Low-Dose Oral Misoprostol for Induction of Labor

A Systematic Review

Timothy W. Kundodyiwa, MB ChB, MRCOG, Zarko Alfirevic, MD, FRCOG, and Andrew D. Weeks, MD, MRCOG

OBJECTIVE: To estimate the efficacy and safety of low-dose oral misoprostol compared with dinoprostone (PGE_2), vaginal misoprostol, and oxytocin for labor induction in women with a viable fetus.

DATA SOURCES: We conducted electronic database searches of PubMed, MEDLINE, EMBASE, and the Cochrane Library for articles published before January 2008 using the keywords *misoprostol*, *labor*, *induction*, *randomized controlled trials*, *dinoprostone*, *oxytocin*, *pregnancy*, and *maternal and fetal side effects*.

METHODS OF STUDY SELECTION: We included randomized controlled trials comparing 20–25 micrograms oral misoprostol with vaginal misoprostol, dinoprostone or oxytocin given to women at 32–42 weeks of gestation for labor induction. From 401 citations identified, results from nine studies were finally analyzed using the Review Manager software. Relative risk (RR) and 95% confidence intervals (CIs) were calculated using fixed and random-effects models.

TABULATION, INTEGRATION, AND RESULTS: Nine articles with 2,937 women met the inclusion criteria. The five trials comparing oral misoprostol and dinoprostone showed significantly fewer women requiring cesarean delivery in the misoprostol group (20% compared with 26%; RR 0.82, 95% CI 0.71–0.96). There were no statistically significant differences in risks of uterine hyperstimulation or need for oxytocin augmentation. Two trials compared oral with vaginal low-dose misoprostol. Women using oral misoprostol were significantly less likely to experience uterine hyperstimulation with fetal heart rate changes (2% compared with 13%; RR 0.19, 95% CI 0.08–0.46), but there were no significant differences in other outcomes.

CONCLUSION: Low-dose oral misoprostol solution (20 micrograms) administered every 2 hours seems at least as effective as both vaginal dinoprostone and vaginal misoprostol, with lower rates of cesarean delivery and uterine hyperstimulation, respectively.

(Obstet Gynecol 2009;113:374–83)

Induction of labor is a common obstetric procedure, accounting for around 20% of all deliveries in the United Kingdom, Canada, and in the United States.[1–3] Adverse effects include failed induction, excessive uterine contraction resulting in fetal heart rate (FHR) abnormalities, and cesarean delivery.[4,5] The choice of induction method depends on both its efficacy and safety profile. Prostaglandin (PG) E_2 (dinoprostone) and oxytocin have been the most commonly used preparations.[6] Factors limiting their use in low-resource settings have been their cost and instability at high ambient temperatures.

Misoprostol is a synthetic PGE_1 analogue marketed for use in the prevention and treatment of peptic ulcer disease caused by nonsteroidal antiinflammatory drugs.[7] It has been shown to be an effective agent for cervical ripening and labor induction,[8–10] but there have been concerns about hyperstimulation associated with its use. Researchers are therefore investigating the lowest effective dose of misoprostol that achieves a balance between high doses, which result in rapid delivery but frequent hyperstimulation, and lower doses which take longer to achieve delivery but have a better safety profile.[11]

Most authorities currently suggest the use of a vaginal dose of 25 micrograms for labor induction, and a number of generic preparations of this strength are becoming available.[6,12–14] However, there is increasing interest in the use of oral preparations for

From the Liverpool Women's NHS Foundation Trust, Liverpool, United Kingdom; and Division of Perinatal and Reproductive Medicine, University of Liverpool, Liverpool Women's Hospital, Liverpool, United Kingdom.

Corresponding author: Dr. A. Weeks, School of Reproductive and Developmental Medicine, Liverpool Women's Hospital, University of Liverpool, Crown Street, Liverpool, L8 7SS, UK; e-mail: aweeks@liverpool.ac.uk.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/09

labor induction due to its simplicity and popularity with women. Also, there has been a long-standing problem with the use of low-dose misoprostol due to the lack of appropriately sized tablets.[15] This means that cutting of the tablets is necessary, which in turn produces inaccurate doses.[16] To solve this problem, Hofmeyr et al[17] pioneered the use of misoprostol solution in 2001. If a 200-microgram tablet is dissolved in 200 mL tap water, then accurate volumes of misoprostol can be measured out for administration (for example 20 micrograms is in 20 mL of water). Furthermore, misoprostol retains its activity in solution for at least 24 hours (Matonhodze BB. Induction of labour in an under-resourced environment [PhD thesis]: University of Witwatersrand; 2005). Although this method produces a more accurate dose of misoprostol than cut tablets; this method is only suitable for oral dosing. For oral administration, a frequent dosing schedule is required due to its relatively brief duration of action (2 hours compared with 4 hours for vaginal administration).[18]

The current Cochrane review of oral misoprostol for labor induction contains 53 studies with more than 11,000 participants.[8] That review, however, is very broad, covering all doses of oral misoprostol, including many that are no longer in use. Furthermore, the subgrouping facility within that review is used for dosage variation, and this prevents a critical examination of the specifics of dosage regimens (eg, solution compared with tablets and dosage frequency). This review has therefore been produced using the Cochrane methodology to examine in more detail those studies included in the above Cochrane review that used oral misoprostol 20–25 micrograms, the dose associated with the greatest potential in clinical practice. A search for articles published after publication of the above Cochrane review in April 2006 resulted in four additional studies meeting our inclusion criteria. The review assesses the efficacy and safety of low-dose oral misoprostol with vaginal misoprostol, dinoprostone, and oxytocin for labor induction in women with a viable fetus.

SOURCES

We searched the Cochrane Pregnancy and Child birth Group Trials Register, PubMed, MEDLINE, and EMBASE for studies published in any language until January 2008 using the keywords *misoprostol*, *labor*, *induction*, *randomized controlled trials*, *dinoprostone*, *oxytocin*, *pregnancy*, and *maternal and fetal adverse effects*. References cited in these articles were manually searched to obtain additional articles.

STUDY SELECTION

Studies eligible for inclusion were randomized controlled trials of women between 32 and 42 weeks of gestation irrespective of membrane or cervical status who were undergoing labor induction with 25 micrograms or less of oral misoprostol. Comparisons of oral misoprostol with the three conventional induction agents, vaginal dinoprostone, vaginal misoprostol, and oxytocin, were included.

The primary outcome measures were those not achieving vaginal delivery within 24 hours (ie, cesarean or vaginal delivery after 24 hours), cesarean delivery rate, and uterine hyperstimulation with fetal heart rate changes. Secondary outcomes were the need for oxytocin augmentation, epidural use, meconium-stained amniotic fluid, Apgar score less than 7 at 5 minutes, admission to neonatal intensive care unit, neonatal morbidity (seizures, birth asphyxia, or neonatal encephalopathy), perinatal mortality, maternal adverse effects (such as nausea, vomiting or diarrhea), serious maternal morbidity (eg, intensive care unit admission, septicemia, or uterine rupture), postpartum hemorrhage, maternal death, and maternal satisfaction. The data were analyzed on an intention-to-treat basis. A prespecified subgroup analysis assessed the different frequency dosing schedules (1 hourly, 2 hourly, 3 hourly, and 4 hourly).

TABULATION AND INTEGRATION

We assessed the validity of the trials included in this review using the criteria established in the Jadad scale (Table 1).[19] Points are given for randomization and adequacy of the method, double-blinding, and adequacy of allocation concealment and description of lost-to-follow-up and exclusions. A maximum score of 5 is possible, and studies with a total of 2 points or less were considered as poor quality. We planned to use the quality of randomization for sensitivity analysis in this review. However, given that all studies were classified as high quality on the Jadad scale,[19] sensitivity analysis based on quality was not performed. Eligibility was assessed by two reviewers (A.D.W. and T.W.K.) independently, following selected criteria. Differences about the inclusion of studies were resolved by discussion with third reviewer (Z.A.) to reach a consensus.

The data were extracted and statistical analysis carried out using the Review Manager (RevMan) 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Data on dichotomous outcomes were combined using the Mantel-Haenszel method, and measures of effect are pre-

Table 1. Characteristics of Included Studies

Study	Country	Methods	Participants	Intervention	Quality According to Jadad Scale[19]
A. Vaginal dinoprostone					
Hofmeyr et al[17] 2001	South Africa/ United Kingdom	Sequentially numbered, opaque envelopes	695 women 34 wk or more gestation undergoing labor induction regardless of membrane or cervical status	Titrated oral misoprostol doses 20 micrograms increased to 40 micrograms every 2 h vs vaginal dinoprostone 2 mg gel followed by another dose 6 h later	3
Matonhodze et al[26] 2003	South Africa	Randomized sealed opaque envelopes	526 women more than 34 wk gestation undergoing labor induction with intact membranes	Titrated oral misoprostol 20 micrograms 2 hourly ×3, then 40 micrograms every 2 h OR dinoprostone gel 2 mg every 6 h ×2, then IV oxytocin OR Foley catheter with 50 mL bulb for 24 h, then titrated oral misoprostol if not in labor	3
Moodley et al[22] 2003	South Africa	Sequentially numbered, opaque envelopes	400 women undergoing induction with viable term pregnancies and Bishop Score less than 6 irrespective of membrane status	Oral misoprostol 20 micrograms every 2 h×4 doses OR vaginal dinoprostone 1 mg every 6 h×3	3
Dallenbach et al[23] 2003	Switzerland	Computer-generated numbers with opaque sealed envelopes in randomly sized blocks	202 women with live single fetus at more than 37 wk gestation and Bishop score 6 or less	Titrated oral misoprostol 20 micrograms every 2 h×2, then 40 micrograms every 2 h×10 until 3 contractions every 10 min, maximal dose 475 micrograms OR dinoprostone gel 2 mg 6 h apart	3
Dodd et al[24] 2006	Australia	Double blind with identical treatment packs sequentially numbered in variable blocks, stratified for parity and center	741 women at 36 6/7 or more wk gestation with intact membranes and a Bishop score of less than 7	Oral misoprostol 20-microgram solution every 2 h 6 OR vaginal dinoprostone 1 mg (primiparous) or 2 mg (parous) every 6 h×2, each with placebo	5

(continued)

Table 1. Characteristics of Included Studies (*continued*)

Study	Country	Methods	Participants	Intervention	Quality According to Jadad Scale[19]
B. Vaginal misoprostol					
How et al[21] 2001	United States	Sequentially numbered, opaque envelopes; double blinded	330 women with singleton pregnancies at more than 32 wk and with Bishop score of less than 6	3 groups: vaginal misoprostol 25 micrograms and 25 micrograms oral OR vaginal misoprostol 25 micrograms and placebo orally OR oral misoprostol 25 micrograms with placebo vaginal, all doses given every 4 h up to 12 doses	5
Cheng et al[27] 2008	China	Computer-generated random numbers with sealed opaque envelopes	220 women between 34 and 42 wk gestation with indications for induction of labor and Bishop score 6 or less	Titrated oral misoprostol 20 micrograms/h×4, then 40 micrograms/h×4, then 60 micrograms×4 until 3 contractions in 10 minutes OR vaginal misoprostol 25 micrograms every 4 h×3 until Bishop score 7 or more or contractions 3 in 10 min	3
C. Oxytocin					
Dodd et al[25] 2006a	Australia	Double blind placebo controlled–but no further details	30 women at term having had artificial or spontaneous rupture of membranes	Oral misoprostol solution given hourly (initially 5 micrograms, then 10 micrograms and 20 micrograms–maximum not specified) or oxytocin infusion; both groups also got placebos	5
D. Oral misoprostol 2 vs 6 doses					
De et al[20] 2006	India	Computer-generated table	200 women 34 wk or more with a Bishop score 5 or less undergoing labor induction	Oral misoprostol 25 micrograms every 3 h×maximum 6 doses until contracting 3 in 10 and oxytocin if contractions inadequate OR oral misoprostol 25 micrograms every 3 h×2 followed by routine oxytocin	3

IV, intravenously.

sented as relative risk (RR) with 95% confidence intervals (CIs). Each forest plot shows a point estimate for each study (with 95% CIs), with a diamond at the bottom representing the pooled point estimate with 95% CIs for each outcome of interest. The presence of significant heterogeneity was explored by I squared (I^2) statistics.[28,29] In cases where I^2 exceeded 50%, we pooled results using random effects models and explored the results for sources of variation.

RESULTS

The search strategy resulted in 401 potentially relevant citations. A Quality of Reporting of Meta-analyses (QUOROM) flow chart[30] (Fig. 1) shows an overview of the study selection process. The remainder were reviewed, and after excluding studies not meeting the criteria, nine studies using 25 micrograms or less of misoprostol were included in the review, with a total of 2,937 women.[17,20–27] One study was only available as a Congress meeting abstract with numbers given as percentages and recruited the smallest sample size of 30.[25]

The most common comparison was between oral misoprostol and vaginal dinoprostone.[17,22,23,24,26] The method of randomization was adequate in all five studies (they all used sequentially numbered, identical sealed envelopes). Blinding of allocation to avoid bias in clinical decision-making assessment was done in only one of the five studies.[24] All studies were considered to be of good quality according to the Jadad scale

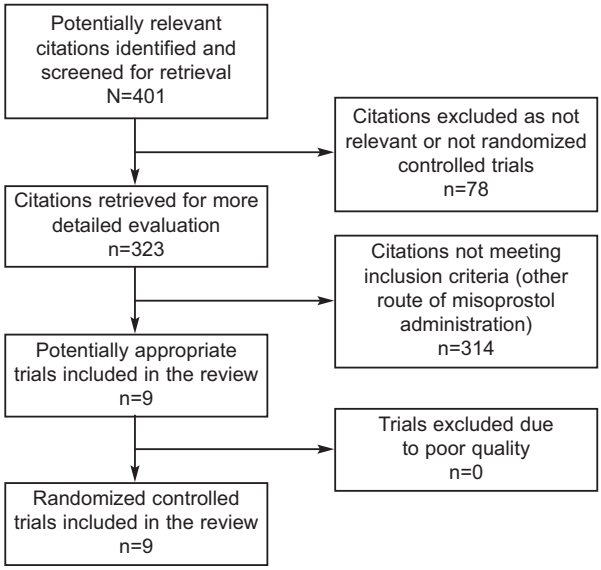

Fig. 1. Quality of Reporting of Meta-analyses flowchart.
Kundodyiwa. Low-Dose Oral Misoprostol for Labor Induction. Obstet Gynecol 2009.

(Table 1),[19] with four studies awarded 3 points[17,22,23,26] and one receiving 5 points.[24]

Thee studies compared oral and vaginal misoprostol[21,22,27] and were of good quality. Two had 3 points,[22,27] and the third had 5 points.[21] The study by Moodley 2003[22] had thee arms, but the third arm (where women were given a mixture of oral and vaginal misoprostol) was excluded from this part of the analysis. The two included studies used computer-generated randomization sequence,[21,27] and only one reported blinding of outcome assessment.[21]

One double-blinded placebo-controlled study comparing oral misoprostol with oxytocin[25] was only available as an abstract. The remaining included study compared a policy of two or six doses of oral misoprostol followed by oxytocin, and the method of concealment used was unclear.[20] Both studies were of good quality according to the Jadad scale[19] (Table 1), being awarded thee[20] and five[25] points.

Table 1 shows the characteristics of the included studies. Titrated oral misoprostol 20 micrograms solution administered every 2 hours until adequate contractions are achieved was the commonest dose regimen used in five of the studies (Table 2). If contractions subsequently became inadequate in labor, thee of the studies using this regimen would augment with further misoprostol, using 5 micrograms titrated every hour to 10 and 20 micrograms maximum.[17,23,26] Other regimens included 25 micrograms every 4 hours, 20 micrograms of solution every hour titrated up to 40 micrograms and 60 micrograms, and 25 micrograms every 3 hours (Table 2). One study comparing oral misoprostol with vaginal dinoprostone had a third group in which women were treated with an initial dose of vaginal misoprostol 25 micrograms followed by subsequent oral doses of 20 micrograms every 2 hours.[22] This arm of the study was excluded from further analysis because it did not fit the selection criteria of the meta-analysis.

The five studies comparing low-dose oral misoprostol with vaginal dinoprostone had 2,281 participants (Table 3). Oral misoprostol was associated with significantly fewer women requiring cesarean delivery (20% compared with 26%; RR 0.82, 95% CI 0.71–0.96) (Fig. 2). There were no statistically significant differences between the groups in any of the other primary or secondary outcomes. There was significant heterogeneity in the analysis for the outcome of need for oxytocin augmentation (I^2=91%, P=.11), hyperstimulation without FHR changes (I^2=83%, P<.001), and all maternal adverse effects (I^2=51%, P=.67). All studies used a similar dose regimen for oral misoprostol (Table 2), but the lack of

Table 2. Detailed Drug Regimens in the Included Studies

	Oral Misoprostol		Comparison Regimen	
Study	Dose	Frequency	Dose	Frequency
Oral misoprostol vs dinoprostone				
Hofmeyr et al[17] 2001	20-microgram solution	Every 2 h	2 mg	Every 6 h × 2 doses
Matonhodze et al[26] 2003	20-microgram solution	Every 2 h	2 mg	Every 6 h × 2 doses
Moodley et al[22] 2003	20-microgram solution	Every 2 h	2 mg	Every 6 h × 2 doses
Dallenbach et al[23] 2003	20-microgram solution	Every 2 h	2 mg	Every 6 h × 2 doses
Dodd et al[24] 2006	20-microgram solution	Every 2 h	2 mg	Every 6 h × 2 doses
Oral vs vaginal misoprostol				
How et al[21] 2001	25-microgram tablet	Every 4 h	25 micrograms	Every 4 h
Cheng et al[27] 2008	20-microgram solution	Every h	25 micrograms	Every 4 h
Oral misoprostol vs oxytocin				
Dodd et al[25] 2006	5-microgram solution	Titrated hourly to 10 and 20 micrograms	Oxytocin	Infusion
De et al[20] 2006	25-microgram tablet	Every 3 h × 6 doses	25-microgram oral misoprostol × 2, then oxytocin	Misoprostol every 3 h × 2, then titrated oxytocin infusion

blinding to the allocated treatment in all except one study[24] made the decision to commence oxytocin and assessment of adverse effects more susceptible to potential bias. Although we planned to explore the possibility of publication bias using Funnel plots, these plots are less useful when there are fewer than 10 included studies and, therefore, formal analysis was not carried out.[31]

Only two trials provided data for women with ruptured membranes.[17,23] There was no statistically significance difference between oral misoprostol and dinoprostone in the need for cesarean delivery (RR 1.17, 95% CI 0.42–3.27) or no vaginal delivery within 24 hours (RR 1.30, 95% CI 0.78–2.18).

Low-dose oral misoprostol was compared with vaginal misoprostol in only two trials[21,27] containing

Table 3. Outcomes of Oral Misoprostol Compared With Dinoprostone

Outcome	Studies	Oral Misoprostol	Dinoprostone	RR	95% CI	Heterogeneity* (%)
Vaginal delivery not achieved within 24 h	5	461/1,090	475/1,191	1.07	0.97–1.18	0
Hyperstimulation+FHR changes	5	64/1,147	47/1,077	1.10	0.76–1.60	29
Hyperstimulation without FHR changes	4	48/896	52/1,003	0.90	0.31–2.62	83
Cesarean delivery	5	220/1,089	310/1,192	0.82	0.71–0.96	6
Oxytocin augmentation	5	338/1,089	449/1,191	0.69	0.45–1.08	91
Epidural use	4	539/985	545/997	1.00	0.93–1.08	34
Meconium-stained liquor	4	103/744	99/845	1.14	0.88–1.48	0
Apgar score less than 7 at 5 min	4	20/983	31/997	0.65	0.37–1.13	0
NICU admission	5	36/1,087	58/1,190	0.81	0.54–1.21	0
Perinatal mortality	4	1/986	2/996	0.60	0.08–4.50	0
Maternal adverse effects (all)	4	307/961	309/987	1.04	0.86–1.26	51
Uterine rupture	4	0/1,089	0/1,191	–	–	–
Postpartum hemorrhage	4	185/985	203/997	0.92	0.77–1.10	0
Maternal death	2	0/711	0/725	–	–	–

RR, relative risk; CI, confidence interval; FHR, fetal heart rate; NICU, neonatal intensive care unit.
* Measured by the Interaction test (I^2). A heterogeneity score of more than 50% suggests a high variability between study outcomes, making the meta-analysis result unreliable.

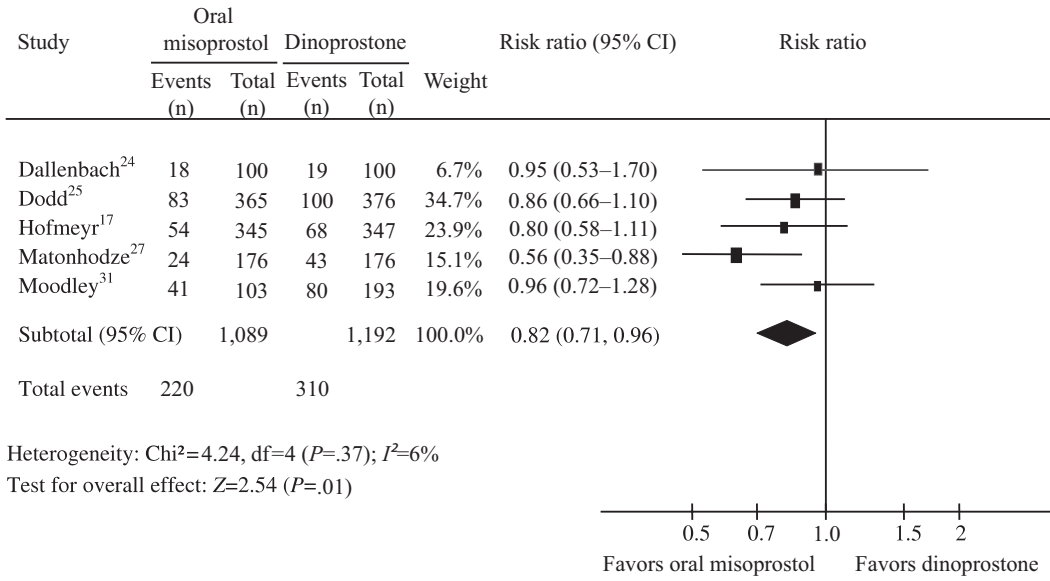

Fig. 2. Forest plot of studies comparing oral misoprostol and dinoprostone, examining the effect on cesarean section. CI, confidence interval.

Kundodyiwa. Low-Dose Oral Misoprostol for Labor Induction. Obstet Gynecol 2009.

426 participants (Table 4). In this comparison, the only statistically significant difference was that women given oral misoprostol were significantly less likely to experience uterine hyperstimulation with fetal heart rate changes (2% compared with 13%; RR 0.19, 95% CI 0.08–0.46) than those in the vaginal misoprostol group (Fig. 3). There were no other statistically significant differences between the groups in either the other primary or secondary outcomes.

In all outcomes other than hyperstimulation there was significant heterogeneity, and we explored the reasons by looking at the effect of the studies' quality and dose regimen. Although the vaginal misoprostol regimen was the same for both studies (25 micrograms tablets every 4 hours), different dose regimens for the oral misoprostol were used (Table 2). Use of frequent titrated oral doses of misoprostol showed more successful vaginal delivery within 24 hours compared with vaginal misoprostol, but the major drawback in this study[27] was the lack of blinding, resulting in a bias among staff toward titrated oral misoprostol. The high cumulative oral dose given in this study could explain its better efficacy.

Only one trial of 30 women compared low-dose oral misoprostol with intravenous oxytocin.[25] This is available in abstract form only, but showed no statistically significant difference in the reported outcomes of vaginal delivery not achieved within 24 hours (RR 0.71, 95% CI 0.30–1.68) or cesarean delivery rate (RR 0.57, 95% CI 0.22–1.50).

One study compared two different regimens of oral misoprostol tablets in women with a low Bishop score.[20]

Table 4. Outcomes of Oral Compared With Vaginal Misoprostol

Outcome	Studies	Oral Misoprostol	Vaginal Misoprostol	RR	95% CI	Heterogeneity* (%)
Vaginal delivery not achieved within 24 h	2	75/210	85/216	0.51	0.03–9.62	98
Hyperstimulation with FHR changes	2	5/211	29/216	0.19	0.08–0.46	48
Hyperstimulation without FHR changes	2	18/211	51/216	0.36	0.22–0.59	0
Cesarean delivery	2	39/210	37/216	0.69	0.09–5.54	92
Oxytocin augmentation	2	92/211	98/216	0.64	0.06–7.03	98
Meconium-stained liquor	1	16/109	11/110	1.47	0.71–3.02	–
Apgar score less than 7 at 5 minutes	2	4/210	11/216	0.35	0.04–3.54	57
NICU admission	2	7/210	11/216	0.44	0.02–8.50	74

RR, relative risk; CI, confidence interval; FHR, fetal heart rate; NICU, neonatal intensive care unit.

* Measured by the Interaction test (I^2). A heterogeneity score of more than 50% suggests a high variability between study outcomes, making the meta-analysis result unreliable.

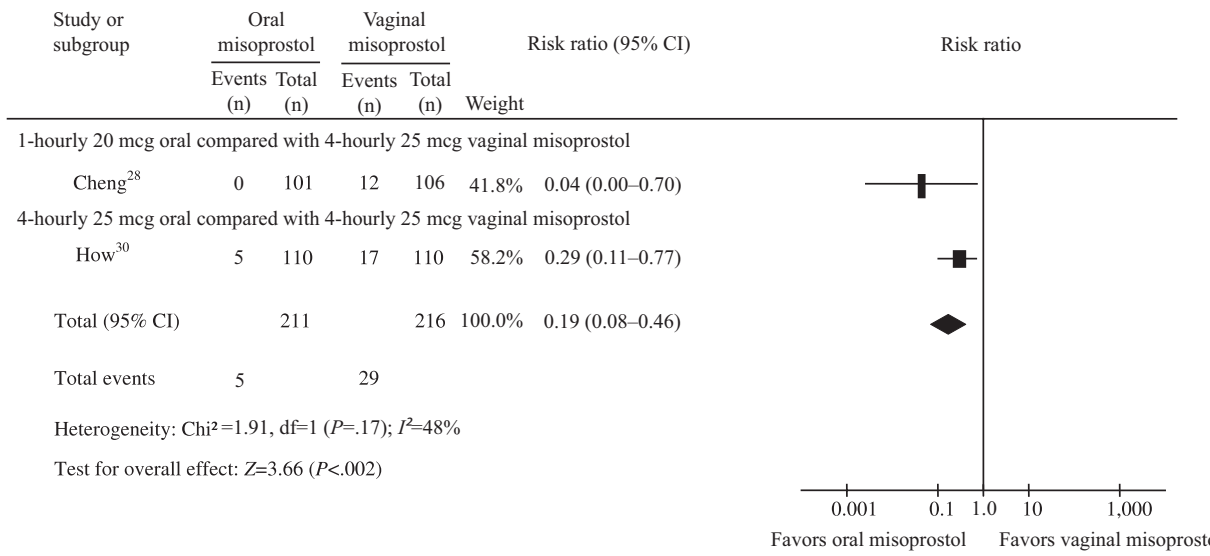

Fig. 3. Forest plot of studies comparing oral and vaginal misoprostol, examining the effect on uterine hyperstimulation with fetal heart rate changes. CI, confidence interval.

Kundodyiwa. Low-Dose Oral Misoprostol for Labor Induction. Obstet Gynecol 2009.

One group received 25 micrograms of oral misoprostol (every 3 hours, maximum 6 times) until they were getting thee contractions every 10 minutes (irrespective of cervical dilatation). Oxytocin was only commenced if contractions later became inadequate or if the woman had received all six doses (this occurred in 77%). The other group received two doses of oral misoprostol 25 micrograms every 3 hours followed by routine oxytocin. There were no significant differences in any of the outcome measures of interest.

Oral misoprostol was continued into labor in four of the studies in this review,[17,23,26,27] with oxytocin only being started if augmentation with oral misoprostol was ineffective. In these four studies, only 17% of women induced with oral misoprostol needed intravenous oxytocin augmentation compared with 38% with the comparator. Women's satisfaction with oral misoprostol was assessed formally in only one study,[24] and more than one half of the women (58.8%) expressed a preference for oral induction agent.

DISCUSSION

In this systematic review we have found that the use of low-dose oral misoprostol administered every 2 hours was as effective as vaginal dinoprostone (PGE_2) in achieving vaginal delivery within 24 hours, and was associated with a significantly lower cesarean delivery rate. Furthermore, this dose of oral misoprostol had lower rates of uterine hyperstimulation with FHR changes than vaginal misoprostol, but was equally effective in other measures of success.

Our results are consistent with other systematic reviews comparing higher doses of oral misoprostol with dinoprostone.[8,32,33] The review by Crane et al[33] only included two oral misoprostol studies which used doses of 100 micrograms and 200 micrograms, respectively. The remainder were excluded because they restricted their reviews to trials of women at term with unfavorable cervices and intact membranes.

High doses of oral or vaginal misoprostol are clearly effective at achieving vaginal delivery, but previous reviews have raised concerns relating to uterine hyperstimulation and adverse fetal outcomes.[8] Lowering the dose of oral misoprostol does not seem to have resulted in lower rates of vaginal delivery. Indeed, the converse seems to have been the case, with significantly lower cesarean delivery rates seen in comparison with the standard dinoprostone regimen. This was not due to a decrease in the incidence of FHR abnormalities, because the overall rate of uterine hyperstimulation with FHR changes was comparable to those in women induced with dinoprostone (4–12%). Studies show that efficacy is not simply a function of contraction frequency and strength, because high-frequency contractions may reduce efficiency though the production of myometrial acidaemia.[34] This provides a mechanism by which lower doses of prostaglandin can be more efficient than high doses. Although the small number of trials included in the analysis did not provide a large enough sample size to address adequately the issue of maternal and

perinatal adverse outcomes, the findings in this review are reassuring.

In this review, we have found that oral misoprostol seems to be as effective as that given vaginally, but with a significantly reduced incidence of uterine hyperstimulation with FHR changes. Earlier systematic reviews containing studies using higher doses of vaginal misoprostol reported slower labors associated with the oral route but lower rates of hyperstimulation.[8] This was probably due to the disparity in dosage between oral and vaginal misoprostol. The greater bioavailability of vaginal misoprostol explains why the same dose of misoprostol seems to produce stronger contractions than the oral route, which has a shorter duration of action. The wide range of dosages in both oral and vaginal misoprostol arms of the studies in previous reviews makes analysis difficult. This review has had similar problems but does suggest that frequent low dosages of oral misoprostol solution are more efficient than the previously used tablets administered every 4 hours.

Apart from the clinical advantages of oral misoprostol over vaginal misoprostol seen in this meta-analysis, oral misoprostol would also seem to offer other advantages in terms of dosage accuracy and patient satisfaction. Dosage accuracy has long been recognized to be a problem with vaginal misoprostol. The general lack of a commercially produced 25-microgram tablet means that a brittle 100-microgram or 200-microgram tablet has to be divided into quarters, resulting in pieces of variable sizes. Williams et al[16] found that only 65% of "free-hand" razor-cut fragments weighed within 10% of that expected. This reduced to only 24% when a pill cutter was used ($P<.001$). This problem is compounded by inconsistent vaginal absorption of misoprostol shown by its greater coefficient of variation of the area under the curve.[35] These problems lead to the frequent inadvertent administration of insufficient or excessive doses, which may result in either induction failure or hyperstimulation, respectively. At present, generic preparations of 25-microgram misoprostol are only available as vaginal pessaries, and until a suitable oral preparation is manufactured, use of titrated oral misoprostol solution allows a more accurate dose administration. Misoprostol in solution has been shown in muscle contraction experiments to retain its efficacy for at least 24 hours, and the solution remains stable at room temperature and so can be made up in batches (Matonhodze BB. Induction of labour in an under-resourced environment [PhD thesis]: University of Witwatersrand; 2005).

Very few studies have evaluated patient satisfaction during labor induction, but those that have report a clear preference toward the oral route.[24,36] It is not surprising that women should find the oral route more acceptable because of the ease of administration and avoidance of vaginal examination. This may be particularly relevant in cultures where women are very reluctant to have intimate examinations. Furthermore, oral doses can continue to be used despite vaginal bleeding or ruptured membranes. All these factors make the oral route an attractive option.

Only 17% of women given oral misoprostol required oxytocin augmentation, whereas the rest used oral misoprostol into labor up to delivery. This provides an additional benefit for settings with no electronic infusion monitors, where the use of oral misoprostol provides a way of giving accurate doses of an oxytocic in labor. This may improve the safety for mother and fetus as well as providing cost savings.

Low-dose oral misoprostol seems to be at least as effective as both vaginal dinoprostone and vaginal misoprostol. More than 2,000 women have now been recruited to trials comparing oral misoprostol and the criterion standard dinoprostone, and they have consistently shown it to be of equal efficacy but with 20% lower cesarean delivery rates. Oral misoprostol solution would therefore seem to be the optimal choice for induction of labor. Practitioners may, however, be concerned about the logistics of making up their own solution of an off-label medication. From the evidence thus far, a commercial oral preparation would not only reduce adverse effects, but would improve the dosage accuracy and is likely to be popular among women.

REFERENCES

1. Macfarlane A, Mugford M. Care of mothers and babies. In: Birth counts: statistics of pregnancy and childbirth. London (UK): The Stationery Office; 2000. p. 191–242.
2. Rayburn WF, Zhang J. Rising rates of labor induction: present concerns and future strategies. Obstet Gynecol 2002;100: 164–7.
3. Zhang J, Yancey MK, Henderson CE. U.S. national trends in labor induction, 1989–1998. J Reprod Med 2002;47:120–4.
4. Royal College of Obstetricians and Gynaecologists. Induction of labour. Evidence-based Clinical Guideline Number 9. London (UK): RCOG Press; 2001.
5. Justus Hofmeyr G. Induction of labor with an unfavorable cervix. Best Pract Res Clin Obstet Gynaecol 2003;17:777–94.
6. American College of Obstetricians and Gynecologists. Induction of Labor. ACOG Practice Bulletin 10. Washington (DC): ACOG; 1999.
7. Watkinson G, Hopkins A, Akbar FA. The therapeutic efficacy of misoprostol in peptic ulcer disease. Postgrad Med J. 1988;64 suppl:60–77.
8. Alfirevic Z, Weeks A. Oral misoprostol for induction of labor. The Cochane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD001338. DOI: 10.1002/14651858.CD001388.

9. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and labour induction in late pregnancy. The Cochane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.
10. Goldberg AB, Wing DA. Induction of labor: the misoprostol controversy. J Midwifery Womens Health 2003;48:244–8.
11. Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction [published erratum appears in Am J Obstet Gynecol 1997;176:1423]. Am J Obstet Gynecol 1996;175:158–64.
12. Wing DA. A benefit-risk assessment of misoprostol for cervical ripening and labour induction. Drug Saf 2002;25:665–76.
13. WHO Expert Committee. The selection and use of essential medicines. World Health Organ Tech Rep Ser 2007;1–162, back cover.
14. Weeks A, Alfirevic Z, Faundes A, Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labor with a live fetus. Int J Gynaecol Obstet 2007;99 suppl:S194–7.
15. Weeks AD, Fiala C, Safar P. Misoprostol and the debate over off-label drug use. BJOG 2005;112:269–72.
16. Williams MC, Tsibris JC, Davis G, Baiano J, O'brien WF. Dose variation that is associated with approximated one-quarter tablet doses of misoprostol. Am J Obstet Gynecol 2002;187:615–9.
17. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG 2001;108:952–9.
18. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet 2007;99 suppl:S160–7.
19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12.
20. De A, Bagga R, Gopalan S. The routine use of oxytocin after oral misoprostol for labour induction in women with an unfavorable cervix is not of benefit. Aust N Z J Obstet Gynaecol 2006;46:323–9.
21. How HY, Leaseburge L, Khoury JC, Siddiqi TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of labor. Am J Obstet Gynecol 2001;185:911–5.
22. Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term–a comparative study. S Afr Med J 2003;93:371–4.
23. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. Am J Obstet Gynecol 2003;188:162–7.
24. Dodd JM, Crowther CA, Robinson JS. Oral misoprostol for induction of labour at term: randomised controlled trial. BMJ 2006;332:509–13.
25. Dodd JM, Crowther CA, Robinson JS. Oral misoprostol versus intravenous oxytocin for induction of labor following artificial or spontaneous rupture of membranes: a randomized controlled trial. In: Perinatal Society of Australia and New Zealand 10th Annual Congress; 2006 April 3–6; Perth (Australia): Perinatal Society of Australia and New Zealand 10th Annual Congress; 2006. p. 258.
26. Matonhodze BB, Hofmeyr GJ, Levin J. Labour induction at term–a randomised trial comparing Foley catheter plus titrated oral misoprostol solution, titrated oral misoprostol solution alone, and dinoprostone. S Afr Med J 2003;93:375–9.
27. Cheng SY, Ming H, Lee JC. Titrated oral compared with vaginal misoprostol for labor induction: a randomized controlled trial. Obstet Gynecol 2008;111:119–25.
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
30. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896–900.
31. Higgins JPT, Green S, editors. Cochane handbook for systematic reviews of interventions version 5.0.0 [Updated September 2008]. Available at: www.cochane-handbook.org Retrieved July 1, 2008.
32. Sanchez-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labor induction: a systematic review of the literature. Clin Obstet Gynecol 2000;43:475–88.
33. Crane JM, Butler B, Young DC, Hannah ME. Misoprostol compared with prostaglandin E2 for labour induction in women at term with intact membranes and unfavourable cervix: a systematic review. BJOG 2006;113:1366–76.
34. Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis [published erratum appears in Obstet Gynecol 2004;103:1344]. Obstet Gynecol 2004;103:718–23.
35. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92.
36. Arvidsson C, Hellborg M, Gemzell-Danielsson K. Preference and acceptability of oral versus vaginal administration of misoprostol in medical abortion with mifepristone. Eur J Obstet Gynecol Reprod Biol 2005;123:87–91.