Accepted: 20 April 2024

DOI: 10.1111/1471-0528.17839

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Oral misoprostol alone, compared with oral misoprostol followed by oxytocin, in women induced for hypertension of pregnancy: A multicentre randomised trial

Shuchita Mundle[1] | Kate Lightly[2] | Jill Durocher[3] | Hillary Bracken[4] | Moushmi Tadas[5] | Seema Parvekar[6] | Poonam Varma Shivkumar[7] | Brian Faragher[8] | Thomas Easterling[9] | Simon Leigh[10] | Mark Turner[2] | Zarko Alfirevic[2] | Beverly Winikoff[3] | Andrew D. Weeks[2]

[1]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India

[2]Department of Women's and Children's Health, University of Liverpool, Liverpool, Merseyside, UK

[3]Gynuity Health Projects, New York, New York, USA

[4]The Patient-Centered Outcomes Research Institute, Washington, District of Columbia, USA

[5]Department of Obstetrics and Gynaecology, Government Medical College, Nagpur, Maharashtra, India

[6]Department of Obstetrics and Gynaecology, Daga Memorial Women's Government Hospital, Nagpur, Maharashtra, India

[7]Department of Obstetrics and Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India

[8]Medical Statistics Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

[9]Department of Obstetrics and Gynecology, University of Washington, Seattle, Washington State, USA

[10]Nexus Clinical Analytics, Charnock Richard, Lancashire, UK

Correspondence
Andrew D. Weeks, Sanyu Research Unit, Department of Women's and Children's Health, Liverpool Women's Hospital, Crown Street, Liverpool, L8 7SS, UK.
Email: aweeks@liverpool.ac.uk

Funding information
Medical Research Council; Foreign, Commonwealth and Development Office; National Institute for Health and Care Research; Wellcome Trust

Abstract

Objective: To assess whether, in those requiring continuing uterine stimulation after cervical ripening with oral misoprostol and membrane rupture, augmentation with low-dose oral misoprostol is superior to intravenous oxytocin.

Design: Open-label, superiority randomised trial.

Setting: Government hospitals in India.

Population: Women who were induced for hypertensive disease in pregnancy and had undergone cervical ripening with oral misoprostol, but required continuing stimulation after artificial membrane rupture.

Methods: Participants received misoprostol (25 micrograms, orally, 2-hourly) or titrated oxytocin through an infusion pump. All women had one-to-one care; fetal monitoring was conducted using a mixture of intermittent and continuous electronic fetal monitoring.

Main outcome measures: Caesarean birth.

Results: A total of 520 women were randomised and the baseline characteristics were comparable between the groups. The caesarean section rate was not reduced with the use of misoprostol (misoprostol, 84/260, 32.3%, vs oxytocin, 71/260, 27.3%; aOR 1.23; 95% CI 0.81–1.85; $P = 0.33$). The interval from randomisation to birth was somewhat longer with misoprostol (225 min, 207–244 min, vs 194 min, 179–210 min; aOR 1.137; 95% CI 1.023–1.264; $P = 0.017$). There were no cases of hyperstimulation in either arm. The rates of fetal heart rate abnormalities and maternal side effects were similar. Fewer babies in the misoprostol arm were admitted to the special care unit (10 vs 21 in the oxytocin group; aOR 0.463; 95% CI 0.203–1.058; $P = 0.068$) and there were no neonatal deaths in the misoprostol group, compared with three neonatal deaths in the oxytocin arm. Women's acceptability ratings were high in both study groups.

Conclusions: Following cervical preparation with oral misoprostol and membrane rupture, the use of continuing oral misoprostol for augmentation did not significantly reduce caesarean rates, compared with the use of oxytocin. There were no hyperstimulation or significant adverse events in either arm of the trial.

KEYWORDS
India, labour induction, misoprostol, oxytocin, pre-eclampsia, randomised trial

1 | INTRODUCTION

Hypertensive disease in pregnancy is a major cause of maternal deaths.[1] Many of the deaths could be prevented by timely and effective delivery, but labour induction itself carries risks. Identifying a safe and effective method suitable for low- and middle-income settings is a critical public health intervention.

Low-dose oral misoprostol (LDOM) is a highly effective method of induction.[2] Oral administration of 25 micrograms of misoprostol every 2 h for cervical preparation has been strongly recommended by both the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE).[3,4] Cochrane reviews of LDOM found that it is more effective than the commonly used vaginal dinoprostone gel,[5,6] and it has the added advantages of being heat stable and of low cost in many settings.

Standard practice for induction is to use a prostaglandin (e.g. misoprostol or dinoprostone) for cervical preparation.[7] Once active labour commences and the amniotic membranes have ruptured, the prostaglandin is replaced with an intravenous infusion of oxytocin, if required.[8] The infusion is titrated every 30 min to stimulate uterine contractions sufficient to progress labour, but not so much as to cause hyperstimulation. In many countries, electronic infusion pumps are not available, and oxytocin is administered through a gravity drip infusion. These poorly regulated infusions require constant supervision as inadvertent overdosing can lead to hyperstimulation, with associated maternal and fetal risks.[9,10] There is a need, therefore, to identify cost-effective means of induction in which the uterotonic can be administered in a safe and standardised way.

In the Cochrane review of LDOM for labour induction, LDOM was continued into active labour in two studies, whereas in the remaining 57 studies the stimulation was changed to oxytocin after the artificial rupture of membranes.[5,11] The main outcomes following the continued use of LDOM into active labour were equivalent or better than in the comparator arms.

The continued use of LDOM allows women to be free to mobilise in labour, unrestricted by an intravenous infusion, and could empower women to be more involved in their care. There could also be significant health system savings, with a reduced use of equipment and staff time.

Despite its promise, an induction protocol with continuing LDOM into labour has never been directly compared with the standard oxytocin regimen in a randomised trial. The study objective was to assess whether, in those requiring continuing uterine stimulation after cervical ripening with oral misoprostol and membrane rupture, augmentation with LDOM is superior to intravenous oxytocin.

2 | METHODS

2.1 | Study design

This was a pragmatic, parallel-group, open-label, superiority randomised control trial of two protocols for labour induction among women with hypertension of pregnancy. All women underwent initial cervical preparation with LDOM, and those who required continuing induction after membrane rupture were randomised in a 1:1 ratio to LDOM or intravenous oxytocin. The study protocol has been published,[12] but the brief methods are outlined below.

2.2 | Participants

Women planning to give birth in three government hospitals in central India were recruited to this trial: Government Medical College, Nagpur; Daga Memorial Women's Hospital, Nagpur; and Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha. Women with an indication for induction for hypertensive disease, irrespective of gestation, and who required cervical preparation for an unfavourable cervix (with a Bishop's score of ≤6) were recruited prior to the start of induction. All consenting women then underwent cervical preparation with LDOM, 25 micrograms, 2-hourly. However, only those who subsequently required augmentation following the artificial rupture of membranes were randomised. Most did not have prior ultrasound unless growth restriction was suspected clinically prior to the development of hypertension or if the onset was before 34 weeks of gestation. Those with a previous caesarean section (CS), aged <18 years, known intrauterine fetal death or multiple pregnancy were excluded.

2.3 | Randomisation and masking

Potential participants were informed of the study through posters in the antenatal areas and labour ward. Once a clinical decision was made for induction, the woman was provided with an own-language information sheet and a brief slide presentation to view on a tablet. If she was unable to read, a member of the research team read the forms to her in her own language in the presence of family members and/or friends. If she wished to participate, then she signed (or placed a thumb print) on the consent form. If she then required continuing induction after membrane rupture as part of the induction process, she was randomised to receive misoprostol or oxytocin, without the need for additional written consent.

For randomisation, the next consecutive, sequentially numbered opaque envelope containing the allocation was drawn from the trial dispenser by the research assistant and opened. The treatment allocation was generated independently using a computerised pseudo-random number generator, stratified by centre, with random block sizes of 6, 8 and 10. The participants, researchers and clinical team were not blinded to the allocated treatment.

2.4 | Procedures

Induction for all women commenced with cervical preparation using 25 microgram oral misoprostol tablets (Cipla, Goa, India) every 2 h. Once painful contractions had begun, labour monitoring commenced with assessments every

30 min and with a vaginal examination performed every 4 h. The next dose of oral misoprostol was omitted when three or more moderate or strong contractions occurred every 10 min. Artificial rupture of membranes (ARM) was performed in accordance with routine clinical practice when the cervix was dilated to 2 cm. If spontaneous rupture of membranes occurred before that point, then the cervical preparation doses of misoprostol were stopped. If contractions were inadequate, then LDOM could be restarted as part of the randomised trial.

After membrane rupture, if the contractions continued at a rate of three or more every 10 min and there was progressive cervical change (defined as dilation of at least 1 cm every 2 h) then no further LDOM was used, and the participants were not randomised. If, however, the contractions slowed to fewer than three every 10 min or if there was no progressive cervical change, then the woman was randomised to either continued LDOM or an oxytocin infusion. This was the point of trial entry. If the cervix was still not favourable for ARM after 24 h of cervical preparation, then the decision regarding continuing management was made by the clinical team, and was usually to perform a caesarean birth.

Misoprostol (25 micrograms) was given orally every 2 h in the absence of adequate uterine activity. There was no titration of the misoprostol dose, but the next dose was withheld in the presence of regular uterine activity and only restarted if contractions became inadequate or if there was inadequate cervical change (<1 cm every 2 h). For the oxytocin infusion, 5 IU of oxytocin (Pfizer Limited, Nani Daman, India) in 500 mL of Ringer's lactate was given through an electronic infusion pump at a rate of 2 mU/min, and increased every 30 min by 2 mU/min to a maximum of 20 mU/min until there were three or four contractions every 10 min. If there was any suspicion of fetal distress caused by excessive uterine activity, then the oxytocin infusion was stopped (or the next LDOM dose was withheld) and the participant was put in a left lateral position and continuous electronic fetal heart rate monitoring began. Oxytocin or LDOM was only restarted if the contraction frequency subsequently dropped to two or fewer every 10 min, at which point the study drug was restarted (oxytocin at half the previous rate or LDOM at 25 micrograms).

Maternal and fetal monitoring was conducted on a one-to-one basis by graduate research assistants, specifically trained in fetal monitoring and uterine contraction strength. Intermittent electronic fetal monitoring was performed every 30 min with continuous electronic fetal monitoring in the case of abnormality. Continuous fetal monitoring was also used routinely in women at high risk, when available. In the case of hyperstimulation, staff were instructed to commence electronic fetal monitoring and, in the event of abnormality, reduce the dose of oxytocin.

2.5 | Outcomes

Outcomes were based on the Cochrane Collaboration induction of labour generic protocol and the induction of labour core outcome set.[13,14] The primary outcome was caesarean birth. Secondary outcomes addressed the success of the induction process, maternal mortality and morbidity, and neonatal mortality and morbidity. Measures of success included the interval between randomisation and birth, the duration of hospital stay and maternal satisfaction. Data was collected using REDCap (Vanderbilt University, Tennessee, USA). A qualitative study, situational analysis and health economic analysis were also conducted, and will be reported separately.

2.6 | Sample size calculation

In a previous study of labour induction conducted in this population, 157 (52%) women required uterine stimulation after membrane rupture with intravenous oxytocin (standard practice), 49 (31%) of whom had a caesarean birth.[15] In a systematic review of LDOM, those whose induction was continued after membrane rupture with LDOM had 42% fewer caesarean deliveries than those who changed to oxytocin (15% vs 26%).[6] Using these data, it was estimated that a total sample size of 520 women would provide: (i) 90% power to detect a reduction in the CS rate from 31.0% to 18.5% (RR 0.6); or (ii) 80% power to detect a reduction in the CS rate from 31% to 20% (RR 0.65) in women who receive LDOM (superiority; two-sided $\alpha = 0.05$). It was proposed to approach and gain consent from 1000 women, of whom an estimated 520 would require continuing induction after cervical preparation. At the point of requiring uterotonics for continuing induction, the consented women would be randomised to either a protocol of continued LDOM ($n = 260$) or the standard oxytocin infusion ($n = 260$).

2.7 | Statistical analysis

The primary outcome was CS, analysed according to the intention-to-treat principle. The primary outcome measure was evaluated using logistic regression models, initially unadjusted and then adjusted for predetermined important potential confounding variables and covariates. Effect sizes are presented as odds ratios for CS delivery rates between the two study treatment arms, along with the 95% confidence intervals. Secondary outcome measures were also evaluated unadjusted and then, where possible, adjusted for the same predetermined variables and covariates using logistic regression, ordinal (ordered) logistic regression, Poisson regression, Cox proportional hazards and standard regression models, according to data type. Stata (StataCorp, College Station, TX, USA) was used for all analyses.

A formal interim analysis was performed by an independent data and safety monitoring committee (IDSMC) after 214 women were randomised, whereas safety data were reported biannually. The 'stopping rules' for the interim analysis were in accordance with O'Brien and Fleming.[16] The IDSMC had the authority to request further interim analyses if indicated, but this was not exercised.

The study was sponsored by the University of Liverpool, registered with ClinicalTrials.gov (NCT03749902) and the Clinical Trial Registry, India (CTRI/2019/04/018827). All trial staff underwent training in Good Clinical Practice. Consumer representatives reviewed the protocol and participant-facing documentation at all stages, and a representative sat on the Trial Steering Committee.

3 | RESULTS

Overall, 1033 women were recruited to participate in the Misoprostol or Oxytocin for Labour Induction (MOLI) study between 6 January 2020 and 14 July 2022, when the sample size was reached (Figure 1). Two of the participating government hospitals, located in Nagpur, India, recruited participants from the launch of the study in 2020 until the end of the trial. Recruitment was temporarily halted on 19 March 2020 for the COVID-19 pandemic, before restarting again from 1 October 2020 with additional precautions against infection for participants and staff, in line with Indian government recommendations. A third site, the Mahatma Gandhi Institute of Medical Science, located in Sevagram, India, was added and began enrolling patients in February 2021.

Of the 1033 women, 520 required continuing induction after membrane rupture following cervical preparation with LDOM. These women were randomised to receive either continued LDOM ($n=260$) or oxytocin infusion ($n=260$). There were no missing data or loss to follow-up. Prior to randomisation, the participants had received a mean (SD) of 2.9 (1.7) and 3.0 (1.7) doses of LDOM, respectively, for cervical preparation. Membrane rupture was spontaneous in 65 (25.0%) and 60 (23.1%) women, respectively; the remainder underwent ARM.

The two randomised groups were well matched by age, parity and severity of disease (Table 1). Most women had not given birth previously, were close to their ultrasound-estimated delivery date and had mild non-proteinuric hypertension.

The primary outcome of CS was similar in the two arms: 84 (32.3%) for women who had continuing induction with LDOM and 71 (27.3%) for those who received oxytocin infusion (adjusted odds ratio, aOR 1.23; 95% CI 0.81–1.85; $P=0.329$; Table 2). This result is consistent with either a 19% reduction in the CS rate or an increase of 85%, with the high degree of uncertainty reflecting the relatively small sample size. The most common reasons for CS were a failure to progress in the first stage of labour and fetal heart rate abnormalities; no statistically significant differences were detected between the two study arms. In an exploratory subgroup analysis, the preterm gestations showed a statistically significant increase in the rate of CS in the misoprostol group (Figure 2).

The rates of fetal heart rate abnormality and meconium-stained liquor were similar in each group. There were no cases of uterine hyperstimulation (i.e. more than five contractions every 10 min) and no statistically significant differences in the rates of placental abruption, postpartum haemorrhage, manual removal of placenta, receipt of blood products or hypertensive complications. A much larger sample size would

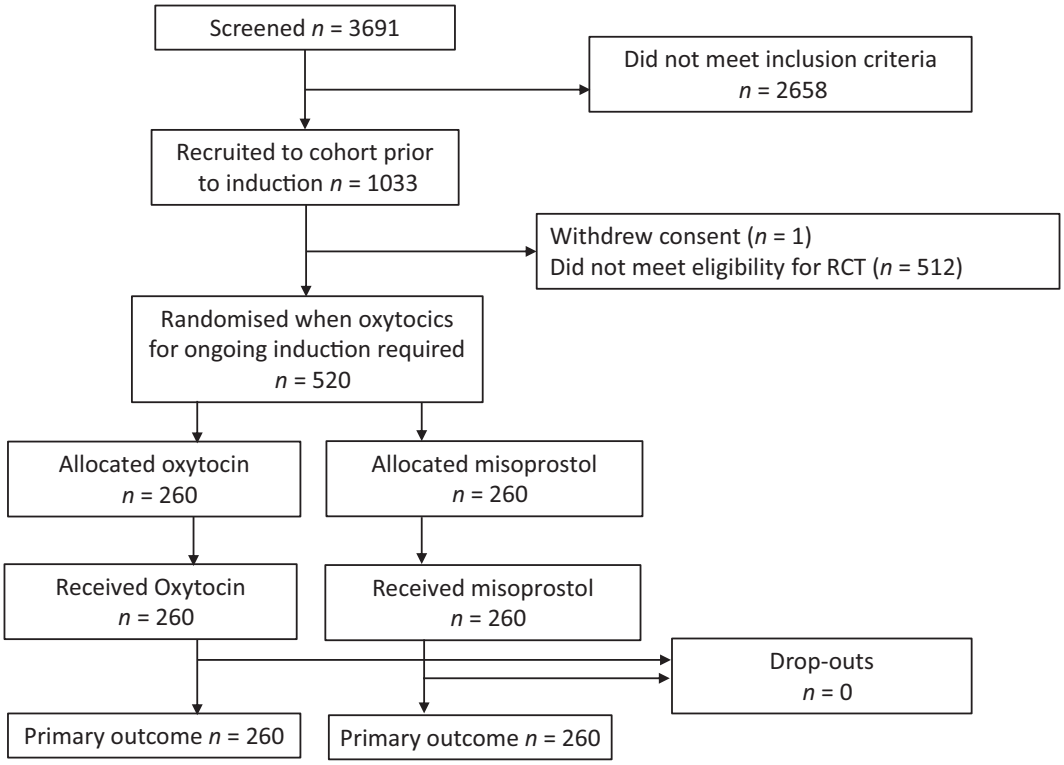

FIGURE 1 CONSORT flow chart.

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 1 Participant demographic and clinical characteristics, *n* (%).

Treatment group	Misoprostol	Oxytocin
Number of mothers	260	260
Woman's age (complete years)		
Mean (SD) [range]	25.2 (3.7) [19–38]	25.6 (4.1) [18–41]
Mother's highest completed education level		
No formal education	4 (1.5)	6 (2.3)
Primary	43 (16.5)	39 (15.0)
Secondary	117 (45.0)	115 (44.2)
Technical/skilled job training	2 (0.8)	10 (3.9)
University/postgraduate studies	94 (36.2)	90 (34.6)
Mother's employment (most time spent doing)		
Housewife/looking after own children	243 (93.5)	239 (91.9)
Other	17 (6.5)	21 (8.1)
Medical conditions affecting this pregnancy (more than one response possible)		
Diabetes	2 (0.8)	10 (3.9)
Chronic hypertension (pre-dating this pregnancy)	5 (1.9)	4 (1.5)
Anaemia	11 (4.2)	6 (2.3)
Sickle cell disease/thalassaemia	9 (3.5)	8 (3.1)
Hypothyroidism	27 (10.4)	17 (6.5)
Heart disease	0	1 (0.4)
Any other medical condition	2 (0.8)	6 (2.3)
Parity		
0	178 (68.5)	182 (70.0)
1	70 (26.9)	60 (23.1)
2/3/4	12 (4.6)	18 (6.9)
Arithmetic mean (SD)	0.37 (0.62)	0.38 (0.65)
Principal clinical indication for induction of labour		
Essential hypertension (predates pregnancy)	2 (0.8)	1 (0.4)
Gestational/pregnancy induced hypertension (no proteinuria)	196 (75.4)	183 (70.4)
Pre-eclampsia	58 (22.3)	73 (28.1)
Eclampsia	1 (0.4)	1 (0.4)
Superimposed pre-eclampsia	2 (0.8)	2 (0.8)
Pre-eclampsia uncategorised	1 (0.4)	0
Mother has attended ≥1 antenatal visits	255 (98.1)	252 (96.9)
At enrolment, prior to start of cervical ripening		
Best estimate of gestational age (weeks)		
Mean (SD) [range]	38.7 (1.3) [34–41]	38.8 (1.3) [34–41]
Estimate obtained by ultrasound at <20 weeks of gestation	252 (96.9)	250 (96.2)
Systolic blood pressure (mmHg)		
Mean (SD) [range]	140.2 (9.9) [120–180]	139.4 (9.9) [100–190]
Diastolic blood pressure (mmHg)		
Mean (SD) [range]	92.6 (6.7) [70–120]	92.2 (6.6) [70–118]
Proteinuria (not recorded for one mother in each group)		
Nil/trace	208 (80.3)	202 (78.0)
1+	34 (13.1)	45 (17.4)
2+/3+	17 (6.6)	12 (4.6)

(Continues)

TABLE 1 (Continued)

Treatment group	Misoprostol	Oxytocin
Mother has had an eclamptic fit	1 (0.4)	1 (0.4)
At randomisation, when continuing induction was needed after membrane rupture		
Time from admission to randomisation (hours)		
Geometric mean (95% CI) [range]	18.0 (16.4–19.7) [2.7–314]	18.9 (17.0–21.0) [2.7–476]
Admission to randomisation <24 h	177 (68.1)	179 (68.9)
No. of doses of misoprostol administered for cervical ripening		
Mean (SD) [range]	2.91 (1.68) [1–12]	3.02 (1.74) [1–12]
Cervical dilatation at randomisation		
Mean (SD) [range]	3.00 (0.76) [1–7]	3.15 (0.77) [1–6]

TABLE 2 Maternal outcomes, *n* (%).

Treatment group	Misoprostol	Oxytocin	Odds ratio (95% CI) [*P*] (misoprostol vs oxytocin)	
Number of mothers	260	260	Unadjusted	Adjusted[f]
Mode of delivery				
Spontaneous vaginal	174 (66.9)	187 (71.9)	–	–
Forceps or vacuum	2 (0.8)	2 (0.8)	–	–
CS (primary outcome)	84 (32.3)	71 (27.3)	1.270 (0.871–1.853) [0.213]	1.226 (0.814–1.847) [0.329]
Fetal monitoring used	254 (97.7)	253 (97.3)	1.171 (0.388–3.537) [0.779]	1.081 (0.297–3.930) [0.906]
Type of fetal monitoring (>1 response possible)				
Intermittent auscultation	229 (90.2)	230 (90.9)	0.916 (0.505–1.662) [0.773]	0.877 (0.470–1.637) [0.681]
CTG intermittent	185 (72.8)	188 (74.3)	0.927 (0.624–1.376) [0.707]	0.877 (0.578–1.331) [0.537]
CTG continuous	73 (28.7)	86 (34.0)	0.783 (0.537–1.141) [0.203]	0.861 (0.570–1.301) [0.478]
Indications for CS delivery(>1 response possible)	***n*=84**	***n*=71**		
Failure to progress in first stage of labour	39 (46.4)	35 (49.3)	0.891 (0.473–1.682) [0.723]	–
Failure to progress in second stage of labour	6 (7.1)	6 (8.5)	0.833 (0.255–2.718) [0.762]	–
Fetal heart rate abnormality	36 (42.9)	34 (47.9)	0.816 (0.432–1.544) [0.532]	0.819 (0.417–1.606) [0.561]
Ante/intrapartum haemorrhage	1 (1.2)	2 (2.8)	0.416 (0.037–4.719) [0.479]	–
Meconium-stained liquor	14 (16.7)	9 (12.7)	1.378 (0.556–3.414) [0.489]	1.644 (0.586–4.613) [0.345]
Cephalopelvic disproportion	1 (1.2)	1 (1.4)	0.843 (0.051–13.86) [0.905]	–
Maternal condition	2 (2.4)[a]	2 (2.8)[b]	0.842 (0.115–6.170) [0.865]	–
Other	1 (1.2)[c]	3 (1.4)[d]	0.843 (0.051–13.86) [0.905]	–
Side-effects during augmentation				
Diarrhoea				
None	259 (99.6)	255 (98.1)	0.198 (0.023–1.717) [0.142]	–
Mild (loose stool)	0	2 (0.8)		
Moderate (watery stool)	0	1 (0.4)		
Severe (uncontrolled watery stool)	1 (0.4)	2 (0.8)		
Vomiting				
None	251 (96.5)	252 (96.9)	1.142 (0.423–3.007) [0.789]	–
Mild (retching only)	5 (1.9)	7 (2.7)		
Moderate (≤1 per hour)	4 (1.5)	1 (0.4)		
Complications of labour or delivery up to time of discharge				
Uterine hyperstimulation	0	0	–	
Fetal heart rate abnormality	39/260 (15.0)	38/260 (14.6)	1.031 (0.635–1.674) [0.902]	1.027 (0.622–1.695) [0.918]

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 2 (Continued)

Side-effects during augmentation				
Placental abruption	0	1 (0.4)	–	–
Diagnosis of postpartum haemorrhage (>1000 mL)	0	3 (1.2)	–	–
Manual removal of placenta	1 (0.4)	4 (1.5)	0.247 (0.027–2.231) [0.213]	–
Blood products after trial entry	7 (2.7)	6 (2.3)	1.171 (0.388–3.537) [0.779]	–
Severe hypertension (SBP ≥ 160 mmHg or DBP ≥ 110 mmHg)	7 (2.7)	11 (4.2)	0.626 (0.239–1.643) [0.342]	0.521 (0.212–1.280) [0.155]
Other	1 (0.4)[e]	0	0.331 (0.034–3.208) [0.340]	–
HELLP (hemolysis, elevated liver enzymes and low platelets)	1 (0.4)	0	–	–
Oliguria (<100 mL in 4 h)	0	1 (0.4)	–	–

Time from randomisation to delivery (minutes)	**Geometric mean (95% CI) [range]**		**(Geometric) mean ratio (95% CI) [*P*] (misoprostol vs oxytocin)**	
All women	225 (207–244) [30–1133]	194 (179–210) [35–1262]	1.159 (1.032–1.301) [0.013]	1.137 (1.023–1.264) [0.017]
CS deliveries only	316 (277–362) [56–1033]	305 (267–348) [79–1262]	1.038 (0.861–1.252 [0.692]	1.064 (0.896–1.264 [0.478]
Normal vaginal deliveries (NVD) only	191 (174–210) [30–1133]	164 (149–179) [35–1057]	1.166 (1.022–1.328 [0.021]	1.141 (1.012–1.286 [0.031]
Number of doses of misoprostol used for continuing induction after randomisation				
All women	Mean (SD) [range]	1.30 (0.85) [1–9]	–	Mean ratio (95% CI) [*P*] (CS vs NVD deliveries)
CS deliveries only	Mean (SD) [range]	1.42 (0.81) [1–5]	–	1.133 (0.967–1.329) [0.123]
NVD deliveries only	Mean (SD) [range]	1.25 (0.87) [1–9]	–	

Duration of hospital stay (hours)	**Geometric mean (95% CI) [range]**		**(Geometric) mean ratio (95% CI) [*P*] (misoprostol vs oxytocin)**	
All women	92 (87–99)[26–365]	98 (93–104)[24–389]	0.968 (0.885–1.059) [0.447]	0.960 (0.878–1.051) [0.379]
CS deliveries only	147 (137–157)[77–365]	142 (133–152)[86–388]	1.042 (0.941–1.155) [0.430]	1.002 (0.904–1.111) [0.966]
NVD deliveries only	74 (69–79)[26–355]	85 (80–91)[24–389]	0.874 (0.783–0.975) [0.016]	0.874 (0.782–0.978) [0.019]

[a]'Early signs of disseminated intravascular coagulation' and 'early signs of disseminated intravascular coagulation and haematuria'.

[b]'Early signs of disseminated intravascular' and 'likely heart disease and tachycardia'.

[c]'Cord prolapse'.

[d]'Cord around neck' (all three cases).

[e]Haematuria.

[f]Adjusted for mother's age, gestational age, parity, mother's diastolic blood pressure, proteinuria and antihypertensive use at enrolment, receipt of magnesium sulphate in last 24 h before enrolment, time from hospital admission to randomisation <24 h, number of misoprostol doses administered for cervical preparation prior to randomisation and dilatation at randomisation.

be required to state with any certainty that there was no clinically important difference in these rare outcomes. No woman in either group experienced uterine rupture, admission to intensive care or death.

Fewer babies allocated to the LDOM group were admitted to the special care baby unit (Table 3); although these babies tended to spend more time there, this difference was not statistically significant ($P = 0.510$). Furthermore, there was no statistically significant difference between babies receiving ventilation, resuscitation or intubation. All other neonatal outcomes were similar between the two arms. Three babies died neonatally, all in the oxytocin arm. The causes of death were: septicaemia in a baby with a birthweight of 2.5 kg; asphyxia in a baby with severe cardiac abnormality and growth restriction, who developed hypoxic-ischaemic encephalopathy without any evidence of uterine hyperstimulation; and severe pulmonary haemorrhage in a severely growth-restricted baby (with a birthweight of 1.1 kg at 36 weeks of gestation). None were thought to be related to the study medications.

After giving birth, participants in both groups reported high levels of acceptability of their augmentation method (Figure 3; Table 4). Only 16 (6.2%) of the women in each group would not be happy to have the same method used again for future inductions, if needed. There was no difference between groups in their acceptability ratings on the time taken to give birth, the amount of pain during the induction and birth or their anxiety.

Women in the LDOM group took a statistically longer time to give birth (with a geometric mean time from randomisation to birth of 225 min, vs 194 min in the oxytocin

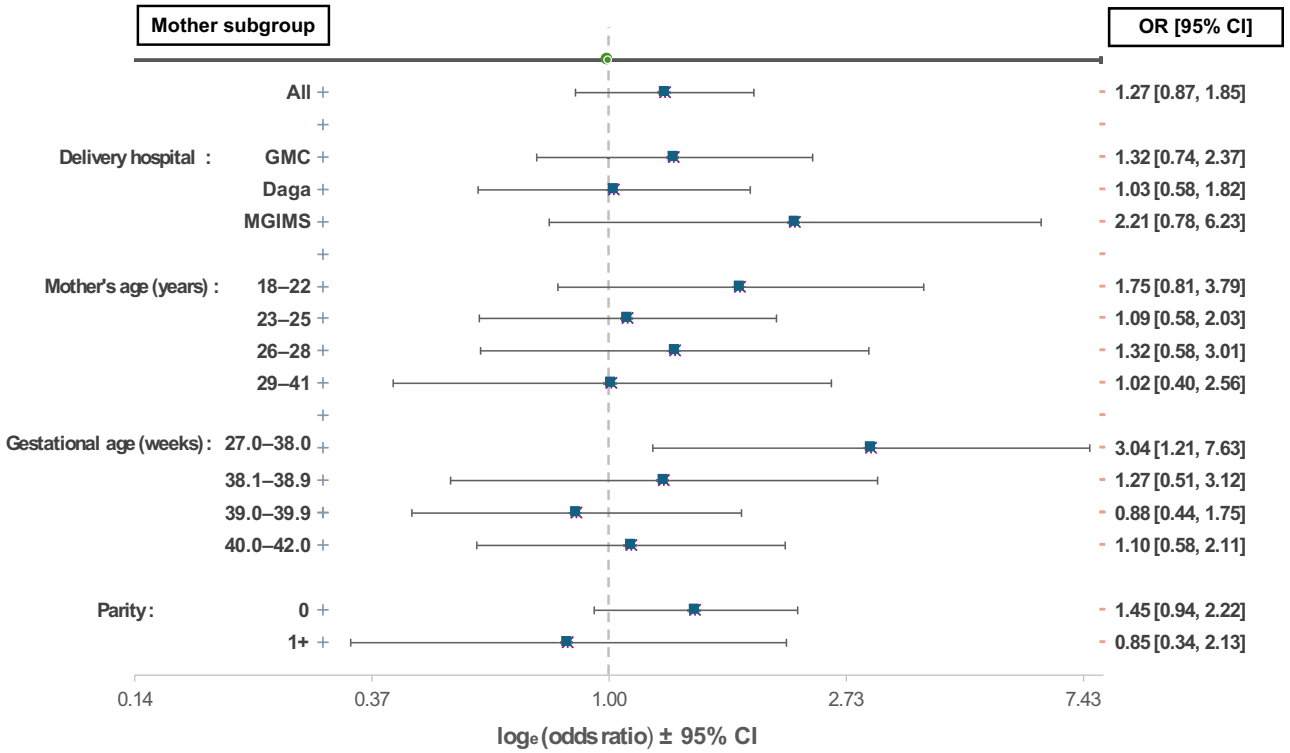

FIGURE 2 Odds ratios (with 95% confidence intervals) for caesarean section with misoprostol in participant subgroups, compared with oxytocin.

group; Figure 4), with the difference driven by those who had normal vaginal births. There was no statistically significant difference for those who underwent CS.

4 | DISCUSSION

4.1 | Main findings

To the best of our knowledge, this is the first randomised trial to compare the safety and efficacy of an induction protocol in which LDOM was used instead of oxytocin following membrane rupture. It demonstrates that in this setting, continuing induction with LDOM after membrane rupture did not reduce the CS rate. However, the confidence intervals are wide for both CS and safety outcomes; larger studies with the resulting narrower confidence intervals will be required to reduce the uncertainty.

4.2 | Strengths and limitations

The strengths of this study are that it was conducted in accordance with international standards, with regular monitoring visits to ensure compliance. The presence of a one researcher allocated to each recruited woman throughout her induction and labour ensured that the data were fully collected and that hyperstimulation, a factor that is often poorly recorded, could be accurately assessed every 30 min throughout labour. Although this process lessened the external validity of the study, it ensured that the study had complete follow-up and no missing data, despite being conducted in busy delivery units. The inclusion of two teaching hospitals, from an urban and a rural setting, and a district hospital allowed us to assess the effect of the intervention across three different types of delivery settings. A detailed comparison of the trial data among the study sites will be published elsewhere.

It is very difficult to blind a study in which a titrated infusion is compared with an oral tablet, and an open-label study is prone to clinician and researcher bias. Furthermore, the use of a placebo infusion would have nullified any mobility effect of the use of LDOM for continuing induction after membrane rupture. Nevertheless, bias is a particular risk in this study, where some clinicians reported being anxious about the risks of LDOM in labour and were reluctant to give more than three doses. This could have led to an excess of CSs in the LDOM group after 6 hours, but this was not seen in the survival curves (Figure 4).

4.3 | Interpretation

There are no previous randomised trials comparing these two stimulation methods during labour induction, although the regimen has been described previously.[11,17] There is also one randomised trial in which LDOM has been used for augmentation of spontaneous labour to accelerate slow progress.[18] In that study the LDOM group had lower rates of tachysystole than the oxytocin group, but there was no

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 3 Neonatal outcomes.

Treatment group		Misoprostol	Oxytocin	OR (95% CI) [*P*]	
Number of mothers		260	260	Unadjusted	Adjusted[a]
Outcome of delivery – live birth	*n* (%)	260 (100)	260 (100)	–	–
Birthweight (g)	Mean (SD)	2702 (414)	2687 (422)	16 (−56, 87) [0.669]	21 (−45, 87) [0.530]
Low birthweight (<2500 g)	*n* (%)	62 (23.9)	71 (27.3)	0.834 (0.561, 1.237) [0.366]	0.812 (0.522, 1.264) [0.356]
Apgar score at 5 min of ≥7	*n* (%)	256 (98.5)	258 (99.2)	0.496 (0.090, 2.737) [0.421]	0.449 (0.092, 2.184) [0.321]
Mean (SD)		8.80 (0.71)	8.83 (0.70)	−0.03 (−0.15, 0.09) [0.620]	−0.08 (−0.19, 0.03) [0.163]
First oral feed (bottle or breast) within 1 h	*n* (%)	232 (89.2)	221 (85.0)	1.462 (0.870, 2.459) [0.152]	1.583 (0.928, 2.699) [0.092]
Neonatal morbidity					
Meconium aspiration syndrome	*n* (%)	0	2 (0.8)	–	–
Neonatal convulsions	*n* (%)	1 (0.4)	0	–	–
Birth asphyxia (clinically diagnosed)	*n* (%)	3 (1.2)	2 (0.8)	1.506 (0.249, 9.103) [0.656]	–
Septicaemia (clinical diagnosed)	*n* (%)	1 (0.4)	1 (0.4)	1.000 (0.062, 16.12) [>0.999]	–
Congenital abnormality	*n* (%)	0	1 (0.4)	–	–
Other	*n* (%)	1 (0.4)[c]	1 (0.4)[d]	1.000 (0.062, 16.12) [>0.999]	–
Baby admitted to special care nursery (SCN)	*n* (%)	10 (3.9)	21 (8.1)	0.455 (0.210, 0.988) [0.046]	0.463 (0.203, 1.058) [0.068]
Time in SCN (days)	Geometric mean (95% CI) [range]	3.52 (1.41, 8.84) [0.18, 14.0]	2.29 (1.35, 3.89) [0.08, 15.3]	1.536 (0.584, 4.042) [0.372][b]	1.390 (0.498, 3.877) [0.510]
Baby was resuscitated	*n* (%)	3 (1.2)	4 (1.5)	0.747 (0.165, 3.376) [0.705]	–
Baby was intubated	*n* (%)	3 (1.2)	1 (0.4)	3.023 (0.312, 29.32) [0.340]	–
Baby was ventilated	*n* (%)	3 (1.2)	4 (1.5)	0.747 (0.165, 3.376) [0.705]	–
If 'yes', how long (hours)	Geometric mean (range)	52 (24, 170)	76 (48, 192)[b]	0.687 (0.084, 5.611) [0.646]	–
Baby was given oxygen	*n* (%)	7 (2.7)	10 (3.9)	0.692 (0.259, 1.848) [0.462]	0.697 (0.255, 1.905) [0.482]
If "yes", how long (hours)	Geometric mean (range)	18.3 (2, 190)	10.9 (0.2, 150)	1.680 (0.223, 12.66) [0.592]	2.182 (0.055, 86.32) [0.609]
Baby *not* alive at time of discharge	*n* (%)	0	3 (1.2)		
Causes of death		Asphyxia; septicaemia; severe uterine growth retardation with large pulmonary bleed			

[a]Adjusted for mother's age, gestational age, parity, mother's diastolic blood pressure, proteinuria and antihypertensive use at enrolment, receipt of magnesium sulphate in last 24 h before enrolment, time from hospital admission to randomisation <24 h, number of misoprostol doses administered for cervical preparation prior to randomisation and dilatation at randomisation.

[b]Time not recorded for one baby who died.

[c]Respiratory distress.

[d]Intrauterine growth restriction.

difference in any other maternal or neonatal outcomes. On the basis of the small size of the studies and the potential risks of misuse, the WHO recommended that LDOM should not be used for augmentation.[19]

This study supports previous evidence suggesting that LDOM is an effective method of continuing stimulation following cervical preparation with LDOM, although the reduction in CS rate that had been anticipated was not achieved. Although this study was not powered for neonatal outcomes, the safety signals of special care baby unit admission and neonatal deaths are both in favour of LDOM. The safety of induction is especially important in settings where there are cases of undetected growth restriction. In this study, the three babies who died were all small (with

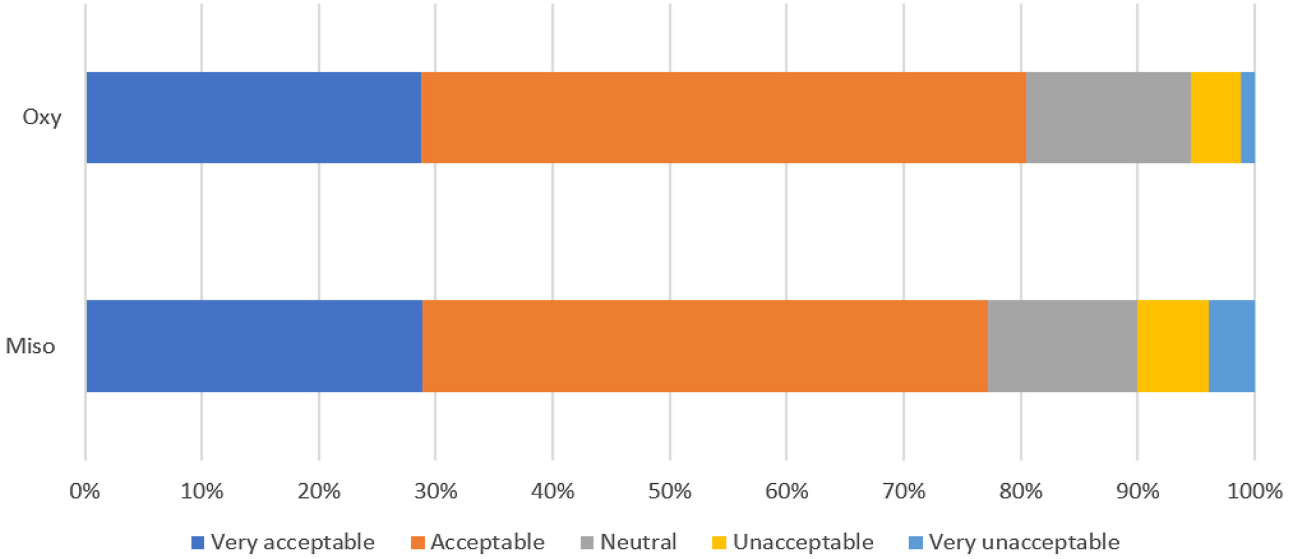

FIGURE 3 Women's acceptability of augmentation method, by study group.

TABLE 4 Participant exit interview.

Treatment group		Misoprostol	Oxytocin	OR (95% CI) [*P*]	
Number of mothers		260	260	Unadjusted	Adjusted[c]
Woman's rating of acceptability of augmentation method (not recorded for three mothers in the oxytocin group)					
Very acceptable	*n* (%)	75 (28.9)	74 (28.8)	1.115 (0.806, 1.542) [0.512]	0.991 (0.712, 1.380) [0.957]
Acceptable	*n* (%)	126 (48.5)	133 (51.8)		
Neutral	*n* (%)	33 (12.7)	36 (14.0)		
Unacceptable	*n* (%)	16 (6.2)	11 (4.3)		
Very unacceptable	*n* (%)	10 (3.9)	3 (1.2)		
Mean (SD)		2.08 (1.00)	1.97 (0.84)	0.10 (−0.06, 0.26) [0.201][d]	0.06 (−0.10, 0.22) [0.449][d]
Woman's rating of amount of time it took for her delivery (not recorded for eight mothers in the misoprostol group and three mothers in the oxytocin group)					
Very acceptable	*n* (%)	40 (15.9)	27 (10.5)	0.936 (0.680, 1.288) [0.683]	0.830 (0.593, 1.161) [0.277]
Acceptable	*n* (%)	104 (41.3)	126 (49.0)		
Neutral	*n* (%)	59 (23.4)	50 (19.5)		
Unacceptable	*n* (%)	31 (12.3)	37 (14.4)		
Very unacceptable	*n* (%)	18 (7.1)	17 (6.6)		
Mean (SD)		2.54 (1.12)	2.58 (1.07)	−0.04 (−0.23, 0.15) [0.679][d]	−0.08 (−0.26, 0.10) [0.384][d]
Woman's rating of amount of pain experienced during induction and delivery (not recorded for one mother in the oxytocin group)					
None	*n* (%)	8 (3.1)	12 (4.6)	0.899 (0.656, 1.232) [0.508]	0.784 (0.563, 1.090) [0.148]
Slight	*n* (%)	32 (12.3)	37 (14.3)		
Moderate	*n* (%)	73 (28.1)	52 (20.1)		
High	*n* (%)	107 (41.2)	110 (42.5)		
Extreme	*n* (%)	40 (15.4)	48 (18.5)		
Mean (SD)		3.53 (1.00)	3.56 (1.09)	−0.03 (−0.21, 0.15) [0.783][d]	−0.09 (−0.26, 0.08) [0.284][d]
Woman's rating of amount of anxiety experienced during induction and delivery (not recorded for one mother in the oxytocin group)					
None	*n* (%)	21 (8.1)	23 (8.9)	0.903 (0.662, 1.230) [0.516]	0.832 (0.609, 1.137) [0.250]
Slight	*n* (%)	70 (26.9)	55 (21.2)		
Moderate	*n* (%)	61 (23.5)	58 (22.4)		
High	*n* (%)	67 (25.8)	94 (36.3)		
Extreme	*n* (%)	41 (15.8)	29 (11.2)		

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 4 (Continued)

Treatment group		Misoprostol	Oxytocin	OR (95% CI) [*P*]	
Mean (s.d.)		3.14 (1.21)	3.20 (1.16)	−0.05 (−0.26, 0.15) [0.600][d]	−0.10 (−0.30, 0.10) [0.329][d]
If woman required another induction, would she be happy to have the same method (not recorded for one mother in the oxytocin group)					
No	*n* (%)	16 (6.2)	16 (6.2)	–	–
Yes	*n* (%)	149 (57.3)	156 (60.2)	0.955 (0.461, 1.980) [0.902]	0.996 (0.480, 2.069) [0.992]
No preference	*n* (%)	95 (36.5)	87 (33.6)	1.092 (0.515, 2.317) [0.819]	1.075 (0.506, 2.284) [0.851]
If woman does not wish induction with same method, what is the reason					
Pain	*n* (%)	10	12	–	–
Side effects	*n* (%)	1	0	–	–
Other	*n* (%)	5[a]	4[b]	–	–

[a]Family planning; second baby (×2); second pregnancy; time in pain.

[b]Family planning (×4).

[c]Adjusted for mother's age, gestational age, parity, mother's diastolic blood pressure, proteinuria and antihypertensive use at enrolment, receipt of magnesium sulphate in last 24 h before enrolment, time from hospital admission to randomisation <24 h, number of misoprostol doses administered for cervical preparation prior to randomisation, and dilatation at randomisation.

[d]Relative risk ratio.

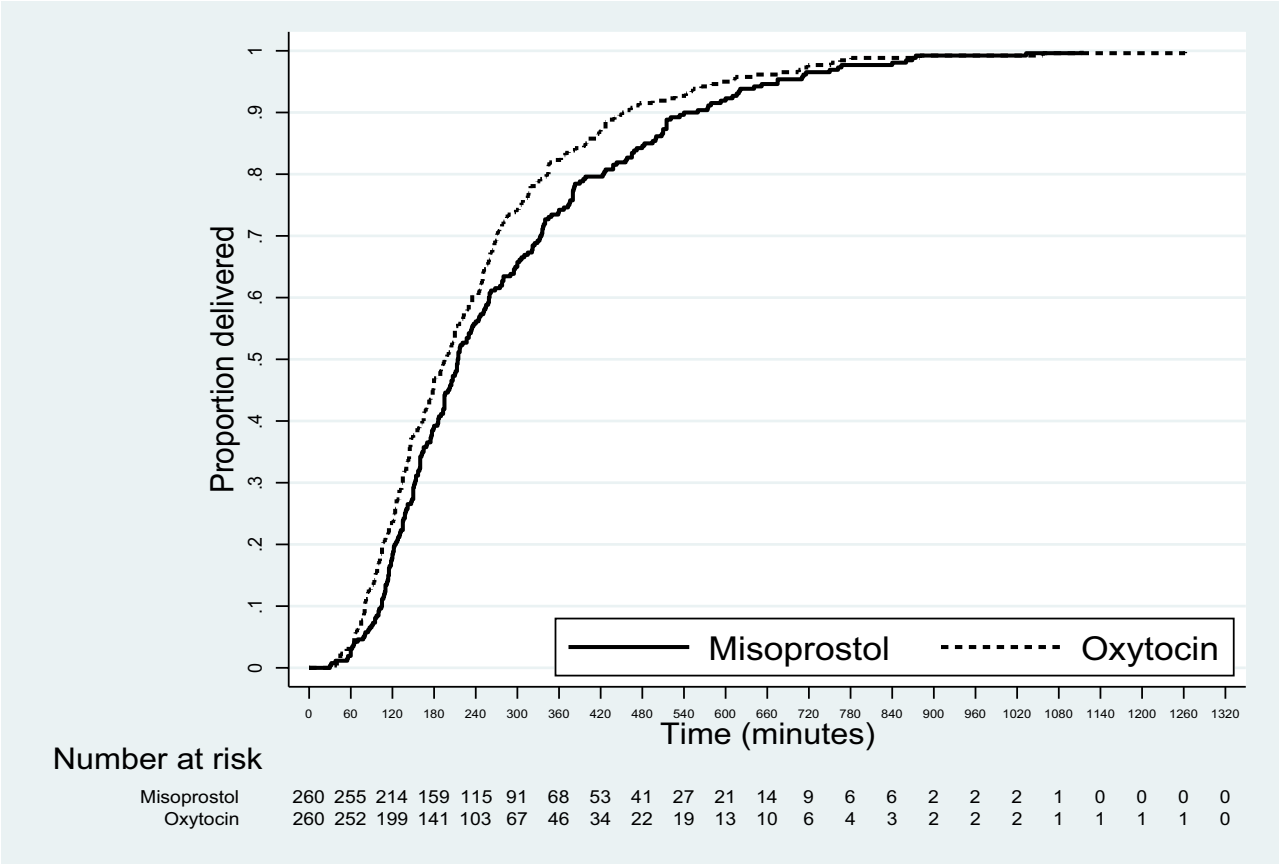

FIGURE 4 Kaplan–Meier survival analysis of time from randomisation (e.g. following membrane rupture and with continuing labour induction with either oxytocin or misoprostol per random assignment) to delivery.

birthweights of 2.5, 1.7 and 1.1 kg) and would have been vulnerable to intrauterine hypoxia even in the absence of hyperstimulation. Given the historical concerns with misoprostol, the increased risk of this patient population and the lack of previous studies on this method, it was important to provide close individual monitoring to detect and treat any hyperstimulation. It was not, however, detected in either arm. Induction with LDOM is recognised to have very low rates of hyperstimulation, equivalent to balloon catheter cervical preparation,[5] so the absence of hyperstimulation in over 500 women undergoing labour induction is not surprising.

Continuing induction with an oxytocin infusion is a complex process, and not only requires a fridge, infusion pump and intravenous set, but also close skilled supervision by an appropriately trained maternity care worker to monitor and titrate the dose. The opportunity to replace this whole process with a standard dose tablet that can be taken orally is attractive to clinical staff, labouring women and health service funders alike. Qualitative and health economic assessments to formally assess these issues have been conducted and will be published separately. However, the maternal satisfaction scales in this study suggest that replacing an intravenous infusion method with an oral tablet did not affect satisfaction rates. This mirrors a qualitative study that found women prioritised the safety of their babies over any particular method of induction.

The simplicity of the LDOM protocol could also have adverse consequences if it encouraged labour induction or augmentation in the community or by unskilled birth attendants. There have been reports of adverse outcomes from unauthorised intrapartum use of both oxytocin and misoprostol in the community,[20,21] and the rate of adverse events is likely to be worsened by the frequent confusion over dosage and routes for both agents. National healthcare regulators should ensure that the public and informal healthcare workers are informed about the risks of the unregulated use of misoprostol in labour, so that woman and their babies are not put at risk.

Further research is needed to understand whether these positive results can be replicated in other settings. The simplified induction protocol using an oral medication combined with the very low rate of hyperstimulation makes the use of LDOM particularly attractive for low-resource settings where fetal monitoring and close intrapartum medical supervision cannot be guaranteed for the monitoring and titration of the oxytocin dose. The other low-cost, low-risk cervical ripening method is the transcervical balloon catheter.[22] Our previous study in the same setting found this to be less effective than LDOM,[15] but it remains to be seen whether combining the two methods results in a more rapid and effective induction without an increase in hyperstimulation. LDOM is also an attractive protocol for high-resource settings where the de-medicalisation of maternity care is valued by many and there are fewer concerns regarding its unregulated use by informal healthcare workers.

5 | CONCLUSION

In this study of continuing labour induction after cervical preparation with LDOM and membrane rupture, the use of LDOM as an alternative to oxytocin infusion did not reduce the need for CS. No cases of uterine hyperstimulation were seen in either group and the maternal and neonatal outcomes were reassuring with LDOM. Satisfaction rates in both groups were high and comparable, even though the time to birth was, on average, 31 minutes longer with LDOM than with oxytocin. We conclude that continuing labour induction with LDOM is an effective option after cervical preparation with LDOM and membrane rupture, especially in settings with limited access to refrigeration, infusion pumps and continuous electronic monitoring.

AUTHOR CONTRIBUTIONS

The idea for the study evolved from the former INFORM study conducted by the same investigator group. ADW led the grant application, chaired the trial management group and wrote the first draft of the article and is the study guarantor. SM, HB, BF, TE, SL, MTu, ZA, BW and ADW wrote the grant application. SM was the lead investigator in India, with MTa, SP and PVS as site principal investigators with local responsibility for study conduct and data collection. KL and HB (replaced in Jan 2021 by JD) were the trial managers. BF was the trial statistician and conducted the analysis. SM, KL, HB/JD, BF, BW and ADW formed the trial management committee. All authors had full access to all the data in the study and accept responsibility for publication.

ACKNOWLEDGEMENTS

Trial Steering Committee: A. Shennan (chair), L. Marions, A. Medina-Lara and U. Sharma. Independent Data and Safety Monitoring Committee: D. Elbourne (chair), A. Muthal-Rathore, J. Vogel and C. Sutton. We thank the MRC, the Wellcome Trust, the NIHR and the UK government for providing funding for the study through the Joint Global Health Trials scheme.

FUNDING INFORMATION

Funding was provided by the UK Medical Research Council (MRC), Foreign, Commonwealth and Development Office (FCDO), the National Institute for Health Research (NIHR) and the Wellcome Trust (MR/R006/180/1), and included external peer review. A funder representative attended Trial Steering Committee meetings, but otherwise played no part in the conduct of the research or writing the paper.

CONFLICT OF INTEREST STATEMENT

Professor Weeks runs an information website called misoprostol.org on a voluntary basis, for which he receives no income. He also acted as a scientific advisor to Norgine from 2021 to 2022. In this role he received no personal remuneration other than travel expenses, but money was paid to the University of Liverpool for his time. The other authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data from this study will be confidential until the database is closed at the end of the study. Following this the study investigators will have exclusive access to the data until the publication of the results in a journal. Once this has happened, the database will be open to other researchers upon request. Open-access databases will also be sought to maximise the availability of our research data with as few

restrictions as possible, in line with MRC and Wellcome Trust policy. The consent form included a clause for women to give their permission for anonymous data to be used for future research studies.

ETHICS STATEMENT

This trial underwent peer review as part of the funding process. It is sponsored by the University of Liverpool (Brownlow Hill, Liverpool, L69 7ZX, UK; UoL001374), which oversees the study quality and has final responsibility for study conduct. The study was approved by the Institutional Ethics Committees at Government Medical College Nagpur (1724 EC/Pharmac/GMC/NGP), Spandan Heart Institute and Research Center (MOLI Study), the Mahatma Gandhi Institute of Medical Sciences (MGIMS/IEC/OBGY/96/2020) and the University of Liverpool (UoL001374). The study is insured by the sponsor (for harm arising from protocol design) and by the recruiting sites (for clinical negligence). The study is registered with ClinicalTrials.gov (NCT03749902) and Clinical Trial Registry, India (CTRI/2019/04/018827). All women enrolled in the trial provided informed written consent.

ORCID

Jill Durocher https://orcid.org/0000-0002-5572-8133

REFERENCES

1. World Health Organization, United Nations Children's Fund (UNICEF) & United Nations Population Fund. Improving maternal and newborn health and survival and reducing stillbirth: progress report 2023. Geneva, Switzerland: World Health Organization; 2023.
2. Weeks AD, Lightly K, Mol BW, Frohlich J, Pontefract S. Williams MJ; Royal College of Obstetricians and Gynaecologists. Evaluating misoprostol and mechanical methods for induction of labour: scientific impact paper No. 68 February 2022: scientific impact paper No. 68 April 2022. BJOG. 2022;129(8):e61–e65.
3. World Health Organization. WHO recommendations for induction of labour. Geneva: World Health Organization; 2011.
4. National Institute of clinical and care excellence (NICE). Inducing labour (NICE guideline NG207). London, UK: NICE; 2021.
5. Kerr RS, Kumar N, Williams MJ, Cuthbert A, Aflaifel N, Haas DM, et al. Low-dose oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2021;6(6):CD014484.
6. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. BMJ. 2015;350:h217.
7. Patabendige M, Chan F, Vayssiere C, Ehlinger V, Van Gemund N, le Cessie S, et al. Vaginal misoprostol versus vaginal dinoprostone for cervical ripening and induction of labour: an individual participant data meta-analysis of randomised controlled trials. BJOG. 2024;00:1–14.
8. World Health Organization. Reproductive health. Managing complications in pregnancy and childbirth: a guide for midwives and doctors. 2nd ed. Geneva, Switzerland: World Health Organization; 2017.
9. Dujardin B, Boutsen M, De Schampheleire I, Kulker R, Manshande JP, Bailey J, et al. Oxytocics in developing countries. Int J Gynecol Obstet. 1995;50(3):243–51.
10. Lovold A, Stanton C, Armbruster D. How to avoid iatrogenic morbidity and mortality while increasing availability of oxytocin and misoprostol for PPH prevention? Int J Gynaecol Obstet. 2008;103(3):276–82.
11. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG: an. Int J Gynaecol Obstet. 2001;108(9):952–9.
12. Bracken H, Lightly K, Mundle S, Kerr R, Faragher B, Easterling T, et al. Oral misoprostol alone versus oral misoprostol followed by oxytocin for labour induction in women with hypertension in pregnancy (MOLI): protocol for a randomised controlled trial. BMC Pregnancy Childbirth. 2021;21(1):537.
13. Hofmeyr GJ, Alfirevic Z, Kelly AJ, Kavanagh J, Thomas J, Brocklehurst P, et al. Methods for cervical ripening and labour induction in late pregnancy: generic protocol. Cochrane Database Syst Rev. 2009;(3):CD002074.
14. Dos Santos F, Drymiotou S, Antequera Martin A, Mol BW, Gale C, Devane D, et al. Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. BJOG. 2018;125(13):1673–80.
15. Mundle S, Bracken H, Khedikar D, Mulik J, Faragher B, Easterling T, et al. Foley catheterisation versus oral misoprostol for induction of labour in hypertensive women in India (INFORM): a multicentre, open-label, randomised controlled trial. Lancet. 2017;390(10095):669–80.
16. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35(3):549–56.
17. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. Am J Obstet Gynecol. 2003;188(1):162–7.
18. Ho M, Cheng SY, Li TC. Titrated oral misoprostol solution compared with intravenous oxytocin for labor augmentation: a randomized controlled trial. Obstet Gynecol. 2010;116(3):612–8.
19. World Health Organization. WHO recommendations for augmentation of labour. Geneva: World Health Organization; 2014.
20. Forna F, Titulaer P, Sesay S, Conteh S, Muoghalu S, Kanu P, et al. Prevalence of use of highly concentrated oxytocin or "pepper injection" in labor among clinicians undergoing emergency obstetric training in Sierra Leone. Int J Gynecol Obstet. 2020;151(3):450–5.
21. Kujabi ML, Mikkelsen E, Housseine N, Obel J, D'Mello BS, Meyrowitsch DW, et al. Labor augmentation with oxytocin in low- and lower-middle-income countries: a systematic review and meta-analysis. AJOG Glob Rep. 2022;2(4):100123.
22. Khan H, Buaki-Sogo MA, Barlow P, Vardanyan R, Zatorska A, Miller G, et al. Efficacy of pharmacological and mechanical cervical priming methods for induction of labour and their applicability for outpatient management: a systematic review of randomised controlled trials. Eur J Obstet Gynecol Reprod Biol. 2023;287:80–92.

How to cite this article: Mundle S, Lightly K, Durocher J, Bracken H, Tadas M, Parvekar S, et al. Oral misoprostol alone, compared with oral misoprostol followed by oxytocin, in women induced for hypertension of pregnancy: A multicentre randomised trial. BJOG. 2024;00:1–13. https://doi.org/10.1111/1471-0528.17839