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Limitations of a Single Extra-Amniotic Injection of Prostaglandins in Viscous Gel to Induce Midtrimester Abortion

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Abstract. A dose-response study using PGE_2 in a viscous gel has been undertaken for induction of midtrimester abortion. A direct relationship was found between the time to abortion and the dose administered. However, even using PGE_2 3.5 mg induced uterine activity was noticed to subside in a significant number of women after approximately 6 h. For routine management it is suggested that PGE_2 3.5 mg be injected and followed by repeat doses 6 h later with removal of the injecting catheter on each occasion.

The principle of suspending a relatively high dose of natural prostaglandins (PGE_2, $PGF_{2\alpha}$) in a viscous gel allowing prolonged activity and improved efficacy compared to that afforded by intermittent or continuous solution administration, was first described by *Lippert and Modly* (1). However, their technique of injecting the gel extra-amniotically every 2–3 h was followed by a report from the United Kingdom describing the efficacy of using a single injection (2).

MacKenzie and Embrey (3) subsequently reported that 75% of patients aborted within 24 h when PGE_2 1.5 mg was injected as a single dose. No significant difference in the time to abortion was noted in those in whom the injection catheter was removed immediately following injection compared with those in whom it was left *in situ*. Those patients who did not abort by 24 h required additional uterine stimulation to complete the process.

The study reported here was undertaken to evaluate a dose-response relationship for a single PGE_2 injection in gel and to establish a satisfactory regime for routine clinical use.

Methods

52 patients who requested termination of pregnancy in the midtrimester under the Abortion Act (1967) acted as the study group. Informed consent was obtained after explanation of the details of the procedure to be performed.

The mean age was 21.8 years with a range from 13 to 43. 10 out of 52 patients were 16 years old or younger. The mean gestation was 18.3 weeks with a range of 13–26 weeks. Of the 7 patients who underwent abortion after 20 weeks, 2 had serious fetal central nervous system malformations, 1 had suffered sexual assault and the 4 others had profound social problems. 81% were single, 15% were married and 4% were either separated or divorced. 65% had never previously been pregnant and 23% had had a previous therapeutic abortion.

Technique of PGE_2 Gel Insertion

This was performed without anaesthesia with the patient placed in the lithotomy position on an ordinary gynaecological examination couch having adjustable leg supports. After preparing the vagina with proper aseptic precautions a sterile speculum was passed and a disposable 12 gauge soft urethral catheter attached to a sterile plastic syringe containing the gel, was then inserted 5–10 cm through the cervical os. The catheter was stabilized by sponge holding forceps being applied at the appropriate distance from the tip of the catheter.

Preparation of PGE_2 Gel

A 4% solution of methyl-hydroxyethyl cellulose powder (Tylose MH300p, Hoechst) was prepared with normal saline and sterilized by autoclaving. PGE_2 solution in normal saline was introduced into the gel aseptically under a laminar flow air cabinet in the hospital pharmacy. 10 ml of gel containing a variable dose of PGE_2 was injected slowly and then the dead space of the catheter cleared through and the catheter removed. After instillation patients returned to the ward to be mobile or recumbent depending on their clinical response.

Dose Schedule

Initially a dose of 1.5–2.0 mg was used with the intention, after 24 h, of either administering the same dose again or using intravenous oxytocin if abortion had not occurred by then or the abortion process at that time was not progressing satisfactorily. The small size of the group studied with this dose schedule was influenced by the limited success experienced. Subsequently increased doses were used of either 2.5–3.0 or 3.5–4.0 mg.

It became apparent at an early stage that the therapeutic effects of the prostaglandin administered in the gel tended to reduce after 6–8 h in those situations where the abortion process had been insufficiently primed to continue to expulsion, and hence with the higher dose schedules used repeat extra-amniotic injections of the same dosage were administered before 24 h.

Table I. Dose-response effects of extra-amniotic PGE_2 in gel

PGE_2 dose mg	Number in group	Abortion with initial dose alone		Mean time to abortion of 'successes' h.min	Additional PGs and/or oxytocin required	Mean time to abortion of 'failures' h.min (range)	Mean overall time to abortion in relation to initial PGE_2 dose h.min (range)
		n	%				
1.5–2.0	9	4	44	12.20	5	31.43 (17.55–52.00)	23.06 (7.31–52.00)
2.5–3.0	20	10	50	10.16	10	27.23 (15.25–48.25)	18.49 (5.15–48.25)
3.5–4.0	23	9	39	7.45	14	18.29 (8.00–30.15)	14.17 (3.50–30.15)

Table II. Side effects of extra-amniotic PGE_2 in gel

PGE_2 dose mg	Number in group	Adverse reaction to PGE_2	Pyrexia >380 °C	Vomiting	Diarrhoea	Haemorrhage requiring transfusion	Cervical laceration	Readmission to hospital
1.5–2.0	9	0	2	1	0	0	0	1
2.5–3.0	20	0	3	13	0	0	0	1
3.5–4.0	23	3	2	9	2	2	0	0

Assessment of Efficacy

The relative success of inducing the abortion with a single injection was evaluated in relation to the initial dose given and the need for other abortifacients. Similarly the mean time to abortion of 'successes' following one application and the overall time to abortion was considered in relation to the initial dose administered. Side effects of vomiting, diarrhoea and pyrexia and the incidence of cervical laceration were also noted.

Results

The dose-response effects are seen in table I. There was little increase in the success rate of inducing abortion with a single injection between the dose ranges used. However, as initial doses increased to a maximum of 3.5–4.0 mg the mean time to abortion of those succeeding with one application reduced from 12 h 20 min to 7 h 45 min. An awareness of the limited duration of activity of the gel in patients in whom the abortion process was not continuing prompted repeated usage of the same strength at earlier time intervals. This is reflected in a reduction in the mean time to abortion for those 'failing to abort' following one application and in the overall time to abortion. The mean time to abortion of 14 h 17 min using the highest dose schedule given as a single or repeated injection is comparable to other extra-amniotic prostaglandin techniques.

The side effects are seen in table II. 3 patients receiving the highest dosage had an adverse reaction which was of short duration and without serious consequences. This was thought to be due to systemic PGE_2 absorption occurring when the catheter had been initially inserted too far into the uterus with possible injection in close proximity to the placenta. It is now our policy to insert the catheter only 5 cm through the cervical os as determined by positioning the sponge holder on the catheter at this site before injection. Each episode occurred with the 4-mg dosage and was manifested by some of the following features, i.e. feeling of coldness and shivering, tightness in the chest, flushing of the cheeks, and abdominal pain due to a contracted uterus.

13% had a pyrexia of 38 °C or more on at least one occasion but this was not associated with intrauterine sepsis and was not obviously dose-dependent. Vomiting occurred in 44% with 1.9 mean episodes. However, 26% of the patients who vomited did so only just before or at abortion. Diarrhoea occurred in only 2 patients each of whom received PGE_2 4 mg. 2 patients required blood transfusion for haemorrhage following curettage and 2 patients were readmitted with irregular bleeding and required subsequent curettage. No patient had a cervical laceration. Some signs of fetal life were occasionally observed but this feature was not specifically assessed quantitatively from the outset of the study.

Discussion

MacKenzie et al. (2) commended the technique of a single extra-amniotic injection of prostaglandins in gel on account of the method being less involved and less likely to be associated with intrauterine sepsis than using prostaglandins in solution form, since the catheter can be withdrawn immediately after injection. However, whilst 75% of patients aborted within 24 h when PGE_2 1.5 mg was injected, no improvement occurred in the success rate with larger doses up to 3.0 mg. On the other hand a direct association was found between the dose injected and the frequency of side effects.

The results of the study reported here confirm these general findings and indicate there are distinct limitations to the use of a single application of PGE_2 in gel as a routine method of inducing midtrimester abortion. However, in those women successfully aborting following a single injection, there was a direct relationship between the time to abortion and the dose administered, being shortest for those receiving the highest dosage. The mean overall time to abortion of 14 h 17 min with the highest dose used is comparable with alternative techniques and the method has not so far been associated with the occurrence of cervical lacerations in our experience.

It is our opinion that if the abortion process has not been sufficiently primed to become progressive with the initial dose used then induced uterine activity will subside after approximately 6 h. We therefore conclude that the technique as originally suggested by *Lippert and Modly* (1) of using repeated injections of the gel has practical advantages. Our routine management is now to inject PGE_2 3.5 mg and to repeat this dose 6 h later irrespective of the stage of the abortion process. The catheter is withdrawn on each occasion rather than be left *in situ* as originally suggested by *Lippert and Modly* (1).

We feel it is important that using this technique care should be given to the location of the catheter ensuring that it is not inserted too far into the uterus with a possibility of rapid intravascular absorption occurring through the retroplacental site. There are also advantages in undertaking ultrasound for placental localisation prior to commencing the procedure to reduce inadvertent bleeding in those patients with a low lying placenta but we have not experienced this problem. However, there are some potential disadvantages of the technique in that signs of fetal activity may be present which we have never previously noticed with intra-amniotic techniques. However, we feel the relative freedom from cervical lacerations using the extra-amniotic, as opposed to intra-amniotic, route outweighs this occasional occurrence.

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