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Induction of labour with a sustained-release prostaglandin E_2 vaginal pessary

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Summary and conclusions

A new polymer vaginal pessary providing sustained constant release of prostaglandin E_2 was administered to 66 patients before planned induction of labour. Effective ripening of the unfavourable cervix was achieved in each of 18 primigravidas, in eight of whom labour was initiated without further treatment. When the cervix was moderately favourable the need for orthodox induction of labour was obviated in 16 out of 23 primigravidas and 21 out of 23 multigravidas.

This method of sustained release of prostaglandin E_2 is simple and convenient and readily acceptable to the patient; it is an important step in the development of non-invasive methods of inducing labour.

Introduction

Several recent studies have shown that the unfavourable prognosis for induction of labour signalled by an unripe cervix may be much improved by vaginal administration of prostaglandin E_2 in simple gels and pessaries and that labour is often promoted without the need for formal induction.[1-4] This method is increasingly favoured and would be still more widely used if a commercial product was available, but hitherto a prostaglandin E_2 preparation with adequate long-term stability has not been developed. Additionally, experience suggests that a sustained-release vaginal preparation would be advantageous.

Initial laboratory studies incorporating prostaglandins in a water-swellable, cross-linked polymer (hydrogel) indicated that such a system should exhibit stability and provide sustained release of prostaglandin over prolonged intervals.[5] We report on our early clinical experience of using a prostaglandin E_2 polymer vaginal pessary in the induction of labour.

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In-vivo studies

We treated 66 patients (41 primigravidas, 25 multigravidas) requiring induction of labour for medical or obstetric reasons at 38-42 weeks' gestation. During the study period the dose of prostaglandin E_2 incorporated in the pessary varied, depending on the formulation of the polymer and its in-vitro release profile. In most cases we used a pessary that in vitro released about 75% of its content over 12 hours; the incorporated dose of prostaglandin E_2 was 10 mg for primigravidas and 5 mg for multigravidas. Some patients who presented early in the trial, when a formulation with a less satisfactory profile was used, received a larger dose (up to 20 mg in primigravidas).

Usually overnight and about 12 hours before induction was planned, the pessary was inserted in the vaginal vault after cervical assessment with a modified Bishop score.[6] The patient remained recumbent for 15 minutes after insertion, and maternal pulse, blood pressure, uterine activity, and fetal heart rate were observed regularly for four to five hours and for longer if labour became established. Internal tocographic records showed that treatment provoked a pattern of frequent contractions (at one- to three-minute intervals) of low amplitude (less than 40 mm Hg) and causing little discomfort, starting after one to two hours: the contractions persisted for four to six hours and then either waned or were augmented as labour became established. The next day, if labour was not established, formal induction was performed by amniotomy followed if necessary by intravenous oxytocin. The pessary was removed when labour was established or at the time of amniotomy. The labour was managed by the duty delivery-suite staff.

Results

The establishment of labour after treatment depended on parity and was related to the initial cervical score (table). Labour was initiated by prostaglandin treatment alone in eight out of 18 primi-

Influence of parity and cervical score (0-4, cervix unfavourable; >5 cervix favourable) on establishment and outcome of labour. Figures are numbers of patients

	Primigravidas		Multigravidas	
	Cervix unfavourable (n = 18)	Cervix favourable (n = 23)	Cervix unfavourable (n = 2)	Cervix favourable (n = 23)
Labour established	8	16	—	21
Oxytocin given	9	6	2	2
Epidural analgesia given	11	8	2	1
Spontaneous vaginal delivery	5	15	—	23
Caesarean section	1	—	1	—

gravidas (44%) with an unripe cervix (cervical score 0-4), while in those with a more favourable cervical score (5+) the proportion was 16 out of 23 (70%). Thus augmentation with oxytocin and epidural analgesia were less often required and spontaneous vaginal delivery was more common in the group with higher cervical scores. One primigravida, with suspected placental insufficiency and an unripe cervix, was delivered by caesarean section for fetal distress at 3 cm dilatation.

Only two multigravidas had low cervical scores (0-4); both required amniotomy and oxytocin. One was delivered by caesarean section for suspected fetal distress at 6 cm, the other by forceps. Of the 23 multigravidas with a favourable cervix, 21 established labour after treatment with prostaglandin. Only two received oxytocin, and all 23 had a spontaneous vaginal delivery.

There were no gastrointestinal side effects attributable to the prostaglandin treatment and no evidence of fetal compromise as judged by the absence of low one-minute Apgar scores (less than 5).

Discussion

There is now considerable evidence confirming that prostaglandin E_2 administered vaginally before planned induction of labour effectively ripens the unfavourable cervix, often obviates the need for formal induction, and improves the prognosis of labour. When the cervix is ripe labour is established in most patients and greater benefits accrue; augmentation with oxytocin and epidural analgesia are needed less often, the incidence of spontaneous vaginal delivery is increased, and caesarean section is rarely required.

These beneficial effects were first achieved by administering prostaglandin E_2 in a viscous cellulose gel,[1 2] while more recently glyceride-based (Witepsol) pessaries have been used.[3 4] Unfortunately the relative instability of these simple formulations of prostaglandin E_2 has deterred commercial production, while an additional disadvantage is that dissolution, and presumably absorption, of the gels and pessaries occur quickly (within two to four hours) with the risk, in some multigravidas, of unduly rapid progress in labour.

In this limited trial a prostaglandin E_2 polymer pessary gave encouraging results in the induction of labour, comparable to those obtained with the alternative vaginal preparations, while additionally possessing the important advantages of controlled sustained release of the prostaglandin and long-term stability. The ability to tailor the pessary to provide a desired release profile—a relatively short release when induction of labour is simple and a more prolonged action for ripening the unfavourable cervix—offers the prospect of improved results as experience increases. Moreover, the delivery system may be adapted to other roles in reproduction: by providing sustained release of promising but hitherto unstable prostaglandin E analogues it has obvious potential in the termination of early pregnancy and induction of menstruation.

The method is simple and convenient, with a high degree of patient acceptability, and this initial study indicates that the sustained release of prostaglandin E_2 provided by this new polymer pessary is an important contribution in the development of non-invasive methods of inducing labour.

Appendix

IN-VITRO STUDIES

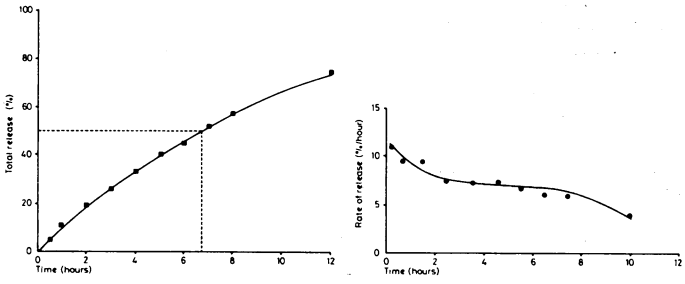
Polyethylene oxide cross-linked polymers from formulations of moderate-molecular-weight polyethylene glycol, 1,2,6-hexane triol, and pure diphenyl methane diisocyanate are hydrophilic and, even when swollen to several times their original dry weight, tough and rubbery. The polymers prepared for this study have an equilibrium swelling in water at 37°C of 400-500 parts per hundred of initial weight.

The reactants were mixed in stoichiometric proportions at 80°C and poured into heated Teflon or high-density polyethylene moulds to cure at 95°C for four hours. After cooling the polyethylene oxide block was cut to the dimensions required for the pessaries. Residual material of low molecular weight was extracted in water and the samples vacuum dried at room temperature. When tested in cell culture system L929 with mouse fibroblasts the material showed no toxic response. Use of the median lethal dose in mice and subcutaneous implantation of the ground material in rats also failed to produce any toxic or abnormal response.

Prostaglandin E_2 was incorporated in the sterilised samples by swelling them in a 1/1 w/w chloroform/ethanol solution of prostaglandin E_2, the concentration of the solution being calculated from the required prostaglandin content of the pessary (usually 10 mg) and the equilibrium swelling of the polymer in the solution. The fully swollen pessaries were vacuum dried to constant weight at ambient temperature, yielding dry prostaglandin E_2/polyethylene oxide pessaries with 10 mg prostaglandin E_2 uniformly dispersed through the matrix, and stored at 4°C until required. In addition to the pessaries for clinical use, identical pessaries containing ^{3}H-prostaglandin E_2 were prepared and their in-vitro release profile in phosphate buffer at 37°C studied as a guide to clinical performance.

Experiment showed that compared with cylindrical pessaries a pessary of rectangular slab design (32 · 10 · 2·5 mm) gave an improved rate of release of prostaglandin E_2. This dry device, as it swells in vivo or in vitro with absorption of water and diffusion of prostaglandin E_2 across the polymer-fluid interface, shows a reasonably constant rate of release (zero order) over a considerable period before changing to a lower value (figure). Its half life is directly proportional to the square of the thickness of the device, making it possible to calculate the optimum thickness for a desired half life and facilitating adjustments in the light of clinical experience. The details of these devices, which offer an attractive and novel way of providing relatively constant profiles of contained drug release, will be published elsewhere.

Methodology for extracting and assaying cold prostaglandin E_2 in the pessary has also been developed, enabling measurements of the prostaglandin E_2 content before and after use to be correlated with clinical events. Other studies have shown the stability of the pessary, with no evidence of loss or degradation of prostaglandin E_2 after storage at 4°C for over a year.



In-vitro release of prostaglandin E_2 polymer pessary, dry size 2·5 · 10 · 32 mm, in phosphate buffer at 37°C. Half life was 6·8 hours.

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ONE HUNDRED YEARS AGO Mr Turnbull, in crossing the Atlantic on board the steamer *Britannia*, writes: "... The sea was lumpy, and during the night the greater number of the passengers were paying their devotions to the sea-fishes. My fellow-passengers in the adjoining state-room soon excited my sympathies. They consisted of a lady about twenty-five years, a young girl of three years and a half, and a maid-servant. The latter was the most noisy by loud efforts and groanings; then followed the lady and girl, but in a quieter manner. I gave the husband three nitro-glycerine lozenges, one each for the adults, and a quarter for the little girl. Soon after, the husband reported the little girl quite better and playing on the floor, with no return; a decided improvement of the wife's condition, and even an amelioration of the noisy demonstrations of the maid. In the little girl, the improvement was entirely permanent; while the other two did vomit after, but soon after became quite comfortable. The next case was my associate in the same state-room, who stated he was always sick crossing. He was young—twenty-six years—robust, weighing two hundred pounds, with a most ravenous appetite. He took one lozenge; but in a few seconds after he stated he vomited it, and would not repeat the dose. Soon after, I gave him fifteen drops of aromatic spirit of ammonia, and from that time he had no return. The fifth case was a celebrated western bishop, who came upon deck and stated he felt nauseated and badly; but he thought by force of will he would not be sick. I told him of the remedy; he desired to take it. I gave him one lozenge; and soon after he told me it gave him such relief, that he was able to go down to the saloon and eat his breakfast; he with two others being all out of ten that were able to do so at our table during the stormy weather. To two adults also I administered the remedy; but in neither case was it of any value, not being retained." These nitro-glycerine tablets are supplied by Mr Martindale, chemist, New Cavendish Street. (*British Medical Journal*, 1880.)