The Value of Intravenous Prostaglandin E_2 after Intra-uterine Death

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SUMMARY

This study records the use of intravenous prostaglandin E_2 in 23 consecutive cases of intra-uterine fetal death in the third trimester of pregnancy. The results presented are related to the causative factors of intra-uterine death and some suggestions are made in regard to the selection of patients and the method of management in these cases.

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The interval between intra-uterine death of the fetus in the third trimester of pregnancy and its spontaneous expulsion is variable and unpredictable.

There does appear to be some correlation between the cause of fetal death and the onset of spontaneous labour. In cases of abruption of the placenta, the onset of labour is usually rapid. When placental insufficiency or rhesus iso-immunisation is responsible for intra-uterine death of the fetus, the delay before the spontaneous onset of labour may be several weeks or even months, especially if death occurs at an early gestational age. Considering the possible mechanisms related to the onset of labour in these cases, it may be possible to modify the form of management to suit all groups of patients.

The value of prostaglandins in the management of intra-uterine fetal death has been shown in several studies using different routes of administration of the prostaglandin. Given by intravenous infusion, prostaglandin E_2 (PGE_2) and prostaglandin $F_2\alpha$ ($PGF_2\alpha$) have been used successfully in the termination of pregnancy following intra-uterine fetal death.[1-6] Given by extra-amniotic injection, PGE_2 and $PGF_2\alpha$ gave good results with minimal complications in a recent series of 22 cases.[7] Karim has achieved success by using a single dose of intra-amniotic prostaglandin.[8]

All these authors stress the desirability of delivering the fetus soon after the diagnosis of intra-uterine death is made, provided it can be done safely, with the minimum of surgical interference or side-effects. There are three reasons given by different authors for expediting delivery in cases of intra-uterine death. The first reason is the emotional and psychological effect on the patient who knows the fetus is dead, and the resultant loss of morale and confidence of the patient and the difficulty in management from the obstetrician's point of view. Secondly, intra-uterine infection in the presence of a dead fetus may occur, especially if any surgical interference is attempted, and this may rapidly proceed to a potentially lethal situation. Thirdly, there is a risk of blood coagulation disorders. This danger is thought to be greater the longer the fetus is retained *in utero*.[9] O'Driscoll and Lavelle[10] have suggested that this is most likely to develop when the fetus is retained for 4 or more weeks after intra-uterine death.

This study reports the use of intravenous prostaglandin E_2 in 23 consecutive cases of intra-uterine fetal death in the third trimester of pregnancy. The results are presented in terms of causative factors of the intra-uterine death, and some suggestions are made in regard to the selection of patients and the method of management of these cases.

PATIENTS AND METHODS

Twenty-three patients, aged from 21 to 39 years (mean 28 years), were studied. In all cases intra-uterine death occurred between 24 and 40 weeks' gestation (mean 29,8 weeks).

In 7 cases the cause of death was due to placental insufficiency. In 2 of these cases essential hypertension was present. In 1 patient severe pre-eclamptic toxaemia complicated pregnancy at 29 weeks' gestation; in another patient persistent proteinuria was present. In 3 cases no specific cause for the placental insufficiency was found, but in 2 cases the fetus showed evidence of chronic malnutrition at postmortem examination. In 16 cases the cause of death was rhesus iso-immunisation with resultant hydrops foetalis.

The time between the occurrence of intra-uterine death and attempted induction of labour varied from 1 to 19 days (mean 4,6 days).

A solution of prostaglandin E_2 5 μg/ml in 0,9% saline was administered intravenously, using a paediatric infusion set, calibrated to deliver 60 drops/ml.

Uterine activity was monitored continuously, using an external tocograph (Hewlett-Packard). Temperature, blood pressure and pulse rate were recorded every half hour.

The infusion was started using 0,125 ml (0,625 μg)min, and maintained at this rate for 60 minutes. If satisfactory uterine contractions were not obtained, the infusion rate was increased at hourly intervals to 0,5 ml (2,5 μg)/min, and then to 1 ml (5 μg)/min.

The infusion was not continued for more than 24 hours. The membranes were not artificially ruptured during the procedure. Analgesics were prescribed when necessary. After expulsion of the fetus, ergometrine 0,5 mg with oxytocin 5 IU was given by intramuscular injection.

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Date received: 6 May 1974.

RESULTS

In the 7 cases where intra-uterine death was due to placental insufficiency, all the cases were successfully delivered by intravenous PGE_2 infusion at the first attempt (Table I). The average period of gestation at the time of intra-uterine death was 31,6 weeks. The mean intra-uterine death-induction interval was 6,9 days. The average duration of infusion was 9,1 hours, and the mean total dose of PGE_2 required was 0,83 mg.

In the 16 cases where intra-uterine death was due to rhesus iso-immunisation, 13 cases were successfully delivered by intravenous PGE_2 infusion at the first attempt (Table III). The average period of gestation at the time of intra-uterine death was 28,4 weeks, and the mean death-induction interval was 3,4 days. The average duration of infusion was 12,5 hours and the mean total dose of PGE_2 required was 1,42 mg.

The amount of PGE_2 required for successful induction of labour in the group where intra-uterine death was due to rhesus iso-immunisation (Table III), was significantly greater than the amount used in the group where intra-uterine death was related to placental insufficiency ($P<0,02$).

There was no statistically significant difference in the duration of intra-uterine death between the two groups. There was also no significant difference in the period of gestation at which IUD occurred.

Taking parity as previous gestations beyond 28 weeks, there was a significantly higher parity in the rhesus group.

In correlating the dose required, the 3 cases in which induction of labour failed at the first attempt (Table V) (all due to rhesus iso-immunisation) were not included.

TABLE I. SEVEN CASES OF INTRA-UTERINE DEATH DUE TO PLACENTAL INSUFFICIENCY (Intravenous PGE_2 0,625 μg - 5,0 μg/min)

Gestation at IUD (weeks)	Parity	Duration of IUD (days)	Total dose PGE_2 (mg)	Induction/delivery interval (to nearest hour)
33	0 + 0	19	0,55	5
36	0 + 2	1	0,15	5
30	2 + 0	4	0,75	10
29	1 + 0	3	1,25	12
29	2 + 0	7	1,27	9
24	0 + 0	10	0,50	5
40	0 + 0	4	1,32	18
Mean 31,6	0,7	6,9	0,83	9,1

IUD = intra-uterine death.
PGE_2 = prostaglandin E_2.

TABLE II. SIDE-EFFECTS RELATED TO TABLE I (7 CASES)

Pyrexia 37,5°C	1
Tachycardia >120 beats/min	nil
Nausea and/or vomiting	1
Diarrhoea	1
Phlebitis	2

TABLE III. INTRA-UTERINE DEATH DUE TO RHESUS ISO-IMMUNISATION. SUCCESSFUL INDUCTION WITH INTRAVENOUS PGE_2 0,625 μg - 5,0 μg/min AT FIRST ATTEMPT (13 CASES)

Gestation at IUD (weeks)	Parity	Duration of IUD (days)	Total dose PGE_2 (mg)	Induction/delivery interval (to nearest hour)
33	2 + 0	3	2,25	18
24	2 + 0	2	0,99	9
29	4 + 3	3	2,11	22
24	2 + 3	3	0,63	3
31	2 + 0	9	1,38	8
24	2 + 1	5	0,83	12
30	2 + 1	2	1,35	18
24	1 + 0	2	1,50	11
28	3 + 0	6	1,82	10
31	2 + 0	2	1,50	15
28	3 + 0	3	0,93	8
33	1 + 0	2	1,49	10
30	2 + 1	2	1,61	18
Mean 28,4	2,2	3,4	1,42	12,5

TABLE IV. SIDE-EFFECTS RELATED TO TABLE III (13 CASES)

Pyrexia 37,5°C	3
Tachycardia >120 beats/min	1
Nausea and/or vomiting	5
Diarrhoea	3
Phlebitis	5

TABLE V. PGE_2 INDUCTION FAILURE AT FIRST ATTEMPT (3 CASES — ALL RHESUS ISO-IMMUNISATION)

Gestation at IUD (weeks)	Parity	Duration of IUD (days)	Total dose PGE_2 (mg)	Induction/delivery interval (to nearest hour)	Total infusion time (hours)
28	1 + 0	6	3,50	81	29
31	2 + 0	6	1,27	28	14
27	4 + 0	11	2,25	6	42
28,7		7,7	2,34	58,3	28,3

In Table V the 3 cases tabulated were those not delivered with a single infusion of PGE_2. In 2 of these the infusion was discontinued before the 24-hour limit, because progress was slow. When infusion was restarted, delivery was completed within a few hours. In the third case a second infusion lasting $18\frac{1}{2}$ hours was required

24 hours after the initial induction.

The side-effects listed in Tables II and IV relate to Tables I and III respectively. Generally, these side-effects appeared to correlate with the infusion rate and concentration of PGE_2.

There were some individual variations not directly related to infusion rate and solution concentration. No accurate prediction of side-effects could thus be made for a particular case before commencement of the infusion. However, sensitivity to low doses of PGE_2 were uncommon.

Nausea and/or vomiting were the most common side-effects, but were only severe in 2 cases, both requiring high-dose infusion rates. Diarrhoea occurred occasionally, but was only troublesome in 3 cases. Phlebitis occurred frequently, but was only noted in 7 cases before delivery. In 1 case it was necessary to transfer the infusion to a large vein in the opposite arm. Other cases of phlebitis (only recorded in the postnatal notes) were mild and not recorded as significant side-effects.

Pyrexia over 37,5°C occurred in 4 cases, but never exceeded 38,5°C. In one case a temperature rise to 39°C was recorded on 3 successive attempts to infuse PGE_2 on different occasions. An infusion rate of 0,625 μg/min produced a marked elevation of temperature within 15 minutes, and attempts at PGE_2 induction were abandoned. This case has not been included as no true trial of prostaglandin could be carried out. The intra-uterine death in this case was related to rhesus iso-immunisation.

Postpartum haemorrhage (over 600 ml of blood) was not recorded in any of the cases.

Evacuation of the uterus after delivery was necessary in 2 cases. One of these was complicated by a secondary postpartum haemorrhage.

There were no cases of puerperal infection and no coagulation disorders occurred.

DISCUSSION

The value of prostaglandin in the management of intra-uterine death is now well established.[1-8] This is supported by the results obtained in our series of 23 cases. However, the most suitable method of administration of the prostaglandin has not yet been established.

The disadvantages of intravenous prostaglandins are the systemic side-effects which arise, and which increase in severity as the infusion concentration and rate are increased. The dose level necessary to obtain the desired effect may therefore not be practical or acceptable in cases where concentration and dose are high. The advantage of this method is that labour can be accurately monitored and the dose level regulated to prevent hyper-stimulation or to diminish side-effects.

The advantage of extra-amniotic or intra-amniotic prostaglandin is that at the dose levels referred to[7,8] the systemic side-effects were fewer when comparable results were obtained. The disadvantages of these methods are that they require some form of surgical intervention with a high risk of infection, especially if the induction should fail or if infection is introduced at the time of induction. In addition, the dose may be more difficult to regulate, and in the third trimester this may be dangerous if the fetus lies in a transverse or abnormal position, which may be difficult to diagnose clinically after intra-uterine death.

The important factor which has emerged in this series is that the amount of prostaglandin necessary to induce labour in cases of intra-uterine death does depend on the cause of death. In this series only 2 groups, placental insufficiency and rhesus iso-immunisation, were compared and they showed a statistically significant difference in dose level of PGE_2 required.

In view of this, and if side-effects are related to the dose of prostaglandin, then it would suggest that cases should be selected for the most suitable method of induction of labour after intra-uterine death. When the cause of death is related to placental insufficiency, significantly smaller doses of prostaglandins can achieve delivery of the fetus and an intravenous route will be the method of choice. However, in cases of rhesus iso-immunisation, where larger doses of prostaglandin are required, with correspondingly more severe side-effects, the extra-amniotic route may be preferable.

As more knowledge is gained of the factors involved in the initiation of labour in these cases, selection of methods and patients may become more clear. Until such time it is suggested that when termination of pregnancy after intra-uterine death is considered, selection of the method used should be modified in relation to the individual as well as to the cause of death of the fetus.

In this series only placental insufficiency and rhesus disease are discussed, and more work will be required to determine the methods of choice in groups where fetal death is due to other factors.

We should like to thank Upjohn Limited, for the supply of prostaglandin E_2 and their assistance in this project.

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