Misoprostol use during the third stage of labor
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CRD summary
This review assessed the effectiveness of misoprostol (in terms of reducing blood loss) compared with placebo and other uterotonic drugs. The authors concluded that misoprostol was less effective than oxytocin and other uterotonics. The evidence presented appears to support the conclusions, although the reliability of the conclusions may be weakened by the presence of statistical heterogeneity for most outcomes.

Authors' objectives
To assess the effectiveness of misoprostol in the third stage of labour, and to compare its effects with placebo and other uterotonics.

Searching
MEDLINE, PubMed, the Cochrane CENTRAL Register and EMBASE were searched from January 1996 to March 2002; the MeSH terms were stated. Published and unpublished studies were eligible and no language restrictions were applied. The reference lists in identified studies, textbooks and abstracts of scientific meetings were also checked. Authors were contacted for additional studies and missing data.

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

Specific interventions included in the review
Studies that compared misoprostol with placebo or other uterotonics were eligible for inclusion. The included studies compared misoprostol (400 microg rectally, or 400 to 600 microg orally) with placebo, intravenous or intramuscular oxytocin (with or without ergometrine), intravenous methylergometrine, or intramuscular Syntometrine.

Participants included in the review
Studies of women in the third stage of labour were eligible for inclusion.

Outcomes assessed in the review
Studies that assessed effectiveness (in terms of reducing blood loss) and side-effects were eligible for inclusion. The review assessed the following outcomes: postpartum haemorrhage (PPH; 500 mL or greater and 1,000 mL or greater); third stage of labour longer than 30 minutes; the use of additional uterotonics to control haemorrhage; shivering; pyrexia, defined as a temperature of at least 37 degrees C; and the haemoglobin change pre- and post-delivery.

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

Assessment of study quality
Validity was assessed and scored from 0 to 9 using the following criteria: randomisation; blinding; explicit inclusion and exclusion criteria; treatment groups similar at baseline with respect to prognostic factors; same methods used to ascertain outcomes for each treatment group; and appropriate statistical analysis. Two reviewers, blinded to the study author and institution assessed validity, but it was not reported whether these assessments were conducted independently.

Data extraction
One reviewer extracted the data. The authors of the primary studies were then contacted for clarification of the data. For each study, the proportions of women with PPH greater than 1,000 mL and other outcomes were calculated for each treatment group. The odds ratio (OR) and 95% confidence interval (CI) were also calculated.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. For binary outcomes, pooled ORs and 95% CIs were calculated using a random-effects model (DerSimonian and Laird) when significant heterogeneity was detected and a fixed-effect model (Mantel-Haenszel) otherwise. For continuous data, pooled weighted mean differences and 95% CIs were calculated using a fixed-effect model. The studies were weighted using the variance. The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared statistic. The influence of each study was assessed by repeating the meta-analysis (for both binary and continuous data) after omitting each study in turn.

Results of the review
Seventeen RCTs (28,170 women) were included.

The validity scores ranged from 5 to 9.

Misoprostol versus any comparator: misoprostol significantly increased PPH; the OR was 1.29, 95% CI: 1.13, 1.48.

Misoprostol versus placebo: there was no significant difference between oral misoprostol and placebo for PPH (500 mL or more, or 1,000 mL or more) or third stage of labour longer than 30 minutes. The OR for PPH of 1,000 mL or more was 0.93 (3 RCTs; 95% CI: 0.64, 1.33). No significant heterogeneity was detected (P=0.25). The OR for PPH of 500 mL or more was 0.94 (2 RCTs; 95% CI: 0.53, 1.65). The OR for third stage of labour longer than 30 minutes was 1.77 (2 RCTs; 95% CI: 0.73, 4.26).

Oral misoprostol significantly reduced the need for additional uterotonics compared with placebo, but it increased shivering and pyrexia. The OR was 0.64 (3 RCTs; 95% CI: 0.46, 0.90) for additional uterotonics, 5.85 (4 RCTs; 95% CI: 4.13, 8.29) for shivering and 9.61 (2 RCTs; 95% CI: 5.70, 16.2) for pyrexia.

Misoprostol versus oxytocin: oral misoprostol significantly increased PPH (greater than 1,000 mL) compared with oxytocin; the OR was 1.42 (5 RCTs; 95% CI: 1.22, 1.66). No significant heterogeneity was detected (P=0.91).

Misoprostol versus Syntometrine: oral misoprostol increased the need for additional uterotonics and shivering compared with Syntometrine. The OR was 1.80 (3 RCTs, random-effects model; 95% CI: 1.39, 2.34) for additional uterotonics and 3.93 (2 RCTs, random-effects model; 95% CI: 3.31, 4.66) for shivering. There was no significant difference between oral misoprostol and Syntometrine for PPH greater than 1,000 mL; the OR was 1.27 (3 RCTs, fixed-effect model; 95% CI: 0.71, 2.26).

One study with 18,530 women provided substantial weight to the results.

Additional results were also reported in the review.

Cost information
The unit cost of misoprostol was $2.00 for 400 microg, compared with $1.20 for 10 IU oxytocin. However, the use of oxytocin involved additional expenses (e.g. refrigeration).

Authors' conclusions
Misoprostol was less effective than oxytocin and other uterotonics for all assessed outcomes of the third stage of labour.
However, misoprostol reduced the need for other uterotonic drugs compared with placebo.

**CRD commentary**

The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched, attempts were made to locate unpublished studies, and no language restrictions were applied. The methods used to select the studies were not described; hence, any efforts made to reduce errors and bias cannot be judged. Only one reviewer extracted the data and it was unclear whether one or more reviewers assessed validity. The lack of duplication may lead to errors and bias. Validity was assessed and scored using specified criteria, but only the total validity scores were reported; there was no mention of specific methodological flaws.

Some relevant information was tabulated. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. The influence of the largest study was discussed. The evidence presented appears to support the authors' conclusions, although it is worth noting that statistical heterogeneity was found for most outcomes.

**Implications of the review for practice and research**

Practice: The authors stated that misoprostol in the third stage of labour may be of benefit in less-developed countries where the administration of parenteral uterotonic drugs may be problematic.

Research: The authors stated that RCTs are required to assess objective outcome measures, and also to clarify the benefits and harms of misoprostol in the third stage of labour. In addition, research is needed to determine the absorption time and peak values for vaginal misoprostol given immediately after delivery.

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