Foley catheterisation versus oral misoprostol for induction of labour in hypertensive women in India (INFORM): a multicentre, open-label, randomised controlled trial

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Summary

Background Between 62 000 and 77 000 women die annually from pre-eclampsia and eclampsia. Prompt delivery, preferably by the vaginal route, is vital for good maternal and neonatal outcomes. Two low-cost interventions—low-dose oral misoprostol tablets and transcervical Foley catheterisation—are already used in low-resource settings. We aimed to compare the relative risks and benefits of these interventions.

Methods We undertook this multicentre, open-label, randomised controlled trial in two public hospitals in Nagpur, India. Women (aged ≥18 years) who were at 20 weeks' gestation or later with a live fetus and required delivery as a result of pre-eclampsia or hypertension were randomly assigned (1:1), via computer-generated block randomisation (block sizes of four, six, and eight) with concealment by use of opaque, sequentially numbered, sealed envelopes, to receive labour induction with either oral misoprostol 25 µg every 2 h (maximum of 12 doses) or a transcervical Foley catheter (silicone, size 18 F with 30 mL balloon). Randomisation was stratified by study centre. The catheter remained in place until active labour started, the catheter fell out, or 12 h had elapsed. If the catheter did not fall out within 12 h, induction continued with artificial membrane rupture and oxytocin, administered through a micro-drip gravity infusion set. Fetal monitoring was by intermittent auscultation. The primary outcome was vaginal birth within 24 h. Due to the nature of the interventions, masking of participants, study investigators, and care providers to group allocation was not possible. We analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01801410.

Findings Between Dec 20, 2013, and June 29, 2015, we randomly assigned 602 women to induction with misoprostol (n=302) or the Foley catheter (n=300; intention-to-treat population). Vaginal birth within 24 h was more common in women in the misoprostol group than in the Foley catheter group (172 [57·0%] *vs* 141 [47·0%] women; absolute risk difference 10·0%, 95% CI 2·0–17·9; p=0·0136). Rates of uterine hyperstimulation were low in both the misoprostol and Foley catheter groups (two [0·7%] *vs* one [0·3%] cases; absolute risk difference 0·3%, 95% CI –0·8 to 1·5; p=0·566) and neonatal deaths did not differ significantly between groups (six [2·0%] *vs* three [1·0%] neonatal deaths; 1·0, –1·04 to 2·97; p=0·322). 17 serious adverse events (3%) were reported during the study: one case of intrapartum convulsion and one case of disseminated intravascular coagulation (both in the Foley group); ten perinatal deaths, including two stillbirths (both in the Foley catheter group) and eight neonatal deaths (n=5 in the misoprostol group and n=3 in the Foley catheter group); and five of neonatal morbidity, comprising birth asphyxia (n=3), septicaemia (n=1), and neonatal convulsion (n=1).

Interpretation Oral misoprostol was more effective than transcervical Foley catheterisation for induction of labour in women with pre-eclampsia or hypertension. Future studies are required to assess whether oxytocin augmentation following misoprostol can be replaced by regular doses of oral misoprostol tablets.

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Introduction

Hypertensive disorders, including pre-eclampsia, are the most common medical complications of pregnancy, affecting 10% of pregnancies. Pre-eclampsia and eclampsia are leading causes of maternal mortality, accounting for about 14% of the 303 000 global maternal deaths annually.[1,2] Effective care, including treatment with magnesium sulphate and antihypertensive drugs, can reduce maternal morbidity and mortality; however, timely delivery, preferably by the vaginal route, is the only definitive cure and is vital to achieve good maternal and neonatal outcomes. Two low-cost cervical ripening methods—low-dose oral misoprostol and the Foley catheter—have been recommended for use in low-resource settings, where most of the morbidity and mortality associated with pre-eclampsia occurs.[3]

Misoprostol, the orally active and heat-stable prostaglandin E1 analogue, has been used for labour induction for almost 20 years. For labour induction, misoprostol is commonly administered vaginally. However, a systematic review[4] of studies that compared oral and vaginal low-dose misoprostol found that women

Research in context

Evidence before this study

We searched PubMed and the Cochrane Database of Clinical Trials (CENTRAL) using the search terms "oral misoprostol", "induction of labour", and "catheter" and MeSH terms and appropriate variations, with no language restrictions for studies from Jan 1, 1980, to Jan 1, 2013. We used standard Cochrane methods to assess quality. The Cochrane Collaboration did a systematic review in 2012 of the effectiveness of Foley catheter for the induction of labour. From these sources we identified just one small study in which 151 women were randomly assigned to receive Foley catheterisation or oral misoprostol (50 µg every 4 h). The investigators reported no significant differences between groups in any of the outcomes. The optimal misoprostol dose is not known. Only one comparative dose-finding study exists, in which oral misoprostol 50 µg every 4 h was compared with 20 µg given every hour, in a double-blind study of 64 women undergoing induction. No differences were found in any of the outcomes. However, evidence from the Cochrane review of oral misoprostol for labour induction suggests that outcomes might be best with the use of low-dose misoprostol (20–25 µg) given every 2 h, and this is the dose recommended in the WHO induction of labour guidelines. WHO guidelines also suggest the use of the Foley catheter for induction as an alternative.

Added value of this study

To our knowledge, this study is the first to directly compare the two regimens for labour induction recommended by WHO: low-dose oral misoprostol (25 µg) and the Foley catheter (both followed by membrane rupture and oxytocin infusion). The study was also done in the highest risk women (those with hypertension who are more likely to be primigravid, preterm, and have growth-restricted babies) and setting (a government facility without routine electronic fetal monitoring or electronic drip counters for the oxytocin). We found that oral misoprostol 25 µg tablets given every 2 h were more effective than Foley catheter induction for a range of measures, including vaginal birth rate, speed of induction, and women's satisfaction. Adverse maternal or neonatal outcomes did not differ between groups.

Implications of all the available evidence

Since we did our study, a large multicentre study has been reported, in which 1859 women were randomly assigned to receive labour induction by either Foley catheter or 50 µg oral misoprostol every 4 h. This dose is higher than that used in our study, but no differences were reported in the main maternal or neonatal outcomes assessed. Our study showed better outcomes with the new 25 µg misoprostol tablets than with the Foley catheter, especially for satisfaction and vaginal birth rate. These findings reinforce those from the Cochrane review of oral misoprostol for labour induction, in which the 20–25 µg doses of oral misoprostol were associated with lower rates of caesarean section delivery than was induction with either higher oral misoprostol doses or standard induction methods. Therefore, we believe that low-dose oral misoprostol (25 µg) given every 2 h is the optimal method for labour induction. Some clinicians give the oral misoprostol during active labour (rather than replacing it with an oxytocin infusion), but whether this method is as effective and safe remains to be seen.

using oral misoprostol were significantly less likely to have uterine hyperstimulation with changes in fetal heart rate (2% *vs* 13%; relative risk 0·19, 95% CI 0·08–0·46), but no significant differences were reported in other outcomes. A Cochrane review[5] included all studies that used oral misoprostol for labour induction, irrespective of dose. Most of the low-dose studies used 20 µg of oral misoprostol solution. The review concluded that "given that safety is the primary concern, the oral regimens are recommended over vaginal regimens. This is especially important in situations where the risk of ascending infection is high and the lack of staff means that women cannot be intensely monitored."[5] This finding is also supported by a network meta-analysis[6] of various methods that use prostaglandin induction.

Although oral misoprostol is very effective, all induction methods can cause uterine hyperstimulation, which in turn can cause fetal hypoxia. The risk of hypoxic damage is increased in pre-eclampsia, when babies might be born prematurely or be affected by intrauterine growth restriction. In low-resource settings, where access to intrapartum fetal monitoring might be poor, avoidance of hyperstimulation is crucial.

The Foley balloon catheter offers an alternative low-cost method for labour induction, which could be safer for the fetus than using current standard methods. Induction with the Foley catheter seems to be as effective as current methods, but with lower rates of uterine hyperstimulation and better fetal outcomes.[7,8] Results of studies have shown no increase in rates of infection.[9] Although this method appears promising, few (eight of 30) of the studies using the Foley catheter were done in low-resource settings.

These two methods, the Foley catheter and low-dose oral misoprostol, seem to be the optimal choices for low-resource settings, but only a few direct comparisons have been done between them. A multicentre Dutch study[10] compared Foley balloon catheter induction with oral misoprostol. The dose was 50 µg misoprostol every 4 h, a regimen that has largely been superseded by the low-dose 1–2 h administration, which is more in keeping with the pharmacokinetic profile for oral misoprostol. The 1859 participants were all at term with an unripe cervix and an intact membrane, but had a wide variety of indications for induction of labour. The study found no differences between groups in any of the major outcomes;

however, general satisfaction with labour was greater in women whose labours were induced with misoprostol.[11]

Labour induction for women with hypertension or pre-eclampsia is a crucial intervention in low-resource settings because it is one of the few indications for which induction is done primarily for the safety of the mother. The induction process is made more difficult and dangerous because nulliparity, preterm gestations, and undiagnosed fetal growth restriction are common. Moreover, after cervical ripening with the Foley catheter, many women require oxytocin infusions, which can be risky in settings with no access to electronic infusion pumps. All these factors increase the risk to mother and baby, especially when antenatal and intrapartum fetal monitoring is scarce.

We undertook the INFORM trial to compare the efficacy, safety, acceptability, and cost-effectiveness of misoprostol treatment with Foley balloon catheter induction of labour in women with gestational hypertension in a low-resource setting.

Methods

Study design and participants

This multicentre, open-label, randomised controlled trial was undertaken at two public hospitals in Nagpur, India: Government Medical College and Daga Women's Hospital. Participants were informed about the study by their doctors when the decision for induction of labour was made, and were enrolled by research staff on the labour ward on the day of induction. We included women who were at least 18 years of age, at 20 weeks' gestation or later with a live fetus, and in whom the decision had been made to induce vaginal birth because of pre-eclampsia or hypertension. The original protocol was changed from "pre-eclampsia or uncontrolled hypertension" when it became clear that induction for hypertension was often done without the aid of urinary protein analysis or prolonged assessment. We excluded women who were unable to give informed consent, those with a history of caesarean section, multiple pregnancy, ruptured membranes, clinically diagnosed chorioamnionitis, or a history of allergy to misoprostol.

The study was approved by the Research Ethics Committees at Government Medical College, Nagpur, and the University of Liverpool, UK. As required by the Drug Controller General of India, participants provided both written and video-recorded oral consent. The study was monitored by independent steering and data monitoring committees. The full protocol has been previously published elsewhere.[12]

Randomisation and masking

After the participant provided informed consent, research staff opened a sequentially numbered, sealed, opaque envelope containing the participant's group assignment and participants were randomly allocated, in a 1:1 ratio, to receive either cervical ripening with transcervical Foley catheterisation or oral misoprostol tablets. The envelopes were generated by staff at Gynuity Health Projects (New York, NY, USA) by use of a randomisation code provided independently by the trial statistician on the basis of computer-generated pseudorandom numbers, with block sizes of four, six, and eight. Randomisation was stratified by centre. Due to the nature of the interventions, masking of participants, study investigators, and care providers to group allocation was not possible.

Procedures

Before randomisation, the resident doctor did a digital examination to establish a baseline Bishop score[13] and cervical dilatation. In the two busy government hospitals in which we did the study, the decision to induce labour was made pragmatically based on gestation and the presence of hypertension. Proteinuria was assessed when possible, depending on the availability of urinary protein dipsticks. Women allocated to the Foley catheter group underwent induction with a transcervical Foley catheter (silicone, size 18F with 30 mL balloon). The catheter was placed either by visualisation with the help of a speculum or blindly, filled with 30 mL saline, and strapped to the thigh under gentle tension. The catheter remained in place until it was expelled when active labour started or until 12 h had elapsed. If the Foley catheter fell out within 12 h, the membranes were ruptured and an oxytocin infusion was started. If the Foley catheter did not fall out within 12 h, it was removed at 12 h and oxytocin started with an artificial rupture of membrane when possible.

Women allocated to the misoprostol group were induced with oral misoprostol tablets (25 µg; Cipla, Mumbai, India) given every 2 h for a maximum of 12 doses or until active labour started. In primigravid women in whom contractions had not started after two doses, the dose could be increased to 50 µg every 2 h. Once in labour (defined as regular, painful contractions, with a cervical dilatation of at least 4 cm), no more misoprostol was given and artificial membrane rupture or oxytocin infusion was used as clinically indicated. In both groups, if labour had not started after 24 h, the induction was classified as failed and the decision on further management was made by the clinical team.

For women in both groups, temperature and uterine tone and contraction frequency were assessed every 2 h and a vaginal examination was done every 4 h to assess cervical dilatation and Bishop score. Oxytocin infusion was given with a micro-drip gravity infusion set, monitored by calculation of the drops per min. One unit of oxytocin was injected in 500 mL of Ringer's lactate, started at a rate of 2 mU/min (15 drops per min), and increased every 30 min by 2 mU/min until three to four contractions happened every 10 min. Intermittent fetal monitoring was done with a Pinard stethoscope or a handheld fetal Doppler every hour before active labour and then every 15–30 min during the active stage of

labour. All participants were monitored by the research staff on a one-to-one basis. Magnesium sulphate and antihypertensives were given to participants with severe pre-eclampsia, as per the hospital protocol. Participant data, including demographic characteristics, medical and pregnancy history, labour course, and outcomes, were collected by the research staff.

Resident staff in both the participating hospitals were familiar with the use of a Foley catheter. However, they underwent brief training in placement of the Foley catheter before the start of the trial to ensure the insertion method was uniform.

Outcomes

The primary outcome was vaginal birth within 24 h. Secondary outcomes included measures of efficacy of the induction process assessed by the induction to birth interval (in vaginal births, caesarean sections, and all births), vaginal births within 12 h, cervix unchanged at 12 h and 24 h, need for oxytocin augmentation, and time from randomisation to start of induction and birth. Secondary outcomes for women in the misoprostol group also included assessment of the total dose of misoprostol used and the number of participants given a 50 µg dose. We also assessed maternal complications, including uterine tachysystole (defined as more than five contractions in 10 min); uterine hypertonus (defined as a single contraction lasting longer than 2 min); caesarean section; uterine rupture; instrumental vaginal birth; severe hypertension; haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; vomiting; diarrhoea; fever; antibiotic use; post-partum haemorrhage; and serious maternal complications, including admission to the intensive care unit, septicaemia, pulmonary oedema, cerebral haemorrhage or oedema, renal failure, eclampsia, and maternal death.

Women's expectations about labour were assessed before the induction process. 48 h after the birth, another questionnaire assessed their opinions about their experience, issues surrounding the induction (including time to induction), and their satisfaction with the actual labour. Women were asked to rate their overall experience on a categorical 5 point scale from very unsatisfied to very satisfied. Outcomes were assessed by the treating clinician and recorded by a research assistant, neither of whom was masked to group allocation.

Fetal or neonatal complications assessed included meconium-stained liquor, Apgar score of less than 5 at 5 min, admission to the neonatal intensive care unit, seizures, birth asphyxia (defined as evidence of antenatal compromise [meconium-stained liquor or fetal heart-rate abnormality] and neonatal compromise [intubation or Apgar score <5 at 5 min] and encephalopathy), clinically diagnosed septicaemia (defined as use of antibiotics for treatment of infection), and stillbirth. Upon discharge, babies admitted to the special care unit were assessed for encephalopathy by the managing neonatologist, and the components of the original Sarnat score were recorded.[14] The score for each baby was assessed by an expert, masked to allocation, who judged the presence of encephalopathy according to a modified Sarnat score.[15] Economic data were also collected and will be reported elsewhere.

Statistical analysis

We created a detailed statistical analysis plan with dummy tables before data analysis. The statistical analysis plan lists all the outcomes to be collected but does not exactly match the outcomes in the protocol. The comprehensive list of outcomes was contained within the case report form and was approved by the ethics committee. Sample size was estimated a priori based on the primary outcome, assuming a vaginal birth rate of 41% with the Foley catheter on the basis of previously published data using the same induction protocol and outcomes as this study.[16–18] Detection of an absolute increase in this rate to 55% or more (ie, a proportional increase of ≥33%), with 90% power and a conventional (two-sided) α level of 0·05, required a total sample size of 546 evaluable women (n=273 per group). To allow for possible losses to follow-up, this number was increased by 10%, giving an actual sample size of 602 women (n=301 per group). The data monitoring committee reviewed the results of one planned interim analysis after half the participants were enrolled, with vaginal birth within 24 h as the primary outcome of interest. Haybittle–Peto boundaries were adopted and the committee concluded that the enrolment should continue.

Generalised linear modelling (regression) methods were used when possible to estimate effect sizes, with their corresponding 95% CIs. Binomial regression was used for the primary outcome measure (difference in the absolute risk of vaginal birth within 24 h) and other binary categorical measures, whereas multinomial regression was used for multicategory variables. Fisher's exact tests were used in the presence of zero or very small frequency counts. We analysed continuous measures using linear regression with mean differences or by Mann–Whitney *U* tests with median differences, according to their distributions. Women were asked to rate their expected (before labour) and experienced levels of both pain and anxiety, so the observed differences in experienced levels were covariate adjusted for the corresponding expected levels. We constructed cumulative frequency curves to compare the time course of induction to delivery in the two study groups.

We did exploratory subgroup analyses of whether attempts to save the fetus would include caesarean section in an emergency or not (determined before randomisation), parity (nulliparous *vs* not), site of birth, and Bishop score (<6 *vs* ≥6). Analyses were by intention to treat. We used SPSS version 22 plus the cendif command in Stata version 13 to obtain confidence intervals for median differences.

Role of the funding source
The study was funded by the UK Department for International Development, Medical Research Council, and Wellcome Trust Joint Global Health Trials Scheme. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. Their only involvement was to approve the membership of the trial steering committee (on which they had one representative) and to comment on the application when submitted. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Dec 20, 2013, and June 29, 2015, we randomly assigned 602 women to the Foley catheter group (n=300) or the misoprostol group (302; figure 1). Four women (1%) in the Foley group had either a failure of placement of the Foley or immediate expulsion of the catheter; three of these women were induced with misoprostol (two vaginally and one orally) and one was induced with oxytocin (figure 1). One woman (<1%) in the Foley group withdrew her consent for induction after randomisation and had caesarean section (figure 1). All these women were included in the final analysis under the intention-to-treat principle.

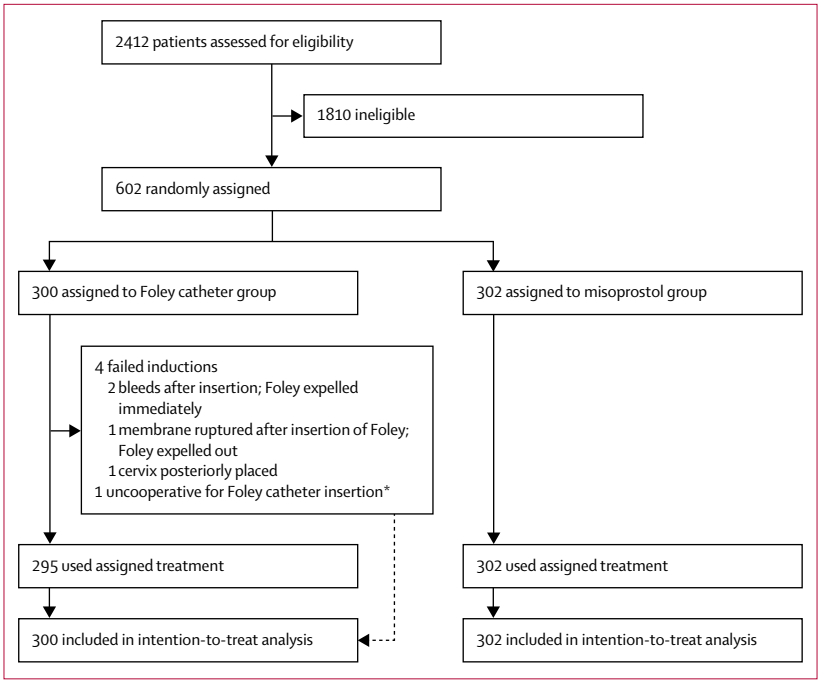

Figure 1: **Trial profile**
*One woman withdrew her consent for induction after being randomly assigned and underwent caesarean section.

No values were missing for the primary outcome. However, for the primary and secondary outcomes, postnatal measurements were not recorded for two babies (<1%) who were stillborn, discharge measurements were not registered for the 11 babies (2%) who died before discharge, and age at first oral feed was not recorded for two babies (<1%) in the Foley group and eight babies (1%) in the misoprostol group.

Baseline characteristics were similar between groups (table 1). Most women were nulliparous with a median gestational age of 39 weeks (table 1). At enrolment, mean systolic blood pressure was 142·5 mm Hg (SD 11·9) and diastolic blood pressure was 94·9 mm Hg (8·3), with virtually all women (96%) receiving antihypertensive medication (table 1). 15% of women in the Foley catheter group and 14% of those in the misoprostol group had received magnesium sulphate in the 12 h before study enrolment (table 1). No HIV-positive women were assessed in the study.

The primary outcome of vaginal birth within 24 h was significantly more common in women in the misoprostol group than in those in the Foley catheter group (172 [57·0%] *vs* 141 [47·0%] women; absolute risk difference 10·0%, 95% CI 2·0–17·9; p=0·0136 table 2). The mean time from induction to delivery was shorter in the misoprostol group than in the Foley catheter group (table 3, figure 2). Women induced with misoprostol were more likely to have a vaginal birth than those induced with a Foley catheter (table 2). Most caesarean sections were done because of failure to progress in the first stage of labour, which occurred more often in the Foley group, whereas more women in the misoprostol group had a caesarean section as a result of meconium-stained liquor (table 2).

The median time from induction to oxytocin infusion was significantly shorter in the Foley catheter group than in the misoprostol group, and the median duration of the infusion was longer (table 2). Membranes were ruptured artificially more often when a Foley catheter was used than when misoprostol was given (table 2).

Rates of uterine hyperstimulation were low in both groups, as were rates of fetal heart-rate abnormality, severe hypertension, and use of blood products after trial entry (table 2). One woman (<1%) induced with the Foley catheter had an intrapartum convulsion and was treated with magnesium sulphate. Another woman (<1%) induced with the Foley catheter delivered vaginally, and was diagnosed with disseminated intravascular coagulation and received blood products after birth. Both women were discharged in good condition. Four women (1%) induced with the Foley catheter were treated for a clinical (wound) infection after the start of the trial. No women were admitted to the intensive care unit or had septicaemia, pulmonary oedema, cerebral oedema or haemorrhage, renal failure, uterine rupture, or died.

Two babies (1%) were stillborn to women induced with the Foley catheter (table 4). Neonatal morbidity was similar in babies born to women in both groups, as was the number of babies admitted to the special care nursery or the number who received oxygen in the

	Foley catheter (n=300)	Misoprostol (n=302)
Study site		
Government Medical College	150 (50%)	151 (50%)
Daga Women's Hospital	150 (50%)	151 (50%)
Age, years		
Mean (SD)	24·0 (3·5)	23·7 (3·1)
Median (range)	23 (18–42)	23 (18–37)
Mother's education		
No formal education	5 (2%)	2 (1%)
Primary	86 (29%)	112 (37%)
Secondary	149 (50%)	131 (43%)
University	60 (20%)	57 (19%)
Mother's employment		
Farming or manual work	16 (5%)	10 (3%)
Professional, office job, or business	6 (2%)	3 (1%)
Housewife	277 (92%)	288 (95%)
Other	1 (<1%)	1 (<1%)
Medical history		
Nulliparous (no previous pregnancies >28 weeks)	247 (82%)	236 (78%)
Previous caesarean section	0	0
Previous hypertension in pregnancy	8 (3%)	16 (5%)
Previous stillbirth	1 (<1%)	5 (2%)
Pre-existing conditions		
Diabetes, renal disease, or liver disease	0	0
Chronic hypertension	0	1 (<1%)
State at recruitment		
Booking status		
Booked	277 (92%)	284 (94%)
Gestational age (best estimate in weeks)	39 (29–42)	39 (29–41)
Estimate made by ultrasound at <20 weeks	131 (44%)	127 (42%)
Gestation of ≥37 weeks	241 (80%)	234 (77%)
Gestation of 32–36^{+6} weeks	56 (19%)	66 (22%)
Gestation of 28–31^{+6} weeks	3 (1%)	2 (1%)
Gestation of <28 weeks	0	0
Systolic blood pressure, mm Hg		
Mean (SD)	142·2 (11·3)	142·8 (12·5)
Median (range)	140 (104–180)	140 (102–190)
Diastolic blood pressure, mm Hg		
Mean (SD)	95·0 (8·3)	94·7 (8·3)
Median (range)	97 (60–130)	90 (66–120)
Proteinuria at enrolment*		
0 or trace	156 (52%)	162 (54%)
+1 or +2	122 (41%)	121 (40%)
+3 or +4	22 (7%)	19 (6%)
Hypertensive symptoms at enrolment	64 (21%)	58 (19%)
Received magnesium sulphate in last 12 h	45 (15%)	42 (14%)
Currently on antihypertensives	292 (97%)	289 (96%)
Time from admission to randomisation, h		
Median (IQR; range)	4 (1–13; 0–335)	3·5 (1–10; 0–849)

Data are n (%), mean (SD), median (range), or median (IQR; range), unless otherwise stated. *Detected on urinary dipstick.

Table 1: **Baseline characteristics**

special care nursery (table 4). In the misoprostol group, the median time from birth to admission was only 17 min and median length of stay only 49 min (table 4), reflecting a high number of babies who were seen for brief assessment only. The time from birth to admission to the special care nursery was longer for babies born following induction with the Foley catheter, but median length of stay was similar between groups (table 4). Neither the proportion of babies with a completed Sarnat score nor the grades of the scores differed significantly between groups (appendix). Nine babies (1%) died: three in the Foley group (all due to prematurity) and six in the misoprostol group (three due to prematurity, one from prematurity plus intrauterine growth restriction, one from intrauterine growth restriction alone, and one from asphyxia). The causes of death did not differ significantly between the two groups.

See Online for appendix

17 serious adverse events (3%) were reported during the study. In addition to the one woman who had an intrapartum convulsion and the woman with disseminated intravascular coagulation (both in the Foley group), we recorded ten incidents of perinatal death (two stillbirths in the Foley group and eight neonatal deaths [five in the misoprostol group and three in the Foley group]) and five incidents of neonatal morbidity, comprising birth asphyxia (n=3), septicaemia (n=1), and neonatal convulsions (n=1), reported as serious adverse events. One neonatal death and one case of septicaemia were not reported as severe adverse events.

Most women in both groups found their assigned method of induction, and the duration of the induction, to be acceptable, and the pain they experienced to be either slight or moderate (appendix). More women in the misoprostol group than the Foley catheter group would use the same method in the future should they require another induction (table 2).

In the prespecified subgroup analysis, we identified few differences in outcomes between nulliparous and parous women (appendix). As expected, parous women delivered more quickly and required fewer caesarean sections, but these outcomes no longer differed significantly between the Foley catheter and misoprostol groups (appendix). The need for oxytocin augmentation remained significantly higher in the Foley group than the

	Foley catheter (n=300)	Misoprostol (n=302)	Absolute difference (95% CI)	p value
Vaginal birth within 24 h	141 (47·0%)	172 (57·0%)	10·0% (–2·0 to 17·9)	0·0136*
Delivered within 24 h	268 (89·3%)	279 (92·4%)	3·1% (–1·5 to 7·6)	0·194*
Vaginal births				
All	149 (49·7%)	178 (58·9%)	9·3% (1·3 to 17·2)	0·0212*
Within 12 h	89 (29·7%)	104 (34·4%)	4·8% (–2·7 to 12·2)	0·209*
Mode of birth				
Spontaneous vaginal birth	146 (48·7%)	176 (58·3%)	9·6% (1·7 to 17·5)	0·0194*
Forceps or vacuum birth	3 (1·0%)	2 (0·7%)	–0·3% (–1·8 to 1·1)	..
Caesarean section	151 (50·3%)	124 (41·1%)	–9·2% (–17·2 to –1·3)	..
Caesarean section indications				
Failure to progress first stage of labour	89/151 (58·9%)	53/124 (42·7%)	–16·2% (–27·9 to –4·5)	0·0068*
Failure to progress second stage of labour	1/151 (0·7%)	3/124 (2·4%)	1·8% (–1·2 to 4·8)	0·251*
Fetal heart-rate abnormality	40/151 (26·5%)	41/124 (33·1%)	6·6% (–4·3 to 17·4)	0·236*
Maternal deterioration	5/151 (3·3%)	0	–3·3% (–6·5 to –0·1)	0·066*
Intrapartum haemorrhage	3/151 (2·0%)	0	–2·0% (–4·5 to 0·5)	0·255*
Cord presentation or prolapse	2/151 (1·3%)	2/124 (1·6%)	0·3% (–2·6 to 3·2)	0·844*
Meconium-stained liquor	22/151 (14·6%)	38/124 (30·6%)	16·1% (6·2 to 26·0)	0·0014*
Analgesia				
Spinal anaesthesia	150 (50·0%)	124 (41·1%)	–8·9% (–16·9 to –1·0)	0·0275*
Local anaesthesia	94 (31·3%)	114 (37·7%)	6·4% (–1·2 to 14·0)	0·097*
Complications of labour and birth				
Uterine hyperstimulation	1 (0·3%)	2 (0·7%)	0·3% (–0·8 to 1·5)	0·566*
Fetal heart-rate abnormality	17 (5·7%)	12 (4·0%)	–1·7% (–5·1 to 1·7)	0·332*
Diagnosis of post-partum haemorrhage	2 (0·7%)	2 (0·7%)	0 (–1·3 to 1·3)	0·995*
Blood products after trial entry	5 (1·7%)	1 (0·3%)	–1·3% (–2·9 to 0·3)	0·099*
Severe hypertension	21 (7·0%)	23 (7·6%)	0·6% (–3·5 to 4·8)	0·772*
Any form of complication	44 (14·7%)	37 (12·3%)	–2·4% (–7·9 to 3·0)	0·385*
Would use same method for future induction				
Yes	216 (72·0%)	250 (82·8%)	..	..
No	59 (19·7%)	35 (11·6%)	..	0·0063†
No preference	25 (8·3%)	17/302 (6%)	..	..
Time from birth to discharge, h	148 (8–1341)	122 (17–559)	–4 (–13 to 3)‡	0·296§

Data are n (%), n/N (%), or median (range). *Binomial regression. †Fisher's exact test. ‡Median difference. §Mann–Whitney *U* test.

Table 2: **Birth outcomes**

misoprostol group for both parous and nulliparous subgroups (appendix). In parous women, the number of babies admitted to the special care nursery was significantly higher in the misoprostol group than the Foley catheter group (appendix). The cause of admission was largely for assessment and observation in babies that were of low birthweight, premature, or had meconium staining of the liquor. Analysis of the remaining subgroups was uninformative. Subgroup analysis by study centre showed no important differences between groups, and the number of participants was too low for analysis by viability or Bishop score (appendix).

Discussion

Our findings show that women undergoing labour induction with oral misoprostol had a quicker labour, were more likely to have a vaginal birth, and were more satisfied than those induced with the Foley catheter. Rates of uterine hyperstimulation were low in both groups and neonatal morbidity did not differ between groups.

Although both methods had been shown to have advantages over other induction methods in systematic reviews,[5,8,19] until recently, neither had ever been directly compared. Ten Eikelder and colleagues[10,11] compared the 30 mL Foley catheter with 50 µg oral misoprostol given every 4 h and found no difference in the prevalence of caesarean section, hyperstimulation, or adverse neonatal outcomes. Participants induced with misoprostol had a higher rate of instrumental vaginal births, a lower rate of caesarean section for failure to progress in the first stage of labour, and were more satisfied than those induced with a Foley catheter. That study is not directly comparable with ours because of the different oral misoprostol regimens, but supports the suggestion that oral misoprostol results in fewer caesarean sections and greater satisfaction.

	Foley catheter (n=299)*	Misoprostol (n=302)	Absolute difference (95% CI)	p value
Bishop score at recruitment				
0–3	118 (39·5%)	115 (38·1%)	..	..
4–6	181 (60·5%)	187 (61·9%)	..	..
Mean (SD)	3·52 (1·29)	3·61 (1·13)	0·09 (–0·10 to 0·29)	0·643†
Cervical dilatation at recruitment, cm				
0–1	242 (80·9%)	198 (65·6%)	..	..
1·5–3	57 (19·17%)	104 (34·4%)	..	..
Mean (SD)	1·03 (0·60)	1·22 (0·66)	0·19 (0·09 to 0·30)	<0·0001†
Oxytocin given	244 (81·6%)	157 (52·0%)	–29·6% (–36·8 to –22·5)	<0·0001‡
Time from randomisation to induction, min				
0–59	281 (94·0%)	301 (99·7%)	..	..
60–119	11 (3·7%)	0	..	..
120–179	6 (2·0%)	1 (0·3%)	..	..
≥180	1 (0·3%)	0	..	..
Median (range)	15 (10–27)	5 (5–15)	10 (5 to 10)	<0·0001§
Time from induction to oxytocin infusion, min	360 (20–1230)	555 (75–1350)	150¶ (95 to 210)	<0·0001§
Duration of oxytocin infusion, min	366 (20–2400)	250 (20–1300)	–125¶ (82 to 175)	<0·0001§
Time from induction to birth, min				
All women				
Mean (SD)	861 (468)	771 (421)	–90 (–161 to –19)	0·0134†
Median (range)	785 (78–2490)	684 (90–2340)	..	..
Vaginal deliveries only				
Mean (SD)	703 (365)	701 (378)	–2 (–82 to 79)	0·967†
Median (range)	660 (120–2100)	633 (90–2155)	..	..
Caesarean sections only				
Mean (SD)	1018 (505)	872 (458)	–146 (–261 to –31)	0·0128†
Median (range)	980 (78–2490)	830 (155–2340)	..	..
No cervical change				
At 12 h	1 (0·3%)	1 (0·3%)	0 (–0·9 to 0·9)	1·000‡
At 24 h	0	0	0	1·000‡
Membrane rupture time recorded	250 (83·6%)	252 (83·4%)	–0·2% (–6·1 to 5·8)	0·956‡
Membrane ruptured artificially	193/250 (77·2%)	153/252 (60·7%)	–16·5% (–24·4 to –8·5)	<0·0001‡
Side-effects during induction				
Mild diarrhoea	2 (0·7%)	7 (2·3%)	1·7% (–0·3 to 3·6)	0·094‡
Vomiting	..	..	1·3% (–2·2 to 4·8)‖	0·465‡
Mild	12 (4·0%)	12 (4·0%)	..	..
Moderate	1 (0·3%)	5 (1·7%)	..	..

Data are n (%), mean (SD), median (range), or n/N (%). *No induction data recorded for one participant who refused to have a Foley catheter inserted and so did not deliver vaginally. †Linear regression. ‡Binomial regression. §Mann–Whitney *U* test. ¶Median difference. ‖Mild and moderate categories combined.

Table 3: **Induction outcomes**

Our study has some limitations. We recruited women on the basis of rapid clinical assessment rather than strict international criteria for pregnancy hypertension. In busy public hospitals in low-income and middle-income countries, pragmatic management decisions need to be made on the basis of rapid clinical assessments, often without the benefit of biochemical tests, urinalysis, or inpatient observation. As such, some women did not eventually fulfil the formal definition of pre-eclampsia because they did not have proven proteinuria; other women's blood pressure settled while they awaited randomisation and induction. Although this method of recruitment makes the population less specific to the treatment of hypertensive disease, it does increase the generalisability of the findings, making them more applicable to other similar settings and to women undergoing labour inductions for other indications.

The study was not masked because of the ethical and logistical difficulties of doing sham cervical catherisation, which increases the risk of bias. However, at the start of the study both oral misoprostol and transcervical Foley catheterisation were rarely in use at the participating hospitals, so clinicians were unlikely to have established opinions as to their relative efficacy to affect decision making. Thus, we believe that the open-label design of the study would not have had major effects on outcomes.

Induction of labour can be hazardous, especially in settings without electronic oxytocin infusion pumps and few facilities for fetal monitoring. The danger comes from the difficulty of balancing inadequate stimulation (safe, but with slow labours and high rates of failure) and hyperstimulation (rapid labours, but with high rates of fetal hypoxia). Additionally, the situation is complicated by interpersonal variation in sensitivity to the induction drugs. Induction with the Foley catheter has the advantage of not directly causing uterine contractions during the cervical ripening phase. Typically, however, 80% of women then need to proceed to an oxytocin infusion, which, in settings without electronic infusion pumps, can be the most dangerous part of the induction process for the fetus. In 1974, Flack and Whyte[20] reported the wide fluctuations in infusion rates that occur when manual drip counters are used. Furthermore, the intrapartum use of oxytocin in low-income settings is closely associated with neonatal morbidity and mortality, and uterine rupture.[21] Therefore, the safety benefits of the Foley catheter for cervical ripening could be neutralised by the dangers of the oxytocin infusion. Conversely, oral misoprostol causes both uterine contractions and cervical ripening. As a result, more women progress through to vaginal birth without requiring an oxytocin infusion, which has potential safety benefits.

Although neonatal morbidity did not differ significantly between the two treatment groups, this study had insufficient power to detect anything other than major differences in rare outcomes. Babies born to women in the misoprostol group more often had meconium-stained liquor, which was also a common cause of caesarean section in that group, accounting for roughly a third of all caesarean sections (compared with 15% in the Foley catheter group). Meconium-stained liquor is a common finding in labours induced with misoprostol, and is believed to occur because of stimulation of fetal intestinal smooth muscle. In settings without access to electronic fetal monitoring, meconium-stained liquor is an important clinical sign of fetal compromise and so might, in itself, be an indication for caesarean sections in these high-risk inductions. Although not associated with fetal hypoxia, meconium-stained liquor does carry risks of meconium aspiration and so can cause clinically significant neonatal morbidity. If electronic fetal monitoring were to be introduced for women with meconium-stained liquor, then the rate of caesarean

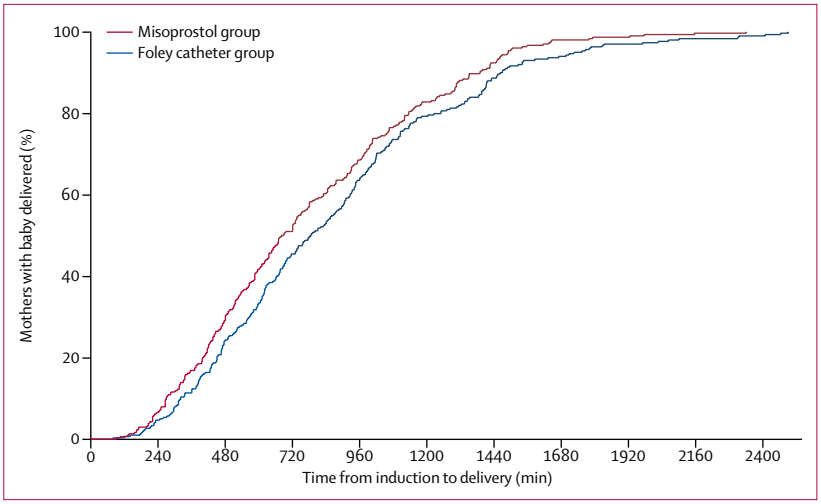

Figure 2: **Cumulative frequency curves showing time from onset of induction to delivery**
All mothers were followed up until delivery, so these curves have no censored observations.

	Foley catheter (n=300)	Misoprostol (n=302)	Absolute difference (95% CI)	p value
Outcome of birth	..	..	..	0·248*
Livebirth	298 (99·3%)	302 (100·0%)	0·7%†	..
Stillbirth	2 (0·7%)	0	..	..
Birthweight, g	..	..	..	0·918‡
Mean (SD)	2612 (464)	2616 (490)	4 (–72 to 80)	..
Median (range)	2600 (1000–3830)	2600 (750–3800)	..	..
Apgar score				
At 1 min	..	..	..	0·687§
<7	10/298 (3·4%)	12 (4·0%)	0·6% (–2·4 to 3·6)	..
≥7	288/298 (96·6%)	290 (96·0%)	..	..
At 5 min	..	..	..	0·058§
<7	1/298 (0·3%)	6 (2·0%)	1·7% (–0·1 to 3·4)	..
≥7	297/298 (99·7%)	296 (98·0%)	..	..
At 10 min	..	..	..	0·431*
<7	0	5 (1·7%)	1·7%†	..
≥7	298/298 (100·0%)	297 (98·0%)	..	..
Median age at first oral feed, min (IQR; range)¶	57 (35–90; 1–18 720)	50 (30–90; <1–3000)	0 (–540 to 300)‖	0·524**
			..	..
Median age at first gasp, s (IQR; range)††	5 (4–6; 2–20)	5 (4–6; 2–120)	0 (–1 to 0)‖	0·060**
			..	..
Median age at heart rate >100 beats per min, s (IQR; range)¶	5 (4–6; 2–20)	6 (4–7; 2–150)	0 (0 to 0)‖	0·103**
			..	..
Worst consciousness level between 30 min and 72 h	..	..	..	0·628*
Normal	294/298 (98·7%)	293 (97·0%)	..	..
Hyperalert	0	1 (0·3%)	..	..
Reduced but rousable	3/298 (1·0%)	6 (2·0%)	..	..
Unrousable	1/298 (0·3%)	2 (0·7%)	..	..

(Table 4 continues on next page)

	Foley catheter (n=300)	Misoprostol (n=302)	Absolute difference (95% CI)	p value
(Continued from previous page)				
Neonatal death	3/298 (1·0%)	6 (2·0%)	1·0% (–1·04 to 2·97)	0·322§
Neonatal morbidity	..	..	..	0·226*
No morbidity	286/298 (96·0%)	289 (95·7%)	..	..
Meconium-stained liquor	6/298 (2·0%)	10 (3·3%)	..	..
Neonatal convulsions	0	1 (0·3%)‡‡	..	..
Birth asphyxia	2/298 (0·7%)	1 (0·3%)	..	..
Septicaemia	1/298 (0·3%)	1 (0·3%)	..	..
Other	3/298 (1·3%)§§	0	..	..
Baby admitted to special care nursery	19/298 (6·4%)	28 (9·3%)	2·9% (–1·4 to 7·2)	0·186§
Median time from birth to special care nursery admission, min (IQR; range)	25 (11–1175; 5–4930)	17 (10–34; 0–3940)	–10 (–60 to 3)‖	0·072**
Median time from special care nursery admission to discharge, min (IQR; range)	51 (20–111; 14–1340)	49 (23–85; 0–525)	–3 (–38 to 22)‖	0·795**
Baby given oxygen	33/298 (11·1%)	42 (13·9%)	2·8 (–2·5 to 8·1)	0·293§
Median length of oxygen administration, min (IQR; range)	30 (10–240; 5–14 400)	60 (10–720; <1–4320)	30 (–60 to 540)‖	0·481**
			..	..
Baby ventilated	4/298 (1·3%)	4 (1·3%)	0 (–1·9 to 1·8)	0·985§
Median length of ventilation, h (IQR; range)	27 (2–156; 0·5–192)	65·5 (15–72; 0·2–72)	17 (–133 to 72)‖	0·886**
Sarnat score completed	19/298 (6·3%)	29 (9·6%)	3·3% (–1·0 to 7·6)	0·138§
Revised Sarnat score	..	..	..	1·000*
Normal	13/19 (68·4%)	20/29 (69·0%)	..	..
Moderate	6/19 (31·6%)	8/29 (27·6%)	..	..
Severe	0	1/29 (3·4%)	..	..

Data are n (%), mean (SD), median (range), n/N (%), or median (IQR; range). *Fisher's exact test. †95% CI not calculable. ‡Linear regression. §Binomial regression. ¶Not recorded for two babies in Foley catheter group and eight babies in misoprostol group. ||Median difference. **Mann–Whitney *U* test. ††Not recorded for one baby in misoprostol group. ‡‡Age was 1090 min. §§One low birthweight, one premature with very low birthweight, and one respiratory distress syndrome.

Table 4: **Neonatal outcomes**

section could be reduced further in the misoprostol group, increasing the difference between the two treatments.

In settings with electronic infusion pumps, oxytocin infusions have an advantage over vaginal induction agents because they produce a very reliable infusion rate and can be stopped rapidly in the event of hyperstimulation or abnormalities in fetal heart rate. The short half-life of oxytocin means that the effect wears off within minutes. By contrast, vaginal misoprostol tablets last for many hours and cannot be removed, which complicates management of hyperstimulation or suspected fetal hypoxia. The production of misoprostol as a vaginal insert has improved this problem, enabling rapid removal of the drug from the vagina. However, the inserts are expensive and scarcely available in low-resource settings. Oral misoprostol is rapidly absorbed with a peak serum concentration of 30 min, and is largely metabolised by 120 min,[22] thus requiring a frequent dosing regimen of 1–2 h. Although this regimen could be deemed inconvenient, it does mean that a woman will be monitored frequently during the induction process and cannot just be given the drug and reviewed 4–6 h later. Furthermore, if a woman starts to experience hyperstimulation, the next dose can be omitted leading to a reduction in contractions within a short space of time. In a low-resource setting with few staff, this regimen is a little more resource intensive, but potentially safer.

The absence of electronic fetal monitoring is typical of many public hospitals in low-income and middle-income countries, and has important implications for the study outcomes. In low-risk pregnancies, electronic fetal monitoring is associated with increased operative intervention, whereas in high-risk pregnancies it might have the effect of reassuring clinicians about fetal health, thus preventing intervention (eg, for meconium-stained liquor). However, the lack of electronic fetal monitoring might make it more difficult to diagnose uterine hyperstimulation and therefore lead to a worsening of fetal outcomes. Certainly, in this study, the rates of hyperstimulation were unusually low compared with the usual rates of about 5%.[5] In our study, attending staff constantly monitored contraction frequency and formally recorded it every 2 h, but there remains the possibility of underdiagnosis. The absence of electronic fetal monitoring means that contraction assessment could not be checked retrospectively or be masked, increasing the risk of bias.

In the parous subgroup of this study, we recorded more admissions to the special care nursery in the misoprostol group than the Foley catheter group. This finding reflects the excess of premature babies recruited in the misoprostol group, as well as the higher rate of meconium-liquor staining in that group, which is thought to relate to a direct smooth muscle effect of misoprostol on the fetal intestine and has not been associated with fetal hypoxia.[5] Most babies stayed in the special care nursery for less than an hour, reflecting their routine transfer for assessment only. This outcome is supported by the finding that the time to transfer to the special care nursery was also lower in the misoprostol group than the Foley catheter group.

Many previous studies[5] of oral misoprostol have given misoprostol every 4–6 h, similar to vaginal misoprostol. Conversely, our study used a 2-h dosing regimen, which is more consistent with the pharmacokinetics of oral misoprostol,[22] and is the first oral misoprostol study to use 25 µg misoprostol tablets. Previous studies[5] have either used divided 100–200 µg tablets, which can lead to inaccuracies because the tablets can shatter and crumble, or oral misoprostol solution, for which the stability is uncertain. The 25 µg tablets should provide a stable and consistent form for the future.

In the present study, more women in the oral misoprostol group than the Foley catheter group would use the same method again if they needed induction in the future. This outcome is not surprising given that women in the Foley group avoided an initial uncomfortable vaginal examination in which a catheter was inserted into the cervix. Some participants also avoided an oxytocin infusion and others avoided a caesarean section. Pain experienced did not differ between the treatment groups; women in the Foley catheter group informally reported discomfort on insertion, but then reported being pain free until active labour. By contrast, although women in the misoprostol group avoided the initial insertion, they often had contraction pain during the cervical ripening process. These findings are in keeping with those of other Foley catheter versus prostaglandin induction studies.[11]

In some studies, oral misoprostol has been used both for cervical ripening and induction, with regular doses of oral misoprostol used in place of the oxytocin infusion characteristic of most induction protocols. In addition to being potentially more satisfying for the woman, this procedure also has logistic advantages due to misoprostol's stability in heat and ease of administration. In settings in which there are no electronic infusion pumps, use of oral misoprostol also ensures a regular and standard dose of stimulant. The fear that misoprostol could be dangerous to the fetus because of irreversible hyperstimulation has not been proven in the studies[5] in which it has been used. One would expect that oral misoprostol used up to birth would be as effective as the misoprostol and oxytocin regimen, but potentially safer in settings without electronic infusion pumps. However, no direct comparisons have been done.

In summary, 25 µg oral misoprostol given every 2 h was more effective and more acceptable to women than a transcervical Foley catheter for induction of labour in women requiring delivery because of pre-eclampsia or hypertension. Oral misoprostol also seemed to be safe, despite the absence of routine fetal monitoring or electronic oxytocin infusion pumps. More studies are required to assess whether the oxytocin augmentation following misoprostol can be replaced by regular doses of oral misoprostol tablets.

Contributors

ADW had the original idea for the study and is guarantor for the study. SM, BW, HB, ZA, BF, TE, and AH developed the idea into a formal grant application. SM led the study team in India, with VK and JM as local principal investigators for the study sites. SL and PG joined AH to do the economic analysis, and MAT joined to provide academic neonatal support. SM, HB, BF, SL, BW, and ADW formed the trial management team with input from other co-investigators as required. HB was the study monitor. BF did the main analysis and ADW wrote the first draft of the clinical paper. All authors reviewed and approved the paper before submission.

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Independent members were Metin Gulmezoglu (Chair), Antonieta Medina-Lara, Lena Marions, and Asha Joshi. Jo Mulligan represented the Medical Research Council and Louise Hardman the Sponsor (University of Liverpool).

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Declaration of interests

ADW is a scientific adviser to Azanta A/S, a Danish pharmaceutical company. The company pays the University of Liverpool for his time and he receives no personal payments. MAT has provided consultancy services to Chiesi, Bristol–Myers Squibb, Novartis, Shire, Janssen, and Grunenthal. The companies pay the University of Liverpool for his time and he receives no personal payments. All other authors declare no competing interests.

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