Single Extra-amniotic Injection of Prostaglandin E_2 in Viscous Gel to Induce Mid-trimester Abortion

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Summary

In a preliminary study a single extra-amniotic injection of 1·5 mg of prostaglandin E_2 incorporated into an aqueous viscous gel was given to 24 patients to induce mid-trimester abortion. Twenty patients aborted within 24 hours, and the mean induction-abortion interval (± S.E. of mean) was 13·5 ± 1·5 hours. Vomiting occurred in seven patients, and transient severe uterine cramps, pallor, nausea, and shivering occurred in one patient immediately after the injection. Complete abortion occurred in 20 patients. A delay in the time taken to abort seemed to be associated with an immediate and rapid rise in uterine tone after the injection which required prompt analgesia; this probably reflected rapid decidual absorption and dissolution of the prostaglandins away from their site of action. The degree of distention of the catheter-retaining balloon did not influence abortion times.

Introduction

The clinical usefulness of prostaglandins for the induction of mid-trimester abortion has been established. Current studies aim at improving the efficacy of techniques and simplifying the method of drug administration.

The intra-amniotic route of administration has been modified to induce abortion within 24 hours by giving two injections with an interval of six hours between them (MacKenzie *et al.*, 1974) or by a single injection combining the prostaglandin with a hypertonic solution (Bowen-Simpkins, 1973; Craft, 1973). Current techniques of extra-amniotic administration (Embrey *et al.*, 1972; Miller *et al.*, 1972; Lippert and Modly, 1973; Midwinter *et al.*, 1973) involve intermittent injections or slow continuous infusions throughout the abortion procedure. Recent experience with 15S-15-methyl prostaglandin $F_2\chi$ in a viscous medium as a single extra-amniotic injection has given good results (Wiqvist *et al.*, 1974).

We report here the results of induction of abortion by a single extra-amniotic injection of prostaglandin E_2 (PGE_2) in a viscous aqueous hydroxyethylmethylcellulose gel.

Patients and Methods

Twenty-four patients (12 primigravidae, 12 multiparae) with a mean gestation of 15·1 weeks were studied: 23 patients were in the second trimester (range 12-26 weeks) and one was at eight weeks gestation.

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With aseptic precautions a 16 French gauge Foley catheter was passed transcervically into the extra-amniotic space, and to observe the effect the retaining balloon size might have on abortion times it was distended with either 5 ml or 30 ml sterile water.

A 6% viscous solution of powdered hydroxyethylmethylcellulose (Tylose MH300, Hoechst) was prepared by adding the granules gradually to water in a glass container and thoroughly mixing to produce an evenly dissolved solution which was subsequently autoclaved at 112°C for 15 minutes. Immediately before administration 1·5 mg of PGE_2 (Prostin E_2, Upjohn) in 1·5 ml ethanol was added to 7·5 ml of the viscous solution to give a final concentration of 5% hydroxyethylmethylcellulose. This was shaken vigorously to give a homogenous solution. The resultant 9 ml of viscous PGE_2 gel was injected as a single dose into the extra-amniotic space. In most cases intrauterine pressure recordings were made linking the extra-amniotic catheter to a pressure transducer connected to a pen recorder (Devices).

All patients were monitored by staff experienced in prostaglandin therapy. In 23 cases analgesia was provided when necessary by 15 mg papaveretum (Omnopon), and 5 mg perphenazine was used if required as an antiemetic. One patient, a primigravida at 26 weeks gestation with fulminating pre-eclampsia, was given an epidural block.

A conservative policy towards postabortion evacuation was followed—patients who aborted completely, as judged by inspection of the products of conception passed and by bimanual pelvic examination, were not surgically explored. Patients who failed to abort within 24 hours received an intravenous infusion of oxytocin at a constant rate of 100 mU/min.

Results

There were no serious complications. In all 24 patients pregnancy was terminated within 29 hours, with a mean abortion time (± S.E. of mean) of 13·5 ± 1·5 hours. The cumulative abortion rate is shown in fig. 1. The mean abortion time for primigravidae was 15·75 ± 2·35 hours and for multigravidae 11·3 ± 1·8 hours. Twenty patients (83·3%) aborted within 24 hours having received only the initial injection. Patients with the Foley balloon distended with 30 ml of sterile water (nine primigravidae,

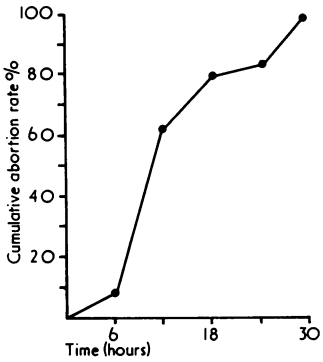

FIG. 1—Cumulative abortion rate in 24 patients receiving a single extra-amniotic injection of 1·5 mg PGE_2 in aqueous viscous gel. At 24 hours an intravenous infusion of oxytocin at 100 mU/min was begun.

six multiparae) had a mean abortion time of 13·2 ± 1·8 hours compared with 14·0 ± 2·8 hours when the balloon was distended with only 5 ml water, but this difference was not statistically significant. No correlation was apparent between gestation, parity, and abortion time.

Side effects observed were vomiting in seven cases (29·1%) and a reaction (pallor, shivering, marked uterine pain, nausea) in one patient immediately after the injection, which persisted for 45 minutes. In one patient mild hypertension was recorded for which no treatment was necessary. No hypotension or pyrexia over 38°C occurred. Twenty patients (83·3%) aborted completely and did not require subsequent curettage. Three patients lost more than 250 ml of blood at abortion, in one of whom the loss amounted to an estimated 1000 ml and a transfusion was needed.

An average of two analgesic injections per patient were given for control of painful contractions. Two patients needed no analgesia during the abortion period and two further patients needed four injections. In seven patients the initial injection of papaveretum was necessary within 60 minutes of the extra-amniotic prostaglandin instillation.

Analysis of the extra-amniotic tocographic records of 17 patients showed that there were two different forms of initial response by the uterus to the injected prostaglandin (fig. 2). In 13 patients a gradual rise in intrauterine pressure (fig. 2, lower trace) was observed and in two analgesia was required within 60 minutes; all aborted within 24 hours. In the remaining four an immediate and rapid increase in tone occurred over three minutes (fig. 2, upper trace), each required analgesia within 60 minutes, and three took longer than 24 hours to abort.

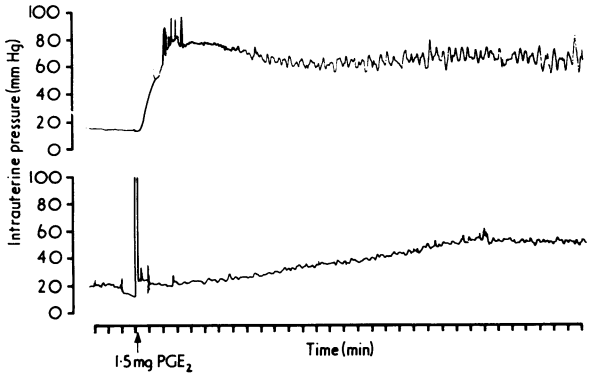

FIG. 2—Upper trace: immediate and rapid rise in intrauterine pressure after extra-amniotic injection of 1·5 mg of PGE_2 gel in four patients associated with need for early analgesia and delayed abortion times. Lower trace: gradual rise in intrauterine pressure after extra-amniotic injection of 1·5 mg PGE_2 gel in 13 patients associated with delayed need for analgesia and abortion within 24 hours.

Discussion

At 12-15 weeks gestation, when amniocentesis is technically difficult and vaginal aspiration is hazardous, the extra-amniotic administration of prostaglandin is the method of choice in terminating pregnancy. With gestations greater than 15 weeks intra- or extra-amniotic administration of prostaglandins may be used.

Intra-amniotic administration of PGE_2 alone (MacKenzie *et al.*, 1974) or in combination with a hypertonic solution of urea (Bowen-Simpkins, 1973; Craft, 1973) or glucose (I. Z. MacKenzie, M. P. Embrey, K. Hillier, unpublished data) has been shown reliably to induce abortion in 24 hours in almost 100% of cases and to require only one or two intra-amniotic injections. Previously reported series of extra-amniotic prostaglandin administration have used intermittent injections, usually at two-hourly intervals, until abortion (Embrey *et al.*, 1972) or a slow continuous infusion (Miller *et al.*, 1972; Midwinter *et al.*, 1973) of prostaglandins into the extra-amniotic space. The mean abortion times and success rates within 24 hours in these series are similar to those we obtained.

The administration of large extra-amniotic doses of PGE_2 (500 μg, 1000 μg, or 1500 μg in 3 ml or 9 ml sterile water) in this unit (I. Z. MacKenzie, M. P. Embrey, K. Hillier, unpublished data) has often caused marked reactions—that is, transient severe uterine pain, pallor, 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 the rapid absorption of prostaglandins into the systemic circulation and leakage through the cervix uteri (Wiqvist *et al.*, 1972; MacKenzie and Hillier, 1974; Read *et al.*, 1974). A conscious attempt to reduce and delay leakage of prostaglandins and decidual absorption by incorporating them in a viscous gel, thus minimizing the necessity for frequent administrations, has produced good results and has decreased the incidence of postinjection reaction. Some leakage through the cervix was observed, however, in each of five cases when the viscous prostaglandin gel was coloured with dye though the volume of leakage was not quantified.

The two basic patterns of uterine pressure response to injection of prostaglandins may be indicative of the speed of initial drug absorption. Thus, an immediate rise in uterine tone suggests a rapid absorption and systemic dissolution of of drug necessitating early analgesia and resulting in long abortion times. A gradual increase in intrauterine tone probably indicates delayed absorption of prostaglandin, prolonging contact with the decidua and resulting in a shorter abortion time.

Lippert and Modley (1973) reported the use of PGE_2 in a 2·5% hydroxyethylmethylcellulose-based solution for mid-trimester abortion. Intermittent extra-amniotic injections of 1·25 mg PGE_2 in 0·5-ml volumes were administered using a thin polythene catheter at two- to three-hourly intervals until abortion in 14 patients. A mean abortion time of 11 hours 35 minutes was achieved with a mean total amount of 4·6 mg PGE_2 (range 2·5-7·5 mg). Compared with the present series the incidence of side effects was similar but in all their patients the placenta was spontaneously expelled; the percentage in which expulsion was complete is not clear. Bearing in mind the similarity of results the reasons for the very marked difference in the total amount of PGE_2 injected between their patients and our patients are not obvious. The smaller volume and lower viscosity of the solution injected and the different catheter used may have influenced prostaglandin absorption and cervical leakage. It is also possible that repeated injections in their series were unnecessary. The very large doses of prostaglandins used did not result in overwhelming side effects, however.

The comparatively short duration of action of the natural prostaglandins has been overcome by incorporating them into a high viscosity solution. The efficacy of the natural prostaglandin in this vehicle is comparable to that of the prostaglandin $F_2\alpha$ analogue, 15S 15-methyl $PGF_2\alpha$, in a viscous solution of 30% dextran 70 (Hyskon Pharmacia, Sweden) (Wiqvist *et al.*, 1974). The analogue does not seem to have any advantages over the natural compound PGE_2.

Further improvement in efficacy might result from the use of larger doses of PGE_2 but this preliminary study already shows the feasibility of a single extra-amniotic injection technique. For the patient this has clear advantages; it both avoids recourse to amniocentesis and obviates the need for repeated extra-amniotic injections while reducing the amount of nursing care required.

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Electrocardiographic Abnormalities Associated with Raised Intracranial Pressure

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Summary

Serial electrocardiographic (E.C.G.) recordings were taken in seven patients suffering from intracranial conditions, for which their intracranial pressure was directly and continuously monitored with a Konigsberg extradural transducer. The E.C.G. changes observed in patients with raised intracranial pressure were prominent U waves, ST-T segment changes, notched T waves, and shortening and prolongation of Q-T intervals. Two patients with normal intracranial pressure showed no E.C.G. abnormalities. The results not only confirm the association between central nervous system diseases and E.C.G. abnormalities but also establish a relationship between E.C.G. abnormalities and changing intracranial pressure.

Introduction

Electrocardiographic (E.C.G.) abnormalities are known to occur in a variety of central nervous system lesions like subarachnoid haemorrhage, cerebrovascular accidents, head trauma, intracranial space-occupying lesions, meningitis, etc. (Byer *et al.*, 1947; Burch *et al.*, 1954; Schuster, 1960; Finkelstein and Nigaglioni, 1961; Hersch, 1961, 1964; Fentz and Gormsen, 1962; Goldman, 1967; Abildskov *et al.*, 1970; Cruickshank and Dwyer, 1974). Bradycardia, extrasystoles, abnormal ST-T deflection, tall, deeply inverted, or notched T waves, prominent U waves, and prolonged Q-T intervals have been described. The possible mechanism responsible for these changes has been discussed by Abildskov *et al.* (1970), who concluded that the E.C.G. abnormalities may be mediated by abnormalities of the sympathetic tone to the heart. Raised intracranial pressure as judged by isolated readings of cerebrospinal fluid pressure at lumbar puncture was thought not to be responsible for E.C.G. abnormalities (Hersch, 1964). It is now well established that intracranial pressure is not a static phenomenon and its dynamics can only be assessed by measuring it directly and continuously (Lundberg, 1960; Langfitt, 1969).

We describe here seven patients in whom serial E.C.G.s were recorded while their intracranial pressure was continuously monitored by placing a pressure-sensitive transducer in the extradural space as part of a different study. To the best of our knowledge similar studies have not been reported in the literature.

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Patients and Methods

Seven patients with varying intracranial conditions and with no evidence of cardiovascular disease were assessed. The intracranial pressure was continuously monitored using a Konigsberg extradural transducer. Whenever the intracranial pressure changed 12-lead E.C.G.s were recorded. Serum electrolytes and blood gases were also assessed in all these patients. Intracranial pressure was measured in millimetres of mercury (1 mm Hg = 0·13332 kPa) and 15 mm Hg was considered as the upper limit of normal. The intracranial pressure was above normal limits in five patients. A combination of dexamethasone and glycerol was used to lower the intracranial pressure to within normal limits and E.C.G. abnormalities were recorded several times as the intracranial pressure changed. In the remaining two patients who were admitted with head injuries the intracranial pressure was within normal limits throughout and they did not show any E.C.G. abnormalities.

Case Reports

Case 1.—A 47-year-old man was admitted with a head injury. He had had no previous cardiac disability. His blood pressure remained between 130 and 150 mm Hg systolic and between 80 and 90 mm Hg diastolic throughout the period of illness. The intracranial pressure went up to 45 mm Hg, and with the changing pressure the E.C.G. abnormalities recorded were tachycardia, changes in ST-T segment, U waves, changes in voltage, and shortening of Q-T interval (fig. 1).

Case 2.—A man aged 50 years with benign intracranial hypertension and with no cardiac disability was admitted for investigations and treatment of raised intracranial pressure. His blood pressure throughout was around 140/85 mm Hg. The E.C.G. abnormalities with changing intracranial pressure were tachycardia, S-T depression, U waves, and shortening of Q-T interval as shown in the table.

Case 3.—A 43-year-old man was admitted with right temporal lobe tumour (glioma). His blood pressure throughout was 130/90 mm Hg. With changing intracranial pressure the E.C.G. abnormalities noted in him were a slightly raised S-T segment, U waves, and prolongation of Q-T intervals as shown in the table.

Case 4.—A 45-year-old woman was admitted with recurrent tumour of right cerebral hemisphere (glioma). Her systolic blood pressure varied between 145 and 160 mm Hg and her diastolic pressure was 90 mm Hg. The intracranial pressure at one time had gone up to 65 mm Hg. Bradycardia, progressive T-wave inversion, U waves, and shortening of the Q-T interval were the abnormalities recorded in her E.C.G.s (fig. 2).

Case 5.—A 21-year-old man was admitted with a head injury. He had sustained extensive cerebral contusion and his intracranial