Induction of labour at term with oral misoprostol versus a Foley catheter (PROBAAT-II): a multicentre randomised controlled non-inferiority trial

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Summary

Background **Labour is induced in 20–30% of all pregnancies. In women with an unfavourable cervix, both oral misoprostol and Foley catheter are equally effective compared with dinoprostone in establishing vaginal birth, but each has a better safety profile. We did a trial to directly compare oral misoprostol with Foley catheter alone.**

Methods **We did an open-label randomised non-inferiority trial in 29 hospitals in the Netherlands. Women with a term singleton pregnancy in cephalic presentation, an unfavourable cervix, intact membranes, and without a previous caesarean section who were scheduled for induction of labour were randomly allocated to cervical ripening with 50 µg oral misoprostol once every 4 h or to a 30 mL transcervical Foley catheter. The primary outcome was a composite of asphyxia (pH ≤7·05 or 5-min Apgar score <7) or post-partum haemorrhage (≥1000 mL). The non-inferiority margin was 5%. The trial is registered with the Netherlands Trial Register, NTR3466.**

Findings **Between July, 2012, and October, 2013, we randomly assigned 932 women to oral misoprostol and 927 women to Foley catheter. The composite primary outcome occurred in 113 (12·2%) of 924 participants in the misoprostol group versus 106 (11·5%) of 921 in the Foley catheter group (adjusted relative risk 1·06, 90% CI 0·86–1·31). Caesarean section occurred in 155 (16·8%) women versus 185 (20·1%; relative risk 0·84, 95% CI 0·69–1·02, p=0·067). 27 adverse events were reported in the misoprostol group versus 25 in the Foley catheter group. None were directly related to the study procedure.**

Interpretation **In women with an unfavourable cervix at term, induction of labour with oral misoprostol and Foley catheter has similar safety and effectiveness.**

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Background

Induction of labour is an obstetric intervention that artificially initiates the process of effacement of the cervix, dilatation, uterine contractions, and eventually delivery of the baby. It aims to end the pregnancy through vaginal delivery, when continuation of the pregnancy could jeopardise the condition of the mother or her baby, and delivery ought to improve outcomes compared with continuing pregnancy. 25% of women in high-resource settings have labour induced.[1–5] In women with an unfavourable cervix, induction of labour starts with cervical ripening, which can be achieved with mechanical methods, such as a Foley catheter, or pharmacologically, with prostaglandin E1 or E2 analogues.[6] Although mechanical methods were predominantly used previously, in the past three decades labour has been induced in high-resource settings mostly with prostaglandins.[7]

The introduction of prostaglandins was not supported by strong evidence of better safety and effectiveness than older methods. Induction of labour with a Foley catheter results in less post-partum haemorrhage and less asphyxia but a similar vaginal birth rate compared with dinoprostone (prostaglandin E2) gel.[8] Misoprostol, a prostaglandin E1 analogue introduced in 1990, seems as effective as dinoprostone in establishing vaginal birth, with fewer side-effects.[9,10] Administration of misoprostol 50 µg orally is associated with less hyperstimulation and asphyxia than is administration of 25 µg vaginally, and has similar effects.[9] Although not licensed for induction of labour, misoprostol is recommended by WHO and the American College of Obstetricians and Gynecologists.[6,11] A well-powered randomised controlled trial to directly compare oral misoprostol with Foley catheter alone for induction of labour has never been done; therefore, we did a multicentre randomised controlled trial on the subject.

Methods

Study design and participants

We did this open-label, non-inferiority trial in six tertiary-care and 23 secondary-care hospitals collaborating in the Dutch consortium for women's health research.

We enrolled women with a vital singleton pregnancy in cephalic presentation, intact membranes, a gestational

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Research in context

Evidence before this study

We searched the Cochrane Library, PubMed, Embase, and Web of Science on June 24, 2015, without date or language restrictions with the terms: ("balloon dilatation" or "mechanical methods" or "mechanical dilatation" or "balloon" or "Foley") and ("prostaglandin E1"or "misoprostol" or "PGE1"). We included randomised controlled clinical trials comparing 30 mL Foley catheter with 50 µL oral misoprostol for induction of labour. Participants were pregnant women who were scheduled for third trimester induction of labour, with an unfavourable cervix, a vital fetus in cephalic presentation, and no previous caesarean section. We identified 1122 articles. After removing duplicates, we assessed 745 articles. One study fulfilled the inclusion criteria. The study participants were randomly assigned to a study procedure, but how this was done was not explained, method of analysis was not mentioned, no outcome measures were mentioned in the method section, and no power calculation was done. Therefore, this study had a high risk of bias. The study showed no difference in caesarean section rate and no difference in Apgar score <7 at 5 min, but, because of a low number of participants (30 in each group) and the high risk of bias, these results should be interpreted with caution.

Added value of this study

Our trial is the first large well-powered randomised controlled study comparing oral misoprostol with Foley catheter for induction of labour. Our results suggest that induction of labour with oral misoprostol or Foley catheter are similarly safe and effective.

Implications of all the available evidence

Alfirevic and colleagues compared all prostaglandins for induction of labour in a systematic review and network meta-analysis. They found that low-dose oral misoprostol has the best safety compared with other prostaglandins. When comparing these data with our trial, oral misoprostol and Foley catheter are the best options of choice for induction of labour. This information will aid physicians in their making clinical decisions, and could prevent serious maternal and neonatal morbidity.

age of 37 weeks or more, and an unfavourable cervix (Bishop score <6), scheduled for induction of labour. We excluded women with known hypersensitivity to any of the products used, age younger than 18 years, a history of caesarean section, placenta praevia, or a fetus known to have lethal congenital anomalies.

This trial was approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Academic Medical Centre, Amsterdam, and by the boards of directors of all participating hospitals. The study protocol has been published.[12] All participants provided written informed consent.

Randomisation and masking

Women were randomly allocated (1:1) to induction with oral misoprostol or induction with a Foley catheter, by use of a web-based program, with block sizes of two and four, and stratified by centre and parity. Because of the nature of the interventions, masking participants or caregivers to the allocation was not possible. Investigators analysing data were not masked to allocation.

Procedures

Trained research staff, the treating midwife, or gynaecologist counselled women for the study. Trained research staff recorded demographics, obstetric information, and medical history, and data about pregnancy and delivery until discharge. Data were entered in an online case-record form with checks for consistency. Women allocated to oral misoprostol received 50 µg capsules once every 4 hours with a maximum of three times per day. Before administration of each dose, fetal condition and uterine activity were monitored. A subsequent misoprostol dose was withheld in the presence of three or more contractions in 10 min or in case of a non-reassuring fetal heart rate as shown on cardiotocography. The capsules were made from misoprostol 200 µg tablets (Searle, Maarssen, Netherlands) manufactured by the hospital pharmacy at the Leiden University Medical Centre.[12] The 200 µg tablets were pulverised with a cube mixer. Capsules were prepared from the powder mixture, optionally supplemented with microcrystalline cellulose to achieve the volume needed for 100 capsules. Each capsule contained 47·5–52·5 µg misoprostol. High-performance liquid chromatography showed the difference between the standard retention time and that of the sample was within 2·5%.

Women allocated to induction with a Foley catheter had a 16F or 18F Foley catheter introduced through the cervix either digitally or using a vaginal speculum. After the Foley catheter had passed the internal os, the balloon was filled with 30 mL 0·9% sodium chloride or sterile water. The external end of the Foley catheter was taped to the thigh without traction. The ripeness of the cervix was assessed every 12 h, or when the Foley catheter was expelled spontaneously. If the Bishop score remained less than 6 after 24 h, the location of the Foley catheter was checked. When still in correct position, the Foley catheter was either left in place, or replaced with a new one after 24 h, according to local preference. If the Bishop score remained less than 6 after 48 h, the catheter was replaced.

After every oral misoprostol dose or Foley catheter placement, women were assigned 1 h of bed-rest while fetal condition and uterine activity were monitored. Induction was considered to have failed if the cervix

remained unfavourable after 4 days of either Foley catheter or misoprostol. At that stage, the study protocol was stopped and further management was determined by the treating physician. In both groups, amniotomy was done when the Bishop score was 6 or greater, and at least 4 h after the last dose of misoprostol. After amniotomy, fetal condition and uterine activity were monitored continuously. If uterine activity was deemed insufficient (as judged by the treating physician), oxytocin was continuously infused through a syringe pump (mostly at an initial dose of 3·3 mIU per min, which was increased by 3·3 mIU every 20–30 min) either until three or four contractions per 10 min were achieved, or progression was considered adequate.

Outcomes

The primary outcome was a composite of neonatal asphyxia (arterial umbilical cord pH ≤7·05 or 5-min Apgar score <7) or post-partum haemorrhage (estimated blood loss ≥1000 mL ascertained over 24 h post partum). Secondary outcomes included mode of delivery, indication for operative delivery, time from induction to delivery, use of analgesics, use of oxytocin, number of misoprostol doses or Foley catheters used, and number of vaginal examinations. Secondary outcomes related to maternal morbidity were post-partum blood transfusion and number of packed cells, hyperstimulation (more than five contractions in 10 min on at least two occasions) without change in fetal heart rate, hyperstimulation with changes of fetal heart rate (defined as a non-reassuring rate tracing by the treating physician), uterine hypertonus (a contraction lasting longer than 2 min with fetal heart rate changes), uterine rupture, maternal infection during labour, maternal infection within 1 week after delivery, use of intravenous antibiotics, endo(myo)metritis or urinary tract infection within 1 week after delivery, and use of other drugs such as tocolytics to convert hyperstimulation. Secondary endpoints related to neonatal morbidity were fetal tachycardia (sustained rate >160 beats per min), meconium-stained liquor, birthweight, Apgar score less than 7 at 1 min, and admission to the neonatal ward or intensive care unit and the reason.

Post-hoc outcomes were failed induction, estimated blood loss of 1000 mL or more and of 500 mL or more, volume of blood loss, duration from randomisation to the first stage of labour, duration from randomisation to birth, duration from induction to first stage of labour, delivery within 24 h, 36 h, and 48 h, Apgar score less than 7 at 5 min, arterial pH of 7·05 or less, and pH 7·10 or less, neonatal death, length of neonatal admission, and maternal admission including duration of stay and reason for admission.

Statistical analysis

We decided to use a non-inferiority design because Foley catheter was considered the standard of care after the PROBAAT trial,[8] and oral misoprostol would be acceptable if its safety and effectiveness was similar. We based our sample size calculation on data from the PROBAAT trial[8] because data for direct comparison between oral misoprostol and Foley catheter were lacking.[13] We expected the primary outcome to occur in 13·7% of patients in the misoprostol group and in 12·7% of the Foley catheter group.[8] We calculated that 1860 participants (930 per group, with a one-sided α of 5%) would provide 80% power to show the non-inferiority of misoprostol on the composite outcome, with a non-inferiority margin of 5%. We considered induction with misoprostol non-inferior to induction with Foley catheter if the upper bound of the 90% CI would exclude an absolute 5% higher rate of composite outcome in the misoprostol group. We did another prospective sample

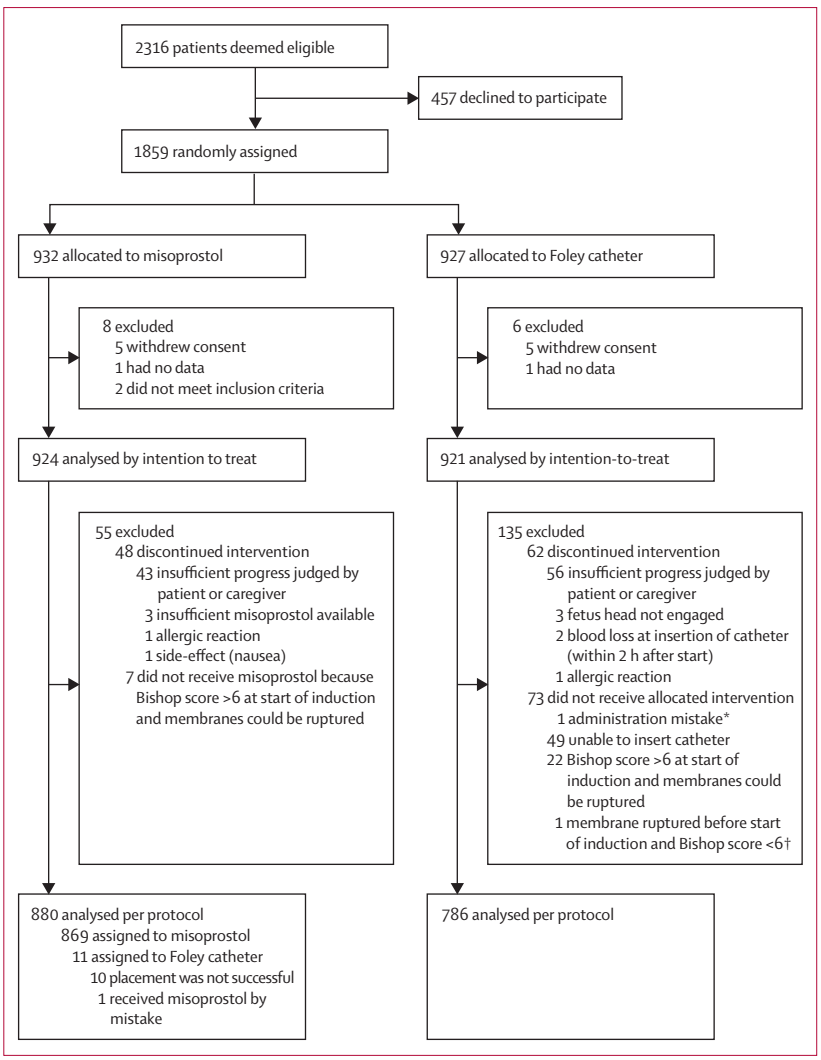

Figure 1: **Trial profile**
1870 randomisations were done, from which 11 participants were mistakenly randomly assigned twice; the result of the second randomisation was used for further management and analysis. *The treating physician wrote oral misoprostol in the participants' chart as randomisation outcome so the participant received oral misoprostol. †Membranes were ruptured before labour was induced and after randomisation; because Bishop score was less than 6 no oxytocin was given and the treating physician decided to use oral misoprostol induction.

	Misoprostol group (n=924)	Foley catheter group (n=921)
Maternal age (years; mean, SD)	31·7 (5·2)	31·4 (4·9)
Ethnic origin		
White	695 (75·2%)	716 (77·7%)
Not white	143 (15·5%)	131 (14·2%)
Unknown	86 (9·3%)	74 (8·0%)
Body-mass index (kg/m²; median, IQR)*	25·1 (22·3–29·0)	24·6 (21·9–28·8)
Parity		
0	610 (66·0%)	596 (64·7%)
1	199 (21·5%)	232 (25·2%)
≥2	115 (12·4%)	93 (10·1%)
Gestational age weeks (median; IQR)	39·5 (38·2–41·1)	39·6 (38·2–41·1)
Gestational age 37–38 weeks	153 (16·6%)	151 (16·4%)
Gestational age 38–39 weeks	222 (24·0%)	206 (22·4%)
Gestational age 39–40 weeks	145 (15·7%)	147 (16·0%)
Gestational age >40 weeks	404 (43·7%)	417 (45·3%)
Total Bishop score <6	917 (99·2%)	899 (97·6%)
Bishop score		
0	95/691 (13·7%)	86/651 (13·2%)
1	137/691 (19·8%)	136/651 (20·9%)
2	167/691 (24·2%)	178/651 (27·3%)
3	155/691 (22·4%)	137/651 (21·0%)
4	78/691 (11·3%)	74/651 (11·4%)
5	57/691 (8·2%)	32/651 (4·9%)
Data missing	235 (25·4%)	278 (30·2%)
Indication for induction†		
Hypertensive disorders	274 (29·7%)	277 (30·1%)
Post-term pregnancy‡	277 (30·0%)	291 (31·6%)
Insulin-dependent diabetes	67 (7·3%)	59 (6·4%)
Oligohydramnios	49 (5·3%)	50 (5·4%)
Intrauterine growth restriction§	64 (6·9%)	69 (7·5%)
Obstetric cholestasis	21 (2·3%)	25 (2·7%)
Decreased fetal movements	72 (7·8%)	75 (8·1%)
Elective¶	233 (25·2%)	226 (24·5%)
Other	72 (7·8%)	57 (6·2%)
Male babies	480 (51·9%)	501 (54·4%)

Data are n (%) unless otherwise indicated. *Data missing for 103 participants in the misoprostol group and 79 in the Foley catheter group. †More than one indication possible. ‡Defined according to local hospital protocol for induction of labour, which in most cases was a gestational age ≥41 weeks. §Defined as estimated fetal weight <10th percentile. ¶Because of pelvic instability, social or psychological reasons, macrosomia, diabetes gravidarum with diet, obstetric history.

Table 1: **Baseline characteristics**

size calculation showing that 1860 participants would give us more than 80% power to show non-inferiority with regard to the proportion of caesarean sections, if the upper bound of the 95% CI would exclude a 5% higher absolute rate of caesarean sections with misoprostol compared with Foley catheter, assuming that 23% of patients have a caesarean section.[8] There is no consensus defining the non-inferiority margin. We set the margin for the primary outcome to achieve a reasonable balance between clinical relevance and the practical size of the sample.

We planned interim analyses for safety and effectiveness by an independent data and safety monitoring board after recruitment of 300 participants and 600 participants. The second interim analysis could not be done because patients were enrolled so quickly that enrolment was almost complete by the time data for 600 participants had been entered. Serious adverse events (intrauterine fetal death, uterine rupture, severe maternal and neonatal morbidity including intensive care admission, and study-related events such as placental abruption directly after insertion of Foley catheter) were reported to the Central Committee on Research Involving Human Subjects and to the ethics committee of the Academic Medical Centre, Amsterdam.

The primary analysis was by intention to treat. Because of the non-inferiority design with one-sided testing, we calculated the primary outcome as relative risk with 90% CI. We adjusted for parity and centre, using a log-binomial model with parity as a fixed effect and centre as a random effect. We also calculated the risk difference with 90% CI. We calculated relative risks and 95% CIs for other binary outcomes, and tested differences between categorical variables with the χ^2 test, or Fisher's exact test if the expected cell count was less than five. We present normally distributed data as means with SDs, and skewed distributions as medians with IQRs. We tested non-normally distributed continuous variables with the Mann-Whitney *U* test. We used Kaplan-Meier analysis to assess time-to-event outcomes. We expected that about a quarter of pH data would be missing because pH is not a standard measurement in all hospitals, whereas we expected almost complete data for 5-min Apgar score. For participants with data missing for umbilical artery pH and a 5-min Apgar score of less than 7, the outcome was classified as abnormal; for patients with missing data for umbilical artery pH and a 5-min Apgar score of 7 or more, the neonatal outcome was classified as normal. For all the other outcomes, we used complete-case analysis.

We also did a per-protocol analysis. We planned a subgroup analysis for parity. We considered $p<0·05$ as statistically significant. We did the statistical analyses with SPSS (version 22). We calculated risk differences using R (version 3.1.2).

The trial is registered with the Netherlands Trial Register, number NTR3466.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 18, 2012, and Oct 10, 2013, we deemed 2316 women eligible, of whom 1859 consented to participate. We randomly assigned 932 women to

	Intention-to-treat analysis				Per-protocol analysis			
	Misoprostol group (n=924)	Foley catheter group (n=921)	Relative risk (CI)	p value	Misoprostol group (n=880)	Foley catheter group (n=786)	Relative risk (CI)	p value
Primary composite outcome	113 (12·2%)	106 (11·5%)	1·06 (0·86–1·31)	..	110 (12·5%)	83 (10·6%)	1·18 (0·95–1·48)	..
Post-partum haemorrhage								
Volume (mL)	300 (200–500)	300 (200–500)	..	0·40*	300 (200–500)	300 (200–500)	..	0·30*
Post-partum haemorrhage ≥1000 mL	79 (8·6%)	82 (8·9%)	0·96 (0·72–1·29)	0·79	76 (8·6%)	64 (8·1%)	1·06 (0·77–1·46)	0·72
Post-partum haemorrhage ≥500 mL	262 (28·4%)	263 (28·6%)	0·99 (0·86–1·15)	0·89	241 (27·4%)	218 (27·7%)	0·99 (0·85–1·15)	0·87
Blood transfusion	22 (2·4%)	21 (2·3%)	1·04 (0·58–1·89)	0·89	22 (2·5%)	13 (1·7%)	1·51 (0·77–2·98)	0·23
Number of packed cells (mean, SD)	2·68 (0·95)	3·00 (1·87)	..	0·48	2·68 (0·95)	2·86 (2·23)	..	0·76
Apgar score <7								
1 min	49 (5·3%)	47 (5·1%)	1·04 (0·70–1·53)	0·85	49 (5·6%)	36 (4·6%)	1·22 (0·80–1·85)	0·36
5 min	17 (1·8%)	15 (1·6%)	1·13 (0·57–2·25)	0·73	17 (1·9%)	12 (1·5%)	1·27 (0·61–2·63)	0·53
Umbilical cord arterial pH								
≤7·10	55/679 (5·1%)	43/668 (6·4%)	1·26 (0·86–1·85)	0·24	53/647 (8·2%)	35/567 (6·2%)	1·33 (0·88–2·00)	0·18
≤7·05	22/679 (3·2%)	16/668 (2·4%)	1·35 (0·72–2·55)	0·35	22/647 (3·4%)	12/567 (2·1%)	1·61 (0·80–3·22)	0·18
Missing data	245 (26·5%)	253 (27·5%)	..	..	233 (26·5%)	219 (27·9%)	..	..
Number of misoprostol doses (mean, SD)	3·7 (2·6)	0·2 (1·0)	..	<0·0001	3·6 (2·5)	0·1 (0·4)	..	<0·0001
Number of Foley catheters used (mean, SD)	0·04 (0·2)	1·15 (0·6)	..	<0·0001	0·02 (0·1)	1·2 (0·5)	..	<0·0001
Number of vaginal examinations (mean, SD)	8·1 (3·9)	6·8 (3·0)	..	<0·0001	7·9 (3·7)	6·6 (2·7)	..	<0·0001
Hyperstimulation								
With fetal heart rate changes	26 (2·8%)	22 (2·4%)	1·18 (0·67–2·06)	0·57	25 (2·8%)	19 (2·4%)	1·18 (0·65–2·12)	0·59
Without fetal heart rate changes	8 (0·9%)	16 (1·7%)	0·50 (0·21–1·16)	0·10	8 (0·9%)	12 (1·5%)	0·60 (0·25–1·45)	0·25
Tocolytic use	30 (3·2%)	29 (3·1%)	1·03 (0·62–1·70)	0·91	28 (3·2%)	22 (2·8%)	1·14 (0·66–1·97)	0·65
Uterine hypertonus	0 (0%)	0 (0%)	..	..	0 (0%)	0 (0%)	..	..
Mode of delivery								
Spontaneous	644 (69·7%)	648 (70·4%)	0·99 (0·93–1·05)	0·76	632 (71·8%)	568 (72·3%)	0·99 (0·94–1·06)	0·84
Vaginal instrumental	125 (13·5%)	88 (9·6%)	1·41 (1·09–1·83)	0·0076	115 (13·1%)	71 (9·0%)	1·45 (1·09–1·91)	0·0090
Caesarean section	155 (16·8%)	185 (20·1%)	0·84 (0·69–1·02)	0·067	133 (15·1%)	147 (18·7%)	0·81 (0·65–1·00)	0·051
Indication vaginal instrumental delivery								
Failure to progress at second stage	53 (5·7%)	43 (4·7%)	1·23 (0·83–1·82)	0·30	47 (5·3%)	35 (4·5%)	1·20 (0·78–1·84)	0·40
Suspected fetal distress	44 (4·8%)	35 (3·8%)	1·23 (0·83–1·81)	0·31	42 (4·8%)	28 (3·6%)	1·34 (0·84–2·14)	0·22
Suspected fetal distress and failure to progress at second stage	32 (3·5%)	13 (1·4%)	2·45 (1·30–4·64)	0·0043	29 (3·3%)	11 (1·4%)	2·36 (1·18–4·68)	0·012
Maternal complication or other	2 (0·2%)	1 (0·1%)	1·99 (0·18–21·95)	1·00†	3 (0·3%)	0 (0·0%)	NA	0·25†
Indication caesarean section								
Failure to progress at first stage	57 (6·2%)	98 (10·6%)	0·58 (0·42–0·79)	0·00054	45 (5·1%)	82 (10·4%)	0·49 (0·35–0·70)	<0·0001
Failure to progress at second stage	19 (2·1%)	15 (1·6%)	1·26 (0·65–2·47)	0·50	19 (2·2%)	10 (1·3%)	1·70 (0·79–3·63)	0·17
Failed instrumental delivery	4 (0·4%)	2 (0·2%)	1·99 (0·37–10·86)	0·69	4 (0·5%)	1 (0·1%)	3·57 (0·40–31·90)	0·38†
Suspected fetal distress	36 (3·9%)	27 (2·9%)	1·33 (0·81–2·17)	0·25	31 (3·5%)	22 (2·8%)	1·26 (0·74–2·16)	0·40
Suspected fetal distress and failure to progress at first stage	19 (2·1%)	27 (2·9%)	0·74 (0·39–1·25)	0·23	17 (1·9%)	20 (2·5%)	0·76 (0·40–1·44)	0·40
Suspected fetal distress and failure to progress at second stage	10 (1·1%)	7 (0·8%)	1·42 (0·54–3·72)	0·47	9 (1·0%)	6 (0·8%)	1·34 (0·48–3·75)	0·61
Maternal complication or other	10 (1·1%)	9 (1%)	1·11 (0·45–2·71)	0·82	8 (0·9%)	6 (0·8%)	1·19 (0·42–3·42)	0·79
Oxytocin augmentation	632 (68·4%)	740 (80·3%)	0·85 (0·81–0·90)	<0·0001	599 (68·1%)	645 (82·1%)	0·83 (0·78–0·88)	<0·0001
Fetal tachycardia	88 (9·5%)	79 (8·6%)	1.11 (0·83–1·48)	0·48	84 (9·5%)	62 (7·9%)	1·21(0·88–1·65)	0·24
Meconium stained liquor	110 (11·9%)	108 (11·7%)	1·02 (0·79–1·30)	0·90	104 (11·8%)	92 (11·7%)	1·01 (0·78–1·32)	0·94
Spontaneous rupture of membranes	258 (27·9%)	91 (9·9%)	2·84 (2·27–3·54)	<0·0001	254 (29·0)	61 (7·8%)	3·73 (2·87–4·85)	<0·0001
Time from induction to birth (h)	29 (17–48)	30 (20–40)	..	0·78	28 (17–44)	30 (20–37)	..	0·97
Delivery <24 h	367 (39·7%)	278 (30·2%)	1·32 (1·16–1·49)	<0·0001	368 (41·8%)	248 (31·6%)	1·33 (1·17–1·51)	<0·0001
Delivery <36 h	575 (62·2%)	623 (67·6%)	0·92 (0·86–0·98)	0·015	575 (65·3%)	569 (72·4%)	0·90 (0·85–0·96)	0·0020
Delivery <48 h	690 (74·7%)	740 (80·3%)	0·93 (0·89–0·98)	0·0035	688 (78·2%)	664 (84·5%)	0·93 (0·88–0·97)	0·0011

Data are n (%) or median IQR, unless otherwise stated. Confidence intervals are 95% except for the primary outcome, which has 90% CIs. NA=not applicable. *Mann-Whitney *U* test. †Fisher's exact test.

Table 2: **Primary outcome and outcomes related to delivery**

	Misoprostol group (n=924)	Foley catheter group (n=921)	Relative risk (95% CI)	p value
Birthweight (g; mean, SD)	3420 (526)	3445 (531)	−24 (−72 to 24)	0·33*
Analgesics used				
Pethidine, promethazine, or nalbuphine	95 (10·3%)	87 (9·4%)	1·09 (0·83 to 1·44)	0·55
Epidural	386 (41·8%)	421 (45·7%)	0·91 (0·82 to 1·01)	0·088
Remifentanil	111 (12·0%)	129 (14·0%)	0·86 (0·68 to 1·09)	0·20
Other	25 (2·7%)	25 (2·7%)	1·00 (0·58 to 1·72)	0·99
Maternal intrapartum infection				
Temperature ≥37·8°C during labour	121 (13·1%)	118 (12·8%)	1·02 (0·81 to 1·30)	0·86
Intravenous antibiotic treatment during labour and delivery, suspected infection	26 (2·8%)	33 (3·6%)	0·79 (0·47 to 1·30)	0·35
Uterine rupture or perforation	0 (0·0%)	0 (0·0%)	NA	NA
Maternal admission				
Ward†	470 (50·9%)	487 (52·9%)	0·96 (0·88 to 1·05)	0·39
Intensive care	2 (0·2%)	1 (0·1%)	1·99 (0·18 to 21·9)	1·00‡
Length of maternal admission (median, IQR; days)	2 (1 to 3)	2 (1 to 3)	..	0·35§
Reason for maternal admission¶				
Suspected infection within 1 week of delivery‖	50 (5·4%)	42 (4·6%)	1·19 (0·80 to 1·77)	0·40
Urinary tract infection within 1 week after delivery (with positive culture)	6 (0·6%)	3 (0·5%)	2·01 (0·52 to 8·18)	0·34‡
Obstructed bowel disease	3 (0·3%)	3 (0·3%)	1·00 (0·20 to 4·93)	1·00‡
Thromboembolic complication**	1 (0·1%)	3 (0·3%)	0·33 (0·04 to 3·19)	0·37‡
Hypertensive disorder	162 (17·5%)	165 (17·9%)	0·98 (0·80 to 1·19)	0·83
Post-partum haemorrhage	54 (5·8%)	59 (6·4%)	0·91 (0·64 to 1·31)	0·62
Post-caesarean	151 (16·3%)	179 (19·4%)	0·84 (0·69 to 1·02)	0·13
Pre-eclampsia or HELLP syndrome	46 (5·0%)	37 (4·0%)	1·24 (0·81 to 1·89)	0·32
Other	108 (11·7%)	100 (10·9%)	1·08 (0·83 to 1·39)	0·57

(Table 3 continues on next page)

misoprostol and 927 to Foley catheter (figure 1). 14 women were excluded from the intention-to-treat analyses, including two who did not meet the eligibility criteria: each had a history of caesarean section and no vaginal examination before randomisation. We believe that these women were enrolled by mistake by the treating physician. At the interim analyses, the data safety and monitoring board advised us to continue the trial.

Baseline characteristics were much the same in each group (table 1). The most common indications for induction of labour were post-term pregnancy and hypertensive disorders (table 1). The primary outcome (asphyxia or post-partum haemorrhage) occurred in 113 (12·2%) of 924 participants in the misoprostol group and 106 (11·5%) of 921 participants in the Foley catheter group (adjusted relative risk 1·06, 90% CI 0·86 to 1·31; risk difference 0·7%, 90% CI −1·8 to 3·2; table 2).

155 (16·8%) of 924 women in the misoprostol group had a caesarean section compared with 185 (20·1%) of 927 women in the Foley catheter group, with no significant difference between groups (relative risk 0·84, 95% CI 0·69 to 1·01, p=0·067; risk difference −3·3%, 95% CI −6·8 to −0·0). There were fewer caesarean sections for failure to progress in the first stage after induction in the misoprostol group than in the Foley catheter group (57 [6·2%] of 924 women *vs* 98 [10·6%] of 921 women; relative risk 0·58, 95% CI 0·42 to 0·79, p=0·00054). Vaginal instrumental delivery was significantly more common in the misoprostol group than in the Foley catheter group (table 2).

More vaginal examinations were done in the misoprostol group than in the Foley catheter group (table 2). Spontaneous rupture of membranes occurred significantly more often in the misoprostol group than in the Foley catheter group (table 2). Labour augmentation with oxytocin occurred less often in the misoprostol group than in the Foley catheter group (table 2). We recorded no significant difference in hyperstimulation either with or without fetal heart rate changes (table 2).

Neonatal medium-care and intensive-care admissions did not differ significantly between the oral misoprostol and Foley catheter groups (table 3). There was no significant difference in suspected maternal infection or neonatal meningitis or sepsis between the groups (table 3).

The individual components of the primary outcome did not differ significantly between groups (table 2). Time from induction to the active phase of labour of less than 24 h was more common with oral misoprostol than with Foley catheter, whereas it was more common with Foley catheter than with misoprostol after 30 h

	Misoprostol group (n=924)	Foley catheter group (n=921)	Relative risk (95% CI)	p value
(Continued from previous page)				
Neonatal admission				
Ward†	270 (29·2%)	279 (30·3%)	0·97 (0·84 to 1·11)	0·61
Medium care	99 (10·7%)	101 (11·0%)	0·98 (0·75 to 1·27)	0·86
Intensive care	25 (2·7%)	24 (2·6%)	1·04 (0·60 to 1·80)	0·89
Neonatal death (≤28 days after birth)	1 (0·1%)	3 (0·3%)	0·33 (0·04 to 3·19)	0·37‡
Length of neonatal admission (days; median, IQR)	2 (1–3)	2 (1–3)		0·43§
Reason for neonatal admission				
Neonatal meningitis				
Suspected	7 (0·8%)	2 (0·2%)	3·49 (0·73 to 16·75)	0·18‡
Proven with culture	0 (0·0%)	0 (0·0%)	NA	NA
Neonatal sepsis				
Suspected	42 (4·5%)	38 (4·1%)	1·10 (0·72 to 1·69)	0·66
Proven	1 (0·1%)	6 (0·7%)	0·17 (0·02 to 1·38)	0·064‡
Fetus immature for gestational age	60 (6·5%)	70 (7·6%)	0·85 (0·61 to 1·19)	0·35
Glucose protocol	176 (19·0%)	184 (20·0%)	0·95 (0·79 to 1·15)	0·61
Hypoglycaemia	31 (3·4%)	36 (3·9%)	0·86 (0·54 to 1·38)	0·53
Infant respiratory distress syndrome	1 (0·1%)	1 (0·1%)	1·00 (0·06 to 15·91)	1·00‡
Meconium aspiration	2 (0·2%)	3 (0·3%)	0·67 (0·11 to 3·97)	0·69‡
Pneumothorax or pneumomediastinum	3 (0·3%)	1 (0·1%)	2·99 (0·31 to 28·69)	0·63‡
Apnoea	0 (0·0%)	1 (0·1%)	NA	0·50‡
Necrotising enterocolitis	1 (0·1%)	1 (0·1%)	1·00 (0·06 to 15·91)	1·00‡
Clinical diagnosis of asphyxia	6 (0·6%)	6 (0·7%)	1·00 (0·32 to 3·08)	1·00‡
Intraventricular haemorrhage	1 (0·1%)	0 (0·0%)	NA	1·00‡
Other	184 (19·9%)	192 (20·8%)	0·96 (0·80 to 1·14)	0·62

Data are n (%) unless otherwise stated. NA=not applicable. *t test. †Maternal admission due to neonatal reasons are not reported, neonatal admissions due to maternal conditions are not reported. ‡Fisher's exact test. §Mann-Whitney *U* test. ¶Individual patients could have more than one reason. ||Endometritis: temperature of more than 37·8°C on two occasions at least 1 h apart after the first 24 h after delivery with associated uterine tenderness; it may be confirmed by positive blood cultures or lochia cultures but not necessarily. Urinary tract infection treated with antibiotics: complaints of cystitis like dysuria or pain in bladder region confirmed by urine dipstick with positive nitrite or leucocytosis or positive urine culture. Pneumonia: clinical signs of pneumonia (eg, cough, dyspnoea) combined with a suspected chest radiograph. **Deep venous thrombosis confirmed by ultrasonography or pulmonary embolism confirmed by spiral CT or ventilation/perfusion scan.

Table 3: **Maternal and neonatal outcomes**

(appendix pp 6, 24). Delivery within 24 h was more common after induction with misoprostol than with a Foley catheter (table 2, figure 2). By contrast, delivery within 48 h was achieved more often in the Foley catheter group than in the misoprostol group (table 2, figure 2). The results were similar when assessing time from randomisation (rather than time from induction) to active phase of labour or delivery (appendix pp 4–21). After 4 days, 59 (6·4%) of 924 patients in the misoprostol group and 23 (2·5%) of 921 patients in the Foley catheter group had not delivered (figure 2). Of these women, 34 (3·7%) in the oral misoprostol group and 15 (1·6%) in the Foley catheter group met the criteria for failed induction—ie, Bishop score less than 6 (relative risk 2·21, 95% CI 1·21–4·04, p=0·0062). These women were subsequently treated according to local protocol. Frequency of, reason for, and length of maternal admission after delivery did not differ significantly between groups (table 3).

204 women were excluded for the per-protocol analysis, 63 in the misoprostol group and 141 in the Foley catheter group (figure 1). The main reasons for exclusion were: discontinuation of intervention, inability to insert Foley catheter, and membranes could be ruptured at the moment of induction. (If the intervention was discontinued or Foley placement failed, local protocol was followed, which could be dinoprostone, vaginal or oral misoprostol, or Foley catheter.) When after local treatment the Bishop score was more than 6, membranes were ruptured, and if thought to be necessary, oxytocin was started, in the same regimen as the study's protocol. In the per-protocol analysis, the primary composite outcome of asphyxia or post-partum haemorrhage occurred in 110 (12·5%) of 880 participants in the misoprostol group and in 83 (10·6%) of 786 participants in the Foley catheter group (adjusted relative risk 1·18, 90% CI 0·95 to 1·48, p=0·22; risk difference 1·9%, 90% CI –0·6 to 4·5; table 2). 133 (15·1%) of 880 participants in the misoprostol group versus 147 (18·7%) of 786 in the Foley catheter group had caesarean section (relative risk 0·81, 95% CI 0·65 to 1·00, p=0·051; risk difference

See Online for appendix

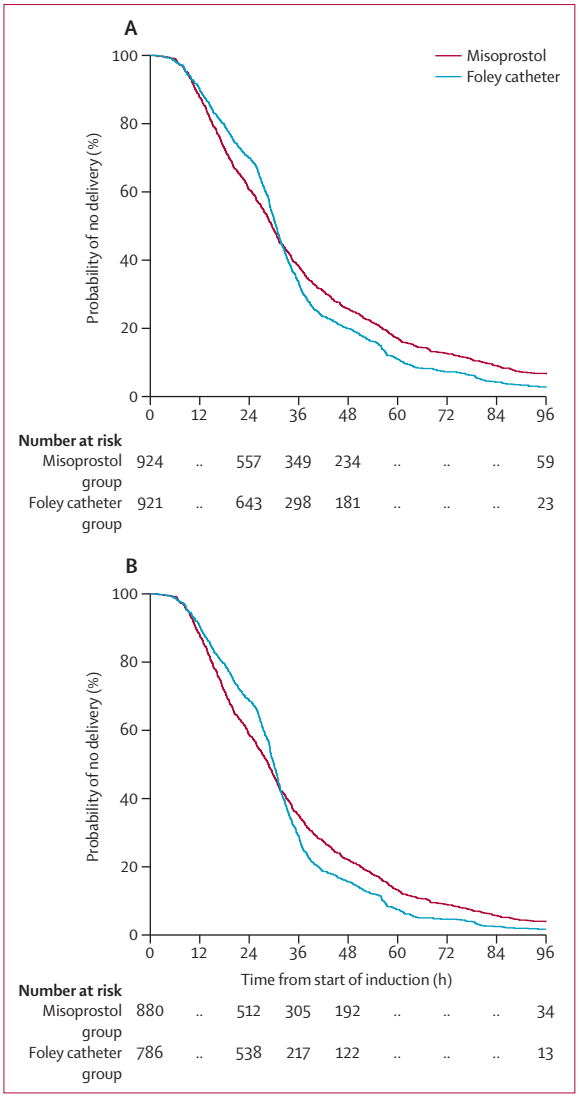

Figure 2: **Kaplan-Meier analysis of time from induction to delivery**
(A) In the intention-to-treat population and (B) in the per-protocol population.

–3·6%, 95% CI –7·2 to 0·0; table 2). The per-protocol analysis did not show significantly different outcomes for any of the secondary outcomes related to maternal or neonatal morbidity (appendix pp 3–4).

52 serious adverse events were reported: 27 in the misoprostol group and 25 in the Foley catheter group (appendix p 2). None were directly related to study procedures. 49 babies were admitted to neonatal intensive care units. Four babies died (one in the misoprostol group *vs* three in the Foley group): three because of lethal congenital malformations diagnosed after delivery (one *vs* two), and one because of asphyxia (none *vs* one). The mother of the child who died by asphyxia was induced because of polyhydramnios and gestational diabetes. After amniotomy, fetal bradycardia occurred, for which an emergency caesarean section was done. There was no hyperstimulation, no use of oxytocin, no cord prolapse, and no blood loss. Apgar score was 1 after 1 min, 0 after 5 min, and 1 after 10 min. Arterial umbilical cord pH was 6·99, base excess –16, and venous umbilical cord pH was 7·15, base excess –7·8. The child was admitted to neonatal intensive care for whole-body cooling. MRI 5 days after birth showed severe brain damage, and treatment was withheld. The child died the same day. A cause for the asphyxia could not be found. Three women were admitted to intensive care (table 3, appendix p 2), two of whom had a major obstetric haemorrhage. The third woman had an allergic drug reaction of unknown origin during caesarean section. All women recovered well.

We recorded four minor procedure-related adverse events. In both groups, there was one mild allergic reaction to the induction agent. In the Foley catheter group, two women had more than 100 mL blood loss on insertion of the catheter, which stopped after removal of the catheter. The effect of induction method on the primary outcome did not differ statistically between nulliparous women (13·8% in the misoprostol group *vs* 13·4% in the Foley catheter group, relative risk 1·03, 90% CI 0·77–1·30) and multiparous women (9·2% *vs* 8·0%, relative risk 1·17, 90% CI 0·77–1·79; $p_{interaction}$=0·70; appendix pp 8–12).

Discussion

In this randomised trial, we found that, in women with an unfavourable cervix at term, induction of labour with oral misoprostol was not inferior to Foley catheter in terms of safety and effectiveness. The composite of post-partum haemorrhage and asphyxia did not occur significantly more often after induction of labour with oral misoprostol than with Foley catheter, and the individual components of the outcome were also similar. The proportion of patients who had caesarean section was similar in each group, but fewer caesarean sections were done in the oral misoprostol group as a result of failure to progress in first stage of labour than in the Foley catheter group. There were more vaginal instrumental deliveries in the misoprostol group than in the Foley catheter group. Thus, misoprostol, although not licensed for use in pregnancy in many countries, is an effective and safe alternative for mechanical cervical ripening with a Foley catheter.

Foley catheter placement did not succeed in 49 women, which could be because not all hospitals were experienced with Foley catheter use, although training was given on how to insert the catheter. Because our study was open-label, knowledge of the method of cervical ripening could have affected the decision to perform a caesarean section because of failure to progress, or could have led to crossover, or the use of dinoprostone. However, only 4·6% of patients in the misoprostol group and 6·1% in the Foley catheter group changed induction method.

We used a Foley catheter taped on the inner thigh without traction because there was no evidence for

superiority of using traction when we designed our study. Subsequent evidence suggests that traction of the Foley catheter does not lead to better outcomes.[14] Jozwiak and colleagues[15] reported more hyperstimulation when using prostaglandins compared with mechanical methods (relative risk 0·19, 95% CI 0·08–0·43). Oral misoprostol results in less hyperstimulation than do other prostaglandins.[16] These results correspond with our finding of no significant difference in hyperstimulation between the two groups.

To our knowledge, oral misoprostol and Foley catheter have been directly compared in only one small study.[17] No significant difference in caesarean section rate, or in Apgar score less than 7 at 5 min was found. In our study, delivery within the first 24 h occurred more often after misoprostol, whereas after 36 h more deliveries had occurred after Foley catheter. Seemingly, misoprostol not only has an effect on cervical ripening but also facilitates the start of the first stage of labour, as do other prostaglandins.[18] In concordance, we recorded less oxytocin use and fewer caesarean sections for failure to progress in the first stage of labour in the oral misoprostol group.

The Cochrane Collaboration, WHO, and UK National Institute for Health and Care Excellence established birth within 24 h of the start of induction as the most clinically relevant measure of effectiveness for trials of methods of labour induction.[9,11,19] This conclusion is arguable, as in our opinion the goal of induction is a safe vaginal delivery for both mother and child soon enough to prevent complications for which the induction is performed. Thus, we believe that delivery within 48 h or 96 h is acceptable, provided the condition of mother and child allow such a delay and the chances are still high to deliver vaginally without complications.[20] We found that very few women needed more than 96 h of induction.

We used a preparation of misoprostol that was reformulated by the study pharmacy. As far as we know, the capsules used in this study are not available to others. The manufacturing is straightforward, cheap, and accurate, and therefore can easily be done by other pharmacists. This preparation would be our first method of choice. Our second method of choice is using two 25 µg capsules, which are available in many countries. Alternatively, one could also divide 200 µg tablets into four pieces.

Where cervical ripening takes place is a point of discussion. Because the process of cervical ripening is usually without complications, this intervention could be done in an outpatient setting, which is probably preferred by women and will reduce hospital costs.[17,21] Although a vaginal prostaglandin, be it misoprostol or dinoprostone, might be related to hyperstimulation and subsequent asphyxia, mechanical induction is unlikely to generate such side-effects. We showed that oral misoprostol is equally safe as mechanical induction with a Foley catheter. More data on safety at home, women's preferences, and costs are needed before a policy of cervical ripening at home can be implemented in routine care.

At present, labour is induced in one of four pregnancies in high-resource settings and in one of ten pregnancies in low-income countries.[11,22] Whether our results are generalisable for other high-income countries should be investigated, especially in countries with a high prevalence of obesity. Oral misoprostol is cheap, easy to store, and has a long shelf-life at room temperature, which makes it also suitable for use in low-resource settings. In countries where there is a reserved attitude towards induction of labour because of a high prevalence of infections and the risk of vertical transmission, oral administration of misoprostol for labour induction could be an option. To address this issue, a randomised controlled trial in low-resource settings is needed.

Contributors

BWM, KOR, MLGtE, MJ, and KWMB designed the study. MLGtE and KOR did the analyses. All authors interpreted the data, critically revised the Article, and approved the final version.

Declaration of interests

We declare no competing interests.

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