Title:

Evaluation of a controlled release vaginal prostaglandin E2 pessary with a retrieval system for the induction of labour

Authors:

Westgate J and Williams JA

Journal:

J Obstet Gynaecol 1994

Journal of Obstetrics and Gynaecology (1994) 14, 146–150

Evaluation of a controlled release vaginal prostaglandin E_2 pessary with a retrieval system for the induction of labour

Jennifer Westgate and J. Anne Williams
Perinatal Research Group, Department of Obstetrics, Postgraduate Medical School, Derriford Hospital, Plymouth

Summary
A slow release hydrogel polymer prostaglandin E_2 pessary with a retrieval system for the induction of labour was studied in 111 women with a cervical score ≤ 6. The pessary was removed with little difficulty and caused no discomfort while *in situ* in 97 per cent of cases. The mean prostaglandin E_2 release rate, assessed by high performance liquid chromatography, was 0·33 ± 0·15 mg/hour (s.d.; 95 per cent confidence interval 0·30–0·36 mg/hour) and was not related to parity, treatment success or failure. There was no dose dumping. Four cases (4 per cent) had fetal heart rate abnormalities during induction, none were hyperstimulated. Two cases (2 per cent) of hyperstimulation resolved with removal of the pessary and in neither case was more than 1 mg of prostaglandin E_2 released from the pessary. This preparation safely allows the obstetrician to control the dose of prostaglandin E_2 administered during induction of labour.

INTRODUCTION

A CONTROLLED release prostaglandin E_2 pessary (Propess; Controlled Therapeutics, Scotland, Ltd., East Kilbride, Scotland) has been developed for cervical ripening in the induction of labour (Embrey and MacKenzie, 1985). It is a hydrogel polymer which releases the drug at a near constant rate as it swells in vaginal fluid (Taylor *et al.*, 1990). In contrast with other vaginal prostaglandin E_2 preparations in current use, this system allows the obstetrician to control the dose administered and, in particular, to terminate drug delivery by removing the pessary should uterine hyperstimulation or abnormal fetal heart rate changes occur during the ripening process. Following its introduction, a letter to *The Lancet* (Bex *et al.*, 1990) described difficulties removing the pessary and another (Khouzam and Ledward, 1990) described two cases of hyperstimulation and one of fetal distress in 30 patients and suggested that dose dumping may have occurred. Experience with Propess in 41 patients in our hospital was more favourable, with no hyperstimulation but we noted that removal could be difficult (Baravilala *et al.*, 1990). The company elected to withdraw the product from the market but in the meantime a retrieval system consisting of a knitted Dacron polyester pouch and withdrawal tape has been developed to assist removal.

The aim of this prospective observational study was to assess ease of removal and patient acceptability of Propess with its retrieval system (Propess-RS) and, secondly, to assess efficacy, safety and investigate whether prostaglandin E_2 dose dumping occurred.

SUBJECTS AND METHODS

The study was performed under a Clinical Trial Exemption Certificate. A sample size of 100 patients was chosen to assess the effectiveness of the retrieval system. As the incidence of adverse events with prostaglandin E_2 preparations reported in the literature varies from 0 to 35 per cent for uterine hyperstimulation and from 0 to 40 per cent for unspecified fetal heart rate 'abnormalities' (Keirse and van Oppen, 1989), the sample size would be adequate to detect any adverse events.

Women with a singleton, cephalic, pregnancy of at least 38 weeks duration who were thought to require induction of labour for medical or obstetric reasons were recruited for the study if their modified Bishop's score was 6 or less. Patients with more than three previous full term pregnancies, a previous caesarean section, ruptured membranes, evidence of fetal compromise or asthma were excluded.

At entry, all patients were examined by a single research midwife who allocated a Bishop's score. Uterine activity and fetal heart rate were monitored by a cardiotocogram at baseline and then again 1 hour after insertion of the pessary, during which time the patients remained in bed. The cardiotocogram was repeated at the onset of tightenings or contractions. The pessary was removed by the research midwife after 12 hours, or earlier if there was concern about fetal or maternal condition or uterine contraction frequency; or if the membranes ruptured or labour ensued. Labour was defined as the onset of regular painful contractions which lasted at least 45 seconds at a frequency of three to four contractions in 10 minutes. In all cases a cervical assessment was made at the time of removal. Ease of removal was assessed by staff and patients on a 4-point scale. Patients also rated their experience of the pessary *in situ* on a 4-point scale. Treatment was considered effective if labour began during the 12 hour observation period or if the Bishop's score increased by three or more points. Patients who did not go into labour or who were unsuitable for amniotomy following the 12 hours observation were managed at the discretion of their attending obstetrician.

Following removal all pessaries were placed in a plastic bag labelled with the study number, date and time of removal and placed immediately into a freezer. The pessaries were analysed by high performance liquid chromatography by Controlled Therapeutics (Scotland) Ltd. (East Kilbride, Scotland). The amount of prostaglandin E_2 released was calculated by subtraction of the residual prostaglandin from the batch potency.

Statistical analysis was by Student's t test, Mann-Whitney U test, analysis of variance or χ^2 analysis. Odds ratios and their 95 per cent confidence intervals are given where appropriate.

RESULTS

One hundred and eleven patients (63 primigravidae, 48 multigravidae) were recruited. The mean gestational age at induction was 40·7 weeks (primigravidae 40·9, multigravidae 40·4) and the mean initial Bishop's score was 4·2 (primigravidae 4·2, multigravidae 4·1).

Ease of removal and patient acceptability

The pessary was removed with little or no difficulty for either staff or patient in 97 per cent of cases (Table). All patients who experienced slight discomfort during removal likened the sensation to removal of a tampon. Removal was very difficult in one case who became very distressed at the onset of labour and developed vaginismus. The retrieval system allowed the pessary to be removed but a full vaginal examination could not be performed until after epidural analgesia was established. No uterine hyperstimulation occurred and the patient did not have a precipitate labour. All 111 patients provided information about their experience of the pessary *in situ*. Ninety-eight patients (88 per cent) were unaware of its presence, 10 (9 per cent) were aware but felt no discomfort, two (2 per cent) were aware with mild discomfort and one (1 per cent) had marked discomfort with the pessary *in situ*.

The pessary fell out in 11 patients. Eight of these occurred in the first 51 patients when the pessary was left lying longitudinally in the vagina following insertion. In the next 60 patients the insertion technique was modified to leave the pessary lying transversely in the posterior fornix. After that only three pessaries were lost, all from patients in early labour; one loss with spontaneous rupture of the membranes, one with a heavy mucous show and one with a contraction.

Efficacy

Treatment success, defined as the onset of labour within 12 hours or an increase in Bishop's score of at least 3, occurred in 78 (70 per cent) of all 111 patients (primigravidae 73 per cent; multigravidae, 67 per cent). If the patients in whom the pessary was lost ($n = 11$) or in whom the pessary was removed early due to an adverse event ($n = 8$) are excluded, treatment success occurred in 70 of 92 patients (76 per cent) of cases (primi-

Table. Ease of pessary removal in 100 patients

	As assessed by	
	Midwife	*Patient*
No difficulty	78	88
Slight difficulty	19	9
Moderate difficulty	2	2
Very difficult	1	1

gravidae 80 per cent; multigravidae, 71 per cent). In this group, although the median pre-treatment Bishop's scores were the same, patients with a treatment success tended to have had higher initial scores compared with those with a treatment failure (difference, $P < 0.05$). The success rate in multigravidae was lower than that of primigravidae. No differences in gestational age or pre-treatment Bishop's scores were found, but when individual components of the Bishop's score were examined there were more multigravidae induced with a very high presenting part (station 3 cm above the ischial spines or higher; 71 per cent *versus* 35 per cent, $P < 0.001$; odds ratio 4·53, 2·01–10·17).

A 3 mg prostaglandin E_2 pessary (Prostin, Upjohn Ltd) was administered vaginally to 27 patients (24 per cent) who did not go into labour within 12 hours and who were not considered suitable for artificial rupture of the membranes. Of these, 10 were treatment successes (with a Bishop's score increase of at least 3); nine received one 3 mg pessary before labour ensued, the other received three 3 mg pessaries before being sent home to return 2 days later in spontaneous labour. These patients had good outcomes with nine normal deliveries and one caesarean section for failure to progress. Of the 17 patients who did not have a satisfactory cervical change with Propess-RS, five patients had one 3 mg pessary, nine had two doses and three had three doses. Eight (47 per cent) were sent home after failing to respond to extra prostaglandin E_2, two were readmitted in spontaneous labour, five were readmitted for further induction attempts and one was delivered by elective caesarean section. The overall caesarean section rate in this group was 35 per cent.

Adverse events with Propess *in situ*

The pessary was removed early from six patients because of an abnormal cardiotocogram and from two patients because of uterine hyperstimulation.

All six cases of cardiotocographic abnormality were associated with uterine activity but none was hyperstimulated. In two cases the record showed an accelerative fetal heart rate pattern which was misinterpreted as a fetal tachycardia, so the true incidence of fetal heart rate abnormalities with the pessary *in situ* was four cases (3.6 per cent). Contractions did not resolve following removal of the Propess in two cases (one was in early labour, the other had the membranes ruptured artificially after removal of Propess) who were delivered by emergency caesarean section. Both neonates were in good condition at delivery although one was postmature and treated for hypoglycaemia neonatally. The two other cases had decelerations accompanying mild, infrequent contractions (one in 5 to 10 minutes) which resolved when the pessary was removed. Both went into spontaneous labour the following day, one with an uneventful labour, normal delivery and good neonatal outcomes. The other had continued decelerations and meconium stained amniotic fluid throughout labour with two normal fetal blood samples before a normal delivery and outcome.

Propess-RS was removed from two multigravidae (2 per cent) because of hyperstimulated uterine activity (> 5 contractions in 10 minutes). Both episodes occurred within 1 hour of insertion and resolved within 30 minutes of removal. Neither case had fetal heart rate changes and both delivered normally after uneventful labours. In six cases the pessary was left *in situ* at the onset of labour. In all these cases the onset of contractions had been slow and gradual and, despite the protocol, staff did not remove the pessary once regular painful contractions were established because they were unable to detect any change in the cervix on vaginal examination. One of the six had a contraction frequency of 5 in 10 minutes in the second stage of labour. All six had normal outcomes.

Residual prostaglandin E_2

One hundred and three pessaries were recovered for analysis of residual prostaglandin content. The amount released from each pessary is shown in the Figure.

The mean rate of prostaglandin E_2 release was 0.33 ± 0.15 mg/hour (s.d.; range 0·12 to 0·78; 95 per cent confidence interval 0·30–0·36 mg/hour). No difference was found in release rates between primigravidae and multigravidae or between treatment successes and treatment failures. Less than two mg of prostaglandin E_2 was released in the 12 hours in 13 (22 per cent) of the 60 patients who had the pessary in for that time, nevertheless treatment success occurred in seven cases (54 per cent). Conversely, five of the 16 patients (31 per cent) who received more than 4 mg of prostaglandin E_2 in the 12 hour period had treatment failures.

DISCUSSION

The inability to remove vaginal prostaglandin pessaries or gels and terminate drug delivery has always been a concern about these preparations.

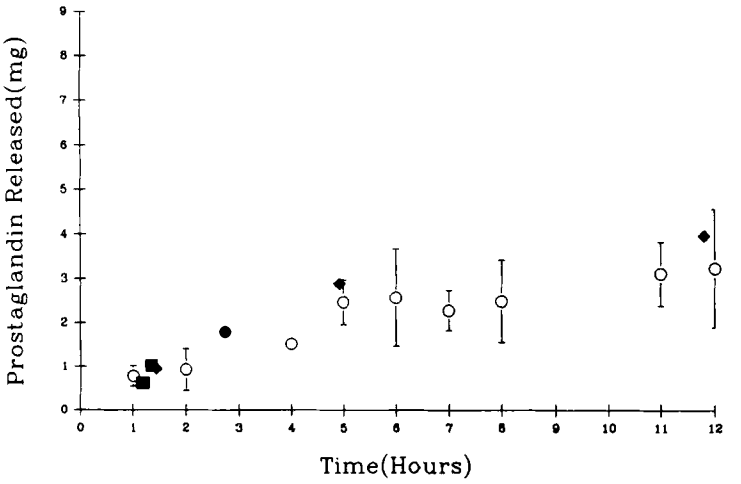

Figure. The amount of prostaglandin E_2 released from each pessary according to the number of hours in the vagina and the occurrence of adverse events. Results are shown as means (○) ± 2s.d. ■ Hyperstimulation, ♦ fetal heart rate abnormalities.

This study has demonstrated that the retrieval system fitted to Propess allows easy removal and has a high patient acceptability. The incidence of excessive uterine activity (2 per cent) and fetal heart rate abnormalities with the pessary *in situ* (4 per cent) were low. Furthermore, neither of the women with hyperstimulation before labour could have received more than 1 mg of prostaglandin E_2. This suggests an individual sensitivity to exogenous prostaglandin rather than an overdose of drug and confirms the advantage both of a slow release preparation and of the ability to rapidly terminate drug delivery.

Uterine hyperstimulation with Propess-RS can also occur if the pessary is left in too long after the onset of labour. This occurred in one case in our study. In two studies where similar controlled release preparations were deliberately left in place at the onset of labour, the overall incidences of hyperstimulation were 15 per cent (Rayburn *et al.*, 1992) and 7 per cent (Witter *et al.*, 1992), but, when removed before the onset of labour, hyperstimulation occurred in only 4 per cent and nil respectively. In all cases, uterine activity reduced with removal of the pessary. Staff must understand that the pattern of uterine activity with the slow release pessary is different to that commonly seen with other vaginal prostaglandin preparations (Miller *et al.*, 1991). We noted a gradual increase in uterine activity over a number of hours with Propess, as opposed to the frequent painful uterine activity seen in the first hour after prostaglandin E_2 pessaries or gel which then often subsides. These pains are not usually associated with change in the cervix and do not necessarily signal the onset of labour. The painful tightenings with Propess-RS were progressive and did not decline unless the pessary was removed. The onset of labour was best judged by the onset of regular painful contractions and not by change in the cervix. A slow steady onset of contractions may be preferable for women who have labour induced. There is no comparative data available for other vaginal prostaglandin E_2 preparations, but it is our impression that analgesia requirements with Propess-RS were reduced. Only 20 (18 per cent) in our study required analgesia with the pessary *in situ*, the vast majority (16) receiving paracetamol, night sedation, baths or the 'pulsar'.

There was no evidence of dose dumping from Propess-RS. The release rate of prostaglandin E_2 found in this study (0·33 mg/hour) was much lower than the 0·9 mg/hour previously reported (Taylor *et al.*, 1990). The pessary used in that study was thinner (0·8 mm thick versus 1·1 mm in this study) which should theoretically have resulted in an increase in release rate. The main reason for the discrepancy is that the pessary was left *in situ* following amniotomy in several cases in Taylor *et al.*'s study. Amniotic fluid has a higher pH than the normal vaginal pH during pregnancy and would cause greater release of prostaglandin from the pessary (Johnson *et al.*, 1992). If the release rate is recalculated excluding the amniotomy cases the mean rate of 0·33 mg/hour is comparable with the rate found in our study (Controlled Therapeutics, personal communication).

Vaginal prostaglandin preparations probably act by stimulating endogenous prostaglandin

production. It has been thought that this is achieved most successfully by a rapid initial rise in prostaglandin E_2 (Greer *et al.*, 1990). A single dose of other prostaglandin vaginal preparations causes a maximal increase in plasma prostaglandin metabolites in the first 40 minutes after administration, which may be responsible for the initial uterine activity described above. Propess-RS released an average of 0·3 mg of prostaglandin E_2 in the first hour, so a rapid initial rise in metabolites was unlikely. Our results suggest that a slow but steady release of exogenous prostaglandin E_2 is also effective in stimulating endogenous production. The amount released from each pessary varied and was not related to the success of the induction. Greer *et al.*, (1990) also found variable absorption rates with prostaglandin E_2 gel. Patients who failed to respond to Propess had a 35 per cent incidence of caesarean section (despite receiving additional prostaglandin) compared with an 11 per cent incidence for those who did respond.

This study has demonstrated the safety and efficacy of a slow release prostaglandin E_2 preparation with a retrieval system. It allows the clinician to control the dose administered and therefore offers particular advantages in cases where there is concern about fetal condition or a risk of uterine over-activity.

Acknowledgements

We thank the medical and midwifery staff at Freedom Fields Hospital, Plymouth for their collaboration and support. We acknowledge the support of Controlled Therapeutics who supplied the Propess-RS pessaries and performed the analysis of residual prostaglandin E_2 content.

REFERENCES

Baravilala W. R., Baker C. and Morsman J. M. (1990) Controlled release prostaglandin E2 pessaries [letter]. *Lancet* **336,** 437.

Bex P., Gunasekera P. C. and Phipps J. H. (1990) Difficulties with controlled release vaginal prostaglandin pessaries [letter]. *Lancet* **336,** 119.

Embrey M. P. and MacKenzie I. Z. (1985) Labour induction with a sustained release prostaglandin E2 polymer vaginal pessary. *Journal of Obstetrics and Gynaecology* **6,** 38–N41.

Greer I. A., McLaren M. and Calder A. A. (1990) Vaginal administration of PGE2 for induction of labour stimulates endodgenous PGF2α production. *Acta Obstetricia et Gynecologica Scandinavica* **69,** 621–625.

Johnson T. A., Greer I. A., Kelly R. W. and Calder A. A. (1992) The effect of pH on release of PGE2 from vaginal and endocervical preparations for induction of labour. *British Journal of Obstetrics and Gynaecology* **99,** 877–880.

Keirse M. N. and van Oppen A. C. C. (1989) Preparing the cervix for induction of labour. In: *Effective Care in Pregnancy and Childbirth*, edited by Chalmers I., Enkin M. and Kierse, M. J. N. C. chapter 61, pp. 988–1056. Oxford, Oxford University Press.

Khouzam M. N. and Ledward R. S. (1990) Difficulties with controlled release prostaglandin E2 pessaries [letter]. *Lancet* **336,** 119.

Miller A. M., Rayburn W. F. and Smith C. V. (1991) Patterns of uterine activity after intravaginal prostaglandin E2 during preinduction cervical ripening. *American Journal of Obstetrics and Gynecology* **165,** 1006–1009.

Rayburn W. F., Wapner R. J., Barss V. A., Spitzberg E., Molina R. D., Mandsager N. and Yonekura M. L. (1992) An intravaginal controlled-release prostaglandin E2 pessary for cervical ripening and initiation of labour at term. *Obstetrics and Gynecology* **79,** 374–379.

Taylor A. V. G., Boland J. and MacKenzie I. Z. (1990) The concurrent in-vitro release of PGE2 from a controlled release hydrogel polymer pessary for cervical ripening. *Prostaglandins* **40,** 89–98.

Witter F. R., Rocco I. E. and Johnson T. R. (1992) A randomised trial of prostaglandin E2 in a controlled-release vaginal pessary for cervical ripening at term. *American Journal of Obstetrics and Gynecology* **166,** 830–834.

Wilson P. (1993) Analysis of 10 mg PGE2 1·1mm hydrogel pessaries fitted with retrieval systems returned to CTS from clinical trial CTC101-500. *Technical Report Number R93008S*, pp 3–6. Controlled Therapeutics, (Scotland) Ltd, Glasgow.

Correspondence should be addressed to: Dr J. Westgate, Department of Obstetrics and Gynaecology, Middlemore Hospital, Private Bag 93311, Otahuhu, Auckland, New Zealand.