Extra-amniotic prostaglandin E_2 and intravenous oxytocin in termination of mid-trimester pregnancy and in the management of missed abortion and hydatiform mole

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INTRODUCTION

SURVEY OF the literature on pregnancy termination has shown that many attempts have been made by a number of workers to establish a safe and efficient method for termination of pregnancy in the mid-trimester. Each technique has its advantages and disadvantages. The long established method of abdominal hysterotomy is best avoided if possible because it leaves uterine scars and carries the risk of anaesthesia and surgery (Stallworthy et al 1971).

Medicated utus pastes were used for abortion induction in Germany in the early 1930's. The pastes are injected through the cervix and they cause direct ovum destruction and served as a stimulant for uterine contractions by causing endometrial necrosis and inflammatory reaction in the myometrium. This method is favourably reported by Lachelin and Burgess (1968) who were successful in inducing abortions in all of 182 cases. Pyrexia requiring antibiotic therapy developed in only 7 per cent of patients. However, complications such as generalised haemolysis, pulmonary embolism, septicaemia and local sepsis have been reported. In view of the recent reports of ruptured uterus and maternal deaths, this method is almost out of favour now. (Confidential enquiry into maternal death 1966 – 1969).

Intra-amniotic injection of hypertonic saline has been preferred by many workers. (Menzies et al 1968, Gillmer 1971). The solution could either be injected abdominally if the uterine size corresponds to 16 weeks gestation or more, or transvaginally if it is less than 16 weeks. However, the induction-abortion interval in most published series is not very satisfactory. Rutlner (1969) had an interval of 26.5 hours whilst Gillmer et al (1971) had an interval of 39.7 hours. When the use of oxytocin is avoided altogether, the injection-abortion interval exceeded 72 hours in 11 to 14 per cent of patients, (Schulman et al 1971). Wagner et al (1962) reported that 6 percent of his cases failed to abort within 6 days, and Schulman et al (1971) found that 4.8 percent did not abort within one week. Watgatsuma (1965) reported serious complications following saline abortions in Japan. In 1948, there were 13 maternal deaths reported among 6,611 saline abortions and in 1950, after reports of another 12 maternal deaths, the technique was largely abandoned in Japan. Among the complications reported by him was fever in 14 percent, haemorrhage 3.7 percent. Other complications reported in other series include coagulation defects, water intoxication and hypernatraemia which could lead to fatal outcome.

Intra-amniotic injection of hypertonic glucose has been used with success by Lewis et al (1969). But severe infections and maternal deaths from the injection has been reported after the use of intra-amniotic glucose solution to induce labour, (Peel 1962, McDonald et al 1965) and it has not achieved much popularity in Britain. Greenhalf and Diggory (1971) described the use of intra-amniotic urea. They were successful in all the 10 cases of their series and comment that inadvertent intravenous or intra-peritoneal injection of the material would be less likely to have harmful effects than hypertonic saline or glucose. However, the induction-abortion interval

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was long, varying from 30 to 96 hours. Craft and Musa (1971) reported considerable shortening of injection-abortion interval if concommitent intravenous infusion of oxytocin was used.

Several methods of mechanical stimulation of the uterus are currently popular among the Japanese. Menabe (1969) in his review of the use of Bougie and Metreurynter as mechanical abortifacients in Japan, found that 90 percent of 597 cases aborted with the use of Bougie, whilst 85.7 percent of 953 patients aborted with the use of metreurynter. Most of the patients required oxytocin stimulation and fever is very commonly encountered. The safety and efficacy of these methods are not clearly demonstrated.

Prostaglandins are currently very popular and many reports have appeared recently demonstrating its safety and efficacy for mid-trimester terminations (Wiqvist et al 1970, Embrey 1970, Karim et al 1970). It was Kurzrok and Lieb (1930) who first reported that fresh human seminal fluid fluid when applied to isolated strips of human uterus produce either relaxation or contraction. A few years later, Goldblatt in England (1933, 1935) and Van Euler in Sweden (1934, 1935) independently observed and studied the stimulating activity of the human seminal fluid on smooth muscles. Von Euler (1935) thought that the active factor was secreted from the prostate gland and named it "prostaglandin".

The chemical structure of prostaglandins was later elucidated by Bergstrom et al (1949). Naturally occurring prostaglandins have 20 carbon atoms and the basic carbon skeleton from which they are derived is named "Prostanoic acid". Differences occurring in the structure of 5 carbon ring are used to subdivide the prostaglandins into four naturally occurring groups called E, F, A and B. Prostaglandins can now be synthesized in appreciable quantities from fatty acids and homogenates of the vesicular glands of sheep and other animals (Bergstrom et al 1964, 1967, Van Dorp et al 1964, 1967).

The oxytocic activity of prostaglandins on the pregnant uterus has now been well-established. The potential of prostaglandins as safe and efficient abortifacient has been vastly explored by many workers using various routes of administration and using different dosage schedules. Karim et al (1972) in a study of 139 women receiving intravenous infusion of PGE_2 for mid-trimester abortions found no significant change in the haematological, biochemical and hormonal status. Clotting factors and renal function were not altered.

Five routes of administration have now been tested, including intravenous, intra-uterine extra-amniotic, intravaginal, intra-amniotic and oral. Each route has its advantages and limitations. Excessive gastro-intestinal symptoms seem to be the most common side-effects. Karim and Filshie (1970) infused intravenously 52 patients with 5 ug./min. of PGE_2 and successfully induced abortion in 50. Vomiting and diarrhoea occurred in 14 of the patients. Hillier et al (1972) using higher dose levels (up to 20 ug./min.) encountered a much higher degree of side-effects with a lower success rate. Intravenous infusion of PGE_2 is also complicated by venous erythema and plebitis. The intravenous route of administration is limited by a higher incidence of side-effects.

Intra-vaginal route of prostaglandin administration has been attempted to facilitate the ease of administration, to decrease side-effects and frequency of administration by a slow continuous release. Karim et al (1971) reported one failure out of 20 cases using PGE_2 with a mean abortion time of 18 hours. Side-effects were negligible. Brenner et al (1972) however reported higher incidence of vomiting, diarrhoea, fever and pain using $PGF_2\alpha$ solutions, tablets and suppositories. Wentz et al (1973) have confirmed these results reporting 95 percent incidence of abortion and 90 percent incidence of side-effects.

The oral route has been limited by unpalatibility of the medication and by its induction of severe gastro-intestinal side-effects (Karim et al 1970). However, Labhsetwar (1972) has reported on the development of an orally active prostaglandin analogue (ICI 74,205) which demonstrated anti-fertility properties in hamsters without gastro-intestinal stimulation. This agent is not available for clinical trials as yet.

The intra-amniotic route has been studied by Karim and Sharma (1971). By using single dose of PGE_2 and $PGF_2\alpha$, they effectively induced abortion in 11 patients with a mean abortion time of 11.4 hours. MacKenzie et al (1974) studied 82 patients using 4 different dosage schedules of intra-amniotic $PGF_2\alpha$ and PGE_2. The most successful results were obtained in 32 patients receiving 2 injections of PGE_2 at 6 hour interval. Thirty-one patients aborted within 24 hours with a mean abortion time of 12.6 hours. However, 22 out of 32 patients had vomiting and 3 had diarrhoea. The intra-amniotic route of prostaglandin administration appears to be promising. However, one should be cautious in the light of recent reports regarding untoward side-effects including sepsis, cervical laceration and cardio-pulmonary reaction (Wentz et al 1973).

The intra-uterine extra-amniotic route of administration was first reported by Wiqvist and Bygdeman (1970) using a thin transcervica lpolyethylene catheter. They reported abortion in 88 percent of 70 women with low incidence of side-effects. Embrey et al (1972) using Foley Catheter gauge 14 – 16 with inflatable balloon into which 20 – 40 ml. sterile water was injected, reported good results. Of the 33 patients given PGE_2 extra-amniotically, 88 percent aborted within 36 hours with the mean abortion time of 19.5 hours and 27.3 percent had vomiting. Several workers including Strickler (1972) and Bruce (1972) had questioned the possible role of the inflated Foley balloon as a mechanical uterine stimulator.

The pharmacologic phenomenon of enhancement and potentiation of uterine response towards combined administration of prostaglandin and oxytocin was initially studied in vitro by Brummer (1971). It was Gillespie (1972) who applied this phenomenon clinically to induce mid-trimester abortions with the aim of reducing the dosage of prostaglandins and hence minimize the incidence of troublesome side-effects. However, he only obtained partial success and in more than half the cases, the induction-abortion interval was greater than 24 hours. Embrey et al (1973) reported induction-abortion interval could be significantly shortened with the concommitant use of extra-amniotic prostaglandins and intravenous oxytocin. The author's experience with concommitant use of extra-amniotic prostaglandin E_2 and intravenous oxytocin in 16 cases of mid-trimester abortions, one missed abortion and one hydatiform mole was described.

MATERIALS AND METHOD

Selection of patients

Eighteen patients were admitted for mid-trimester termination of pregnancy, of which 15 were induced because of psychosocial reasons, one because of rubella infection which was confirmed by rising titre of rubella antibody; of the remaining two cases, one had a missed abortion and the other an hydatiform mole. The diagnosis of missed abortion and hydatiform mole was confirmed by ultrasonic scanning.

All but one patient were under 30 years of age and three patients were under 15 years. Twelve patients were primigravidae, four were gravida two and two patients were gravida four. All but one pregnancy were between 15 to 19 weeks. The odd one was a case of missed abortion which was 27 weeks by dates but the uterine fundus corresponded to 16 weeks' gestation size.

Method of study

The method employed was similar to the one described by Embrey et al (1972). Prostaglandins E_2 were supplied by Upjohn Company. A small size Foley Catheter (French gauge 12 or 14) was inserted transcervically into the extra-amniotic space under aseptic condition. Sixteen patients had the Foley catheters inserted in the ward with premedication of Pethidine 100 mg. intramuscularly half-hour prior to insertion while two patients who were extremely apprehensive had the insertion done under general anaesthesia. The catheter balloon was inflated with 20 ml. of sterile water in all cases. In three patients, the catheters were expelled before abortion was achieved and reinsertion was done.

Dosage of Prostaglandin E_2 and intravenous oxytocin

The patients were divided into two groups according to the dosage regime of PGE_2 employed. In Group 1, which consisted of the first 12 cases, the dosage recommended by the manufacturer (Upjohn) was used. An initial dose of 200 ug. of PGE_2 was injected into the catheter after filling the dead space in the catheter with 5 ml. of sterile normal saline. Subsequent instillations of 100 – 200 ug. of PGE_2 were done hourly. If abortion was not achieved by 12 hours, intravenous oxytocin was commenced starting with 32 mU./min. and doubling the dose every half hour. Three patients in this group did not require intravenous oxytocin. The mean total dosage of PGE_2 required per patient was 2.02 mg.

In Group 2 which consisted of six patients, an initial dose of 500 ug. of PGE_2 was injected extra-amniotically. Subsequent instillations with 500 ug. of PGE_2 were done at four, six and eight hours respectively. If abortion was not achieved by six hours, intravenous infusion of oxytocin was commenced with a dose of 80 units at a steady rate of 30 drops per minute. All six patients in this group required the intravenous infusion of oxytocin. The mean total dosage of PGE_2 required per patient was 2.0 mg.

All the patients were carefully monitored by experienced medical and nursing staff. The blood pressure and pulse were recorded hourly while the temperature was charted every four hours. Analgesia with 100 mg. of Pethidine was given intramuscularly if the patient was distressed with pain.

RESULTS

Induction-abortion interval (Table I and II)

Abortion was achieved in all patients. Fifteen out of 18 patients (72%) aborted within 24 hours. The mean induction abortion interval was 17.4 hours.

Table I

Details of Patients – Group I

Case No.	Age (yrs)	Gravida	Gestation (weeks)	Total Dose PGEt (mg.)	Induction – Abortion interval (hours)
1	15	1	16	1.6	5.5
2	19	1	17	4.0	42.5
3	15	1	18	2.0	34.0
4	14	1	18	1.2	14.5
5	16	1	17	2.0	27.5
6	31	2	18	1.2	7.5
7	19	1	15	4.0	42.5
8	19	1	19	2.0	11.5
9	19	1	16	2.0	17.5
10	17	1	16	2.0	24.0
11	28	5	16	2.0	14.0
12	20	1	16	3.0	53.0

Table II

Details of Patients – Group II

Case No.	Age (yrs)	Gravida	Indication	Gestation (week)	Total Dose PGEt (mg.)	Induction – Abortion interval (hours)
13	14	1	legal abortion	19	2.0	11.5
14	25	2	legal abortion	16	2.0	13.0
15	27	2	hydatidiform mole	17	2.0	8.5
16	26	2	missed abortion	27	2.0	9.0
17	17	1	legal abortion	17	2.0	12.0
18	17	5	legal abortion	17	2.0	11.5

The mean abortion time for the Group 1 patients was 24.8 hours. However, the interval was much shorter in Group 2 patients, 11.0 hours.

Only 5 out of 18 patients had complete abortions (27%). Thirteen patients needed evacuation of uterus under general anaesthesia. One patient, Case 6, was initially diagnosed as complete abortion, but was readmitted one week later for evacuation of the uterus under general anaesthesia. Also included was a case of hydatiform mole who had uterine evacuation by vacuum aspiration.

Side-effects (Table III)

Nausea and/or vomiting occurred in 5 patients (27%). None of the patients vomited more than three times. All patients except one vomited once only. One patient had diarrhoea (6%) which stopped spontaneously. Two patients (12%) experienced transient attack of dizziness which lasted not more than ten minutes. Only one patient (6%) experienced severe uterine cramp immediately after extra-amniotic instillation of 500 ug. of PGE_2. This was however relieved by 100 mg. of intra-muscular injection of Pethidine.

Table III: Side-Effects

Side Effects	No. of Patients		Total
	Group I	Group II	
1. Vomiting	4	1	5
2. Diarrhoea	1	0	1
3. Dizziness	1	1	2
4. Uterine Cramps	0	1	1

Complications – Haemorrhage, Sepsis and Cervical Laceration (Table IV)

The average blood loss during abortion varied between 200 – 300 ml. However, 4 patients (22%) had blood loss of about 500 ml. or more. Only one patient needed transfusion of two units of blood.

Table IV: Complications

Complications	No. of Patients		Total
	Group I	Group II	
1. Haemorrhage (500 ml. or more)	1	3	4
2. Sepsis	0	0	0
3. Cervical laceration	0	0	0

No cases of pelvic sepsis or cervical laceration were noted in this small series of 18 cases.

DISCUSSION

The safety and efficacy of extra-amniotic prostaglandin E_2 with concommitant intravenous infusion of Syntocinon for inducing mid-trimester abortion, missed abortion and hydatiform mole, is demonstrated in this series of 18 cases. It is the author's impression that the use of larger doses of extra-amniotic prostaglandins E_2 administered at four-hourly intervals is more efficient in inducing abortions. The induction-abortion intervals of patients in Group 2 was only 11.0 hours as compared to 24.8 hours in Group 1 patients. MacKenzie et al (1975) claimed that administration of large extra-amniotic doses of PGE_2 produces marked reactions – that is transient severe uterine pain, pallour, nausea, shivering and hypotension – and has proved insufficiently reliable for inducing abortion within 24 hours. Radiological studies have suggested that possible reasons for these results could be rapid absorption of prostaglandins into the systematic circulation and leakage through the cervix uteri (Wiqvist et al 1972, MacKenzie and Hillier 1974, Read et al 1974). Leakage of prostaglandins and decidual absorption could be reduced by incorporating the PGE_2 in aqueous viscous gel. MacKenzie et al (1975) reported favourable results in 24 patients who received a single injection of 1.5 mg. PGE_2 incorporated into an aqueous viscous gel, with the mean abortion time of 13.5 hours. Vomiting occurred in 7 patients, transient severe uterine cramps, pallour, nausea and shivering occurred in only one patient immediately after injection. Complete abortion occurred in 20 patients.

The disadvantage of intermittent extra-amniotic administration of PGE_2 is the need of a doctor to be present at hourly interval to give the injections. Miller et al (1972) reported favourable results by administering PGE_2 continuously using a Palmer infusion pump. Midwinter et al (1973) found that the optimum dose of extra-amniotic PGE_2 given by continuous infusion for the termination of 10 to 20 weeks' pregnancies seemed to be from 66.5 to 133.5 ug. per hour.

The majority of the patients in this series (73%) required evacuation of uterus under general anaesthesia because of retained bits or whole placenta. It is disappointing to note that the abortion was complete in only 27 percent of the patients. The percentage of complete abortion varies a great deal in different series of study, Embrey et al (1972) 60 percent, Miller et al (1972) 48 percent and Gillmer et al (1971) 70 percent. Embrey et al (1972) claimed that 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 to some extent, it is influenced by the skill of the attendant, who can often avoid retention of the placenta by a well-conducted third stage.

The incidence of vomiting (27%) and diarrhoea (6%) is comparable to other reported series. Embrey et al (1972) had 27.3 percent incidence of vomiting and 6 percent of diarrhoea with PGE_2. The occurrance of gastro-intestinal side-effects is related to the stimulatory action of prostaglandins on the smooth muscles of gastro-intestinal tract. Two patients (12%) experienced transient attack of dizziness and pallour. This is probably due to rapid decidual absorption of PGE_2 into the systemic circulation.

Another advantage of this abortion technique as opposed to hysterotomy and intra-amniotic injection of hypertonic saline or glucose, is that it carries very little risk of haemorrhage, sepsis and trauma. It is interesting to note that the average blood loss is between 200 – 300 ml. Only one patient (6%) needed blood transfusion because of blood loss of 800 ml. Despite the introduction of a foreign body into the uterus, namely the Foley Catheter, the incidence of sepsis following abortion is almost

negligible. No case of sepsis is reported from this small series. Embrey et al (1972) reported an incidence of 6 percent of pyrexia of more than 1°C. However, he reported no case of sepsis which required antibiotic treatment.

No cases of ruptured cervix were noted in this series. However, four cases were reported following prostaglandin-induced abortion by Shearman et al (1972), Bradley-Watson et al (1973) and Wentz et al (1973). Kojanoja (1974) analysed 5 cases of cervical rupture in 412 prostaglandin abortions (incidence of 2.7%). All the 5 patients were young primigravidae treated with intra-amniotic $PGF_{2\alpha}$. No cervical rupture was observed in patients treated with PGE_2. The association between cervical rupture and the use of $PGF_{2\alpha}$ may be related to the fact that strips of pregnant cervix contract with $PGF_{2\alpha}$ hile they are relaxed by PGE_2 (Hillier and Karim 1970, Najak 1970). Infusion of oxytocin in high doses has been found to reduce the induction-abortion interval in intra-amniotic $PGF_{2\alpha}$-abortions (Seppala et al 1972). The concommitant administration of oxytocin reduces the amount of PG required to bring about abortion but it is interesting to note that in his series, this combination treatment was used in 4 out of 5 patients with cervical rupture.

CONCLUSION

Concommitant administration of extra-amniotic prostaglandin E_2 and intravenous oxytocin is shown to be a safe and efficient way of inducing mid-trimester abortion, missed abortion and hydatiform mole. It is currently the most popular method and is associated with minimum side-effects and complications. The use of high dosage of PGE_2 extra-amniotically may be effective in producing short induction-abortion interval. However, further study is required to show that large doses are not associated with a higher incidence of side effects.

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