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Review of Propess — a controlled release dinoprostone (prostaglandin E_2) pessary

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Introduction

A controlled release hydrophilic matrix (Controlled Therapeutics Ltd., East Kilbride, Scotland) which provides a gradual release of dinoprostone (prostaglandin E_2) was introduced in 1995 (Propess-RS, Ferring Pharmaceuticals). This preparation is used for the initiation or enhancement of cervical ripening in women at or after term with a singleton pregnancy and a cephalic presentation. Prostaglandin E_2 causes softening and dilatation of the cervix and subsequently produces uterine contractions which may induce labour. This review summarises the pharmaceutical, pharmacokinetic, pharmacological and clinical studies conducted with controlled release prostaglandin E_2 and related products.

Pharmacology

The role of prostaglandin E_2 in the induction of cervical ripening

During spontaneous labour, prostaglandin E_2 has a major role in the physiological changes associated with parturition and is an important mediator of both cervical softening and dilatation and uterine contractions. It is believed to relax the smooth muscle of the cervix (Bryman *et al.*, 1982) and also to induce an increase in the production of glycosaminoglycans within the collagen fibres of the cervix which result in softening and ripening for parturition (Novy and Liggins, 1980).

The pharmacological action of prostaglandin E_2 on the uterus is influenced by pregnancy. In the non-pregnant uterus, it produces relaxation of the uterine smooth muscle, but during pregnancy causes contractions. Uterine responsiveness is related to the duration of pregnancy, the uterus being much more responsive at term than during pregnancy (Dollery, 1992).

In view of the physiological actions of endogenous prostaglandin E_2, it is not surprising that it has been administered as a pharmacological agent to enhance cervical ripening and induce labour. Early studies with the extra-amniotic administration of prostaglandin E_2 led to the more convenient intravaginal administration as a gel or pessaries (MacKenzie and Embrey, 1977; Shepherd *et al.*, 1979).

Miller *et al.* (1991) and Smith *et al.* (1994) compared the efficacy of intravaginal prostaglandin E_2 by gel or controlled release hydrogel pessary for the induction of cervical ripening and initiation of labour. In both studies, the controlled release preparation was more effective in producing cervical ripening and inducing labour, with less need for oxytocin.

Miller *et al.* (1991) recorded mean uterine activity during 12 hours of treatment (Figure 1). The gel formulation produced peak uterine activity within the first 4 hours, whereas the peak was at 5 to 8 hours with the controlled release pessary. High amplitude uterine contractions, that is, ≥ 6 mm on the tocograph tracing, lasting at least 30 seconds and occurring at less than 1-minute intervals, were recorded in 50 per cent of women at 11 hours after gel application and in 80 per cent after the pessary. Prostaglandin E_2 delivered by the controlled release hydrogel pessary produced a more gradual increase in uterine activity and more sustained high amplitude contractions for 9 to 12 hours.

In general terms, labour induction should attempt to replicate spontaneous labour as closely as possible. Labour is the culmination of a gradual transition from pregnancy through the phase of 'pre-labour' and active labour to delivery. The closer the pregnancy to term the easier and safer is the induction of labour.

Cervical ripening is by nature a gradual process and probably requires several hours of exposure to

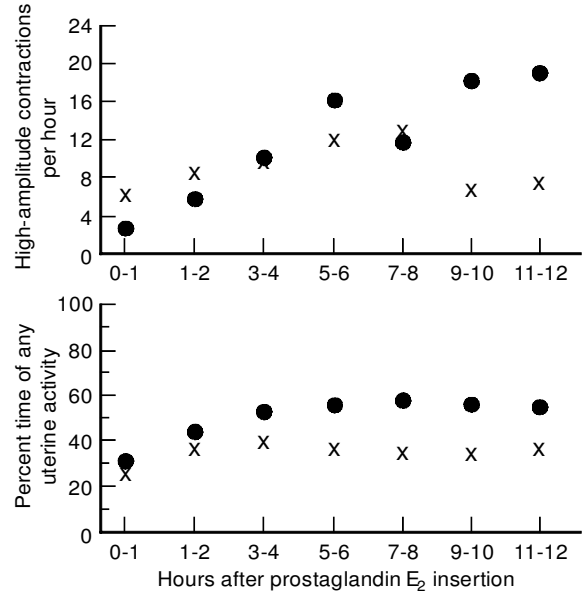

Figure 1. Mean hourly high amplitude contraction frequencies and the proportion of time occupied by any uterine activity (low amplitude, high frequency or high amplitude) following intravaginal prostaglandin E_2 treatment with gel (x) or controlled-release hydrogel pessaries (●) (Miller *et al.*, 1991).

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endogenous or exogenous prostaglandin E_2. In the absence of a sustained release delivery system, women with an unripe cervix may require repeated applications of vaginal gel or pessaries. Sustained, steady and controlled release of prostaglandin within the vagina close to the cervix presents theoretical advantages compared with the irregular bolus doses with rapid and unpredictable release which are associated with simple pessary and water-based gel formulations.

Controlled release prostaglandin E_2 pessaries

These consist of a polyethylene glycol-based hydrogel polyurethane polymer which releases prostaglandin E_2 (dinoprostone) from the solid reservoir within the matrix as the pessary takes up moisture from the vaginal environment. The polymer has the property of releasing prostaglandin E_2 at a predetermined constant rate and is not biodegradable. It does not break up when *in situ*. This latter property allows retrieval of the pessary and hence cessation of the administration of prostaglandin E_2 at any point in time.

Glyceride-based (Witepsol) pessaries dissolve and the prostaglandin E_2 is absorbed through the vagina, generally within 2 to 4 hours. In contrast, the hydrogel pessary swells within the vagina to 2 to 3 times its original size. The pessary becomes soft and pliable but maintains its physical integrity, allowing removal.

Development of the hydrogel pessaries

The initial formulation had an estimated *in vitro* release rate of 0·7–0·8 mg/hour (Embrey *et al.*, 1980) and was found to be effective in causing cervical ripening and labour (Embrey *et al.*, 1980; Embrey and MacKenzie, 1985). A number of problems were reported within a year. Khouzam and Ledward (1990) reported two cases of rapid onset of contractions and a very short second stage of labour following pessary insertion. In a third woman, fetal heart rate changes occurred despite pessary removal. In one of the women, severe vaginismus impeded pessary removal. Difficulty in pessary recovery was reported in 5 out of 15 women (Bex *et al.*, 1990) and 14 out of 41 women (Baravilala *et al.*, 1990). In 11 of these women, the pessary was not recovered from the vagina, although it may have been expelled unseen.

As a result of these difficulties, the initial formulation was withdrawn, re-formulated and relaunched with a retrieval system to aid pessary removal. Calder and Johnston (1995b) assessed the feasibility of using a tampon-style retrieval cord attached to a placebo pessary. The acceptability of the pessary was assessed in seven pregnant volunteers. After eight hours *in situ*, gentle traction on the cord enabled retrieval of the pessary from five subjects, but in two the pessary was torn. A simple cord was not sufficiently reliable to use as a retrieval system. An alternative retrieval system was required to enable the pessary to be removed easily without tearing.

This retrieval system consists of a one piece knitted pouch made from a polyester that is used in the manufacture of long-term vascular implants, with an attached withdrawal tape. The knitted construction allows the pouch to stretch as the pessary hydrates and swells. The retrieval system does not alter prostaglandin E_2 release or the pessary stability characteristics.

Pharmacological and toxicological studies with controlled release pessaries

No untoward effects due to the polymer, potential impurities or breakdown products have been found in repeated dose oral toxicity studies. Studies using a radio-labelled hydrogel polymer have also confirmed that the pessary is inert and not biodegradable (Kynoch *et al.*, 1983; Elliot, 1984; Comelli *et al.*, 1988).

Potential for toxic shock syndrome

In theory, the formulation, in common with the use of tampons, has potential risk factors for the development of toxic shock syndrome. It contains hydrogel polymer which absorbs water; the retrieval system has a textile content; and the product is intended to remain *in situ* for up to 12 hours and possibly longer by accident.

An *in vitro* study utilising a reproducible model has been conducted to predict the potential for causing toxic shock syndrome (Holland, 1993). The controlled release preparation had little effect on *Staphylococcus aureus* growth and *Staph. aureus* toxin production was reduced. Whilst these *in vitro* results cannot guarantee a lack of toxicity *in vivo*, the acid pH of the vagina during late pregnancy may also reduce the chances of *Staph. aureus* growth and toxin production.

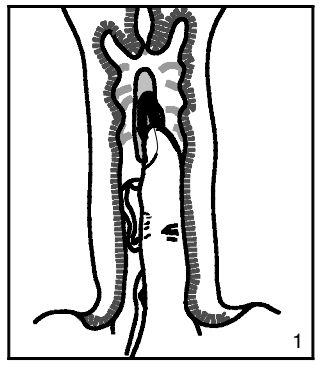
Administration and acceptability

The pessary is inserted into the vagina (Figure 2) using a small amount of water-soluble lubricant to aid insertion. Rotation of the pessary, so that it lies transverse to the posterior fornix, is advisable to prevent accidental loss. Westgate and Williams (1994) reported loss of eight pessaries from 51 women (16 per cent) in whom the pessary was left in a longitudinal position. Modification of the insertion technique, with rotation of the pessary, resulted in the loss of only three pessaries from the next 60 women (5 per cent), all during early labour.

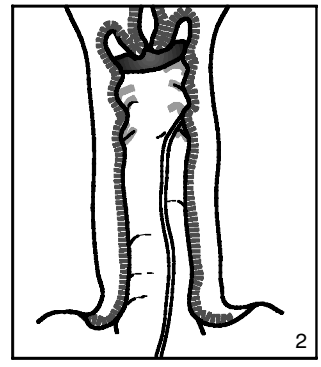
One hundred and eleven women reported on acceptability of the pessary *in situ* (Westgate and Williams, 1994). One hundred and eight (97 per cent) felt no discomfort from the pessary, with 88 per cent being unaware of its presence. Two women were aware of mild discomfort (2 per cent), whilst only one (1 per cent) reported marked discomfort from the use of the pessary.

The ease of removal of the pessary using the retrieval system was also assessed in 100 women (Table I). The pessary was removed with no or slight difficulty in 97 per cent of cases (Westgate and Williams, 1994).

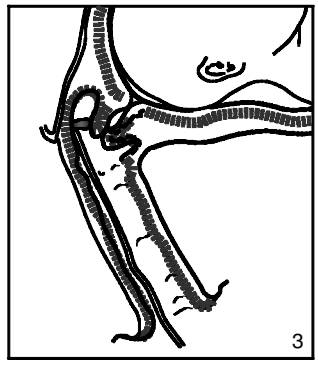
Mowat *et al.* (1995) found no difficulty inserting the pessary into seven women and only minor difficulty in two. All nine women found the pessary and its retrieval system to be acceptable and there were no adverse comments. The pessary was retrieved from the vagina without difficulty in every case. The retrieval system proved acceptable to



(1) Holding the pessary between the fingers of the examining hand, insert the pessary high into the posterior vaginal fornix using only small amounts of water soluble lubricants.



(2) To ensure that the pessary remains *in situ*, it should be turned through 90° so that it lies transversely in the posterior fornix.



(3) Allow sufficient tape to remain outside the vagina to permit retrieval.

(4) After insertion, ensure that the patient remains recumbent for 20 to 30 minutes to allow time for the pessary to swell.

Figure 2. Diagrammatic representation of the recommended method for insertion of the controlled release pessary.

women and clinicians, and enabled easy removal from the vagina in all cases, by gentle traction on the retrieval tape.

The controlled release pessaries should not be used: (1) when strong, prolonged uterine contraction would be inappropriate, such as in patients: (a) who have had previous major surgery; (b) who have had previous surgery to the cervix; (c) with a major degree of cephalopelvic disproportion; (d) with fetal malpresentation; (e) with a history of difficult or traumatic deliveries; (f) who have had more than three full term deliveries; (2) when there is a history of, or current, pelvic inflammatory disease, unless adequate prior treatment has been instituted; (3) when there is reason to believe there may be hypersensitivity to prostaglandin E_2; or (4) when there is multiple pregnancy.

The controlled release pessaries should be removed: (1) when labour has started; (2) when it is proposed to rupture the membranes artificially; (3) when the membranes rupture spontaneously; (4) when oxytocin is given; and (5) with suspicion or evidence of fetal distress.

Westgate and Williams (1995) found the pessaries could be removed without undue difficulty from all women with adverse events, and in all except one incident, the symptoms diminished on removal of the pessary.

Pharmacokinetics

Prostaglandin E_2 release

In vitro *studies*. The *in vitro* release of prostaglandin E_2 from a hydrogel polymer pessary has been studied by a number of investigators (Embrey *et al.*, 1980; Taylor *et al.*, 1990) who have confirmed consistent release of prostaglandin E_2 over 12 and 8 hours, respectively.

Johnston *et al.* (1992) compared the effect of pH on the *in vitro* release of prostaglandin E_2 from gels,

Table I. Ease of controlled release vaginal pessary removal in 100 patients. Investigators assessed difficulty, patients assessed discomfort (Westgate and Williams, 1994)

	Assessment by	
	Investigator	*Patient*
No difficulty or discomfort	78	88
Slight difficulty or discomfort	19	9
Moderate difficulty or discomfort	2	2
Very difficult or marked discomfort	1	1

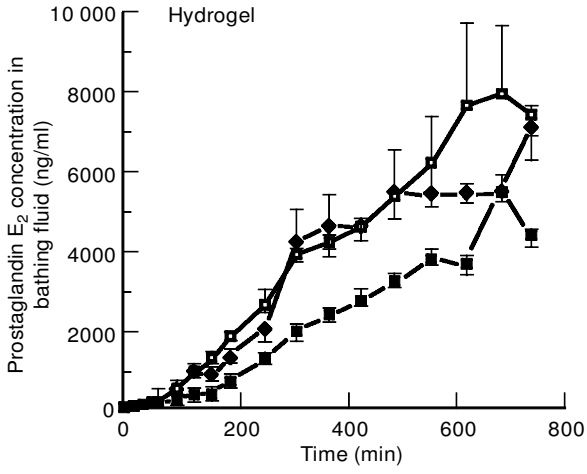


Figure 3. *In vitro* release of prostaglandin E_2 from hydrogel polymer pessary at 37°C. The results are shown as means with standard error bars. Where no error bars are shown, the standard error was too small to be apparent on the graph (Johnston *et al.*, 1992). □ pH 7·4; ◆ pH 5·4; ■ pH 3·4.

a vaginal tablet and a controlled release hydrogel polymer pessary. The release rates from the four formulations were compared at pH's 3·4, 5·4 and 7·4. The lactose-based vaginal tablet had a very low prostaglandin E_2 release rate for most of the study time but there was a sudden and variable increase in release after about six hours, especially at the lower pH. The release from the gels was initially rapid but the release was lowest at the low pH.

Johnston *et al.* (1992) confirmed that the controlled release hydrogel pessary provided linear release of prostaglandin E_2 *in vitro* (Figure 3). The release rate was greatly influenced by the pH of the buffer solutions, with the greatest release from pessaries tested at pH 7·4 (Table II). These investigators also found that precoating the pessary with obstetric cream greatly reduced prostaglandin E_2 release, probably due to the prevention of water uptake into the pessary. MacDonald and Weir (1993) confirmed that the *in vitro* release of prostaglandin E_2 from a hydrogel polymer pessary was relatively consistent over the pH range of 3·5 to 5·0 (Figure 4). The rate of prostaglandin E_2 release from pessaries at pH 6·5 to 7·5, including pessaries in amniotic fluid, was far higher.

In the clinical situation, vaginal fluid around term (37–42 weeks) has a pH of approximately 4·1, enabling a slow and consistent release of prostaglandin E_2 from a hydrogel pessary. The pH of amniotic fluid is approximately 7·5, therefore a more rapid release may be expected if the pessary remains *in situ* after rupture of the membranes (Taylor and MacKenzie, 1993). This concern is balanced by the fact that at the pH of amniotic fluid, prostaglandin E_2 will be predominantly ionised (pKa 4·9) and presumably less available for absorption (MacDonald and Weir, 1993).

In vivo studies. Four clinical reports or studies have been made of the prostaglandin E_2 release rate from intravaginal controlled pessaries (Taylor *et al.*, 1990; Westgate and Williams, 1994; Calder and Johnston, 1995a; Johnston and Calder, 1995).

In three studies, a single pessary was placed in the posterior fornix of the vagina of each suitable woman and removed from the vagina after intervals of 30 minutes to 8 hours, according to a pre-determined scheme, frozen and subsequently analysed for residual prostaglandin E_2. Each pessary was immediately replaced by a pessary which had been stored for the same length of time in saline, in order to allow treatment to continue up to the planned 8 or 12 hours. In the fourth study (Westgate and Williams, 1994) the pessaries were stored and assayed for residual prostaglandin E_2 following removal for clinical reasons or at the end of the study. Release rates where membrane rupture occurred with the pessary *in situ* were excluded.

The rate of release of prostaglandin E_2 was broadly consistent in the four studies (Table III). A plot of the prostaglandin E_2 release characteristics from the pessaries confirmed drug release at a near constant rate of approximately 0·3 mg/hr *in vivo* (Westgate and Williams, 1994; Figure 5). Based on this release rate, the maximum dose over 12 hours is of the order of 4 mg prostaglandin E_2. This compares with doses of 1 to 3 mg prostaglandin E_2 administered as single 'immediate release' doses, which often have to be repeated 6 hours later and give a maximum dose of up to 6 mg in under 12 hours (MacKenzie and Boland, 1993).

Westgate and Williams (1994) found that the amount of prostaglandin E_2 released from the controlled release pessary was not related to the success of induction of labour or the incidence of adverse events, such as uterine overstimulation. As exogenous prostaglandin E_2 has been shown to stimulate endogenous production of oxytocic agents such as prostaglandin $F_{2\alpha}$ (Greer *et al.*, 1990), this finding is perhaps not unexpected.

Taylor *et al.* (1990), found a correlation between prostaglandin E_2 release from a controlled release hydrogel polymer pessary and the increase in cervical score (correlation coefficient 0·65; $P < 0·001$).

Table II. Residual content of prostaglandin E_2 in 10 mg controlled release hydrogel pessaries following *in vitro* release over 12 hours (Johnston *et al.*, 1992)

pH of buffer solution	*Mean residual prostaglandin E_2 content*
3·4	4·50 mg
5·4	2·00 mg
7·4	1·08 mg

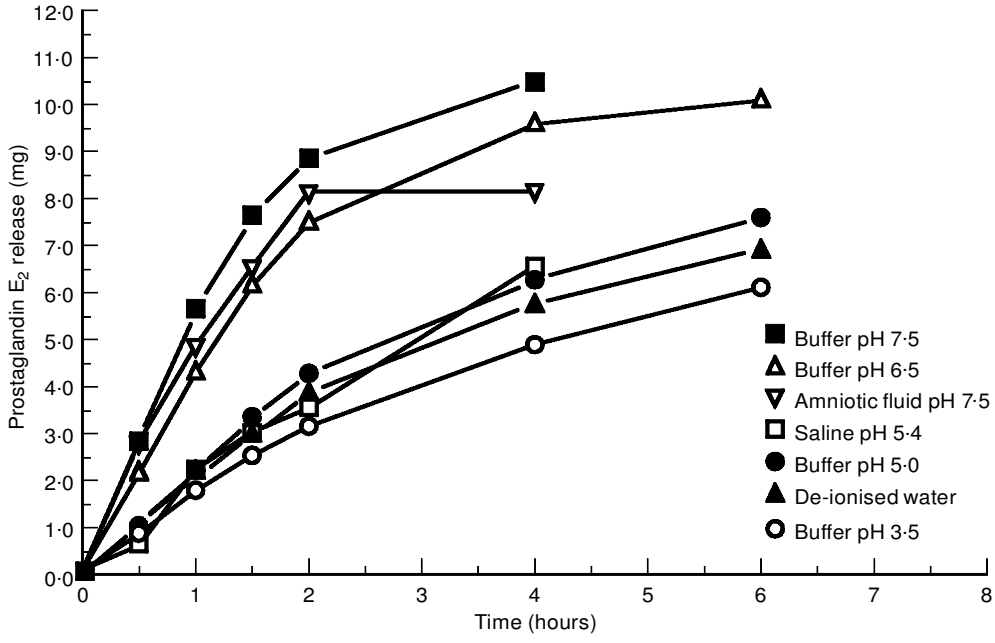


Figure 4. Effect of pH on the rate of prostaglandin E_2 release *in vitro* from hydrogel pessary at 37°C(MacDonald and Weir, 1993).

Table III. *In vivo* release rate of prostaglandin E_2 from controlled release pessaries

Reference	*Rate of prostaglandin release Mean (± s.d.) mg/hour*
Taylor *et al.*, 1990	0·30 ± 0·13
Westgate and Williams, 1994	0·33 ± 0·15
Calder, 1995a	0·32 ± 0·08
Calder, 1995b	0·27 ± 0·05

Maternal prostaglandin E_2 levels

During spontaneous labour, amniotic fluid concentrations of prostaglandin E_2 and prostaglandin $F_{2\alpha}$ increase substantially (Greer *et al.*, 1990). In order to assess the effects of intravaginal prostaglandin E_2 administration, changes in prostaglandin E_2 metabolites and prostaglandin $F_{2\alpha}$ metabolite have been recorded.

Taylor *et al.* (1991) measured prostaglandin E and F metabolite concentrations in peripheral plasma following induction of labour with a controlled release prostaglandin E_2 hydrogel pessary, designed to release 0·6 mg/hour. A significant rise in prostaglandin E metabolite occurred, reached a peak at 2 to 4 hours after pessary insertion, and returned towards baseline levels at 8 hours (Figure 6).

Prostaglandin F metabolite levels increased slowly throughout the 8 hours of treatment. Both prostaglandin E and F metabolite levels were higher in those women delivering during the 8 hours of observation. The results suggested that prostaglandin E_2 released by the pessary stimulated endogenous prostaglandin production (Taylor *et al.*, 1991).

Maternal plasma prostaglandin metabolite levels were measured in three studies on controlled release pessaries (Calder and Johnston, 1995a; Johnston and Calder, 1995; MacKenzie, 1995a). Prostaglandin E metabolites increased over the first 1 to 2 hours after insertion of the pessary and then maintained a constant level over the rest of the 8 hours. There was no direct relationship between the release of prostaglandin E_2 from the pessary and maternal plasma prostaglandin E metabolite levels. Prostaglandin F metabolites also increased over the first few hours, but levelled off and then increased again at around 8 hours; prostaglandin F metabolite levels were highest postpartum.

The above findings support the hypothesis that intravaginal administration of prostaglandin E_2 may stimulate endogenous production of prostaglandin E_2 and $F_{2\alpha}$ and induces cervical ripening and labour in a way that mimics spontaneous labour.

Clinical efficacy

Clinical trial programme

The controlled release hydrogel polymer prostaglandin E_2 pessary has been the subject of a programme of clinical studies to assess its efficacy and safety alone or, with the retrieval system. A total of eight reports or studies, in the form of clinical trials or postmarketing surveillance studies, have evaluated efficacy in causing cervical ripening and inducing labour. The eight clinical studies are summarised in Table IV.

All the clinical reports or studies utilised a similar set of inclusion and exclusion criteria, generally reflecting standard clinical practice for inducing

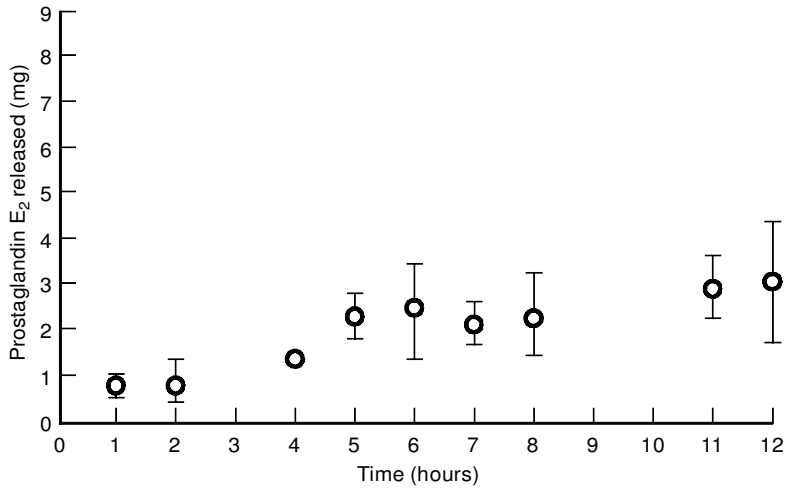


Figure 5. Amount of prostaglandin E_2 released from controlled release hydrogel pessary in relation to the time in the vagina (111 patients). The mean rate of prostaglandin E_2 release was $0{\cdot}33 \pm 0{\cdot}15$ mg per hour (s.d. range $\pm 0{\cdot}12$ to $0{\cdot}78$; 95 per cent confidence interval $0{\cdot}30$ to $0{\cdot}36$ per hour) (Westgate and Williams, 1994).

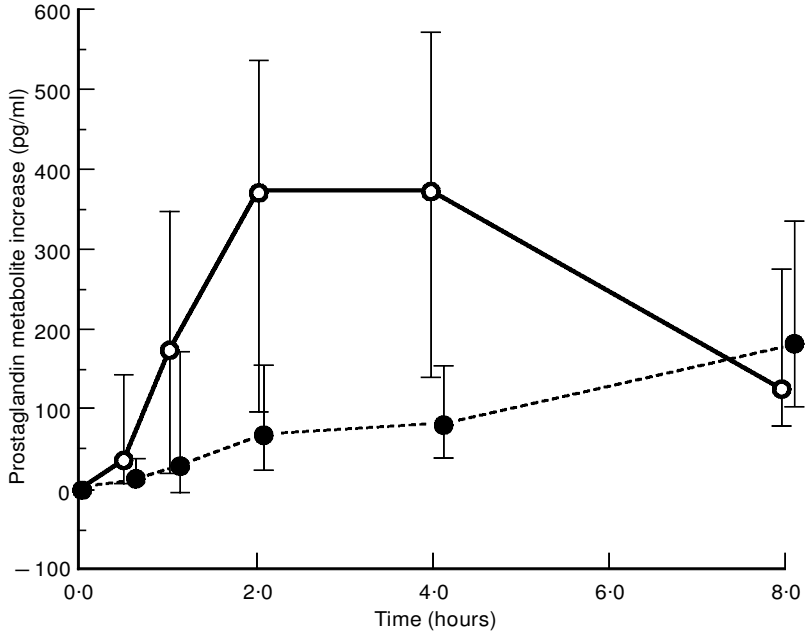


Figure 6. Median and interquartile changes in plasma concentration of (○) prostaglandin E metabolites and (●) prostaglandin F_2 metabolites following insertion of controlled-release hydrogel vaginal pessaries. Means and s.d.'s: $n = 25$ at 0·5, 1, 2 and 4 hours; $n = 17$ at 8 hours (8 patients delivered) (Taylor *et al.*, 1991).

labour. The women included in the studies all had a gestational age in excess of 37 weeks, a singleton pregnancy with cephalic presentation, intact membranes and an unfavourable or only partially favourable cervix with a Bishop (1964) score of 6 or less. Exclusions from the studies included any patients with a uterine scar, a history of vaginal bleeding, pyrexia, hypersensitivity to prostaglandins, asthma or glaucoma, evidence of fetal distress, suspected hydramnios or hypertension; and those in spontaneous labour.

Standard controlled release pessaries containing 10 mg dinoprostone were used in all but one of the clinical studies; the exception was MacKenzie (1995b) where a 5 mg controlled release hydrogel pessary was employed for the induction of labour in multigravidae. In clinical studies, the pessaries were left *in situ* for 8 or 12 hours, or until the start of labour or removal because of adverse maternal or fetal events.

Oxytocin or artificial rupture of membranes was also employed, generally after the 8 or 12 hour prostaglandin E_2 treatment, to assist induction of labour in appropriate women in many of the studies. In one study (Taylor *et al.*, 1995), women requiring further uterine stimulation beyond the initial 12 hours of treatment, were allocated at random to receive either a second pessary or an oxytocin infusion.

Overall efficacy of controlled release dinoprostone pessaries (Propess)

Treatment success was assessed in all the studies using similar end points. Cervical ripening was defined as an increase in the Bishop score of 3 or more (2 or more by Calder and Johnston, 1995a), or

Table IV. Summary of patients evaluated for efficacy in clinical trial programmes for controlled release prostaglandin E_2 (PGE_2) pessaries

Reference	*Study description*	*Number of patients receiving the pessaries*
Browning *et al.* (1995)	Post-marketing survey of efficacy in nulliparae and multiparae	192
Calder and Johnston (1995a)	PGE_2 release and efficacy in nulliparae	33
Calder and Johnston (1995b)	PGE_2 release rates and efficacy in multiparae	24
MacKenzie (1995a)	PGE_2 release rates and efficacy in nulliparae and multiparae	27
MacKenzie (1995b)	Controlled release *versus* Witepsol PGE_2 pessary in nulliparae and multiparae	74
Taylor *et al.* (1995)	Efficacy in nulliparae and comparison of delayed induction of labour: second controlled release pessary *versus* oxytocin	27
Mowat *et al.* (1995)	Post-marketing survey of controlled release PGE_2 efficacy in nulliparae and multiparae	9
Westgate and Williams (1995)	Efficacy of controlled release PGE_2 in nulliparae and multiparae	111

the achievement of vaginal delivery within the defined observation period, 8 or 12 hours).

MacKenzie (1995b) compared the relative efficacy of the controlled release prostaglandin E_2 pessary, with a Witepsol-based prostaglandin E_2 pessary. No differences were found between the two prostaglandin E_2 formulations with respect to efficacy. The efficacy data from this study were not directly comparable with those from other studies, as amniotomy and oxytocin infusion were routinely performed within the treatment period. Furthermore, nulliparae were given twice the intravaginal dose of prostaglandin E_2 given to multiparae.

Thirty-three nulliparous women, with a median gestational age of 41 weeks (range 37–42), were treated with a controlled release prostaglandin E_2 pessary for up to 8 hours (Calder and Johnston, 1995a). Treatment success, defined as vaginal delivery or an increase in Bishop score of 2 or more within the observation period, was achieved in 28 women (85 per cent).

In a second study (Johnston and Calder, 1995b), 24 multiparae, with a median gestational age of 41 weeks (range 39–42), were treated with a controlled release pessary for up to 8 hours. Treatment success, defined as an increase in Bishop score of 3 or more or vaginal delivery within the observation period, was achieved in 22 women (92 per cent).

MacKenzie (1995a) treated 27 women, with a mean gestational age of 40·7 weeks, with controlled release prostaglandin E_2 pessaries for up to 8 hours to achieve cervical ripening and induction of labour. The pessaries were thought to be a valuable addition to the procedures available for the induction of labour in both nulliparous and multiparous women. Cervical ripening occurred in 89 per cent with 82 per cent of the women achieving a spontaneous vaginal delivery.

Twenty-seven nulliparous women, at a mean gestational age of 40·1 weeks and Bishop scores ≤ 6, received prostaglandin E_2 as a controlled release pessary for up to 12 hours (Taylor *et al.*, 1995). More stringent criteria for treatment success were used in this study. Six women (22 per cent) delivered within 12 hours and a further nine achieved sufficient cervical ripening (Bishop score ≥ 9) or the onset of labour within the 12 hours. The remaining women were allocated at random to receive a second pessary or an oxytocin infusion. Vaginal delivery was achieved in 50 per cent of those receiving a second pessary.

Westgate and Williams (1995) employed the controlled release prostaglandin E_2 pessary with a retrieval system for the induction of cervical ripening and labour in 111 women (mean gestational age 40·7 weeks). Treatment success (an increase in Bishop score of 3 or more or onset of labour within the 12 hours of treatment) was achieved in 70 per cent of women and spontaneous vaginal delivery in 66 per cent. There was a high degree of acceptability for both the women and clinicians; 97 per cent of patients had no or little discomfort or retrieval difficulty (Westgate and Williams, 1994).

Browning *et al.* (1995) reported on an open post-marketing surveillance study conducted in 15 British centres to assess the efficacy and tolerance of the controlled release pessary (without the retrieval system). The pessary was retained for up to 12 hours by women at a mean gestational age of 40 weeks with a low Bishop score (0–4). The efficacy was assessed in 188 women and demonstrated that the pessaries encouraged cervical ripening. Treatment was judged successful (an increase in Bishop score of 3 or more or vaginal delivery within 12 hours of pessary insertion) in 82 per cent of women.

Nine women had labour induced with a controlled release prostaglandin E_2 pessary as part of a post-

Table V. Summary of cervical ripening with controlled release prostaglandin E_2 pessaries. Mean increase in Bishop score in each of six clinical studies and estimation of overall mean increase in Bishop score

	Nulliparae		*Multiparae*	
	n	*Mean increase in Bishop score*	*n*	*Mean increase in Bishop score*
Browning *et al.* (1995)	(123)	4·6	(69)	5·5
Calder and Johnston (1995a)	(33)	4·4	(33)	6·3
MacKenzie (1995a)	(13)	4·3	(14)	6·3
Mowat *et al.* (1995)	(3)	8	(6)	5·7
Westgate and Williams (1995)	(63)	2·9	(48)	2·7
Totals	(235)	4·1	(161)	4·9

marketing surveillance study by Mowat *et al.* (1995). The women had a mean gestational age of 39 to 40 weeks and were thought to need cervical ripening (mean initial Bishop score around 3). Treatment was judged successful in 89 per cent and all the women achieved vaginal delivery.

The results of the studies that interpreted 'treatment success' in a similar manner, an increase of ≥ 2 (Calder and Johnston, 1995a) or ≥ 3 in Bishop scores or onset of labour or vaginal delivery during treatment, are presented in Table V. Overall, induction of labour in a mixed group of 392 nulliparae and multiparae achieved 'success' in around 80 per cent.

Induction of cervical ripening

The prime indication for the vaginal administration of prostaglandin E_2 is to induce cervical ripening when this is to be initiated by intervention. Late cervical ripening is thought to result from a delay in the production of endogenous maternal prostaglandin E_2, and intravaginal application of prostaglandin E_2 both relaxes the cervical smooth muscle and stimulates endogenous prostaglandin E_2 production.

In all studies, the status of the cervix was assessed by a modified Bishop score which evaluates five pelvic features: cervical dilatation, the length of the cervix, the station of the head and the consistency and position of the cervix (Bishop, 1964).

MacKenzie (1995b) required an initial modified Bishop score of between 4 and 8, inclusive, before random allocation of nulliparae and multiparae to induction of labour with either the controlled release pessary or a Witepsol-based prostaglandin E_2 pessary. Similar increases in the Bishop score were found in the two treatment groups.

Nulliparous women entering a study by Calder and Johnston (1995a) all had a Bishop score of 4 or less on admission. The median increase in Bishop score was 4 after up to 8 hours treatment with controlled release pessaries. The increase in Bishop scores for the 33 nulliparae ranged from 0 to 11.

Johnston and Calder (1995) treated 24 multiparous women with Bishop scores of 6 or less at study entry (median baseline Bishop score 4). Treatment for up to 8 hours achieved increases from 1 to 11, with a median increase of 7.

Both nulliparae and multiparae with a Bishop score of 6 or less on admission were treated for up to 8 hours by MacKenzie (1995a). The mean Bishop score of the 27 women at entry was 4·5. Treatment resulted in a mean increase in the Bishop score of 5·3 (median 6·0; range 0–9).

Westgate and Williams (1995) also included both nulliparous and multiparous women, all with a Bishop score of 6 or less on admission (mean score 4.2). After treatment with controlled release prostaglandin E_2 pessaries for up to 12 hours, increases in the Bishop score ranged from 0 to 7, with a mean increase of 2·8.

In the post-marketing surveillance studies (Browning *et al.*, 1995; Mowat *et al.*, 1995) the increase in cervical ripening was recorded according to parity. With controlled release pessaries for up to 12 hours, the mean increase in Bishop score was 4·6 for nulliparae and 4·4 for multiparae; whilst with the retrievable pessaries for up to 12 hours, the mean increases were 8·0 and 5·7, respectively.

Overall, the mean increase in Bishop score in these nulliparous and multiparous women in the above six studies was about 4·4, which should be sufficient to enable vaginal delivery in the majority of women.

Induction of labour

Calder and Johnston (1995a) treated 33 nulliparous women with controlled release prostaglandin E_2 for up to 8 hours. The mean times from insertion of the pessary to onset of labour and delivery were 9·8 hours (s.d. $\pm$ 9·7) and 19·0 hours (s.d. $\pm$ 9·7), respectively, for those judged a treatment success, which was achieved in 28 women (85 per cent), with 73 per cent having spontaneous vaginal delivery.

Johnston and Calder (1995) used the pessaries to induce cervical ripening and labour in 24 multiparous women. The mean times from insertion of the pessary to onset of labour and delivery were 5·5 hours (s.d. $\pm$ 2·4) and 9·9 hours (s.d. $\pm$ 5·0), respectively, for those judged a treatment success, which was achieved in 22 women (92 per cent), with 79 per cent having spontaneous vaginal delivery.

The report by MacKenzie (1995a) involved the treatment of 27 women (13 nulliparous and 14 multiparous) with controlled release prostaglandin E_2 pessaries for up to 8 hours. The mean times from pessary insertion to onset of labour and delivery were 4·3 hours and 10·1 hours, respectively for the treatment successes which were achieved in 24 women (89 per cent) with 22 having spontaneous vaginal delivery.

Primiparae in the study by MacKenzie (1995b) were administered half the intravaginal dose of prostaglandin E_2 (5 mg) given to multiparae. Since these results are not comparable with the other studies

Table VI. Median times for onset of labour and delivery for patients treated successfully with controlled release prostaglandin E_2 pessaries for the induction of cervical ripening and labour

Reference	No. of patients NP:MP	Median time (hours)				No. of patients needing CS
		Onset of labour		Time of delivery		
		NP	MP	NP	MP	
Calder and Johnston (1995a)	(33:0)	9·8[a]	—	19·0[a]	—	9
Johnston and Calder (1995)	(0:24)	—	5·5[a]	—	9·9[a]	2
MacKenzie (1995a)	(13:14)	5·3	3·2	13·5	7·2	2
MacKenzie (1995b)	(38:0)	6·0	—	13·0	—	0
Westgate and Williams (1995)	(29:25)	12·1[b]	7·0[b]	20·3[b]	15·3[b]	NS

[a]mean value; [b]subset of patients not discharged or treated with additional PGE_2; NP nulliparae; MP multiparae; NS not stated; CS caesarean section.

Table VII. Relative efficacy of controlled release prostaglandin E_2 and oxytocin in the induction of labour following failed induction after 12 hours' initial treatment with the controlled release preparation in nulliparous patients (Taylor *et al.*, 1995)

	Oxytocin (n = 5)	Controlled release prostaglandin E_2 (n = 8)
Mean time to spontaneous or artificial rupture of membranes (hours)	3·7 (range 3·0–4·4)	8·3 (range 0–23·0)
Mean time from induction to delivery (hours)	11·4 (range 7·1–17·4)	17·2 (range 7·6–33·5)
Type of delivery:		
spontaneous vaginal	1	2
assisted vaginal	2	2
caesarean section	2	3
vacuum extraction	—	1

only the data from the 38 nulliparae receiving 10 mg are summarised in Table V. The median time from controlled release pessary insertion to the onset of labour in the nulliparae was 6 hours and the median time to delivery was 13 hours. Spontaneous vaginal delivery was achieved in 36 women (95 per cent).

Westgate and Williams (1995) allowed some women to be discharged home to await a second induction attempt or spontaneous labour. As a result some of the times to onset of labour and delivery were very long. The mean insertion of controlled release pessaries to onset of labour was 29·7 hours for nulliparae and 35·6 hours for multiparae and the mean time from pessary insertion to delivery was 38·8 hours and 44·6 hours, respectively. Seventy-three women had a spontaneous delivery and the remaining 38 were assisted, 19 by caesarean section. The data were then reanalysed to exclude those who were discharged home, if 48 hours or longer elapsed until delivery, or who subsequently received a prostaglandin E_2 pessary. From insertion of the controlled release pessaries to onset of labour the median times for nulliparae and multiparae were 12·1 hours and 7·0 hours respectively. Similarly, the median times to delivery were 20·3 hours and 15·3 hours respectively.

The median times from prostaglandin E_2 pessary insertion to the onset of labour and delivery are summarised in Table VI.

Failed induction of labour with a single controlled release pessary

Taylor *et al.* (1995) treated 27 nulliparous women, with a mean gestational age of 40·1 weeks, with a controlled release pessary.

Treatment success was defined as vaginal delivery or an increase in the Bishop score ≥ 3 within the 8 hour study period. Treatment success was achieved in 15 out of 27 nulliparae (56 per cent). Those whose Bishop score remained 8 or less after the initial pessary were allocated at random to receive either a second pessary or an intravenous infusion of oxytocin 12 hours after insertion of the controlled release pessary.

Thirteen women entered the second phase of the study (including one with a Bishop score of 9). Five received oxytocin and eight received a second pessary. The relative efficacy of labour induction and delivery is summarised in Table VII.

The numbers included in the two treatment groups were too small to allow definitive conclusions on the comparative efficacy of the two regimens. There was in general earlier rupture of membranes and delivery after failure with the prostaglandin E_2 pessaries following uterine stimulation with oxytocin. In clinical practice, the decision to continue induction of labour with prostaglandin E_2 or change to an intravenous infusion of oxytocin was influenced by whether addi-

Table VIII. Requirements for induction of labour with oxytocin following attempted induction with controlled release prostaglandin E_2 pessaries

Reference	Total no. of patients	No. of patients requiring oxytocin	Treatment success* after oxytocin use	Treatment failure after oxytocin use
Browning *et al.* (1995)	192	90 (47%)	NS	NS
Calder and Johnston (1995a)	33	20 (61%)	15	5
Johnston and Calder (1995b)	24	3 (13%)	2	1
MacKenzie (1995a)	27	19 (70%)	16	3
MacKenzie (1995b)	36	23 (64%)	NS	NS
Westgate and Williams (1995)	111	51 (46%)	NS	NS

Overall incidence of patients needing oxytocin 206/423 (49%). *Bishop score increase ≥ 2 on vaginal delivery within 8 hours. NS Not stated.

Table IX. Type of delivery achieved after induction of labour with controlled release prostaglandin E_2 pessaries

	Type of delivery		
Reference	Spontaneous vaginal	Assisted vaginal	Caesarean section
Calder and Johnston (1995a)	17 (52%)	7 (21%)	9 (27%)
Johnston and Calder (1995b)	19 (79%)	3 (13%)	2 (8%)
MacKenzie (1995a)	22 (82%)	3 (11%)	2 (7%)
Mowat *et al.* (1995)	7 (78%)	2 (22%)	0
Westgate and Williams (1995)	73 (66%)	19 (18%)	19 (17%)
Overall ($n = 204$)	138 (68%)	34 (17%)	32 (16%)

Some with oxytocin — numbers not specified by authors.

tional cervical ripening or uterine contractions were thought to be the primary requirement.

Completion of induction of labour with oxytocin was a common feature in many of the clinical trials, and there was a requirement for oxytocin in 206 out of 423 women (49 per cent) who did not have treatment success with the pessaries (Table VIII).

Mode of delivery after induction of labour with controlled release pessaries

Five studies allowed an evaluation of the delivery following induction of labour with controlled release pessaries. The data are presented in Table IX.

Relative efficacy in nulliparous and multiparous women

A number of clinical studies included both nulliparae and multiparae, with separate efficacy analyses for the two groups. These studies, together with the single parity studies, allow a comparison of the efficacy data according to parity.

MacKenzie (1995a) compared the efficacy of controlled release prostaglandin E_2 pessaries in the induction of cervical ripening in 13 nulliparae and 14 multiparae. Treatment success as defined by vaginal delivery or an increase in Bishop score ≥ 3 within the 8 hour study period was recorded in 85 per cent of nulliparae and 93 per cent of multiparae. There was a lower incidence of oxytocin use in multiparous women, 50 per cent compared with 92 per cent in nulliparous women. Multiparae had earlier median times for onset of labour and delivery, 3·2 hours multiparae and 5·3 hours nulliparae, and 7·2 hours multiparae and 13·5 hours nulliparae, respectively. All the multiparous women achieved spontaneous vaginal delivery compared with only 62 per cent of the nulliparous group. Thirty eight per cent of the nulliparous women needed assisted vaginal delivery or caesarean section.

Westgate and Williams (1995) evaluated the efficacy of controlled release pessaries in 111 women, 73 were nulliparous and 48 were multiparous. Treatment success, as defined by an increase in Bishop score of 3 or more or onset of labour within the 12 hour observation period, occurred in 78 women (70 per cent: nulliparae 73 per cent; multiparae 67 per cent). Oxytocin was used in 25 per cent of multiparae compared with 62 per cent of nulliparae. Spontaneous vaginal delivery was obtained in 79 per cent of multiparae and 56 per cent of nulliparae.

It was noted that some of the times to onset of labour and delivery were very long. This was due to some women being discharged home to await a second induction attempt or spontaneous labour. For this reason, the median times to onset of labour and delivery were calculated for the 70 per cent of women with successful cervical ripening with the controlled release pessary. Thus, the median time from the first insertion of the controlled release pessary to onset of labour was 14·0 hours (14·0 hours for the nulliparae and 13·6 hours for the multiparae) and the time to delivery was 23·0 hours (23·8 hours for the nulliparae and 19·8 hours for the multiparae). Three women were withdrawn from the study after admission because of an abnormal lie; one of these had a spontaneous vaginal delivery and two had caesarean sections. The remainder had spontaneous vaginal deliveries. Ninety women required augmentation of labour with oxytocin.

The British post-marketing surveillance study on the controlled release pessary (Browning *et al.*, 1995)

Table X. Overall efficacy data from three double-blind placebo-controlled clinical studies with 0·8 mm controlled release prostaglandin E_2 pessaries (Saulter, 1995). Treatment success was defined by vaginal delivery within 12 hours or Bishop score ≥ 6 at 12 hours or increase in Bishop score ≥ 3 at 12 hours

Achievement within 12-hour treatment period	Rayburn et al. (1992)		Witter et al. (1992)		Rayburn et al. (1991)	
	Active	Placebo	Active	Placebo	Active	Placebo
n	(150)	(184)	(41)	(36)	(92)	(101)
Vaginal delivery	20·0%	1·1%	24·3%	0·0%	2·2%	5·9%
Bishop score ≥ 6	5·3%	5·4%	4·9%	5·6%	44·6%	33·7%
Bishop score increase ≥ 3	47·3%	15·2%	43·9%	22·2%	14·1%	9·0%
Mean treatment success	73·0%**	22·0%	73·0%*	28·0%	65·0%*	45·0%

Comparison with placebo: *$P < 0.01$; **$P \leq 0.001$.

Table XI. Median times to delivery in nulliparous and multiparous patients from three double-blind placebo-controlled clinical studies with the 0·8 mm pessary (Saulter, 1995)

Study	n		Median time to delivery (hours)	
			Nulliparae	Multiparae
Rayburn *et al.* (1992)	150	Active	28·1	17·0
	184	Placebo	N/A	N/A
Witter *et al.* (1992)	41	Active	25·7**	11·8**
	36	Placebo	35·1	28·6
Rayburn *et al.* (1991)	92	Active	26·8**	20·6**
	101	Placebo	38·3	27·0

Comparison with placebo: **$P \leq 0.001$. N/A No formal comparison with placebo-treated women was made.

evaluated 192 women, 123 nulliparae and 69 multiparae. The multiparous women had an earlier onset of labour, shorter mean duration and earlier delivery following the pessary enclosed in a prototype retrieval system than the nulliparae. The mean interval from insertion of the pessary to onset of labour was 22·6 hours for nulliparae and 11·9 hours for multiparae, whilst the mean interval to delivery was 33·5 hours and 17·0 hours, respectively. The mean duration of labour was 8 hours in nulliparae against 4·8 hours in multiparae.

In a smaller post-marketing surveillance study in nine women (3 nulliparae and 6 multiparae) receiving the pessary enclosed in a prototype retrieval system, the mean times from insertion of the pessary to onset of labour were 12·9 hours for nulliparous women and 6·8 hours for multiparous women and from insertion to delivery 18·6 hours and 16·1 hours, respectively. Seven women had spontaneous vaginal deliveries and two had instrumental assistance. There were no caesarean sections (Mowat *et al.*, 1995).

The mean increase in the Bishop score in nulliparae was 4·1 compared with an increase of 4·9 in multiparae. Multiparous women tend to have a reduced requirement for oxytocin, reduced time to labour and delivery, and an increased incidence of vaginal delivery.

Efficacy of an alternative type of controlled release pessary

The controlled release pessary available in the United Kingdom is a 1·1 mm thick pessary containing 10 mg dinoprostone with the prostaglandin released from a hydrogel polymer core. An alternative but essentially similar pessary only 0·8 mm thick has also been investigated. Three double-blind clinical studies and five open studies were conducted to assess the efficacy of this 0·8 mm controlled release hydrogel prostaglandin E_2 pessary. These largely unpublished studies are summarised and discussed together in a review (Saulter, 1995); some individual centres have also published study results (Rayburn *et al.*, 1992; Witter *et al.*, 1992).

Double-blind placebo-controlled studies

Three double-blind comparative studies against placebo were conducted with the 0·8 mm controlled-release prostaglandin E_2 pessary. One study utilised the pessaries fitted with a retrieval system, consisting of a polyester 'net' and withdrawal cord. All three studies involved women with singleton pregnancies and cephalic presentations, for whom there were medical or obstetric grounds for the induction of labour, and who had a Bishop score of 4 or less. The women were at least 37 weeks pregnant. Both treatment groups were stratified for nulliparae and multiparae.

Three key measures of efficacy were monitored and used to assess the achievement of treatment success: vaginal delivery with 12 hours, a Bishop score ≥ 6 at 12 hours and an increase in Bishop score ≥ 3 at 12 hours.

The results for each of these efficacy end points were summarised in Table X. In all three double-blind studies, the active pessary produced a greater

Table XII. Overall efficacy data from five open studies with 0·8 mm thick controlled release prostaglandin E_2 pessaries (Saulter, 1995)

Study	No. patients	Delivery within 12 hours	Bishop score ≥ 6 at 12 h	Bishop score increase ≥ 3 at 12 h	Treatment success
1(a)	39	46·0%	—	52·8%	67·0%
2(b)	142	—	—	—	66·0%
3	53	17·0%	2·0%	41·5%	58·0%
4	31	3·2%	61·0%	12·9%	77·0%
5	30	6·6%	80·0%	0	87·0%
	33 (with RS)	3·0%	66·0%	3·0%	83·0%

(a) open active study in patients with initial Bishop score 4–5; (b) open cross-over for placebo treatment failures; RS retrieval system.

success rate than the placebo pessary. In one study the incidence of vaginal deliveries was greater in the early part of the study where the pessary was left *in situ* after the onset of labour (Rayburn *et al.*, 1992).

The median times to delivery were also recorded in these studies and compared according to parity (Table XI). In the two studies, where the times to delivery were recorded for placebo-treated women, the time to delivery was significantly shorter in the active treatment groups.

In the study by Witter *et al.* (1992) the median time to onset of labour was also significantly less in the actively treated group; in nulliparae, 12·0 hours compared to 19·2 and, in multiparae, 7·0 compared to 21·6 hours ($P < 0{\cdot}001$). In this study, following active treatment, multiparous women had a greater incidence of vaginal delivery than the nulliparous group ($P < 0{\cdot}05$).

Open studies

Five open studies with the 0·8 mm controlled release prostaglandin E_2 pessary have yielded efficacy results. Two of these studies included women originally recruited that by Witter *et al.*; an open study for women with a presenting Bishop score of 5 to 6 (outside the inclusion criteria of Bishop score ≤ 4 for the double-blind study), and an open comparison of placebo treatment failures with active therapy.

As with the double-blind studies, the three primary end points of efficacy were vaginal delivery within 12 hours, Bishop score ≥ 6 at 12 hours or increase in Bishop score ≥ 3 at 12 hours. The primary efficacy results from the five open studies are summarised in Table XII.

In conclusion, double-blind controlled studies with the 0·8 mm pessary demonstrated greater treatment success for the active controlled release prostaglandin E_2 pessary than with a placebo pessary.

Clinical safety

Dinoprostone (prostaglandin E_2) is a naturally occurring prostaglandin used predominantly in obstetric practice. Serious adverse events in association with the local administration of prostaglandin E_2 are very rare. Excessive uterine stimulation can occur and very rarely may result in uterine rupture or amniotic fluid embolism (Dollery, 1992).

Overstimulation of the uterus during cervical ripening or induction can cause severe pain and acute fetal distress. The incidence of hyperstimulation is related to the dose administered, the route of administration and the sensitivity of the individual women to prostaglandin E_2. An incidence of 0·6 to 20·0 per cent has been cited for uterine hyperstimulation with an intravaginal dinoprostone preparation. Hyperstimulation due to dinoprostone was commonest after the onset of active labour (Rayburn *et al.*, 1992). Local administration of dinoprostone rarely causes systemic adverse effects, such as fever, diarrhoea or vomiting.

Uterine hyperstimulation

Calder and Johnston (1995a) recorded one case of uterine hyperstimulation with variable decelerations and fetal bradycardia, which occurred two hours after pessary insertion and was thought to be due to the prostaglandin E_2. The incident resolved spontaneously on removal of the pessary.

Taylor *et al.* (1995) recorded two instances of hyperstimulation associated with controlled release pessaries. Both were associated with fetal heart rate decelerations and occurred during the first 12 hours. Removal of the pessary diminished the intensity of the contractions in both cases.

Westgate and Williams (1994) recorded three (2·7 per cent) cases of uterine hyperstimulation and hypertonus, with no associated fetal distress, which were thought to be related to controlled release prostaglandin E_2 pessaries. Hyperstimulation resolved within 30 minutes of removal of the pessary (Westgate and Williams, 1994). Westgate and Williams (1995) also commented on the relatively low analgesic requirements of women receiving the preparation. Only 18 per cent of women required analgesia whilst the pessary was *in situ*, with the majority requiring only simple measures, such as paracetamol or night sedation.

A post-marketing surveillance study (Browning *et al.*, 1995) evaluated the adverse event profile of controlled release pessaries treatment of 192 women. Nine women (4·7 per cent) had uterine hyperstimulation or hypertonus attributed to the use of the pessary. In two of the above nine incidents, the pessary had been left *in situ* after the onset of labour. Most adverse events were controlled by the removal of the pessary; only one woman required tocolytic treatment to control contractions, but a precipitous delivery occurred in another.

Five studies involving 139 women reported no adverse events attributable to controlled release prostaglandin E_2 pessary (Johnston and Calder, 1995; Calder and Johnston, 1995b; MacKenzie, 1995a and 1995b; Mowat *et al.*, 1995).

Table XIII. Incidence of drug-related uterine hyperstimulation and fetal hyperstimulation in clinical trials with controlled release prostaglandin E_2 pessaries

Reference	n	Incidence of adverse events		
		Maternal uterine hyperstimulation	Fetal distress with hyperstimulation	Fetal distress without hyperstimulation
Browning *et al.* (1995)	192	9 (5%)	6 (3%)	5 (3%)
Calder and Johnston (1995a)	33	1 (3%)	1 (3%)	1 (3%)
Calder and Johnston (1995b)	7	0	0	0
Johnston and Calder (1995)	24	0	0	0
MacKenzie (1995a)	27	0	0	0
Taylor *et al.* (1995)	27	2 (7%)	2 (7%)	0
Mowat *et al.* (1995)	9	0	0	0
Westgate and Williams (1995)	111	3 (3%)	0	3 (3%)
Totals	430	15 (3·5%)	9 (2·1%)	9 (2·1%)

Other maternal adverse events

Westgate and Williams (1995) reported one case of vomiting with the pessary *in situ*. The event was described as mild and required no treatment.

The post-marketing surveillance studies, which assessed the tolerability of the controlled release pessaries in the induction of labour in 201 women, recorded a low incidence of drug-related maternal adverse events: backache 2·5 per cent; abdominal pain 2·0 per cent; nausea and vomiting 1 per cent; and diarrhoea and headache 0·5 per cent (Browning *et al.*, 1995; Mowat *et al.*, 1995).

Fetal adverse events

Calder and Johnston (1995a) recorded one incident of hyperstimulation and fetal bradycardia (3 per cent) and one case of fetal tachycardia (3 per cent). Both neonates were healthy at delivery.

Johnston and Calder (1995) noted six incidents of fetal distress, but all occurred after removal of the pessary or oxytocin administration and were not attributed to use of the pessary.

Taylor *et al.* (1995) recorded two incidents of fetal distress associated with uterine hyperstimulation. One baby was subsequently delivered by caesarean section. There was also one case of intra-uterine death, in which the umbilical cord was found to be tightly wrapped round the upper arm of the fetus. This event was not considered related to the prostaglandin pessary.

Westgate and Williams (1995) identified three incidents (2·7 per cent) of fetal distress (fetal heart rate decelerations) which were thought to be related to the use of the pessary. A healthy neonate was delivered in all cases.

In the post-marketing surveillance study, a total of 11 cases of fetal heart rate changes (5·7 per cent) were recorded by fetal cardiotocography (Browning *et al.*, 1995). Six cases of fetal complications were recorded in association with hypertonus, and a further five cases in the absence of uterine hyperstimulation. In three of the latter cases, the abnormal rhythm continued after removal of the pessary and throughout the subsequent labour.

No fetal adverse events attributable to the pessaries were recorded in four studies (Johnston and Calder, 1995; Calder and Johnston, 1995b; Mackenzie, 1995a; Mowat *et al.*, 1995).

In a comparative study of prostaglandin E_2 treatment using a controlled release pessary or a Witepsol-based pessary followed by artificial rupture of the membranes, MacKenzie (1995b) reported an incidence of fetal adverse events of 41 per cent for nulliparae and 13 per cent for multiparae with Witepsol pessaries. The incidence of adverse events was similarly high in the controlled release pessary group (34 per cent of nulliparae and 28 per cent of multiparae). This study was not comparable with other studies on controlled release prostaglandin E_2 pessaries as the protocol required artificial rupture of the membranes after 3 hours and oxytocin administration within the 8 hours of starting treatment.

Although the adverse fetal and maternal effects resolved when the pessary was removed, it is now advised that the pessary should be removed before the membranes are ruptured artificially, and removed promptly if the membranes rupture spontaneously.

Neonatal and paediatric safety

Apgar scores were recorded for neonates at both one minute and five minutes after delivery (Calder and Johnston, 1995a; Johnston and Calder, 1995; MacKenzie, 1995a; Taylor *et al.*, 1995; Westgate and Williams, 1995). The median Apgar scores at one minute ranged from 7·6 to 8·4 (range of scores 1 to 10) and at five minutes ranged from 9·0 to 9·9 (range of scores 3 to 10). The median values at five minutes confirm that induction using controlled release prostaglandin E_2 pessaries does not have an adverse effect on neonatal condition at birth.

MacKenzie and McKinlay (1995) presented a retrospective comparison of the child health records of 313 children delivered at a single centre whose mothers had spontaneous vaginal delivery after spontaneous labour or had labour induced with prostaglandin E_2 pessaries, either controlled release or Witepsol-based, or by artificial rupture of membranes or oxytocin infusion, or had been delivered by elective caesarean section. No adverse effects of these procedures on infant health, or psychomotor or physical development over the first three years of life were detected, with no differences between the groups.

Overall safety profile of controlled release prostaglandin E_2 vaginal pessaries

The interpretation of maternal and fetal adverse events is partly hampered by the absence of a univer-

sally accepted definition for fetal distress or hypertonus. In clinical studies, investigators have applied their own interpretation of potential adverse events. In particular, interpretation of fetal cardiotographic tracings is frequently variable and inconsistent.

Double-blind and open studies with the alternative 8 mm diameter controlled release prostaglandin E_2 pessary have indicated that this form of treatment is less well tolerated. An incidence of 8 to 14 per cent of uterine hyperstimulation was reported, which was usually rapidly controlled by removal of the pessary. Fetal heart rate changes or fetal distress were recorded in about 7 per cent of cases, with half of these associated with maternal uterine hyperstimulation (Saulter, 1995).

The similarity of the protocols applied to the majority of the British clinical trials and the post-marketing surveillance studies allows an overview of the safety profile of the current controlled release prostaglandin E_2 pessaries. The incidence of the two main adverse events, uterine hyperstimulation and fetal cardiac events, is presented in Table XIII.

The mean incidence of uterine hyperstimulation following induction of labour in 430 nulliparous and multiparous women was 3·5 per cent, with a range of 0 to 7 per cent. Similarly, the mean incidence of fetal distress assessed by heart rate changes was 4·2 per cent with a similar range of 0 to 7·4 per cent. Half the fetal rate changes were associated with uterine hyperstimulation. Only a few adverse events needed medical or surgical intervention, and the majority were managed by removal of the pessary.

Retention of the controlled release pessary after the onset of labour has been identified in a number of studies as a risk factor for uterine hyperstimulation (Browning *et al.*, 1995; Westgate and Williams, 1994), as there is likely to be greater release of prostaglandin E_2 from the pessary at the pH of amniotic fluid (see Pharmacokinetics section).

In studies evaluating the release rate for prostaglandin E_2 from the controlled release pessary, no evidence of 'dose dumping' was found (Westgate and Williams, 1994; Calder and Johnston, 1995a; Johnston and Calder, 1995; MacKenzie, 1995a). No correlation was found between the release of prostaglandin E_2 and the incidence of maternal or fetal adverse events. Two cases of uterine hyperstimulation before the onset of labour occurred in women who had received no more than 1 mg of prostaglandin E_2 (Westgate and Williams, 1994). Thus, the occurrence of adverse events appears to relate to individual sensitivity to exogenous and endogenous prostaglandin.

Conclusion

Prostaglandin E_2 has an important preparatory role in parturition, producing first softening and dilatation of the cervix and then uterine contractions. In order to enable labour induction to replicate the gradual transition present in spontaneous labour, research began on a controlled release prostaglandin E_2 pessary.

The pessary consists of a hydrophilic polymer containing 10 mg of prostaglandin E_2. The hydrogel polymer swells in vaginal fluid and releases the prostaglandin E_2 at a near constant rate of around 0·3 mg/hour, releasing approximately 4 to 5 mg prostaglandin E_2 over 12 hours. The pessary swells within the vagina to 2 to 3 times its original size; as it swells, it becomes soft and pliable but maintains its physical integrity, so facilitating removal.

The preparation utilises a retrieval system consisting of a one-piece knitted pouch made from polyester with an attached withdrawal tape to allow the pessary to be removed at the onset of labour or rupture of membranes, or in the event of a maternal or fetal adverse event. A high degree of acceptability has been shown for the preparation with 99 per cent of women reporting little or no discomfort with its use. Retrieval of the pessary has also been achieved with little or no difficulty in 97 per cent of women.

Efficacy. The controlled release prostaglandin E_2 pessary has been evaluated in eight clinical studies involving nearly 500 women. Treatment induced cervical ripening, with a mean increase in the Bishop score of around 4·4. Spontaneous vaginal delivery was achieved in 68 per cent of women.

About half the women treated with the pessary required additional oxytocin.

As might be expected the time to cervical ripening and onset of labour is usually better in multiparous women who also tend to have a reduced requirement for oxytocin and an increased incidence of vaginal delivery.

Safety. The mean incidence of uterine hyperstimulation following induction of labour with the pessaries was 3·5 per cent and the mean incidence of fetal distress was 4·2 per cent. Half the adverse fetal events were associated with uterine hyperstimulation. No adverse effects on neonatal or paediatric development have been recorded.

The majority of adverse events were managed by removal of the pessary.

Controlled release prostaglandin E_2 vaginal pessaries are effective and well tolerated in achieving cervical ripening and labour in both nulliparous and multiparous women. The presentation enables the pessary to be efficiently removed at the onset of labour or rupture of the membranes and also allows its rapid removal in the event of maternal or fetal adverse events.

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