CLINICAL RESEARCH

Comparative study of oestradiol and prostaglandin E₂ vaginal gel for ripening the unfavourable cervix before induction of labour

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Abstract

Oestradiol 150 mg and prostaglandin E₂ (PGE₂) 4 mg suspended in viscous gel and applied intravaginally were compared with regard to ripening the unfavourable cervix of patients randomly allocated to two study groups.

In primigravidae no significant difference was observed in the efficacy of the two substances. Some multiparous patients, however, had considerably more uterine sensitivity to PGE₂ than to oestradiol. Two patients in the group given PGE₂ quickly developed decelerative cardiotocographic tracings after insertion of the gel. In the group given oestradiol there was a significant absence of uterine activity after gel application.

The findings suggest that oestradiol applied vaginally is a safe, comfortable, cheap, and equally effective alternative to PGE₂ for ripening the cervix, without the disadvantages of uterine stimulation frequently encountered with PGE₂.

Introduction

The purpose of this study was to compare the cervical ripening effect of oestradiol and prostaglandin E₂ (PGE₂) applied intravaginally in a viscous gel. Much work has been published on cervical ripening by prostaglandins used intravenously,^{1,2} by mouth,³⁻⁵ extra-amniotically,⁶⁻⁸ intravaginally as gels,^{9,10} and as wax pessaries.¹¹ The efficacy of other substances, such as oestrogens, progesterone, and relaxin, has not been explored clinically to the same extent. Nevertheless, Gordon and Calder¹²

showed a significant increase in cervical ripening in patients in whom oestradiol valerate in viscous gel was instilled into the extra-amniotic space by means of a Foley catheter.

Reasonable search of published work disclosed no comparative study on the use of oestradiol and PGE₂ for cervical ripening.

Patients and methods

Patients selected for study gave informed consent and were allocated to two treatment groups according to the odd or even date of their month of birth. Table I gives the comparability of the two groups, including maternal age, height, parity, gestational age, and pre-treatment cervical score. Parity ranged from nil to three. The gestational ages of all pregnancies, which were singletons, ranged from 37 to 42 weeks. All fetal presentations were cephalic, and non-engagement was not a contraindication to inclusion in the trial. In all patients the initial cervical state was clinically unfavourable, as denoted by a modified Bishop score¹³ of 0-3. The indications for induction of labour were pregnancy hypertension, suspected intrauterine growth retardation, and prolonged gestation.

TABLE 1—Matching of patients in treatment groups (ranges in parentheses)

	PGE ₂ group (n = 30)	Oestradiol group (n = 30)
Mean maternal age (years)	25.4 (19-44)	25.5 (19-39)
Mean maternal height (cm)	161.4 (150-180)	160.3 (150-178)
Mean gestation (days)	277 (259-294)	278 (259-294)
Mean pre-gel cervical score	1.9 (0-3)	2.2 (0-3)
Primigravidae	1.6	1.8
Multiparae	2.2	2.4
No of primigravidae	20	18
No of multiparae	10	12

PREPARATION OF GELS

PGE₂ (Prostin E₂; Upjohn) 4 mg in ethanol (11.4 ml) was suspended in sterile viscous gel (4% methylhydroxyethylcellulose; Tylose MH 300). The total volume was 20 ml in Tylose 3% gel. For the second treatment group oestradiol 150 mg (Organon) was first dissolved in ethanol, heated momentarily to 37°C, and suspended in a similar

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viscous gel as above, with a total volume of 20 ml Tylose 3% gel. Both PGE₂ and oestradiol gels were prepared by the hospital pharmacist and stored in sterile bottles at 4°C ready for use.

CLINICAL METHOD

Treatment began on the night before induction, but before insertion of the gel the cervix was assessed with minimal manipulation. With the patient in the dorsal position the respective viscous gel was applied intravaginally by a latex contraceptive diaphragm. Cardiotocography for 40 minutes was performed immediately before and 15 minutes after gel insertion, with patients in a semi-reclining position. Uterine activity was assessed by the appearance or increase in frequency of uterine contractions recorded in the post-gel cardiotocogram compared with the control cardiotocogram taken before gel application. These data were analysed for significance of difference using χ^2 (with Yates's correction) and one degree of freedom.

After a mean overnight interval of 12 hours after gel insertion patients were transferred to the delivery suite for cervical assessment. If their cervical score was three or less formal induction of labour was delayed for 24 hours. Meanwhile, the gel application was repeated. Labour was then induced, irrespective of cervical ripeness. The mean changes in cervical score (after first gel application only) for primigravidae and multiparae in each treatment group were analysed for significance of differences using the Wilcoxon rank sum test.

In patients whose cervix was found to be suitable after the first gel application forewater amniotomy was performed and intravenous oxytocin infusion begun immediately, using the regimen described by Beazley *et al.*¹⁴

Throughout labour the fetal heart rate was recorded continuously via a scalp electrode, and uterine activity was recorded via a Gaeltec intrauterine pressure transducer.

Results

Of the 60 patients studied, 30 received PGE₂ 4 mg in 3% gel, of whom 23 were treated once only; and 30 received oestradiol 150 mg in 3% gel, of whom 23 were treated once only. Table II summarises the results in the two treatment groups.

TABLE II—Results of comparative study groups (numbers of patients given in parentheses)

	PGE ₂ group (n = 30)	Oestradiol group (n = 30)	Significance
Subjective symptoms	90% (27)	17% (5)	p < 0.0005
Uterine activity increased (cardiotocographic findings)	83% (25)	17% (5)	p < 0.0005
Spontaneous onset of labour	7% (2)	0	NS
Decelerative cardiotocographic recording	7% (2)	0	NS
Surgical induction rate after first application	77% (23)	77% (23)	NS
Overall surgical induction rate after second application	87% (26)	90% (27)	NS
Mean cervical score improvement in primigravidae (± 1 SD)	3.4 $\pm$ 2.0 (20)	2.6 $\pm$ 1.3 (18)	NS (NED = 1.85)
Mean cervical score improvement in multiparae (± 1 SD)	4.7 $\pm$ 2.6 (10)	2.7 $\pm$ 0.6 (12)	p < 0.01 (NED = 2.71)
Epidural analgesia	80% (24)	80% (24)	NS
Mean duration of labour in hours (± 1 SD)	7.0 $\pm$ 3.6 (23)	8.3 $\pm$ 4.3 (22)	NS
Patients requiring caesarean section	23% (7)	27% (8)	NS
Mean Apgar score at one minute (± 1 SD)	8.5 $\pm$ 0.9 (30)	9.0 $\pm$ 0.7 (30)	NS

NS = Not significant (p > 0.05).
NED = Normal equivalent deviate.

Subjective symptoms—The incidence of backache and lower abdominal pain resulting in disturbed sleep was increased very significantly (p < 0.0005; χ^2 , 1 df) in patients receiving PGE₂ gel compared with those receiving oestradiol. Symptoms occurred within two hours of PGE₂ gel insertion in 27 patients. Only five women receiving oestradiol had any discomfort; all of them slept satisfactorily overnight.

Uterine activity—In the PGE₂ group tocography showed an increase in uterine activity after insertion of the gel in 25 patients. This increased incidence of uterine activity was highly significant (p < 0.005;

χ^2 , 1 df). Two of the patients began labour spontaneously overnight and delivered vaginally after one and 16 hours. In a further two patients decelerative cardiotocographic recordings were observed, and in one of these the severity and persistence of the tracing necessitated emergency caesarean section four hours after insertion of the gel. In the oestradiol group only five patients developed increased uterine activity; no patient began labour spontaneously or exhibited decelerative fetal heart tracings.

Induction of labour—On the first morning after gel insertion the cervical score had increased significantly (p < 0.01; Wilcoxon signed rank test) in both treatment groups, and 23 patients from each group were suitable for surgical induction. If patients who received a second gel application are included surgical induction of labour was possible in a total of 26 women in the PGE₂ group and 27 women in the oestradiol group. This difference was not significant. Hence there remained four patients in the PGE₂ group and three in the oestradiol group in whom, despite two applications of gel, surgical induction was not feasible. Among primigravid patients no significant difference in the increase of cervical ripeness was found between the two treatment groups (p > 0.05; Wilcoxon rank sum test). Among multiparous patients, however, the mean improvement in cervical ripeness was significantly greater after PGE₂ than oestradiol (p < 0.01; Wilcoxon rank sum test). Only the results from first gel applications were analysed for statistical significance.

Progress in labour—After induction of labour epidural analgesia was administered to 24 patients in each group. The mean duration of labour was 7.0 $\pm$ SD 3.6 hours in the PGE₂ group and 8.3 $\pm$ 4.3 hours in the oestradiol group. This difference was not significant. Delivery by caesarean section was necessary for seven patients in the PGE₂ group. In one of these fetal distress occurred before the onset of labour. In another patient the cervical substance effaced completely but the external os remained closed despite two gel applications and further stimulation by intravenous PGE₂; primary cervical dystocia was diagnosed. In the remaining five patients the indications for caesarean section were cephalopelvic disproportion (three patients), intrapartum fetal distress (one), and primary dysfunctional labour (one). In the group treated with oestradiol eight patients required emergency caesarean section. Of these, three were performed for intrapartum fetal distress, two for cephalopelvic disproportion, and three for failure to progress in labour. There was no significant difference in the one-minute and 10-minute Apgar scores in the two treatment groups, and there were no perinatal deaths in either group.

Discussion

The mechanisms controlling cervical ripening are poorly understood. Glycosaminoglycans in the cervical ground substance are believed to be concerned, together with prostaglandins and oestrogens. Pinto *et al.*¹⁵ claimed that oestradiol serves to soften the cervix, and Leppe and Kinnison¹⁶ showed in the cervical tissue of mice that oestradiol alters the bonding of collagen fibres and cervical compliance. Clinically, Gordon and Calder¹² showed that extra-amniotic application of oestradiol valerate effects a significant increase in cervical ripeness.

Our study shows that oestrogens applied vaginally will ripen the cervix of most patients; also, the technique we employed is simple and causes minimal discomfort to the patient. It also has the advantage of avoiding the complications which may accompany an invasive instillation of gel into the extra-amniotic space.

The role of PGE₂ administered via the extra-amniotic route⁸ or, more conveniently, into the posterior fornix⁹ has been well established as a method of ripening the clinically unfavourable cervix before induction of labour. In our study PGE₂ applied vaginally was as effective as oestradiol in ripening the primigravid cervix. In multiparous patients, however, though both agents were effective, prostaglandin excited more uterine activity than oestradiol.

To ripen the cervix PGE₂ apparently "storms the gate" with uterine contractions, while oestradiol simply "unlocks it." The latter is preferable, therefore, for use in patients suspected of having placental insufficiency; and, in our view, when PGE₂ is employed cardiotocography is essential.

We thank Mr P A Deeks and Miss P M Love for preparing the gels, the consultants at Liverpool Maternity Hospital who allowed us

access to their patients, all the medical and nursing staff concerned for their co-operation, and Mr M C K Tweedie, of the department of biostatistics, University of Liverpool.

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(Accepted 11 December 1980)

Systemic lambda light-chain deposition in a patient with myeloma

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Abstract

Systemic lambda light-chain deposition occurred in a 73-year-old man with myeloma. An initial renal biopsy specimen showed the features of myeloma kidney. When he died 22 months later lambda light chains were detected by immunofluorescence in kidneys, liver, spleen, and heart. They were probably responsible for cardiac dysfunction and the fatal arrhythmia.

It is suggested that in this patient deposition was due to a structural alteration of the light chains, possibly induced by cyclophosphamide.

Introduction

Renal tubular casts due to precipitation of M component are the classical lesions of multiple myeloma. Recently unusual histological features have been described attributable to deposition of light chains, which react with specific antisera by immunofluorescence and are sometimes associated with nodular glomerulosclerosis.¹⁻⁵ In some patients light-chain deposits have been found in other organs,^{3,6} so-called "systemic light-chain deposition disease."³ Until now all patients have shown deposits of kappa light chains. We describe a patient with a typical myeloma kidney who subsequently developed systemic, lambda light-chain deposition.

Case report

A 73-year-old man was admitted in May 1976 with rapidly progressive renal failure after an episode of diarrhoea. A diagnosis of multiple myeloma was established by finding 20% abnormal plasma cells in the bone marrow aspirate and monoclonal free lambda light chain by serum immunoelectrophoresis. Urine output ranged from 1 to 2 l/day, with 1.5 g protein, mainly lambda light chains. Serum creatinine concentration varied between 980 and 1100 μ mol/l (11.1 and 12.4 mg/100 ml), with a calculated clearance of about 3 ml/min. Renal biopsy was performed on the third day, and haemodialysis was started on the fifth day and continued until death. Cyclophosphamide (150 mg/day) and prednisone (30 mg/day) were given for 15 days.

The patient remained well until December 1977, when he had two episodes of supraventricular tachycardia. Over the next two months intracardiac conduction defects recurred, with bouts of tachycardia, one of which resulted in transient cardiovascular collapse. He died in March 1978 after cardiac arrest. Two weeks before death the myeloma had shown no progression; there were no visible osteolytic lesions, and bone marrow plasma cells (23%) had not increased. Free lambda light chains were still detectable in serum, and light chains in the urine represented half of the 2.8 g protein excreted daily.

PATHOLOGICAL INVESTIGATIONS

Biopsy specimens were frozen in isopentane, cooled by liquid nitrogen, and cut at 2 μ m. Sections were incubated with fluorescein-labelled antisera against human immunoglobulins G, A, and M (heavy-chain specific; Behringwerke Lab) and kappa and lambda light chains (light-chain specific; Atlantic Antibodies).

Initial renal biopsy specimen—Microscopical examination showed typical myeloma kidney, characterised by numerous polychromatophilic casts surrounded by giant cells. There was extensive interstitial fibrosis without plasma cell infiltration. Glomeruli showed segmental ischaemic changes related to non-specific vascular lesions (fig 1). Stains for amyloid were negative. Immunofluorescence showed a weak reaction with antilambda light-chain antiserum of tubular casts but no staining of tubular basement membrane or glomeruli. Electron microscopy disclosed thickening of glomerular and tubular basement membranes but no abnormal deposits.

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