Labour induction at term — a randomised trial comparing Foley catheter plus titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone

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Objectives. To compare three methods of labour induction.

Design. Randomised controlled trial.

Setting. Academic hospitals in Johannesburg, South Africa.

Subjects. Women with intact membranes due for induction of labour.

Method. Randomised, sealed opaque envelopes were used to allocate women to labour induction with extra-amniotic Foley catheter/titrated oral misoprostol solution ($N = 174$), titrated oral misoprostol solution alone ($N = 176$), or vaginal dinoprostone ($N = 176$). Misoprostol was dissolved in water and 20 - 40 g was given 2-hourly.

Outcome measures. These were failure to deliver vaginally within 24 hours, additional measures for induction or augmentation of labour, analgesia, and maternal and fetal complications.

Results. In the Foley catheter group, misoprostol was required in all but 1 case. Failure to deliver vaginally within 24 hours was similar for the three groups (79/174 v. 70/176 v. 70/176 respectively). Labour augmentation, caesarean section and instrumental delivery were used somewhat more frequently in the Foley/misoprostol group than in the misoprostol alone group, but these differences were not statistically significant. More analgesia was used in the Foley catheter/misoprostol group than in the misoprostol group (64/172 v. 46/175). Side-effects and neonatal complications were similar for the three groups.

Conclusions. Use of extra-amniotic Foley catheter placement showed no measurable benefits over the use of oral misoprostol alone, or vaginal dinoprostone.

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Mechanical methods (catheters or hygroscopic dilators introduced into the extra-amniotic space via the cervical canal) were among the first methods of cervical ripening and labour induction developed.[1] Potential advantages include simplicity of use, low cost and few side-effects. Despite the availability of pharmacological methods over recent decades, the Foley catheter[2] and the 'Atad' double balloon catheter[3] are still in use, with or without the injection of saline solution or prostaglandins into the extra-amniotic space.[4] In a systematic review of 45 randomised trials, mechanical methods of labour induction were found to be less effective than prostaglandins and reduced the risk of uterine hyperstimulation; compared with oxytocin, there were fewer caesarean sections with mechanical methods.[5] A recent small study[6] found that the combination of an extra-amniotic Foley catheter with vaginal misoprostol was not significantly more effective than misoprostol alone, although there was a trend to fewer cases of tachysystole.

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Prostaglandin E_2 (PGE2) is regarded as the 'gold standard' for labour induction, but is unaffordable in many resource-poor settings.

Misoprostol is a unique prostaglandin E_1 analogue that has found wide application in clinical medicine including cervical ripening and labour induction.[7-11] One of the major problems has been finding the ideal dose to minimise its side-effects, particularly uterine hyperstimulation. Several cases of uterine rupture have also been reported.[12] Following completion of a small dose-finding pilot study,[13] we developed a novel approach to the use of misoprostol for labour induction, administering 20 - 40 g of misoprostol solution orally every 2 hours, titrated against the uterine response. This new method was compared with conventional labour induction using vaginal dinoprostone in a multicentre trial in Johannesburg and Liverpool.[14] Because it may be difficult to eliminate uterine hyperstimulation completely with this method, we also investigated the effectiveness of a mechanical method (Foley's catheter) followed when necessary by oral misoprostol titration. A randomised study design was used, nested within the larger trial. Those women with intact membranes enrolled at the South African sites were randomly allocated to Foley catheter/oral misoprostol, oral misoprostol alone or vaginal dinoprostone. This report presents the results of that three-way comparison.

Methods

Eligible women with clinical indications for labour induction at or after 34 weeks' gestation and intact membranes were recruited into the study at Coronation Women's and Children's Hospital and at Chris Hani Baragwanath Hospital in Johannesburg. The study protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Signed and informed consent was obtained from each participant and baseline demographic details were completed. Exclusion criteria were: uterine scar, uncontrolled medical complications such as diabetes mellitus and severe hypertension, non-vertex presentations, multiple pregnancy, fetal distress and antepartum haemorrhage. Baseline cardiotocography was performed to rule out fetal compromise, followed by a cervical score assessment. A modified Bishop's score of < 7 was classified as unfavourable.[15] Membrane status was noted. The next in a series of opaque, sealed and numbered treatment envelopes in computer-generated random sequence was taken out of one of four dispensers for: intact membranes/unfavourable cervix, intact membranes/favourable cervix, ruptured membranes/unfavourable cervix and ruptured membranes/favourable cervix. The first two categories reflected the three-way randomisation reported here. Management followed the protocol indicated in the envelope unless clinical imperatives dictated otherwise. Analysis was by 'intention to treat', The protocols were as follows:

Foley catheter/titrated oral misoprostol solution

The cervix was visualised using a sterile bivalved vaginal speculum. An 18 - 20-gauge Foley catheter with a 30 ml bulb was passed through the cervix, and the bulb inflated with 50 ml sterile saline or water. The speculum was removed and the catheter taped to the woman's slightly flexed leg with light traction. If the bulb did not fall out within 24 hours it was deflated and removed. If, after removal or spontaneous expulsion of the catheter, labour contractions had not commenced, titrated oral misoprostol solution was started. A 200 µg misoprostol tablet was dissolved in 200 ml tap water in a medicine bottle and shaken before use. Twenty ml (= 20 µg), increasing to 40 ml after three doses, was taken orally every 2 hours until active labour (three contractions per 10 minutes, with each contraction lasting 30 seconds or more). If after established labour the contractions became inadequate, augmentation with misoprostol solution (5 µg hourly, increasing if necessary to 10 and 20 µg) was used. If the clinician judged that misoprostol augmentation was ineffective, standard oxytocin augmentation was used.

Titrated oral misoprostol

Titrated oral misoprostol solution was used as described above.

Conventional method (dinoprostone)

Dinoprostone gel 2 mg was inserted into the posterior vaginal fornix, and repeated after 6 hours if the patient was not in established labour. If not in active labour after 12 hours, oxytocin infusion was commenced, starting at 2 mIU (6 drops) per minute and increased every 20 minutes until adequate contractions occurred. Labour was augmented with oxytocin if contractions became inadequate.

If hypersystole (more than five contractions per 10 minutes for at least 20 minutes) or hypertonus (a contraction lasting at least 2 minutes) occurred, the woman was placed in the left lateral position with continuous fetal heart rate monitoring. If there were accompanying fetal heart rate abnormalities, oxygen was administered using a face mask, and 5 - 10 µg hexoprenaline was administered intravenously over 5 - 10 minutes.

Routine artificial rupture of membranes to augment labour was discouraged in all three groups because of a high prevalence of hepatitis, HIV and other perinatal infections. Artificial rupture of membranes, therefore, was generally used only if additional augmentation was considered necessary or delivery was imminent. Continuous fetal heart rate monitoring was not possible in all low-risk women, because of the shortage of cardiotocograph machines and personnel. In most cases intermittent electronic monitoring was used. The cardiotocograph tracings were analysed by one of the authors (BBM), blinded to the treatment, for uterine contraction and fetal heart rate abnormalities, and entered separately onto the database.

The sample size calculation was based on the incidence of the primary outcome, failed vaginal delivery within 24 hours, of 58% in randomised trials of vaginal misoprostol versus dinoprostone.[11] To detect a reduction to 40% with 95% certainty and 90% power required 171 women in each group.

Data were entered into the Epi-info 6 statistical package and analysed independently by one of the authors (JL). Differences between groups were expressed as relative risks with 95% confidence intervals (CIs). Prespecified subgroups for analysis were by cervical status.

Results

The baseline data are shown in Table I. There were slightly more primiparous women in the Foley catheter/misoprostol group (44%), compared with the misoprostol group (37%) and the dinoprostone group (36%). In all other respects the groups were well matched.

In the Foley catheter group, misoprostol was used in addition to the Foley catheter in all but 1 woman.

The primary outcome, failure to deliver vaginally within 24 hours, was similar for the three groups (79/174 v. 70/176 v.

Table I. Baseline data expressed as mean values (standard deviation), or proportions (%)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)	
Maternal age (yrs) (mean (SD))	26.7	(6.0)	27.8	(6.5)	27.3	(6.2)
Gestation (wks) (mean (SD))	40	(1.9)	39.9	(2.1)	39.7	(2.4)
Primiparous	76/173	(44%)	65	(37%)	63/174	(36%)
Cervical score < 7	129	(74%)	132	(75%)	128	(73%)
Primary indication for IOL:						
Impaired growth	21	(12%)	17	(10%)	22	(13%)
Post-term	97	(56%)	90	(51%)	96	(55%)
Hypertension	37	(21%)	48	(27%)	38	(22%)
Poor obstetric history	10	(6%)	12	(7%)	10	(6%)
Maternal request	1	(0.69%)	2	(1%)	1	(0.6%)
Maternal health concerns	2	(1%)	2	(1%)	1	(0.6%)
Fetal concerns	6	(3%)	4	(2%)	7	(4%)
Other	0	-	1	(0.6%)	1	(0.6%)

IOL = induction of labour.

Table II. Primary* and secondary outcomes expressed as proportions (%). Differences are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
	N	%	*N*	%	*N*	%	Combined v. misoprostol	Combined v. dinoprostone
No vaginal delivery < 24 hours*	79	45	70	40	70	40	1.14 (0.89 - 1.46)	1.14 (0.89 - 1.46)
Amniotomy	50/168	30	47/174	27	44/165	26	1.10 (0.79 - 1.57)	1.12 (0.79 - 1.57)
Oxytocin augmentation	23	13	11	6	43	24	2.11 (1.06 - 4.21)	0.54 (0.34 - 0.86)
Misoprostol augmentation	20	11	21	12	0	–	0.96 (0.54 - 1.71)	–
Any augmentation	38	22	29	16	43	24	1.33 (0.86 - 2.05)	0.89 (0.61 - 1.31)
Vaginal bleeding	9/168	5	4	2	6/174	3	2.36 (0.74 - 7.51)	1.55 (0.57 - 4.27)
Uterine tachysystole	6/163	4	13/161	8	12/164	7	0.46 (0.18) - 1.17)	0.50 (0.19 - 1.31)
Uterine hypersystole	1/163	1	1/161	1	1/164	1	0.99 (0.06 - 15.66)	1.01 (0.06 - 15.95)
Hyperstimulation syndrome	6/163	4	7/161	4	8/164	5	0.85 (0.29 - 2.46)	0.75 (0.27 - 2.13)
Fetal heart rate (FHR changes)	8/163	5	7/161	4	8/164	5	1.13 (0.42 - 3.04)	1.01 (0.39 - 2.62)
Tocolysis	9/164	5.5	7/170	4	7/170	4	1.18 (0.44 - 3.19)	1.38 (0.49 - 3.90)
Analgesia (epidural or opioid)	64/172	37	46/175	26	56/175	32	1.42 (1.03 - 1.94)	1.16 (0.87 - 1.55)
Meconium	17/168	10	13/174	7.5	15/171	8.8	1.35 (0.68 - 2.70)	1.15 (0.6 - 2.23)
Caesarean section*	36	21	24	14	43	24	1.52 (0.95 - 2.43)	0.85 (0.57 - 1.25)
Instrumental delivery (vacuum or outlet forceps)	4	2	5	3	4	2	0.81 (0.22 - 2.96)	1.01 (0.26 - 3.98)
Indication for caesarean or instrument delivery								
Delay	25/173	14	14/175	8	23/172	13	1.81 (0.97 - 3.36)	1.08 (0.64 - 1.83)
Fetal distress	13/173	8	13/175	7	17/172	10	1.01 (0.48 - 2.12)	0.76 (0.38 - 1.52)
Other	2/173	1	2/175	1	3/172	2	1.01 (0.14 - 7.10)	0.66 (0.11 - 3.92)

70/176 respectively) (Table II). Overall augmentation, caesarean section and instrumental delivery were somewhat more frequent in the Foley/misoprostol group than in the misoprostol alone group, but the differences were not statistically significant.

Analgesia was used more frequently in the Foley catheter/misoprostol than the misoprostol group (64/172 v. 46/175, relative risk 1.42, 95% CI 1.03 - 1.94).

Side-effects were very similar between the three groups, except that diarrhoea was more common in the

Table III. Maternal side-effects and complications, expressed as proportions (%). Differences are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
	N	%	*N*	%	*N*	%	Combined v misoprostol	Combined v. dinoprostone
Blood loss > 500 ml	42/174	24	43/175	25	43/174	25	0.98 (0.58 - 1.64)	0.98 (0.67 - 1.41)
Pyrexia > 38°C	3/172	2	1/174	1	2/175	1	3.03 (0.32 - 28.99)	1.53 (0.26 - 9.02)
Retained placenta	1/172	1	1/174	1	0	-	1.01 (0.06 - 16.04)	
Other	6/172	3	5/174	3	7/175	4	1.20 (0.37 - 3.86)	0.86 (0.30 - 2.51)
Nausea	31/149	21	23/151	15	19/151	12	1.37 (0.84 - 2.23)	1.65 (0.98 - 2.79)
Diarrhoea	20/148	14	6/150	4	6/165	4	3.38 (1.4 - 8.17)	3.72 (1.53 - 9.0)
Shivering	57/149	38	69/150	46	66/164	41	0.83 (0.64 - 1.09)	0.95 (0.72 - 1.25)
Any side-effect	86/149	58	82/151	54	82/165	50	1.06 (0.87 - 1.30)	1.02 (0.84 - 1.24)

Table IV. Neonatal outcomes and complications expressed as proportions (%) or mean values (standard deviation, SD). Differences between proportions are expressed as relative risk with 95% confidence intervals (CI)

	Foley/misoprostol (*N* = 174)		Titrated oral misoprostol (*N* = 176)		Dinoprostone (*N* = 176)		Relative risk (95% CI)	
							Combined v. misoprostol	Combined v. dinoprostone
Birth weight (g) (mean (SD))	3 066	(518)	3 129	(505)	3 103	(542)		
Missing data	1	-	0	-	1	-		
5 min Apgar < 7	6/171	(3%)	6/173	(3%)	9/175	(5%)	1.01 (0.33 - 3.08)	0.67 (0.24 - 1.84)
Neonatal ICU admission	2/171	(1%)	3/174	(2%)	3/175	(2%)	0.68 (0.11 - 4.01)	0.68 (0.12 - 4.03)
Perinatal death	1/171	(0.6%)	0	-	1/174	(0.6%)	-	1.02 (0.06 - 16.1)
Neonatal seizures	1/170	(0.6%)	1/173	(0.6%)	0	-	1.02 (0.06 - 16.0)	-
Neonatal sepsis	1/171	(0.6%	0	-	0	-	-	-
Other	6/171	(4%)	6/173	(3%)	4/174	(2%)	1.01 (0.33 - 3.08)	1.53 (0.44 - 5.31)

Foley/misoprostol group (Table III). There were no cases of uterine rupture or sepsis.

Neonatal complications were also very similar (Table IV), although the event rates were too low for meaningful statistical comparison.

Discussion

In terms of inducing labour contractions, Foley catheter insertion was less successful than has been reported previously. In all but 1 case, misoprostol was required to induce labour contractions. Neither did preliminary 'ripening' of the cervix with the Foley catheter produce measurable benefits in terms of shorter labour or fewer complications, although the numbers studied were too small to exclude the possibility of a reduction in infrequent events such as uterine tachysystole.

This study provides no evidence of an advantage to using the Foley catheter method followed when necessary by misoprostol induction in women with intact membranes, particularly as this adds expense to the procedure, and is uncomfortable for the woman. However, the fact that failure to deliver within 24 hours of randomisation was similar across groups does suggest that the Foley catheter had an influence on the process of labour induction. Misoprostol was used only after expulsion or removal (at 24 hours) of the Foley catheter, and greatly increased randomisation to delivery times would be expected had the Foley catheter been ineffective.

The cardiotocographic data may underestimate complications as electronic monitoring was intermittent in some cases. As this limitation applied to all three groups, the data are presented for comparative purposes.

Further research should focus on the use of the Foley catheter technique in situations in which prostaglandin preparations are not available, or contraindicated. A particular problem is induction of labour in women with previous caesarean section,[16,17] in whom use of prostaglandin preparations, particularly misoprostol, may be hazardous. Although this problem was not addressed directly in this

study, the results suggest that Foley catheter placement alone is unlikely to be adequate. Additional procedures such as extra-amniotic saline infusion, or artificial rupture of membranes after expulsion of the catheter, are worth investigating in these circumstances.

Conclusions

Use of extra-amniotic Foley catheter placement followed when necessary by titrated oral misoprostol solution for induction of labour showed no measurable benefits over the use of oral misoprostol alone, or vaginal dinoprostone.

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