed by clinical ultrasonographic and hormonal evaluation were treated with PGF_2a via extra-amniotic route. The group consisted of 3 patients in whom intrauterine fetal death had occurred between 25 and 29 weeks of gestation and of 15 patients in whom fetal death occurred between 16 and 22 weeks. There were also 12 patients referred for therapeutic second trimester

2nd Department of Obstetrics and Gynecology of the University of Athens,
"Areteion" Hospital, Athens (Greece)

Table 1. – *Induction of labor with extra-amniotic prostaglandins.*

	Patients no.	Parity	Gestational age (weeks)	Induction-expulsion interval (hours)	
Missed abortion	3	0	16-17	6-8.5 (mean 6.8)	(mean 6.5)
Missed abortion	9	≥2	16-22	3.5-8 (mean 6.2)	
Fetal death	2	2	27-29	6-8 (mean 7)	

abortion due to fetal genetic abnormalities or because of a maternal indication. The gestational age of these patients varied from 17 to 23 weeks.

Following admission all patients had routine laboratory studies including fibrinogen assessment. All had normal profiles. In the cases of extra-amniotic administration, a No. 16 Foley catheter was inserted in the internal cervical os, right up to the fundus, between the amniotic membrane and the uterine wall. The balloon of the catheter was filled with 5 ml physiological saline to prevent it slipping out of the uterus. Following this, 20 mg of Prostaglandin F_2a (Enzaprost-F, Chinoin Budapest) diluted in 50 ml physiological saline were injected at a rate of 5 ml every twenty minutes. In the patients with intrauterine instillation of prostaglandin, amniocentesis was performed after ultrasound evaluation in order to find the optimal site for abdominal puncture. After establishing a free flow of amniotic fluid an amount of 70-100 ml was removed and 25-40 mg of prostaglandin F_2a were slowly injected. At intervals and in order to confirm that the needle remained properly placed a small amount of fluid was withdrawn. After completion of the injection the needle was removed.

RESULTS

Successful induction of labour was achieved in 12 patients with missed abortion (Tab. 1). The mean induction-abortion interval was 6.5 hours (range 3.5 to 8.5 hours). Treatment was successful in two patients with fetal death. The mean induction-delivery interval was 7 hours (range 6 to 8 hours).

In the remaining four patients the method failed. The first of these patients received additionally 10mg of PGF_2a in 1000 cc dextrose 5% solution in a continous drip (Tab. 2). The second one received additionally 15 I.U. oxytocin in 1000 cc dextrose 5% solution also in a continuous drip. The last two patients of this group, were treated initially with PGF_2a and having falled to respond to this regime were treated with oxytocin. The first patient aborted after 12 hours, the second after 13 hours and the last two patients aborted after 16 and 48 hours respectively.

Of the group of patients with intra-amniotic prostaglandins, successful induction of labor was achieved in 7 patients. Four of them were nulliparas and the mean induction expulsion time was 9.7 hours (range 4-20 hours); three were multiparas with mean induction-expulsion time 11 hours (range 7-16 hours) (Tab. 3). In the remaining four patients where the above method failed, 15 IU oxytocin were administered in 1000 cc dextrose 5% solution in a continuous drip. There was also one patient in whom previous extra-amniotic prostaglandin administration failed, who

Table 2. – *Combined treatment (PGF_2a extraamniotic and/or in PGF_2a and/or in oxytocin).*

	Patients no.	Parity	Gestational age (weeks)	Total time till expulsion (hrs)
Extraamniotic+intravenous PGF_2a	1	2	18	12
Extraamniotic PGF_2a+oxytocin	1	3	21	13
Extraamniotic+intravenous PGF_2a +oxytocin	2	>2	20-25	16-48

Table 3. – *Induction of labor with intra-amniotic prostaglandins.*

	Patients no.	Parity	Gestational age (weeks)	Induction-expulsion interval (hours)
Therapeutic abortion	4	0	17-21	4-20 (mean 9.75)
	3	≥2	21-23	7-16 (mean 11)

was treated with additional intra-amniotic administration of 25 mg prostaglandin $F_{2}a$. The mean induction abortion time for the 3 patients was 11.3 hours (range 3-24 hours). One patient delivered after 16 hours and the patient with extra-intra-amniotic administration delivered 18 hours after the intra-amniotic instillation of prostaglandins, (Tab. 4).

In all patients the expulsion of the products of conception was complete. Blood loss was minimal. Curettage was performed in all patients. The side effects in the extrauterine group were gastrointestinal symptoms in two patients, tachycardia and increase in blood pressure in one, and slight increase of temperature in two. The side effect found in the intra-amniotic group was vomiting in three patients.

All patients received antibiotics following initiation of the extra-amniotic infusion. In the intra-amniotic group antibiotics were not administered.

DISCUSSION

Missed abortions and intrauterine fetal death have always been medical and social dilemmas. Various methods of delivery have been advocated. Large studies over the past 40 years have demonstrated that when fetal death occurs labor will begin between 2 to 3 weeks in 77% to 93% of women (Tricomi and Kohl 1957, Kent and Goldstein 1976). When spontaneous labor takes place there are no complications. When the dead fetus is retained for more than 3 to 4 weeks there may be a progressive decline in serum fibrinogen and platelets.

Most authorities still agree that a surgical intervention is contraindicated because of the dangers of infection. The use of high dose intravenous infusion of oxytocin with or without amniotomy has achieved some success (Ursell 1972). However, amniotomy is considered to be potentially dangerous because if the uterus fails to respond to stimulation, there is a high risk of infection (Naismith and Wallace 1974). There is now good evidence of the value of the prostaglandins PGE_2 of PGF_{2a} as agents for induction in patients with missed abortion, fetal death and premature labor. Gordon and Pipe (1975) suggest that prostaglandins given intravenously have some advantage over oxytocin in inducing labor after intrauterine death of the fetus. However, prostaglandins create side effects, which include nausea, vomiting, diarrhoea, hyperthermia, and hypotension, in approximately

Table 4. – *Induction of labor with intra-amniotic prostaglandins and extraamniotic/or oxytocin.*

	Patients no.	Parity	Gestational age (weeks)	Induction-expulsion interval (hours)
Intraamniotic+oxytocin	4	1: 0 3: ≥1	22 20-22	16 3-24 (mean 11.3)
Extraamniotic +intraamniotic	1	1: 0	18	18

60% to 70% of patients (Schulman *et al.* 1979).

Kerekes and Domokos (1977) studied the usefulness of extra-amniotic administration of one single dose of undiluted PGF_2a in 16 patients with missed abortion and fetal death. The mean time of duration of intervention was 5.0 hours. Embrey *et al.* (1974) report successful treatment in 22 patients with missed abortions and fetal death using PGF_2a extra-amniotically with mean time of duration 14.2 and 7.6 hours respectively. However, Scher *et al.* (1980) in their study did not report any difference between extra-amniotic administration of PGF_2a suppositories. The induction-delivery intervals in their study are similar, namely, 8.6 hours for the intrauterine extra-amniotic route and 9.2 hours for the vaginal route.

The present study suggests that by local extra-amniotic administration, good results can be achieved with a low incidence of side effects in the cases of missed abortion. Vomiting occurred only in two patients. Our group of patients, although at great risk carrying a dead fetus showed no evidence of intrauterine or pelvic infection. The pyrexia commonly seen during intravenous infusion did not occur. Compared to the other methods used in the management of fetal death in utero we believe that PGF_2a, administered via extra-amniotic route can offer a high degree of efficacy and safety with few side effects.

The intra-amniotic instillation of prostaglandin F_2a is most effective for termination of pregnancy at 15 to 20 weeks gestation. Several satisfactory dose schedules have been used. Among these are 25 mg repeated after six hours, or a single dose of 40 mg to 50 mg. Reinstallation of 20-40 mg PGF_2a may be required after 24-48 hours. If the primary method fails, an intravenous infusion of oxytocin may be added (Kajanoja, 1983). Karim *et al.* (1972) reported that repeated intra-amniotic administration of 5 mg PGE_2 or 25 mg PGF_2a at ten hour intervals had a success rate over 95%, with a mean induction-abortion interval of 17 hours. Perry *et al.* (1977) reported an induction abortion interval of 19.6 hours in cases with single dose of 40 mg PGF_2a augmented by intravenous oxytocin. In all of our cases the induction abortion interval was 10.6 hours probably, because we withdrew 70 to 100 ml of amniotic fluid thus increasing PGF_2a concentration.

REFERENCES

1) Embrey M. P., Calder A. A., Hillier K.: "Extra-amniotic prostaglandins in the management of intrauterine fetal death, anencephaly hydatidiform mole". *J. Obst. Gyn. Brit. Comm.*, *81*, 47, 1974.
2) Gordon H., Pipe N. G. J.: "Induction of labor after intrauterine fetal death". *Obst. Gyn.*, *45*, 44, 1975.
3) Kajanoja P.: "Induction of abortion by prostaglandins in the second trimester of pregnancy". *Acta Obst. Gyn. Scand.*, *suppl. 113*, 145, 1983.
4) Karim S. M. M., Sharma S. D., Filsie M. B.: "Termination of second trimester pregnancy with intra-amniotic administration of prostaglandines E_2 and F_2a". *J. Reprod. Med.*, *9*, 427, 1972.
5) Keirse M. J.: "Termination of pregnancy after intrauterine death". In: "Second trimester pregnancy termination", edited by Keirse M. J., Gravenhorst J. B., Van-Lith D. A., Embrey M. P., chapter 14, pp. 138-154, London, Leiden University Press, 1982.
6) Kent D. R., Goldstein A. I.: "Prostaglandin E_2 induction of labor for fetal demise". *Obst. Gyn.*, *48*, 475, 1976.
7) Kerekes L., Domokos N.: "Termination of mid-term spontaneous and missed abortions by extra-amniotic injection of a single Prostaglandin F_2a dose". *Therapia Hungarica*, *25* (3), 1, 1977.
8) Naismith W. C. M. K., Wallace B.: "Simultaneous intravenous infusion of prostaglandin E_2 (PGF_2) and oxytocin in the management of intrauterine death of the fetus, missed abortions end hydatidiform mole". *J. Obst. Gyn. Brit. Comm.*, *81*, 146, 1974.

9) Perry G., Siegal B., Held B.: "Second trimester abortion: single dose intra-amniotic injection of prostaglandin F_2a with intravenous oxytocin augmentation". *Prostaglandin, 13*, 987, 1977.
10) Scher J., Jeng D. Y., Moshirpur J., Kereynyi T.: "A comparison between vaginal prostaglandin E_2 suppositories and intrauterine extraamniotic prostaglandins in the management of fetal death in utero". *Am. J. Obst. Gyn., 137*, 769, 1980.
11) Schulman H., Saldana L., Lin C. C., Randolph G.: "Mechanism of failed labor after fetal death and its treatment with prostaglandin E_2". *Am. J. Obst. Gyn., 133*, 742, 1979.
12) Tricomi V., Kohl S. G.: "Fetal death in utero". *Am. J. Obst. Gyn., 74*, 1092, 1957.
13) Ursell W.: "Induction of labor following fetal death". *J. Obst. Gyn. Br. Comm., 79*, 260, 1972.

Address reprint requests to:
Prof. E. SALAMALEKIS M. D.
2nd Department of Obstetrics and Gynecology
Areteion Hospital
76 Queen Sophias Ave.
Athens 11528 - Greece