Misoprostol compared with prostaglandin E2 for labour induction in women at term with intact membranes and unfavourable cervix: a systematic review

Crane J M, Butler B, Young D C, Hannah M E

CRD summary
The authors concluded that in women at term with intact membranes and unfavourable cervix, misoprostol did not reduce the Caesarean section rate, and increased the risk of tachysystole and hyperstimulation, compared with prostaglandin E2. Overall, the review was well conducted and the authors' conclusions appear appropriate. However, the absence of evidence of consistent results across studies weakens the robustness of the conclusions.

Authors' objectives
To compare misoprostol with prostaglandin E2 (PgE2) for the induction of labour in women at term with intact membranes and unfavourable cervix.

Searching
MEDLINE (via PubMed), EMBASE and the Cochrane Library were searched from 1987 to December 2005 without any language restrictions; the search terms were reported. Reference lists were screened. Abstracts and unpublished studies were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with losses to follow-up of 20% or less in either group were eligible for inclusion.

Specific interventions included in the review
Studies that compared oral, vaginal, sublingual or buccal misoprostol with vaginal or intracervical (IC) PgE2 for labour induction were eligible for inclusion. The included studies compared oral or vaginal misoprostol (starting doses ranged from 25 to 200 microg) with various forms of vaginal PgE2 (including controlled release, gel, pessary and tablet) or IC PgE2 gel. The studies evaluated different regimens; misoprostol was given from once up to six times and PgE2 was given from one to four times (details of the regimens were reported). In one study, misoprostol followed by high-dose oxytocin after the last dose was compared with PgE2 plus concurrent low-dose oxytocin.

Participants included in the review
Studies of women at term (at least 37 weeks' gestation) with intact membranes and unfavourable cervix were eligible for inclusion. Most of the primary studies included a large proportion of nulliparous women; some studies only included nulliparous women. The mean maternal age ranged from approximately 22 to 29 years. The definition of an unfavourable cervix varied from a Bishop score of four or less to a score of less than eight.

Outcomes assessed in the review
The studies had to report intention-to-treat data for any of the outcomes of interest. The primary review outcome was Caesarean delivery. The secondary outcomes were tachysystole (defined as 'more than five contractions in 10 minutes in each of two consecutive 10-minute periods') and hyperstimulation (defined as 'excessive uterine activity with a nonreassuring foetal heart rate pattern'). Other outcomes included Caesarean delivery or prolonged time to vaginal delivery (24 hours or more), operative delivery, use of oxytocin or epidural, meconium staining, Apgar score less than 7 at 5 minutes, admission to neonatal intensive care unit (NICU), neonatal morbidity, perinatal mortality, maternal morbidity, adverse effects, postpartum haemorrhage, maternal mortality and women not satisfied. The review only included data on neonatal and maternal adverse effects if methods of ascertainment were reported. Data on neonatal and maternal morbidity were only included if individual morbidities were specifically reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion and any disagreements were resolved through recourse to a
Assessment of study quality
The studies were assessed for method of randomisation, allocation concealment and blinding. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted data on the primary and secondary outcomes.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model (DerSimonian and Laird). The main comparison was between any misoprostol (oral or vaginal) and any PgE2 (IC or vaginal).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. A subgroup analysis was used to examine the effects of interventions on nulliparous women only. The review also compared vaginal misoprostol with any PgE2; oral misoprostol versus any PgE2; misoprostol with a starting dose of 25 microg versus any PgE2; misoprostol with a starting dose greater than 25 microg versus any PgE2; any misoprostol versus vaginal PgE2; and any misoprostol versus IC PgE2.

Results of the review
Fourteen RCTs (n=2,172) were included.

All of the studies reported randomisation. Twelve studies reported the methods used for randomisation, and the majority of these used opaque, sealed envelopes in an attempt to conceal treatment allocation. Two studies did not report either the randomisation method or if allocation was concealed. One study reported blinding of the patient and the delivering physician.

Any misoprostol versus any PgE2.

There was no significant difference between any misoprostol and any PgE2 in the rate of Caesarean section delivery (RR 0.99, 95% CI: 0.83, 1.17).

Any misoprostol was associated with a significantly higher risk of tachysystole (RR 1.86, 95% CI: 1.01, 3.43) and hyperstimulation (RR 3.71, 95% CI: 2.00, 6.88) compared with PgE2.

Among all vaginal deliveries, misoprostol was associated with a higher rate of vaginal delivery within 24 hours than PgE2 (RR 1.14, 95% CI: 1.00, 1.31).

Among all deliveries, misoprostol was associated with a significantly lower rate of oxytocin use (RR 0.71, 95% CI: 0.60, 0.85) compared with PgE2, but a non significant increase in meconium staining (RR 1.22, 95% CI: 0.96, 1.55).

The results were similar when the analysis was restricted to misoprostol starting doses of more than 25 microg. Studies evaluating starting doses of misoprostol of 25 microg showed no significant differences in outcomes between misoprostol and PgE2, but the authors reported that the analyses might have been underpowered (n=304).

For nulliparous women (3 RCTs, n=348), there was no significant difference between any misoprostol and any PgE2 in the risk of Caesarean section or hyperstimulation, but misoprostol was associated with an increased risk of tachysystole (RR 2.68, 95% CI: 1.14, 6.29).
Oral and vaginal misoprostol versus any PgE2.

There were no significant differences in the rate of Caesarean section or tachysystole between oral or vaginal misoprostol and any PgE2.

Vaginal misoprostol was associated with a significantly increased risk of hyperstimulation compared with any PgE2 (RR 3.80, 95% CI: 1.91, 7.58).

Any misoprostol versus vaginal and IC PgE2.

There were no significant differences in the rate of Caesarean section between any misoprostol and either vaginal or IC PgE2.

Any misoprostol was associated with a significantly increased risk of tachysystole compared with IC PgE2 (RR 8.32, 95% CI: 2.27, 30.55), but not compared with vaginal PgE2.

Hyperstimulation was significantly more common with any misoprostol compared with both vaginal PgE2 (RR 2.99, 95% CI: 1.25, 7.16) and IC PgE2 (RR 4.61, 95% CI: 1.91, 11.09).

The results for the other outcomes were also reported.

**Authors’ conclusions**
In women at term with intact membranes and unfavourable cervix, misoprostol increased the rate of vaginal delivery within 24 hours compared with PgE2, but did not reduce the Caesarean section rate either in all women or only nulliparous women, and increased the rates of tachysystole and hyperstimulation.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise the potential for language bias. The restriction to published studies raises the possibility of publication bias and missing studies. Methods were used to minimise reviewer errors and bias in the study selection and data extraction processes, but it was unclear whether similar steps were taken in the assessment of validity. Only RCTs with a low drop-out rate were included and validity was assessed.

Although the authors stated that they assessed statistical heterogeneity, the results were not reported. In the absence of results from individual studies, it was not possible to determine whether the results were consistent amongst the studies. Overall, the review was well conducted and the authors’ conclusions appear appropriate, but the absence of evidence for consistency across studies weakens the robustness of the conclusions.

**Implications of the review for practice and research**
Practice: The authors stated that in resource-poor countries, the advantages and disadvantages of inducing labour with misoprostol compared with other induction methods, or awaiting the onset of spontaneous labour, need to be taken into account. They also stated that in view of the increased risk of hyperstimulation found with misoprostol, misoprostol should only be used when the possible benefits outweigh the potential harms.

Research: The authors stated that there may be a need for more studies to evaluate a low starting dose of 25 microg misoprostol for the induction of labour and to evaluate the effect of misoprostol on admissions to NICU. In future studies, assessors of foetal heart tracings should be blinded to treatment allocation and, ideally, a placebo control should be used.

**Bibliographic details**
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