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Misoprostol for induction of labour at term: a more effective agent than dinoprostone vaginal gel

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

Design A single-blind randomised comparative trial.

Setting Induction and labour wards of a UK teaching hospital.

Participants Two hundred and eleven pregnant women at term in whom induction of labour was indicated, and with no contra-indication to the use of prostaglandins for the induction of labour.

Intervention The women were randomly assigned to receive vaginal administration of either misoprostol 50 μg four hourly (to a maximum of four doses) or dinoprostone gel 1 mg six hourly (to a maximum of three doses).

Main outcome measures Time from induction to delivery, oxytocin requirement in labour, analgesic requirement, mode of delivery, neonatal outcome.

Results The misoprostol group had a highly significant reduction in median induction–delivery interval compared with the dinoprostone group (14·4 hours *vs* 22·9 hours; $P < 0{\cdot}00001$). In addition, more women delivered after only one dose (77% *vs* 49%; $P < 0{\cdot}0001$, OR 3·51, 95% CI 1·94–6·35), and within 12 and 24 hours. There was a reduced need for oxytocin augmentation in labour (21% *vs* 47%; $P < 0{\cdot}0001$, OR 0·30, 95% CI 0·16–0·54). There was no difference in analgesia requirement in labour, or in mode of delivery. There were no adverse neonatal outcomes associated with the use of misoprostol. Women in the misoprostol group experienced more pain in the interval between induction and being given analgesia in labour, but this did not reach statistical significance.

Conclusions Misoprostol 50 μg vaginally is a more effective induction agent than 1 mg dinoprostone vaginal gel, with no apparent adverse effects on mode of delivery, or on the fetus. The higher pain scores in the misoprostol group must be balanced against the reduction in time spent having labour induced, and the reduction in need for intravenous oxytocin augmentation. Further randomised studies must continue to exclude the possibility of rare adverse side effects.

INTRODUCTION

Misoprostol is a synthetic prostaglandin E_1 analogue widely used for the treatment of gastric ulcer in patients taking non-steroidal anti-inflammatory drugs. It has been shown to be a useful agent for termination of pregnancy in the first, second and third trimesters[1–3], and more recently has been used for cervical ripening and induction of labour. There are now many trials investigating its use vaginally for induction of labour at term compared with either placebo[4] or with intracervical dinoprostone gel[5–8], vaginal dinoprostone tablets[9], or a combination of dinoprostone vaginally and oxytocin intravenously[10,11]. These trials have used various dose intervals and maximum dosage, ranging from single 25 μg to 100 μg doses up to a maximum total dose of 600 μg[12,13]. All these studies showed misoprostol to be an effective induction agent. In addition, misoprostol does not need to be stored in a refrigerator, and has a significant cost advantage compared with dinoprostone gel.

A dose of 50 μg misoprostol, 4 hourly to a maximum of five doses has been demonstrated to be effective for induction of labour and cervical ripening, and appears to have a low incidence of adverse side-effects such as uterine hypertonus[8], which were unacceptably high in other higher dosage regimens.

A recent meta-analysis of these studies has shown that misoprostol offers advantages in terms of a shorter induction–delivery interval, a reduction in the total

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number of doses required, an increase in the number of patients delivering after one dose, an increase in the rate of delivery within 24 hours, and a reduction in the requirement for oxytocin augmentation of labour. There appears to be no increase in operative delivery rates or any other complication for the mother or infant[14].

Most of these studies have been carried out in the USA, with control groups using induction methods not used in the UK. Although one Canadian trial has compared vaginal misoprostol with dinoprostone vaginal gel[10], the control group also included women who had intracervical dinoprostone gel or oxytocin for induction of labour. This is, therefore, the first UK study to describe the use of misoprostol for induction of labour, and the first to compare it solely with dinoprostone vaginal gel (the most widely used induction agent in the UK), rather than intracervical gel or vaginal pessaries. The aim of the study was to establish a safe and effective dose regimen of vaginal misoprostol for induction of labour at term.

METHODS

The study was approved by the local Ethics Committee. Eligible women were at term (between 37 and 42 completed weeks of pregnancy, with ultrasound confirmed dates), with a singleton fetus of cephalic presentation, with intact membranes, in whom induction of labour was indicated. Women who had had more than one previous caesarean section or any other uterine surgery, any other significant fetal or maternal medical condition, or known hyper-sensitivity or contra-indication to prostaglandins were excluded. Women who participated in this trial did so voluntarily, having given written informed consent to one of the investigators. After recruitment, the woman was assigned to receive either misoprostol or dinoprostone by random numbers allocated by the hospital pharmacy. The investigators were blind to the allocation. Blinding of the woman and the midwife administering the drug was not possible due to the dissimilar preparations used (i.e. misoprostol tablet and dinoprostone gel). A cardiotocogram and vaginal examination to assess the cervix were performed prior to administration of either preparation. Women with any abnormality of the fetal heart rate, significant uterine activity or with a Bishop score of ≥ 8 were excluded.

If the cervical score was less than eight, the patient received either 1 mg dinoprostone gel (Prostin E2 vaginal gel, Upjohn Ltd, Crawley, West Sussex, UK) as currently used in our unit for induction of labour, or 50 μg misoprostol (a 200 μg tablet quartered by the hospital pharmacy) (Cytotec, Searle Pharmaceuticals, High Wycombe, Bucks, UK) placed digitally in the posterior vaginal fornix.

The dose of dinoprostone gel was repeated every six hours to a maximum of three doses, (which was then the standard induction protocol in our unit), and the misoprostol repeated every four hours (to a maximum of four doses). Cardiotocography was performed prior to each dose, and if uterine contractions ensued. If the Bishop score was eight or more, the patient was transferred to the labour ward for artificial rupture of the membranes. No further doses were given if there were uterine contractions, if membranes ruptured spontaneously or if there were any fetal heart rate abnormalities. Oxytocin was used for augmentation of labour subsequent to artificial rupture of the membranes if necessary, according to departmental protocols.

A previously validated questionnaire with visual-analogue scales (from 0 to 100 mm) for severity of pain at insertion of the induction agent, and before, during, and after labour was given to the patients to complete postnatally.

Outcome measures

The primary outcome measure was induction–delivery interval. Analgesia requirements in labour, oxytocin requirement in labour, the incidence of fetal heart rate abnormalities in labour, mode of delivery, Apgar scores at one and five minutes, umbilical venous pH and base deficit, presence of meconium in the amniotic fluid and neonatal unit admission, and pain scores, were also compared between the dinoprostone and misoprostol groups.

Uterine tachysystole was defined as six or more contractions in any 10 minute period, and hyperstimulation as fetal heart rate abnormality associated with tachysystole. Tachysystole and hyperstimulation were determined from a standard cardiotocogram.

The demography of the two groups was compared in terms of maternal age, height, weight, parity, gestational age, Bishop Score at induction, and birthweight.

Statistical analysis

Continuous variables were compared using the Student's *t* test or Mann-Whitney *U* test, and discrete data with the Fisher's exact test or χ^2 test as appropriate. Analysis was performed using readily available statistical software (SPSS for Windows, SPSS Inc, Chicago, USA).

Power calculation

We considered that a six hour reduction in induction–delivery interval would be of clinical significance, and calculated that 100 patients in each group would show a true difference of this magnitude with $\alpha = 0{\cdot}01$ and power of 95%.

RESULTS

Two hundred and eleven women were recruited, of whom 105 received misoprostol, and 106 dinoprostone gel. There were no maternal demographic differences between the two groups. There were 54 (51%) primiparae in the misoprostol group and 63 (59%) in the dinoprostone gel group (Table 1). There were no cases in which labour could not be induced. There were no post-randomisation exclusions, and no woman withdrew from the trial after consent had been given.

The median induction–delivery interval was 14·4 hours in the misoprostol group and 22·9 hours in the dinoprostone group (U = 3238, P < 0·00001). In addition, more women in the misoprostol group were delivered after a single dose (77% *vs* 49%, P < 0·0001; OR 3·51, 95% CI 1·94–6·35), and more in the misoprostol group were delivered within 12 hours or within 24 hours from induction (Table 2). The number requiring oxytocin augmentation of labour was significantly fewer in the misoprostol group, (21% *vs* 47%, P < 0·0001; OR 0·30, 95% CI 0·16–0·54), and in those cases requiring oxytocin, the median total dose used was less in the misoprostol group (0·96 U) than in the dinoprostone group (1·86 U) (U = 3886, P = 0·002) (Table 2).

There were more cases of uterine tachysystole in the misoprostol group (5% *vs* 4%) but this did not reach statistical significance (Table 2). There was only one case of hyperstimulation which required intravenous tocolysis, and this occurred in the dinoprostone group.

There were no differences between the groups in analgesia used in labour (Table 3) or mode of delivery (Table 4).

During labour, there were no significant differences in the presence of meconium (14% *vs* 11%), abnormal fetal heart rate patterns (29% *vs* 24%), or need for fetal scalp blood sampling (9% *vs* 8%) (Table 5). The birthweight of the babies in each group was similar, and there were no differences in umbilical vein pH or base deficit, Apgar scores at one and five minutes, or admission to the neonatal unit (Table 5). There were no cases where the meconium was of any clinical significance.

In total, 14 babies were admitted to the neonatal unit, eight in the misoprostol group, and six in the dinoprostone group. In the misoprostol group, two babies were admitted with transient tachypnoea, two with anaemia (of which one case was due to Rhesus iso-immunisation), one with fits after 24 hours thought to be secondary to congenital anomaly, one with feeding problems, one because of maternal drug abuse, and one for 'stress at delivery', although cord pH and base deficit were normal. The duration of stay in the neonatal unit ranged from one to eight days. In the dinoprostone group, three babies were admitted with transient tachypnoea, two following cyanotic episodes and one because of jaundice. Stay ranged from three to nine days.

The median patient pain scores were all higher in the misoprostol group. These did not reach statistical significance, but only a small number of questionnaires (42) were received for analysis (Table 6).

Table 1. Maternal demographic details at induction of labour. Values are given as median (range), mean [SD] or n {%}.

	Misoprostol (n = 105)	Dinoprostone (n = 106)	P
Age (years)	28 (16–42)	27 (16–39)	0·15
Parity	0 (0–3)	0 (0–4)	0·37
Gestation (weeks)	41 (38–42)	41 (37–42)	0·94
Height (cm)	163 [5·9]	163 [6·5]	1·00
Weight (kg)	70 [15]	70 [15]	0·73
Initial Bishop score	4 (1–7)	4 (2–7)	0·35
No. of primigravidae	54 {51}	63 {59}	0·27

Table 2. Comparison of outcomes in labour for women randomly allocated to receive vaginal misoprostol or dinoprostone gel. Values are given as median (range), or n [%], unless otherwise indicated.

	Misoprostol (n = 105)	Dinoprostone (n = 106)	OR (95% CI)	P
No. delivered				
After single dose	81 [77]	52 [49]	3·51 (1·94–6·35)	< 0·0001*
< 12 h	38 [36]	15 [14]	3·44 (1·75–6·77)	0·0002*
< 24 h	84 [80]	54 [51]	3·85 (2·09–7·10)	< 0·0001*
Induction–delivery interval (h)	14·4 (4·4–66·2)	22·9 (7·0–92·8)	—	< 0·00001†
No. needing oxytocin augmentation	22 [21]	50 [47]	0·30 (0·16–0·54)	< 0·0001*
Median dose oxytocin required (U)	0·96 (0·2–3·6)	1·86 (0·15–30·4)	—	0·002‡
Tachysystole	5 [5]	4 [4]	1·28 (0·33–4·89)	0·75*

*Fisher's exact test (two-tailed).
Mann-Whitney U test (two-tailed) = †3238; ‡3886.

Table 3. Analgesia used in labour. Values are given as *n* (%).

	Misoprostol	Dinoprostone
None	15 (14)	15 (14)
Entonox only	19 (18)	15 (14)
Morphine ± Entonox	45 (43)	47 (44)
Epidural ± morphine ± Entonox	16 (15)	22 (21)
Other	10 (10)	7 (7)

Entonox = 50% oxygen/50% nitrous oxide (BOC Medical Gases Ltd, Manchester, UK).
$\chi^2 = 1{\cdot}99$; d.f. = 4; $P = 0{\cdot}74$.

Table 4. Mode of delivery. Values are given as *n* (%).

	Misoprostol	Dinoprostone
Unassisted vaginal delivery	73 (70)	74 (70)
Operative vaginal delivery	20 (19)	18 (17)
Caesarean section	12 (11)	14 (13)

$\chi^2 = 0{\cdot}26$; d.f. = 2; $P = 0{\cdot}88$.

DISCUSSION

This trial is the first study to compare vaginal misoprostol with vaginal dinoprostone gel (the most widely used agent in the UK) for induction of labour. Misoprostol appears to be a more effective induction agent than dinoprostone vaginal gel in the regimens compared in this trial. At the time of the study, our departmental induction protocol did not use 2 mg doses of dinoprostone gel. Although it is possible that this reduced the efficacy in the dinoprostone arm of the trial, audit within the department had previously shown no benefit from the higher dose.

There is a reduction in induction delivery interval of over 8 hours, with 77% of cases delivering after a single dose and 80% of women were delivered within 24 hours compared with only 54% with dinoprostone gel. The requirement for oxytocin augmentation in labour was reduced from 50% to 22%, and the amount of oxytocin required in the augmented cases was also reduced. There was no increase in the number of cases of uterine tachysystole, and the only case of hyperstimulation requiring tocolysis occurred in the dinoprostone group. The analgesia required in labour, and the method of delivery were the same in both groups. There were no clinically relevant adverse effects on the fetus, although it is acknowledged that this study does not have sufficient power to detect changes in serious rare adverse outcomes.

The 50 μg dose regimen was selected with regard to the then published trials, as a compromise between efficacy and unacceptable side effects. It may be possible that efficacy can be retained and side effects reduced even further with a 25 μg dose. A more recent meta-analysis[15] has recommended that all future trials involving misoprostol for induction of labour should not use a dose of more than 25 μg given four to six hourly. It also recommends that such trials should be double-blind and of sufficient size to detect small differences in important, but uncommon, complications such as serious perinatal morbidity and mortality.

Neither meta-analysis[14,15] has found any significant increase in such clinically relevant adverse effects, but even the combined numbers of subjects do not give sufficient power for this to be a robust conclusion. However in this study, if anything, there were more adverse neonatal outcomes in the dinoprostone group.

The women given misoprostol did experience more pain in the interval between administration and receiving analgesia than those given dinoprostone. It is likely that this would have been significant even with slightly larger numbers of subjects.

Table 5. Comparison of neonatal outcomes. Values are given as median (range), mean [SD], or *n* {%}. CTG = cardiotocography.

	Misoprostol ($n = 105$)	Dinoprostone ($n = 106$)	*P*
Birthweight (g)	3639 [460]	3601 [469]	0·55†
Umbilical vein pH	7·26 [0·1]	7·28 [0·1]	0·29†
Umbilical vein base deficit	7·77 [5·0]	7·31 [4·2]	0·48†
Apgar at 1 min	9 (6–10)	9 (7–10)	0·32‡
Apgar at 5 min	9 (4–9)	9 (4–9)	0·29‡
No. with Apgar < 7 at 5 min	21 {20}	24 {23}	0·74*
No. with meconium staining of amniotic fluid	15 {14}	12 {11}	0·54*
No. needing fetal blood sampling in labour	9 {9}	9 {8}	1·00*
No. with fetal heart rate abnormality on CTG	30 {29}	25 {24}	0·44*
No. of admissions to neonatal unit	8 {8}	6 {6}	0·59*

*Fisher's exact test (two-tailed).
†Student's *t* test (two-tailed).
‡Mann-Whitney *U* test (two-tailed).

Table 6. Patient pain scores (on visual-analogue scale from 0 to 100 mm) during induction and delivery. Values are given as median (range).

	Misoprostol ($n = 18$)	Dinoprostone ($n = 24$)	$P^{\dagger}$
Pain at induction	20 (0–100)	16 (0–53)	0·51
Pain before analgesia given in labour	84 (50–98)	66 (16–100)	0·07
Second stage pain	90 (0–98)	77 (3–100)	0·09
Pain at delivery	79 (0–98)	75 (6–100)	0·51

†Mann-Whitney *U* test (two-tailed).

It is possible that oral misoprostol may be associated with fewer adverse side effects. There has been one study comparing oral misoprostol with vaginal or intracervical dinoprostone which found it to be equally, but not more effective[16]. The maternal side effects traditionally associated with oral prostaglandins (diarrhoea, nausea, vomiting)[17] were not found in this study.

In conclusion, misoprostol 50 μg vaginally is a highly effective induction agent, with no apparent adverse effects on the outcome of labour; in other studies it seems to cause more tachysystole and meconium passage, but not so as to cause fetal compromise. It has the benefit of being very inexpensive in comparison with other available prostaglandins, and does not need to be stored in a refrigerator. We have found that the increased efficacy is at the expense of a small increase in the degree of pain suffered by the patient, but this did not result in more analgesia being used in labour, and must be balanced by the benefits of a much shorter induction–delivery interval, and reduced need for intravenous oxytocin to augment labour.

There is a need for further larger studies to enable the safety of misoprostol to be firmly established, and to investigate other dosage regimens and the use of oral misoprostol for induction of labour. In the meantime, misoprostol should be used only within the context of appropriate clinical trials.

References

1 El-Refaey H, Templeton A. Early induction of abortion by a combination of mifepristone and misoprostol administered by the vaginal route. *Contraception* 1994; **49**: 111–114.

2 El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU486) and oral or vaginal misoprostol. *N Engl J Med* 1995; **332**: 983–987.

3 Webster D, Penney GC, Templeton A. A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996; **103**: 706–709.

4 Fletcher H, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol as a cervical ripening agent. *Br J Obstet Gynaecol* 1993; **100**: 641–644.

5 Varaklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin E2 gel for induction of labor at term. *Obstet Gynecol* 1995; **86**: 541–544.

6 Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E2 gel for pre-induction cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; **172**: 1804–1810.

7 Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: an effective agent for cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; **172**: 1811–1816.

8 Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E2 gel (Prepidil Gel): randomized comparison. *Am J Obstet Gynecol* 1995; **173**: 1137–1142.

9 Fletcher H, Mitchell S, Frederick J, Simeon D, Brown D. Intravaginal misoprostol versus dinoprostone as cervical ripening and labor-inducing agents. *Obstet Gynecol* 1994; **83**: 244–247.

10 Mundle WR, Young DC. Vaginal misoprostol for induction of labor: a randomised controlled trial. *Obstet Gynecol* 1996; **88**: 521–525.

11 Sanchez-Ramos L, Kaunitz AM, Del Valle GO, Delke I, Schroeder PA, Briones DK. Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: a randomized trial. *Obstet Gynecol* 1993; **81**: 332–336.

12 Farah LA, Sanchez-Ramos L, Rosa C et al. Randomized trial of two doses of the prostaglandin E1 analog misoprostol for labor induction. *Am J Obstet Gynecol* 1997; **177**: 364–369.

13 Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. *Am J Obstet Gynecol* 1996; **172**: 158–164.

14 Sanchez-Ramos L, Kaunitz AM, Wears RL, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstet Gynecol* 1997; **89**: 633–642.

15 Hofmeyr GJ. Misoprostol administered vaginally for cervical ripening and labour induction in the third trimester (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update Software, 1998.

16 Windrim R, Bennett K, Mundle W, Young DC. Oral administration of misoprostol for labor induction: a randomized controlled trial. *Obstet Gynecol* 1997; **89**: 392–397.

17 Keirse MJNC. Any prostaglandin (by any route) vs oxytocin (any route) for induction of labour [revised 22 April 1993]. In: Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C, editors. Pregnancy and Childbirth Module of *The Cochrane Pregnancy and Childbirth Database. The Cochrane Collaboration*; Issue 2, Oxford: Update Software, 1995.

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