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A randomised controlled trial comparing low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term

Sarah Gregson,[a] Mark Waterstone,[a] Ian Norman,[b] Trevor Murrells[c]

Objective To compare the efficacy of low dose vaginal misoprostol and dinoprostone vaginal gel for induction of labour at term.

Design A single-blind randomised controlled trial.

Setting Antenatal and labour ward of a UK district general hospital.

Participants Two hundred and sixty-eight women requiring induction of labour at term (>37 weeks of gestation) with no significant fetal or medical condition, no previous uterine surgery and no contraindication to prostaglandin.

Methods Misoprostol 25 μg (one-quarter of a 100 μg tablet) was inserted into the posterior vaginal fornix every 4 hours (to a maximum of six doses) or dinoprostone vaginal gel 1–2 mg 6 hourly (maximum of 3 mg in 24 hours).

Main outcome measure Induction-to-vaginal delivery interval.

Secondary outcome measures Requirements for oxytocin, mode of delivery, number of women delivering <24 hours, incidence of uterine contraction abnormalities, incidence of abnormal cardiotocograph (CTG) recordings, 5-minute Apgar scores, umbilical cord pH recordings, analgesia requirements, admission to NICU and blood loss at delivery.

Results There were no significant differences between the two groups in induction-to-vaginal delivery interval, mode of delivery, number of women delivering within 24 hours and neonatal outcomes. The incidence of uterine contraction abnormalities (tachysystole and hyperstimulation) and the incidence of abnormal CTG recordings were also similar for both groups.

Conclusion Low dose vaginal misoprostol is as effective as dinoprostone gel for inducing labour at term. There would be substantial cost savings, estimated at around £3.9 million per annum, for maternity services if low dose misoprostol became the agent of choice for inducing labour in the UK.

INTRODUCTION

The main problems associated with induction of labour are ineffective labour and excessive uterine action, which may cause fetal hypoxia leading to an increased risk of caesarean section, particularly if the cervix is unfavourable at the onset of the induction.[1] At present, most maternity units in the United Kingdom use a regimen of dinoprostone vaginal gel, in doses of 1–2 mg, as the agent of choice for inducing labour,[1] but this is a relatively expensive drug (£15.25 for a 1-mg dose and £16.80 for a 2-mg dose).[2] Dinoprostone gel also requires refrigeration for storage, which can cause significant problems for maternity units in developing countries.

There has been a growing interest in using misoprostol, a prostaglandin E_1 analogue, as an alternative agent for inducing labour since the first reported use of it for this indication in 1988.[3] It is considerably less expensive than dinoprostone gel (£0.14 for a 100-μg tablet) and requires no special storage arrangements. Replacing dinoprostone with misoprostol would allow considerable cost savings. Although misoprostol can be administered vaginally, orally or rectally, the vaginal route appears, at present, to offer the most benefits in terms of efficacy and minimising side effects.[4–6] Danielian *et al.*[7] found that 50 μg of misoprostol was more effective than dinoprostone gel and had a similar side effect profile, but others have demonstrated that a dosing regimen of 50 μg or higher is associated with an increased incidence of uterine contraction abnormalities.[8,9]

[a]*Maternity Unit, Queen Mary's Sidcup NHS Trust, Sidcup, Kent, UK*
[b]*Mental Health Section and Graduate Research Studies, Florence Nightingale School of Nursing & Midwifery, King's College, University of London, UK*
[c]*Nursing Research Unit, Florence Nightingale School of Nursing & Midwifery, King's College, UK*

Correspondence: Ms S. Gregson, Maternity Unit, Queen Mary's Sidcup NHS Trust, Frognal Avenue, Sidcup, Kent, DA14 6LT, UK.

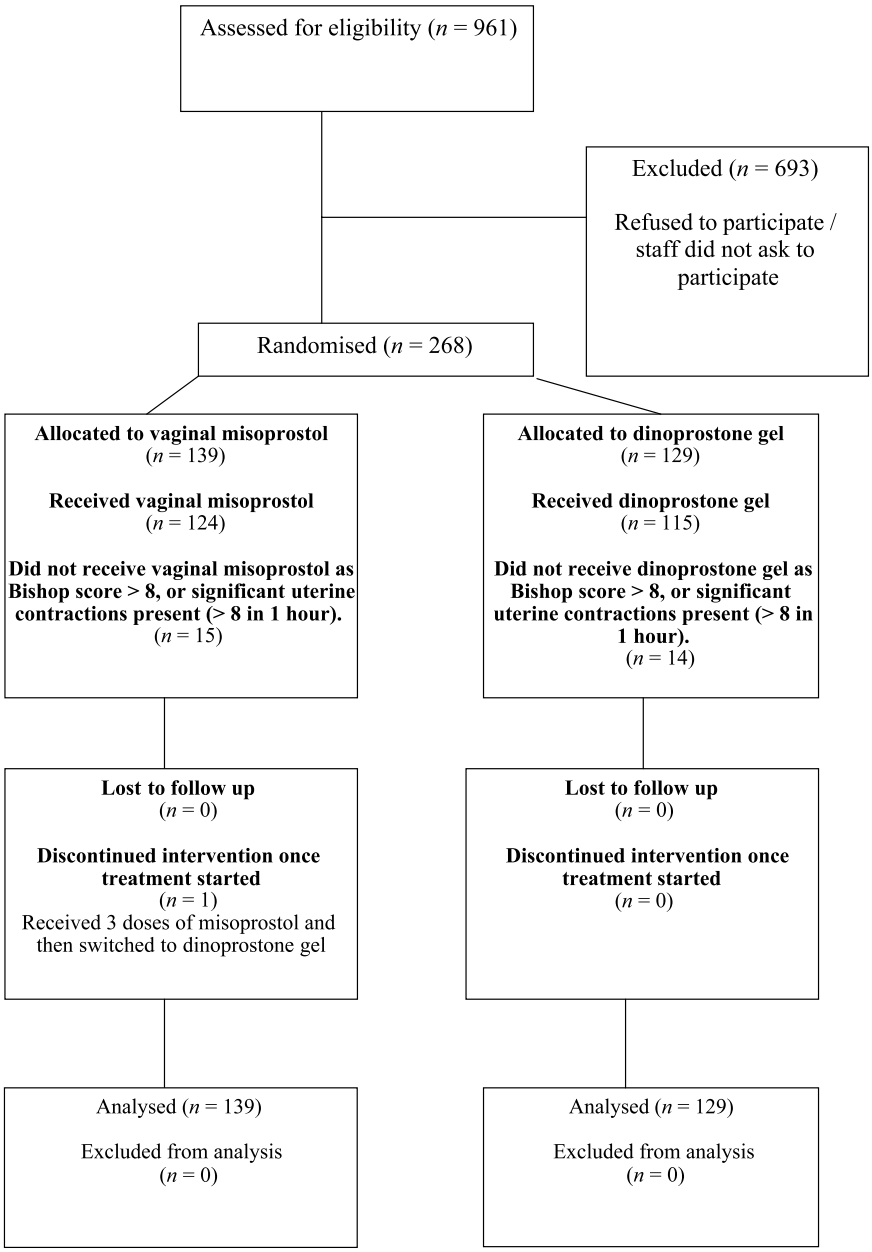

Fig. 1. CONSORT diagram for misoprostol trial.

Higher doses have also been associated with a higher incidence of meconium-stained amniotic fluid[9] and uterine rupture in women with or without previous uterine surgery.[10–12] Although not all trials have confirmed these findings, they are of sufficient concern for the authors of a systematic review, the Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) to recommend a cautious approach to its use, and further investigation into lower dose misoprostol regimens.[1,13,14]

At present, there is only limited information available on low dose regimens (25 μg) of misoprostol. However, studies to date indicate that it is as effective as other prostaglandin preparations and oxytocin for inducing labour in terms of induction-to-delivery times, requirements for oxytocin and achieving vaginal delivery.[15–19] These studies also indicate that low dose regimens of misoprostol have a similar incidence of uterine contraction abnormalities and meconium-stained amniotic fluid as conventional methods of inducing labour, except in women who have had previous uterine surgery. The first study to compare a low dose regimen of vaginal misoprostol with dinoprostone vaginal gel used a 25-μg tablet of misoprostol that was pulverised and encased in a cellulose capsule.[20] This study found that the median induction interval in the misoprostol group was longer than in the dinoprostone group (25 *vs*

Table 1. Maternal demographic details at induction of labour. Values are presented as mean [SD] or *n* (%).

	Misoprostol ($n = 139$)	Dinoprostone ($n = 129$)
Age (years)	28.73 [5.34]	29.57 [5.19]
Parity	0.54 [0.73]	0.60 [0.76]
Gravidity	1.99 [1.24]	2.00 [1.19]
Gestation (days)	289.02 [24.91]	290.31 [9.52]
Height (cm)	163.86 [6.54]	165.01 [6.60]
Weight (kg)[1]	71.05 [15.28]	72.37 [16.67]
Birthweight of baby (g)	3720 [445]	3819 [472]
Bishop score at induction[2]		
0–4	86 (63)	83 (65)
5–7	43 (31)	36 (28)
8+	8 (6)	9 (7)
Ethnicity		
White	130 (94)	128 (99)
Black, Asian or Chinese	9 (6)	1 (1)

[1] Misoprostol, $n = 136$; Dinoprostone, $n = 126$.
[2] Misoprostol, $n = 137$; Dinoprostone, $n = 128$.

19 hours, $P = 0.008$), but the side effect profile was similar in both groups. To date, there has been no comparison of low dose misoprostol and prostaglandin gel in the UK.

METHODS

A randomised controlled study was set up to test the following null hypothesis:

> There is no significant difference in efficacy of low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term.

The trial sample size was calculated using a joint statistical and pragmatic assessment, based on the number of women that could be recruited within an acceptable timescale and the size of effect (difference between treatments) that could be measured. Sample size calculations were based on mean induction-to-delivery times and standard errors from one study using the same dosage regime for misoprostol,[17] and from an internal audit of 100 randomly selected women who had a vaginal delivery at Queen Mary's Hospital. Previous research had shown that the mean induction-to-delivery interval for women receiving misoprostol could vary from 13 to 22 hours depending on the dose regimen. The induction-to-delivery interval with misoprostol varies from 3.8 hours longer[21] to 8.5 hours shorter.[7] Calculations suggested that a sample size of 224 (112 in each arm) would be sufficient to show a true mean difference of 6 hours in induction-to-delivery interval with a power of 95% at the 5% level of significance (two-tailed).

The study took place at Queen Mary's Sidcup NHS Trust between 18th July 2000 and 2nd December 2003. Approval for the study was obtained from the Local Research Ethics Committee. Women were eligible to be included in the trial if they met the following criteria: singleton pregnancy at term (between 37 and 42 completed weeks of pregnancy), cephalic presentation, no significant maternal or fetal medical condition, no previous uterine surgery, parity <4 and no contraindication to prostaglandin. Membranes could be intact or ruptured. Those willing to participate in the trial were asked to give written consent. After recruitment participants were randomly allocated to receive vaginal misoprostol or dinoprostone vaginal gel.

The allocation of treatment was generated using a computer random schedule in blocks at the start of the study and assignment was concealed by placement in consecutively numbered, opaque, sealed envelopes drawn in consecutive order by a manager, who was unaware which agent was allocated until the envelope was opened. The investigators were blind to allocation, but blinding of the participant and the midwife administering the treatment was not possible due to the differences in preparations used.

A cardiotocograph (CTG) and vaginal examination were performed prior to treatment. Women with a Bishop score of 8 or more, any abnormalities of the fetal heart rate or any significant uterine activity were excluded. Women received 1 mg dinoprostone vaginal gel, if the Bishop score was 5 or <5 and 2 mg if the Bishop score was >5, (Prostin E_2 vaginal gel, Upjohn, Crawley, West Sussex, UK) or 25 μg misoprostol (a 100-μg tablet quartered by the midwife or doctor; Idis, Millbank House, Surbiton, Surrey, UK) inserted digitally into the posterior fornix. Dinoprostone vaginal gel was repeated every 6 hours to a maximum of 3 mg in 24 hours, and the misoprostol was repeated every 4 hours, to a maximum of six doses, until an adequate contraction pattern (eight or more contractions in an hour) was achieved or the Bishop score was 8 or more, in which case artificial rupture of the membranes was performed. No further doses of either agent were given if there were

Table 2. Comparison of induction-to-vaginal delivery interval.

All subjects ($n = 267$)*	Misoprostol ($n = 138$)	Dinoprostone ($n = 129$)	Mann–Whitney *U* (*P* value)
Median	971	990	8675
Range	150–8223	224–5229	(0.72)
Nulliparous only ($n = 152$)	Misoprostol ($n = 81$)	Dinoprostone ($n = 71$)	
Median	1380	1390	2686
Range	179–8223	317–5229	(0.48)
Multiparous only ($n = 115$)	Misoprostol ($n = 57$)	Dinoprostone ($n = 58$)	
Median	663	718	1536
Range	150–5351	224–3330	(0.51)

* Data missing for one participant.

Table 3. Outcomes in labour. Values are presented as *n* (%) or mean [SD].

	Misoprostol ($n = 139$)	Dinoprostone ($n = 129$)	Relative risk (95% CI)
Women delivering <24 hours			
All subjects ($n = 268$)	96 (69)	88 (68)	1.01 (0.86 to 1.19)
Nulliparous only ($n = 152$)	45 (56)	37 (52)	1.07 (0.79 to 1.43)
Multiparous only ($n = 116$)	51 (88)	51 (88)	1.00 (0.87 to 1.14)
Requiring oxytocin augmentation			
All subjects ($n = 268$)	50 (36)	46 (36)	1.01 (0.73 to 1.39)
Nulliparous only ($n = 152$)	42 (52)	41 (58)	0.90 (0.67 to 1.20)
Multiparous only ($n = 116$)	8 (14)	5 (9)	1.60 (0.56 to 4.60)
Mode of delivery			
All subjects ($n = 268$)			
Vaginal	74 (53)	72 (56)	0.95 (0.77 to 1.19)
Instrumental (forceps or vacuum)	29 (21)	26 (20)	1.04 (0.65 to 1.66)
Caesarean	36 (26)	31 (24)	1.08 (0.71 to 1.63)
Nulliparous only ($n = 152$)			
Vaginal	22 (27)	23 (32)	0.84 (0.51 to 1.37)
Instrumental	25 (31)	20 (28)	1.10 (0.67 to 1.80)
Caesarean	34 (42)	28 (39)	1.06 (0.72 to 1.57)
Multiparous only ($n = 116$)			
Vaginal	52 (90)	49 (84)	1.06 (0.92 to 1.22)
Instrumental	4 (7)	6 (10)	0.67 (0.20 to 2.24)
Caesarean	2 (3)	3 (5)	0.67 (0.12 to 3.84)
Tachysystole*			
All subjects ($n = 263$)	19 (14)	24 (19)	0.72 (0.41 to 1.24)
Nulliparous ($n = 147$)	9 (11)	11 (16)	0.69 (0.30 to 1.55)
Multiparous ($n = 116$)	10 (17)	13 (22)	0.77 (0.37 to 1.61)
Hyperstimulation^			
All subjects ($n = 263$)	1 (1)	4 (3)	0.23 (0.03 to 2.00)
Nulliparous ($n = 147$)	1 (1)	2 (3)	0.42 (0.04 to 4.52)
Multiparous ($n = 116$)	0 (0)	2 (3)	0.00
Abnormal cardiotocograph¬			
All subjects ($n = 260$)	24 (18)	27 (22)	0.80 (0.49 to 1.31)
Nulliparous ($n = 146$)	21 (26)	18 (27)	0.96 (0.56 to 1.65)
Multiparous ($n = 114$)	3 (5)	9 (16)	0.33 (0.10 to 1.17)
	Misoprostol ($n = 139$)	**Dinoprostone ($n = 129$)**	**Mean difference (95% CI)**
Estimated blood loss at delivery (mL)			
All subjects ($n = 268$)	434 [363]	419 [538]	14 (−96 to 124)
Nulliparous ($n = 151$)	534 [428]	473 [333]	61 (−63 to 185)
Multiparous ($n = 116$)	296 [170]	354 [710]	−58 (−248 to 132)

* 6 cardiotocograph recordings uninterpretable re fetal heart.
^ 3 cardiotocograph recordings uninterpretable re uterine action.
¬ 2 carditocograph recordings unobtainable.

uterine contractions, if the membranes ruptured spontaneously or if there were fetal heart rate abnormalities. After artificial rupture of the membranes, subsequent management of labour was identical for the experimental and control group: 4 hourly cervical assessments were performed and failure of the cervix to dilate at a rate of 1 cm per hour was an indication to commence oxytocin augmentation. Augmentation was delayed for 4 hours after administration of the last dose of ripening agent. Continuous fetal heart rate and uterine activity monitoring was performed on all subjects.

The primary outcome measure was induction-to-delivery interval.

Secondary outcome measures were: mode of delivery, incidence of uterine contraction abnormalities and abnormal CTG recordings and neonatal outcomes including 5-minute Apgar scores and umbilical arterial pH recordings, requirement of oxytocin, analgesia use in labour, presence of meconium, neonatal intensive care admission and blood loss at delivery.

The experimental and control groups were compared for factors that could potentially affect the induction process:

Table 4. Comparison of neonatal outcomes for the experimental and control groups. Values are presented as *n* (%).

	Misoprostol ($n = 139$)	Dinoprostone ($n = 129$)	Relative risk (95% CI)
Umbilical artery pH[1] <7.2	12 (15)	14 (23)	0.63 (0.31 to 1.26)
Umbilical artery base deficit[2] < −12	2 (2)	2 (3)	0.71 (0.10 to 4.90)
Apgar score below 8 at 5 minutes	2 (1)	1 (1)	1.86 (0.17 to 20.23)
Meconium-stained amniotic fluid	22 (16)	17 (13)	1.20 (0.67 to 2.16)
Admission to neonatal unit	1 (1)	2 (2)	0.46 (0.04 to 5.06)

[1] Misoprostol, $n = 82$; Dinoprostone, $n = 60$.
[2] Misoprostol, $n = 83$; Dinoprostone, $n = 59$.

parity, age, gravid, height, weight, ethnicity, gestational age, birthweight and Bishop score at the onset of induction.

Data were collected from the participants' computer and hospital records by the researchers and entered onto a SPSS for Windows version 11 database. The assessment of CTG recordings for uterine contraction abnormalities and abnormal fetal heart rate patterns was performed prior to collection of other data so that the investigators were 'blinded' to treatment group. Uterine tachysystole was defined as six or more contractions in a 10-minute period for two consecutive 10-minute periods. Hyperstimulation was defined as fetal heart rate abnormality associated with tachysystole.

The process for categorising fetal heart rate patterns was as follows: One researcher (SG) scrutinised the CTG recordings and identified any recordings that had suspicious or pathological features as defined by the International Federation of Gynaecology and Obstetrics.[22] These 'abnormal' CTGs were further scrutinised by a second researcher (MW), a consultant obstetrician, who gave final judgement as to how the CTG was to be categorised. This process avoided the problem of inter-observer variation.[23] Both researchers were blind to treatment group prior to analysing the CTG.

The experimental hypotheses were tested using statistical procedures available in SPSS for Windows version 11. All tests were two-tailed and a significance level of $P < 0.05$ was accepted as statistically significant. Ninety-five percent confidence intervals (two-tailed) have been presented alongside summary measures (mean and relative risk) throughout. Median induction delivery times are shown for both the experimental and control groups alongside the range rather than the means because the data were non-normal.

RESULTS

A total of 268 women were recruited, of whom 139 were allocated to receive misoprostol and 129 dinoprostone vaginal gel. Twenty-nine women entered the trial without receiving either induction agent; 28 of these had labour induced or augmented by artificial rupture of the membranes and 1 required delivery by caesarean section for an abnormal CTG. All 29 were included in data analysis as 'intention to treat' (Fig. 1).

There were three incidences of protocol violation; one participant was inadvertently given a dose of 50 μg misoprostol instead of the prescribed 25 μg, and one participant received three doses of misoprostol and was then switched to dinoprostone gel. In addition, one participant refused the allocated misoprostol and was given dinoprostone instead. Data for these three women were also analysed on an intention-to-treat basis.

Maternal demographic details were compared across experimental and control groups (Table 1). There were no important differences except for a higher proportion of Black, Asian and Chinese women in the experimental group.

The most common reason for induction was postmaturity (misoprostol 95%, $n = 132$; dinoprostone 94%, $n = 121$). A small number of women were induced for spontaneous rupture of the membranes (misoprostol 2%, $n = 3$; dinoprostone 5%, $n = 6$) or for maternal request (misoprostol 3%, $n = 4$; dinoprostone 2%, $n = 2$).

Table 2 summarises the induction-to-vaginal delivery interval for all subjects and in parity groups (i.e. data for nulliparous and multiparous women analysed separately). While the misoprostol group had a shorter median induction-to-vaginal delivery interval in all groupings, these differences were not significant.

The number of women who delivered <24 hours was similar in each group (Table 3), as was the number requiring oxytocin augmentation. Mode of delivery and estimated blood loss were also similar in the experimental and control groups. There were no significant differences in the incidence of tachysystole, hyperstimulation or abnormal fetal heart rate recordings.

There were no significant differences between the two groups in analgesic requirements.

There were no significant differences detected between the two groups in umbilical cord pH and base deficit recordings, incidence of meconium, incidence of Apgar scores below 8 at 5 minutes or admission to the neonatal unit (Table 4).

Six hundred and ninety-three women eligible to take part in the study declined to do so. Analysis of this cohort showed no differences in demographic details between participants and non-participants, except there were fewer Black, Asian and Chinese women in the study than in the non-participants group, 4% *versus* 10% (relative risk 0.37, 95% CI 0.19 to 0.71), a finding that is consistent with

other studies.[24] Parity was significantly higher among non-participants than participants (0.85 *vs* 0.57; mean difference 0.28, 95% CI 0.14 to 0.42), and gravidity was significantly higher among non-participants when compared with participants (2.41 *vs* 2.00; mean difference 0.41, 95% CI 0.21 to 0.62).

DISCUSSION

This is the first UK study to compare a low dose regimen of vaginal misoprostol with dinoprostone vaginal gel. In this study, we found no significant difference between the groups in terms of efficacy, thus confirming the results of previous studies.[9,15–18,25,26]

A similar study in the Netherlands concluded that the median induction-to-vaginal delivery interval was approximately 6 hours longer in the misoprostol group than in the dinoprostone group.[20] It is possible, however, that the efficacy of the misoprostol may have been reduced as it was given in gel form. A previous comparison of an extemporaneous form of misoprostol with misoprostol tablets demonstrated that tablets were more efficacious.[27]

The main concern raised by previous studies into higher dose vaginal misoprostol for inducing labour has been that of safety.[11] Wing and Paul[16] hypothesised that vaginal misoprostol, 25 μg 4 hourly, would maximise efficacy while minimising side effects, and this was the rationale for this study. The misoprostol group tended to have a lower incidence of side effects, although this did not reach statistical significance.

Although women with medical problems have been included in trials investigating vaginal misoprostol,[20,25] this study excluded women with medical complications because concerns for safety were paramount.

The majority of the participants who received neither agent to induce labour (28 out of 29) could have been avoided if another vaginal examination had been performed prior to randomisation, but this was not considered ethically acceptable. While this group of women were included in the study on an 'intention-to-treat' basis, it should be noted that similar results were obtained when this cohort was excluded and the data re-analysed.

To allow comparison with previous studies, the present study categorised CTGs as 'normal' or 'abnormal', with the 'abnormal' category reserved for CTGs that required delivery of the fetus. However, nine months after the start of the trial, the National Institute for Clinical Excellence published guidelines ('The use of electronic fetal monitoring') which give much clearer guidance for classifying fetal heart rate patterns.[28] The use of this categorising scheme by future studies would enable more valid comparisons to be drawn between different studies in this country.

At present, misoprostol is unlicensed for use in obstetrics, and the previous manufacturer of misoprostol (G.D. Searle) was accused of actively trying to prevent its use in this area.[29] The company also declined to manufacture a smaller dose tablet (personal communication, 2001), which means that the dose of 25 μg can only be obtained by cutting a 100-μg tablet into four. While this method was employed in this study and others, it means that an exact dose of 25 μg cannot be guaranteed. This method, however, seems to be preferable to putting misoprostol into a gel form which appears to make it less efficacious.[27]

Approximately 20% of the 600,000 women who give birth in the UK each year have labour induced, costing the NHS approximately £4 million per annum (assuming that each woman requires on average two doses of dinoprostone vaginal gel). If the same number of women were induced with vaginal misoprostol, it would cost approximately £35,000, resulting in an overall saving of £3.9 million to the NHS, which could be directed into improving other aspects of maternity services. As well as cost, misoprostol has other important implications for obstetrics in developing countries as, unlike dinoprostone gel, it does not require refrigeration.

In conclusion, this study demonstrates that low dose (25 μg) vaginal misoprostol in tablet form is an effective and extremely cheap method of inducing labour at term. We would recommend that misoprostol is accepted as a method of induction of labour and that a central database is set up in order to monitor any rare untoward effects (such as uterine rupture).

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