Labor induction with 25 microg versus 50 microg intravaginal misoprostol: a systematic review

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Authors' objectives
To compare the safety and efficacy of 25 microg versus 50 microg of intravaginal misoprostol for cervical ripening and labour induction.

Searching
MEDLINE, PubMed, Current Contents, the Cochrane CENTRAL Register, and EMBASE were searched with no language restrictions from January 1987 to March 2001. The MeSH terms used included 'labor induction', 'cervical ripening', 'misoprostol' and 'randomised controlled trial'. In addition, references from published articles and chapters from textbooks were used, and abstracts from relevant scientific meetings during the 14-year period were handsearched. Authors were contacted for advice on missed trials and queries with respect to additional information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies that assessed the use of repeated doses of 25 or 50 microg of intravaginal misoprostol were eligible for inclusion in the review. Five included studies compared 25 and 50 microg dose regimens, whilst two further studies compared intravaginal misoprostol with intracervical dinoprostone gel. Of these two studies, one used a 50 microg dose regimen and the other a 25 microg dose regimen.

Participants included in the review
Women with indications for cervical ripening and labour induction. The majority of patients were those requiring labour induction due to pregnancy induced hypertension, post-dates and intrauterine growth restriction.

Outcomes assessed in the review
The authors did not state any specific inclusion criteria relating to the outcomes. The outcomes assessed included the incidence of tachysystole and hyperstimulation, the need for oxytocin augmentation, start of induction-to-vaginal delivery interval, Caesarean rate, Caesarean deliveries resulting from foetal heart rate (FHR) abnormalities, vaginal delivery within 24 hours of drug application, abnormal Apgar scores, and the neonatal intensive care unit admission rate. Tachysystole was defined as at least six uterine contractions in 10 minutes for two consecutive 10-minute periods. Hyperstimulation was defined as the presence of tachysystole or a prolonged uterine contraction lasting at least 2 minutes associated with FHR abnormalities (foetal tachycardia, late decelerations, or loss of beat-to-beat variability). Not all of the included trials evaluated each of the outcome variables; therefore, specific outcome analyses were based on a variable number of studies.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The validity of the primary studies was graded from 0 to 9 on the basis of the following: randomisation; masking; explicit inclusion and exclusion criteria; baseline similarity between the groups for important prognostic features; equal detection of outcomes between the groups; and appropriate statistical analysis. Two reviewers independently assessed the validity of the included studies. This was undertaken blind to the original study authors and institutions. However, the authors do not state how any disagreements between the reviewers were resolved.
Data extraction
The data were extracted independently by two reviewers. The authors do not state how any disagreements were resolved.

Data on the authors, study period, location, number of study participants, dosing interval and the outcomes of interest were extracted and presented in tabular format.

Methods of synthesis
How were the studies combined?
The odds ratio (OR) for each outcome and 95% confidence intervals (CIs) were calculated for the 25-microg misoprostol group and compared with the 50-microg group. Estimates of OR for dichotomous outcomes were calculated using the random-effects (DerSimonian and Laird) and fixed-effect (Mantel-Haenszel) models (see Other Publications of Related Interest no.1). When statistical analyses revealed significant heterogeneity (p<0.10), the random-effects results were reported.

The continuous outcomes were pooled using a variance-weighted average of within-study differences in means.

The outcomes reflecting maternal and perinatal safety and efficacy from the two trials comparing different doses of intravaginal misoprostol with intracervical dinoprostone gel were compared using chi-squared analyses. The ORs and 95% CIs were also calculated. For all analyses, a P-value of less than 0.05 was considered statistically significant. Publication bias was examined using the test of Egger et al. (see Other Publications of Related Interest no.2), and by visual inspection of funnel plots of the ORs versus study sample size.

How were differences between studies investigated?
The homogeneity of the treatment effect across studies was formally tested using the method of Breslow and Day (see Other Publications of Related Interest no.3). In addition, there was a qualitative visual inspection of L’Abbe’s plots (see Other Publications of Related Interest no.4). A sensitivity analysis was performed by sequentially omitting each study and analysing the overall impact on the pooled results.

The proportion of patients who experienced hyperstimulation syndrome was lower for the group receiving 25 microg misoprostol (4.4%) than for those receiving 50 microg (9.3%). When the sensitivity analysis was performed for this variable, it was observed that the outcome of the meta-analysis was dominated by one trial. The omission of other studies made little or no difference. After temporarily omitting the trial, no significant difference in the overall rate of hyperstimulation remained between the two groups.

Results of the review
Five RCTs compared 25 microg versus 50 microg of misoprostol; these included a total of 933 women (461 and 472 allocated to receive 25 and 50 microg, respectively). Two RCTs compared misoprostol with intracervical dinoprostone; of the 206 women enrolled in the misoprostol groups, 138 were randomised to receive 25 microg and 68 to receive 50 microg intravaginally.

The incidence of tachysystole was significantly lower among patients who received 25 microg misoprostol. The rates of tachysystole ranged from 1.6 to 15.6% for patients in the 25-microg group, compared with 3.2 to 32.8% in the 50-microg group. The overall rate of uterine tachysystole was 8.9% for patients who received 25 microg and 20.8% for those who received 50 microg (OR 0.36, 95% CI: 0.24, 0.53).

The time from start of labour induction to vaginal delivery for study participants receiving 50 microg was nearly 5 hours shorter than for those receiving the 25 microg dose. While no significant differences were noted for Caesarean (OR 1.01, 95% CI: 0.73, 1.41) and operative vaginal delivery rates (OR 1.11, 95% CI: 0.70, 1.75), the use of the 50-microg dose was associated with a greater proportion of deliveries within 24 hours (OR 0.68, 95% CI: 0.47, 0.98), a greater proportion of patients delivering after a single dose (random-effects OR 0.57, 95% CI: 0.32, 0.99), and less frequent need for oxytocin augmentation (OR 1.93, 95% CI: 1.44, 2.59).
No dose-related differences were noted with regard to the proportion of patients requiring Caesarean deliveries for FHR abnormalities, abnormal Apgar scores, and admissions to the neonatal intensive care unit.

There was no evidence of publication bias, either from the visual inspection of funnel plots or from the use of Egger et al's test, for the main outcomes analysed.

The indirect comparison of the two studies that assessed either 25 or 50 microg misoprostol compared with intracervical dinoprostone gel supported the findings of the meta-analysis.

**Authors' conclusions**
The published data indicate that a 50-microg dose of intravaginal misoprostol for cervical ripening and labour induction is more efficacious than a 25-microg dose, but it is unclear whether it is as safe.

**CRD commentary**
The authors addressed a clear review question in terms of the interventions, participants and study designs that were to be included in the review. The literature search was adequate, but since it was limited to published papers and abstracts only, publication bias could have been introduced into the review process. However, the authors further examined this issue and their funnel plot analysis revealed no evidence of publication bias in the reviewed studies. The authors did not state how the papers were selected for inclusion in the review, and once again bias may have been introduced in this process. A systematic validity assessment was undertaken by more than one reviewer, allowing the reader to assess the quality of the included studies. The statistical analysis undertaken was appropriate, and heterogeneity between the studies was formally explored. A sensitivity analysis was also undertaken to assess the impact of excluding different studies. Overall, this is a reasonably well-conducted review in which the authors' results and conclusions are consistent with the evidence base reviewed.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

**Bibliographic details**

**PubMedID**
11777525

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Administration, Intravaginal; Adult; Cervical Ripening /drug effects; Confidence Intervals; Dose-Response Relationship, Drug; Female; Humans; Labor, Induced /methods; Misoprostol /administration & dosage; Odds Ratio; Oxytocics /administration & dosage; Pregnancy; Randomized Controlled Trials as Topic; Treatment Outcome
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.