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Induction of labour in nulliparous and multiparous women: a UK, multicentre, open-label study of intravaginal misoprostol in comparison with dinoprostone

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Objective To compare the efficacy and safety of a 25-microgram vaginal tablet of misoprostol (APL202) with dinoprostone (3-mg vaginal tablet) in cervical ripening and labour induction.

Design A randomised, open-label, noninferiority, comparative study in two maternal populations.

Setting Eighteen NHS study centres across the UK.

Population Nulliparous or multiparous women with a singleton pregnancy eligible for induction of labour.

Methods Women were randomised to receive either misoprostol, initially 25 micrograms (50 micrograms in nulliparous women with Bishop score ≤4) followed by 25 micrograms after 4 and 8 hours, or dinoprostone, initially 3 mg followed by 3 mg after 6 hours. Clinical noninferiority of misoprostol was defined as an absolute difference between treatments of no more than 10% for the primary outcome.

Main outcome measures The number of vaginal deliveries achieved within 24 hours of labour induction. Maternal and fetal safety outcomes.

Results A total of 626 women were randomised to misoprostol (n = 318) or dinoprostone (n = 308) treatment. The rate of vaginal deliveries achieved within 24 hours of induction did not significantly differ between the misoprostol and dinoprostone (43 versus 47%; 3.74% difference, 95% CI –3.58 to 11.05, respectively) treatment groups. The treatments were generally comparable for other secondary efficacy measures. Maternal and fetal adverse events were similarly distributed across the misoprostol and dinoprostone groups.

Conclusions Low-dose misoprostol is efficacious in cervical ripening and labour induction and demonstrates a similar fetal and maternal safety profile to dinoprostone.

Keywords Cervical ripening, dinoprostone, induced labour, intravaginal, misoprostol.

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Introduction

Labour induction is a common obstetric intervention, employed in response to a broad range of conditions in which prompt delivery may be perceived to reduce the risk of maternal or neonatal morbidity and mortality. The proportion of pregnancies undergoing induction varies widely between countries, but it is estimated that approximately 20% of labours in the UK and the USA are induced.[1–3] The physiological processes surrounding the initiation and promotion of labour are complex, but a successful vaginal delivery is less likely if the cervix is unfavourable (or unripe). Prostaglandin E_2 (e.g. dinoprostone) is widely used for cervical ripening and labour induction. Vaginal prostaglandins increase the likelihood of a vaginal delivery within 24 hours compared with placebo, but their use is associated with an increased rate of uterine hyperstimulation and fetal heart rate abnormalities.[4] Furthermore, dinoprostone is costly and must be refrigerated or frozen during transportation and storage because of its thermal instability.[5–7]

Misoprostol (APL202) is a potential alternative to currently licensed labour induction agents. It is a prostaglandin E_1

analogue that is stable at room temperature and easy to administer.[8] Misoprostol has been widely used in the prevention and treatment of gastrointestinal ulcers for more than 20 years, but it also has uterotonic properties and there is a growing body of literature exploring its 'off-label' use for cervical ripening and labour induction. Misoprostol, administered orally or intravaginally, has previously been shown to be effective for labour induction.[9–17] A meta-analysis of eight randomised studies comparing intravaginal misoprostol with dinoprostone, oxytocin or placebo showed a higher rate of vaginal delivery within 24 hours of administration, significantly lower overall rate of caesarean sections, and a reduced need for oxytocin augmentation with misoprostol.[18] Nevertheless, there has been continuing concern that misoprostol may be associated with uterine hyperstimulation and tachystole[16,19] and that, particularly in women with a prior caesarean delivery, this may be associated with uterine rupture and fetal death.[20,21] The incidence of these rare events appears to be dose related as most studies and case reports have evaluated doses of at least 50 micrograms intravaginally or total doses in excess of 100 micrograms.[11,12,16,21] A 25-microgram dose of misoprostol appears to be better tolerated than a 50-microgram dose,[11] but dosing in these studies may have been confounded by the need to split 100 or 200 micrograms misoprostol tablets to obtain the required lower dose, potentially leading to dosing inaccuracies.[22]

The American College of Obstetricians and Gynecologists[8] currently recommends use of a 25-microgram dose of misoprostol for labour induction, but their guideline was developed in the absence of large, well-designed clinical studies. A systematic review of 70 randomised controlled trials of misoprostol was, however, carried out in 2003. This reported that low-dose misoprostol (25 micrograms, administered 4-hourly or less frequently) was as effective as standard labour induction agents and that its use did not increase the incidence of uterine contraction disorders.[12]

We therefore conducted a large, randomised, open-label, noninferiority clinical study to compare the efficacy and safety of intravaginal misoprostol, using a specifically developed 25-microgram vaginal tablet, with that of dinoprostone (3-mg vaginal tablet) in cervical ripening and labour induction in nulliparous and multiparous women.

Methods

Study population

Nulliparous or multiparous women with a singleton pregnancy who were eligible for induction of labour with prostaglandins were included in the study. All women provided informed consent prior to participation in the study and were aged 18 years or older, had a pregnancy duration of at least 37 weeks and demonstrated an unfavourable cervix (Bishop score <9). Women who required insulin to control diabetes were excluded from the study, as were women who had a multiple pregnancy. Women in whom oxytocic drugs were contraindicated, women with a uterine scar, women with a history of prior conditions for which labour was inappropriate and women who had already ruptured their membranes were also excluded. Additional exclusion criteria were an intercurrent vaginal, ascending or systemic infection; placenta praevia, placental abruption or unexplained vaginal bleeding during the pregnancy; active cardiac, pulmonary, renal or hepatic disease; a contraindication to vaginal delivery or a known allergy to prostaglandins.

Study design

This randomised, open, noninferiority, comparative study of misoprostol (Isprelor®; Alliance Pharmaceuticals Limited, Chippenham, UK) and dinoprostone (Prostin E2 Vaginal Tablets; Pharmacia Ltd, Sandwich, UK) was conducted in 18 NHS study centres across the UK from January 2005 to March 2007 inclusive. The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by two appropriate independent ethics committees. Blinding was not performed as differences in the dosage timing of the two treatments would have necessitated up to five vaginal examinations in a 12-hour period with a consequent theoretically increased risk of maternal infection and discomfort.

Nulliparous women were stratified by their Bishop score (≤4 or ≥5).[23] All subjects were then independently randomised to treatment with misoprostol or dinoprostone using a randomisation list to assign a randomisation number. The identity of the allocated treatment was not revealed to the investigator until the randomised treatment pack was opened at the start of induction. Dinoprostone tablets were used as the standard treatment in preference to dinoprostone gel in line with National Institute of Health and Clinical Excellence (NICE) and Royal College of Obstetricians and Gynaecologists recommendations.[24,25] Recommended dosing guidelines were followed for both treatments.[5,8,24,25] Thus, women randomised to the misoprostol group received an initial dose of 25 micrograms (50 micrograms in nulliparous women with Bishop score ≤4) of misoprostol followed by further administrations of 25-microgram misoprostol after 4 and 8 hours, and women randomised to the dinoprostone group received an initial dose of 3 mg of dinoprostone followed by a further 3 mg of dinoprostone after 6 hours. Study medication was inserted into the posterior fornix of the vagina. Second and/or third doses were not administered to women who were experiencing three uterine contractions per 10 minutes, had a Bishop score >8 or spontaneous rupture of membranes. Unrestricted concomitant medications and amniotomy were allowed at any time during the study at the investigator's discretion.

Outcome measures

The primary outcome measure of the study was the number of vaginal deliveries achieved within 24 hours of the start of

labour induction. Secondary outcome measures included vaginal deliveries within 12 hours of the start of labour induction, caesarean sections and instrument-assisted vaginal deliveries. The mean and distribution of the induction–delivery interval and the requirement for oxytocin augmentation were also recorded.

Safety and tolerability

Maternal and fetal safety outcomes assessed were the incidence of tachysystole, uterine hyperstimulation with fetal heart rate changes, pyrexia during labour, serious neonatal or maternal morbidity or death and maternal and fetal complications (including uterine rupture, use of epidural analgesia, meconium-stained liquor, an Apgar score of less than 7 at 5 minutes and maternal nausea, vomiting or diarrhoea). In addition, all adverse events (AEs) were recorded from the time of the first dose of study treatment until discharge from hospital.

Statistical analysis

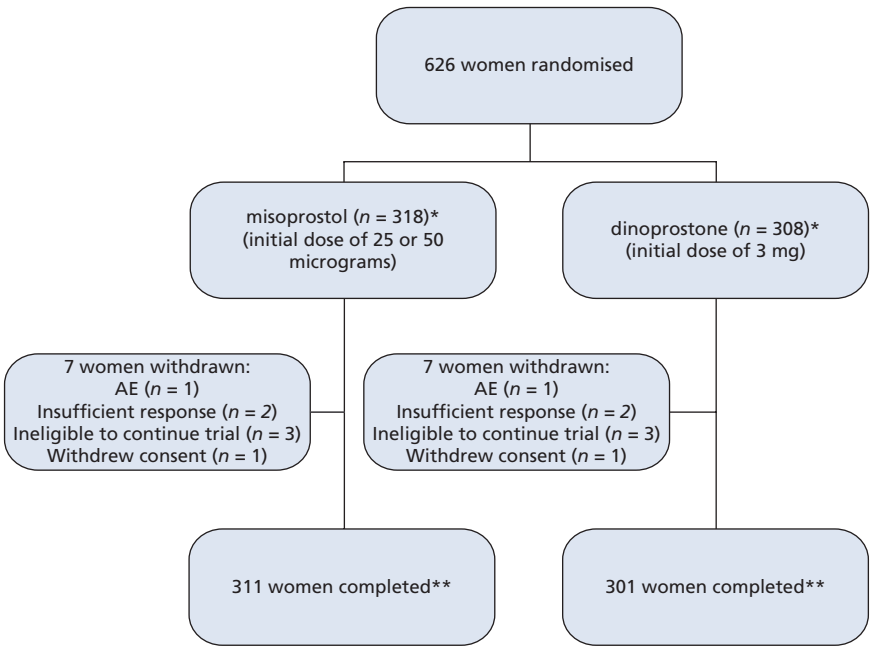
For the primary outcome measure, clinical noninferiority was defined as an absolute difference between treatments of no more than 10% as this was considered to be a clinically acceptable difference in efficacy. The selection of this noninferiority limit was informed by the expert opinion of an advisory group of obstetricians familiar with misoprostol and labour induction. To demonstrate this with a two-sided 95% CI and 90% power, it was calculated that a total of 622 women would be required. Data from the nulliparous and multiparous groups were combined using an inverse variance-weighted meta-analysis. Primary and secondary outcome measures were analysed in the intention-to-treat population, which consisted of all randomised women.

In the analysis of secondary outcome measures, categorical variables were compared using logistic regression, and continuous variables were compared using a normal linear model. Comparisons between treatments were tested at the 5% level of significance without adjustment for multiple testing. The safety population included those women who received at least one dose of study medication.

Results

A total of 626 women were randomised to treatment with dinoprostone (n = 308) or misoprostol (n = 318) (Figure 1). Of these, 14 women withdrew from the study (7 women from each treatment group). Baseline demographic characteristics were similar between the groups, except that the median weight was higher in the misoprostol group (with nine women weighing more than 125 kg in the misoprostol group versus one woman in the dinoprostone group) (Table 1).

A total of 56 (18%) women received one dose (25 or 50 micrograms only), 104 women (33%) received two doses (25 + 25 micrograms or 50 + 25 micrograms) and 156 (49%) received three doses (25 + 25 + 25 micrograms or 50 + 25 + 25 micrograms) of misoprostol over approximately an 8-hour



*Following analysis of the data,it was confirmed that 307 women received dinoprostone and 319 women received misoprostol.
**Primary end-point data,were not recorded for seven participants: misoprostol n = 4, dinoprostone n = 3.

Figure 1. Flow chart of women progressing through the study.

Table 1. Baseline characteristics of the study population*

Characteristic	Misoprostol (*n* = 318)	Dinoprostone (*n* = 308)	Total (*n* = 626)
Age, years	*n* = 316	*n* = 306	*n* = 622
Median (range)	29.87 (17.74–44.70)	29.71 (18.16–45.81)	29.79 (17.74–45.81)
Height, m	*n* = 300	*n* = 290	*n* = 590
Median (range)	1.65 (1.45–1.83)	1.65 (1.45–1.81)	1.65 (1.45–1.83)
Weight, kg	*n* = 247	*n* = 253	*n* = 500
Median (range)	83.50 (50.00–174.60)	81.20 (51.00–145.00)	83.00 (50.00–174.60)
Parity, *n* (%)			
0	179 (56)	179 (58)	358 (57)
1	81 (25)	74 (24)	155 (25)
2	43 (14)	40 (13)	83 (13)
3	13 (4)	12 (4)	25 (4)
4	2 (1)	2 (1)	4 (1)
5	0	1 (0)	1 (0)
Gestation, days			
Median (range)	290 (259–297)	290 (259–297)	290 (259–297)
Induction reason, *n* (%)			
Post-dates	237 (75)	214 (69)	451 (72)
Hypertension	14 (4)	15 (5)	29 (5)
Pre-eclampsia	16 (5)	11 (4)	27 (4)
Intrauterine growth restriction	5 (2)	8 (3)	13 (2)
Other	46 (14)	60 (19)	106 (17)
Bishop score	*n* = 307	*n* = 296	*n* = 603
Median (range)	4.00 (0.00–10.00)	4.00 (1.00–8.00)	4.00 (0.00–10.00)

*Baseline characteristic data were not recorded for all participants.

dosing period. Over the approximately 6-hour dosing period for dinoprostone, 140 (46%) women received one dose and 163 (54%) received two doses. A number of women, in whom labour was not established after their final dose of study medication, received subsequent doses of a cervical ripening agent, generally dinoprostone, either as gel or tablet from pharmacy stock, according to the investigator's standard clinical practice. More women in the dinoprostone group than in the misoprostol group (33 compared with 22, respectively) received additional nonstudy cervical ripening agents.

Efficacy

Primary outcome

One hundred and thirty seven (43%) of 315 women in the misoprostol group achieved vaginal delivery within 24 hours of the start of labour induction compared with 143 (47%) of 304 in the dinoprostone group. This difference did not reach statistical significance (3.74%, 95% CI –3.58 to 11.05). The upper limit of the 95% CI (11.05%) did not fully meet the predefined criterion for noninferiority. However, this criterion was met at the 90.6% CI level.

The rate of vaginal deliveries achieved within 24 hours was similar between the misoprostol and dinoprostone groups in nulliparous (52 [29%] of 179 and 54 [31%] of 175, respectively) and multiparous (85 [63%] of 136 and 89 [69%] of 129, respectively) women. The differences between the treatments were not statistically significant in the nulliparous (1.81%, 95% CI –7.74 to 11.35) or multiparous (6.49%, 95% CI –4.91 to 17.89) groups, although the study was not powered for these subgroup comparisons.

Secondary outcomes

Outcomes for the majority of the secondary efficacy measures were similar for both treatments (Table 2). Overall, mean induction–delivery intervals were similar for misoprostol and dinoprostone (24.67 versus 25.06 hours, respectively). In nulliparous women, the mean induction–delivery interval was 28.04 hours for misoprostol and 29.61 hours for dinoprostone. Corresponding values in multipara were 21.77 and 20.54 hours, respectively (Figure 2). The median induction–delivery intervals were also comparable (21.13 hours [interquartile range {IQR} 14.43–29.67] versus 19.72 hours [IQR 12.45–31.20], respectively). Comparison of the median induction–delivery intervals using a Wilcoxon–Mann–Whitney test showed no statistically significant difference between the two treatment groups ($P = 0.33$).

There were more caesarean section deliveries in the misoprostol group (Table 2). However, when adjusted *post hoc* for confounding variables, such as parity, age, weight and baseline Bishop score, the difference in caesarean section deliveries

Table 2. Secondary efficacy outcome measures in intention-to-treat population

Outcome measure	Misoprostol	Dinoprostone	Treatment difference (OR for dinoprostone versus misoprostol [95% CI])
Vaginal deliveries <12 hours from start of induction, *n* (%)	*n* = 315	*n* = 304	
	35 (11)	56 (18)	1.93 (1.20–3.11), *P* = 0.007
Caesarean section deliveries, *n* (%)	*n* = 318	*n* = 308	
	90 (28)	67 (22)	0.66 (0.45–0.98), *P* = 0.037
Induction–delivery interval in hours, mean (SD)	*n* = 227	*n* = 237	
	24.67 (15.61)	25.06 (18.87)	0.12 (−2.98–3.21), *P* = 0.94
Oxytocin augmentation requirement, *n* (%)	*n* = 318	*n* = 308	
	157 (49)	152 (49)	0.98 (0.70–1.37), *P* = 0.91
Instrument-assisted vaginal deliveries, *n* (%)	*n* = 318	*n* = 308	
	53 (17)	60 (19)	1.20 (0.79–1.83), *P* = 0.38
Women experiencing tachysystole, *n* (%)	*n* = 318	*n* = 308	
	8 (3)	8 (3)	1.01 (0.37–2.76), *P* = 0.98
Uterine hyperstimulation with fetal heart rate changes, *n* (%)	*n* = 318	*n* = 308	
	19 (6)	20 (6)	1.08 (0.56–2.08), *P* = 0.81
Pyrexia during labour, *n* (%)	*n* = 318	*n* = 308	
	14 (4)	16 (5)	1.18 (0.56–2.47), *P* = 0.67

was no longer significant (OR 0.73, 95% CI 0.45–1.19, *P* = 0.21). A greater proportion of women who received dinoprostone had vaginal deliveries within 12 hours of induction compared with misoprostol recipients.

Safety and tolerability

Maternal and fetal complications were observed at similar rates in the misoprostol and dinoprostone groups, with the exception of a significantly higher rate of maternal nausea in the dinoprostone group than in the misoprostol group (Table 3). There were no cases of uterine rupture during the study.

Perineal laceration and vomiting were frequently experienced AEs among women in both treatment groups (Table 4). Compared with misoprostol, there was a relatively higher frequency of vomiting (24.1 versus 19.6%), episiotomy (17.8 versus 11.7%) and perineal laceration (41.6 versus 38.0%) in the dinoprostone group. Rates of postpartum haemorrhage and uterine hypertonus were similar between groups.

Fetal heart decelerations were reported more frequently in the dinoprostone group (27.4 versus 23.1%), but other fetal heart rate abnormalities were reported more frequently in the misoprostol group (14.9 versus 10.2% [Table 5]). The proportion of labours associated with reports that could be indicative of fetal distress (including any fetal heart rate- or meconium-related abnormality) was similar between the dinoprostone and misoprostol groups (50.2 versus 53.5%).

All women received concomitant medications during the study. More women in the dinoprostone group received antiemetics and antinauseants (30.7 versus 24.1%) and drugs for functional gastrointestinal disorders (22.4 versus 15.2%). More women in the misoprostol group received antibacterials (39.9 versus 33.3%).

One woman from each treatment group discontinued the study due to an AE; of these, only one AE was judged likely to be treatment related (moderate uterine hypertonus in the misoprostol group). There were no fetal or maternal deaths in either treatment group.

Discussion

This open-label, comparative study is one of the largest studies to date to assess the safety and efficacy of low-dose intravaginal misoprostol in the induction of labour. Furthermore, this is the only such study to use a specifically developed vaginal tablet of 25-microgram misoprostol; all studies hitherto having relied on informally prepared tablets, fragments or suspensions. No significant difference between misoprostol and dinoprostone was found in the proportion of women achieving vaginal delivery within 24 hours of the start of induction. Misoprostol and dinoprostone demonstrated similar efficacy on most secondary end-points, including mean induction–delivery interval and requirement for oxytocin augmentation. Moreover, misoprostol was as well tolerated as dinoprostone.

Findings for the nulliparous and multiparous populations were similar to the observations for the overall population. However, as expected, the rate of vaginal deliveries achieved within 12 or 24 hours in both treatment groups was lower for

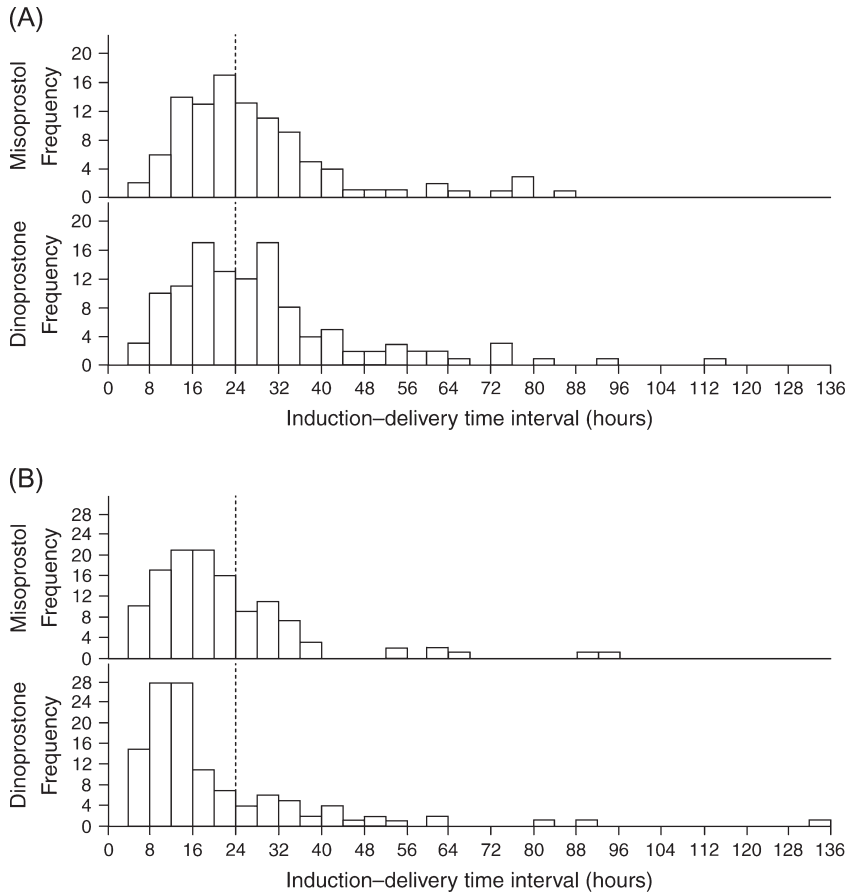


Figure 2. Distribution of induction–delivery intervals in nulliparous (A) and multiparous (B) women with vaginal delivery.

nulliparous women compared with multiparous women. Although the mean induction–delivery intervals did not significantly differ between treatments in either subpopulation, the relatively skewed distribution of the induction–delivery intervals for dinoprostone, more prominent in the multiparous population, may reflect additional dosing with dinoprostone and also a tendency for investigators to be more comfortable with the standard agent, thus allowing labour

Table 3. Maternal and fetal complications*

Outcome measure	Misoprostol (n = 316)	Dinoprostone (n = 303)	Treatment difference (OR for dinoprostone versus misoprostol [95% CI])
Uterine hyperstimulation without fetal heart rate changes, *n* (%)	11 (3)	14 (5)	1.33 (0.59–2.99), P = 0.49
Uterine rupture, *n* (%)	0 (0)	0 (0)	Undefined (no events in either group)
Use of epidural analgesia, *n* (%)	148 (47)	142 (47)	0.98 (0.71–1.37), P = 0.91
Maternal nausea, *n* (%)	42 (13)	61 (20)	1.65 (1.06–2.54), P = 0.025
Maternal vomiting, *n* (%)	56 (18)	69 (23)	1.36 (0.91–2.04), P = 0.13
Maternal diarrhoea, *n* (%)	3 (1)	3 (1)	1.05 (0.21–5.25), P = 0.95
Meconium-stained liquor, *n* (%)	48 (15)	42 (14)	0.91 (0.58–1.43), P = 0.69
Apgar score <7 at 5 minutes, *n* (%)	1 (0)**	3 (1)***	3.14 (0.32–30.48), P = 0.32

*The safety population (n = 619) comprises all participants who received at least one dose of study medication.
**n = 315.
***n = 302.

Table 4. Common maternal AEs (>5% frequency in any group, *n* [%])

AE	Misoprostol (*n* = 316)	Dinoprostone (*n* = 303)	Total (*n* = 619)
Any event	281 (88.9)	271 (89.4)	552 (89.2)
Perineal laceration	120 (38.0)	126 (41.6)	246 (39.7)
Vomiting	62 (19.6)	73 (24.1)	135 (21.8)
Arrested labour	51 (16.1)	51 (16.8)	102 (16.5)
Postpartum haemorrhage	50 (15.8)	46 (15.2)	96 (15.5)
Anaemia	48 (15.2)	47 (15.5)	95 (15.3)
Episiotomy	37 (11.7)	54 (17.8)	91 (14.7)
Failed induction of labour	33 (10.4)	40 (13.2)	73 (11.8)
Uterine hypertonus	24 (7.6)	23 (7.6)	47 (7.6)
Pyrexia	19 (6.0)	19 (6.3)	38 (6.1)
Nausea	18 (5.7)	18 (5.9)	36 (5.8)
Amniotic cavity disorder	12 (3.8)	20 (6.6)	32 (5.2)
Prolonged labour	13 (4.1)	17 (5.6)	30 (4.8)

induction to proceed longer than with misoprostol before intervening.

Although the absolute difference (3.74%) between treatments for the primary end-point of the number of vaginal deliveries within 24 hours did not reach statistical significance, the upper limit of the 95% CI exceeded the predefined noninferiority limit of 10% by 1.05%. The initial selection of the noninferiority limit for the primary analysis, informed by expert opinion, was based on the assumption that 82% of deliveries in the dinoprostone group would be achieved within 24 hours.[4] In fact, only 47% of deliveries in the dinoprostone group occurred within 24 hours. There was wide variation in the proportion of vaginal deliveries within 24 hours recorded across the 18 enrolling study centres for misoprostol (27–75%) and dinoprostone (17–100%). Inconclusive demonstration of noninferiority in this study population can be attributed to a greater variability in the clinical data than was originally anticipated at the time of the design of this clinical study.[26] Although noninferiority was not formally demonstrated, misoprostol was shown to have, at worst, a 24-hour delivery rate within 11% of that of dinoprostone. Nonetheless, the study provides more than 90% confidence of the noninferiority of misoprostol.

The ultimate objective of this noninferiority study was to ensure that APL202 is superior to a putative placebo. Data from the Cochrane review[4] indicate that the relative risk for failure to achieve vaginal delivery within 24 hours under vaginal dinoprostone versus standard care is 0.12 (95% CI 0.08–0.17). From the current study, the relative risk for failure to achieve vaginal delivery within 24 hours under APL202 versus dinoprostone is 1.07 (95% CI 0.94–1.23). A conservative analysis, using the extremes of these two confidence intervals, indicates that APL202 retains at least 95% of the relative effect of vaginal dinoprostone over standard care.

Furthermore, comparison with other studies is limited as they generally used higher drug doses or different regimens. However, in a trial conducted by van Gemund *et al.*,[15] which employed a similar dosing schedule to the one used in this

Table 5. Common fetal AEs (>2% frequency in any group, *n* [%])

AE	Misoprostol (*n* = 316)	Dinoprostone (*n* = 303)	Total (*n* = 619)
Any event	227 (71.8)	207 (68.3)	434 (70.1)
Fetal heart rate deceleration	73 (23.1)	83 (27.4)	156 (25.2)
Umbilical cord around neck	41 (13.0)	44 (14.5)	85 (13.7)
Meconium in amniotic fluid	47 (14.9)	38 (12.5)	85 (13.7)
Fetal heart rate abnormal	47 (14.9)	31 (10.2)	78 (12.6)
Neonatal jaundice	40 (12.7)	34 (11.2)	74 (12.0)
Fetal distress syndrome	36 (11.4)	27 (8.9)	63 (10.2)
Fetal bradycardia	28 (8.9)	29 (9.6)	57 (9.2)
Fetal tachycardia	10 (3.2)	11 (3.6)	21 (3.4)
Umbilical cord abnormality	11 (3.5)	3 (1.0)	14 (2.3)
Birth trauma	6 (1.9)	7 (2.3)	13 (2.1)

study, 48% of women who received misoprostol 25 micrograms 4-hourly achieved vaginal delivery within 24 hours. The baseline characteristics for the populations in the current study and that by van Gemund *et al.* were broadly comparable with the exception of the main indications for induction. In this study, it was post-dates gestation (n = 451, 72%), followed by hypertension (n = 29, 5%) and then pre-eclampsia (n = 27, 4%). In the study by van Gemund *et al.*, the indications were the same as in the current study but with a significantly smaller number for post-dates gestation (n = 167, 25%) and significantly more for hypertension including pre-eclampsia (n = 176, 26%).

The rate of caesarean section deliveries in the dinoprostone group (22%) was similar to that generally observed in the UK in induced labours (20.4%)[3] and in the van Gemund study (21%) in which dinoprostone 1-mg gel 4-hourly was the active comparator. The 28% caesarean section rate observed in the misoprostol group in this study was higher than previously reported in the van Gemund study (16%) and higher than that reported in other published studies of intravaginal misoprostol 25 or 50 micrograms (approximately 19%),[11] while a recent meta-analysis reported no difference in the risk of caesarean delivery between intravaginal misoprostol and dinoprostone.[16] A possible reason for the higher rate in caesarean section in misoprostol-treated women compared with dinoprostone-treated women is that by chance, more women at high risk of requiring caesarean section were randomised to the misoprostol group. For example, obesity is a recognised risk factor for caesarean section,[25,27] and more women in the misoprostol group had a weight consistent with morbid obesity (>125 kg) compared with the dinoprostone group. In addition, there were more women in the misoprostol group than in the dinoprostone group with a baseline Bishop score <3 (62 and 48, respectively) or pre-eclampsia (16 versus 11, respectively). A covariate analysis, adjusting for confounding factors for caesarean section such as parity, age, weight and baseline Bishop score, found the difference in caesarean section rates between the treatment groups to be nonsignificant.

Misoprostol was at least as well tolerated as dinoprostone. Most maternal and fetal AEs occurred at comparable frequencies in the treatment groups, including the incidence of postpartum haemorrhage (15.8 versus 15.2% for dinoprostone) (Table 4), which confirms observations elsewhere.[12,16] A notable difference between the two treatments was the significantly greater proportion of women in the dinoprostone group who experienced nausea compared with those in the misoprostol group (20 versus 13%). The relatively higher incidence of maternal vomiting in the dinoprostone treatment group (22 versus 17% for misoprostol) may even have been underestimated due to the higher incidence of antiemetic and antinauseant use (31 versus 24%) among the dinoprostone group. Of particular interest is the incidence of uterine tachysystole (defined as more than five contractions per 10 minutes for at least 20 minutes) and hyperstimulation (defined as tachysystole or uterine hypersystole/hypertonus—a contraction lasting at least 2 minutes), which were similar in the two groups. Numerous studies have investigated misoprostol at higher doses than used in the current study[16,28] and have generally recorded high rates for each of these events. When misoprostol has been used at lower doses, the rates of these uterine events have been similar to those of comparator agents.[12] Thus, confirming this observation, this study found that low-dose misoprostol was as well tolerated as dinoprostone by both the mother and fetus. These findings are reassuring when considering previous suggestions of an increased risk of fetal distress-related events with misoprostol in a meta-analysis by Crane *et al.*[16] In the meta-analysis, the sample size of those receiving low-dose misoprostol was small (i.e. 155 women from only four studies).

The present study was subject to some methodological limitations. It was not blinded because of the differences in the regimens, and this may have resulted in an inadvertent bias for or against one type of treatment. For example, caesarean sections may have been considered in preference to other interventions or considered at an earlier stage if the woman was receiving the unfamiliar, investigational agent rather than the familiar, well-accepted agent. This is suggested by the tendency for caesareans to take place earlier in the misoprostol group (e.g. the induction-to-caesarean section interval ranged from 20 to 38 hours in the misoprostol-treated group across the respective enrolling sites compared with 20–86 hours in the dinoprostone-treated group). A potential for such bias was recognised by Hofmeyr and Gülmezoglu[12] in their meta-analysis of intravaginal misoprostol studies. Similarly, certain events may have been more likely to be reported to occur with one agent (e.g. uterine tachysystole with misoprostol) if the investigator was aware of published studies, suggesting an association between the agent and the event. More women in the dinoprostone group than in the misoprostol group (33 compared with 22, respectively) received additional nonstudy cervical ripening agents. This use may have resulted in some caesarean sections being avoided or may have affected the primary outcome of vaginal deliveries within 24 hours in this subgroup of women. Variation in the dosage timings for the two study treatments (three doses of misoprostol over approximately 8 hours compared with two doses of dinoprostone administered over approximately 6 hours) may also have influenced the number of vaginal deliveries at the 12-hour time period because measurements of this study end-point would have occurred 6 hours after the completion of the dinoprostone dosing but only 4 hours after the misoprostol dosing was completed. Ultimately in any study comparing the potency and efficacy of drugs, outcome measures may be influenced not only by the formulations being compared but also by the dosages and dosage intervals used in the study.

Conclusions

This large study was designed to assess a specifically developed 25-microgram vaginal tablet of misoprostol (APL202). The findings confirm the efficacy of low-dose misoprostol in cervical ripening and labour induction and demonstrate a similar fetal and maternal safety profile to dinoprostone. Therefore, this 25-microgram vaginal misoprostol tablet provides an effective and well-tolerated option for cervical ripening and labour induction.

Lead investigators

A.A.C. stood down as lead investigator in November 2006 when he was appointed chairman of the NICE Induction of Labour Guidelines Development Group and was succeeded then by A.D.L.

Investigators

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Conflict of interest

A.A.C. and A.D.L. were study investigators and their sites received research funding from Alliance Pharmaceuticals Limited for their participation in the studies. In addition, both received sponsorship to attend a scientific meeting. The employer of C.J.W. has undertaken contract research in collaboration with Alliance Pharmaceuticals Limited. J.W.B. is a paid employee of Alliance Pharmaceuticals Limited.

Contribution to authorship

A.A.C contributed to the initial review of the study designs. C.J.W. contributed to the statistical analysis. All authors contributed to the critical review and revision of the study results and to final version for publication. All authors reviewed and approved the final paper.

Details of ethics approval

The protocols and amendments for two separate studies were reviewed and approved by Huntingdon Research Ethics Committee, Victoria House, Capital Park, Fulbourn, Cambridge, on 12 November 2004, reference number: 04/Q0104/94, and South East Multicentre Research Ethics Committee, South East Coast Health Authority, Preston Hall, Aylesford, Kent, on 4 November 2004, reference number: 04/MREC01/45. Ethics approval for combining the studies was granted by both ethics committees on the 29 and 7 September 2006, respectively.

The study was conducted and informed consent was obtained in accordance with the Declaration of Helsinki (revised Edinburgh 2000) and according to European Good Clinical Practice.

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