Misoprostol for termination of pregnancy with intrauterine fetal demise in the second and third trimester of pregnancy: a systematic review

Gomez Ponce de Leon R, Wing DA

CRD summary
The review concluded that among women with foetal death in the second or third trimester, vaginal misoprostol was less effective than oral misoprostol at achieving uterine evacuation within 24 hours, but not within 48 hours. In view of the limitations of the evidence base, small sample sizes and heterogeneity between studies, the authors' conclusions may not be reliable.

Authors' objectives
To assess the risks and benefits of misoprostol alone and to assess the optimum regimen for its use to terminate pregnancy among women with foetal death in the second or third trimester.

Searching
Cochrane Pregnancy and Childbirth Group's Specialised Register, MEDLINE, POPLINE, LILACS and CINAHL were searched from 1987 to 2008 for published studies. Search terms were reported. References of articles retrieved were checked.

Study selection
Randomised controlled trials (RCTs) of vaginal, oral or sublingual misoprostol for uterine evacuation of women with a foetal death at more than 14 weeks gestation were eligible for inclusion. Controls could receive placebo, no treatment or any other medical, surgical or mechanical method of uterine evacuation. Studies that evaluated misoprostol given in combination with other interventions or that compared different routes or regimens were eligible. Outcomes of interest in the review included uterine evacuation at 24 and 48 hours (main outcome), surgical evacuation, analgesia, blood transfusion, antibiotics and side effects and complications (listed in the review). Studies were excluded if foetal death was the indication for termination of pregnancy in less than 40% of the study population.

Participants in most of the included studies were women in the second trimester of pregnancy. There was wide variation (between and within studies) in size, frequency and number of doses of misoprostol administered. More than half of the studies compared different misoprostol regimens with each other or compared misoprostol with and without adjunctive treatment (such as oxytocin, laminaria tents, acetic acid). Some studies compared misoprostol with other prostaglandins by various routes (such as vaginal, extra-amniotic) or with oxytocin. No studies were placebo-controlled. The review reported time to induction and other outcomes.

Three reviewers independently selected the studies. Disagreements were resolved by discussion.

Assessment of study quality
The following components of study quality were assessed: randomisation, allocation concealment, blinding, follow-up rate and use of intention-to-treat (ITT) analysis.

Three reviewers independently conducted the assessment. Disagreements were resolved by discussion.

Data extraction
Relative risks (RRs) with 95% confidence intervals (CIs) were extracted or calculated for dichotomous outcomes. Mean differences were extracted or calculated with 95% CI for continuous outcomes. Authors of some primary studies provided data specific to women with foetal deaths, in which case only this subset was analysed.

Three authors independently extracted data. Disagreements were resolved by discussion.
Methods of synthesis
Studies were grouped by comparison and outcome. Data were combined to calculate pooled relative risks, weighted mean differences (WMDs) and 95% CIs. Heterogeneity was assessed using the $\chi^2$ test. Potential causes of heterogeneity were explored. Fixed-effect models were used unless there was substantial clinical or statistical heterogeneity, in which case random-effects models were used.

Results of the review
Fourteen RCTs were included in the review (n=866). Eleven studies used satisfactory methods of randomisation. Six studies used satisfactory methods of allocation concealment. Only one study was double-blinded. None of the studies described losses to follow-up or use of ITT analysis. The authors noted that most studies were of acceptable quality overall.

Four RCTs compared vaginal versus oral misoprostol (n=229). Misoprostol by either route achieved uterine evacuation within 48 hours in all participants. The rate of uterine evacuation within 24 hours was significantly lower with vaginal administration (RR 0.79, 95% CI 0.68 to 0.93; two RCTs, n=123). The direction of effect was inconsistent for mean time to uterine evacuation, with the vaginal and oral routes each significantly favoured by two RCTs. Vaginal administration was associated with a significantly lower rate of diarrhoea (RR 0.26, 95% CI 0.07 to 0.93; three RCTs). There was no statistically significant difference between the groups for any other side effects.

When vaginal misoprostol was evaluated with and without oxytocin, rates of evacuation at 48 hours did not differ significantly between the groups. Misoprostol alone was significantly less effective in achieving uterine evacuation at 24 hours (RR 0.45, 95% CI 0.24 to 0.85; one RCT, n=49) and mean time to induction was significantly longer (WMD 11.5 hours, 95% CI 3.9 to 19.2).

Other results were reported in the review.

Authors' conclusions
Among women with foetal death in the second or third trimester, vaginal misoprostol was less effective than oral misoprostol at achieving uterine evacuation within 24 hours, but not within 48 hours.

CRD commentary
The objectives and inclusion criteria of the review were clear in most respects, although it was unclear whether all outcomes and all exclusion criteria were determined in advance. Relevant sources were searched for studies, but exclusion of published studies and of a study in Polish meant that the review was potentially subject to publication and language biases. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, assess validity and extract data. Statistical pooling of data in at least one of the analyses was questionable in view of highly significant statistical heterogeneity that resulted from opposite directions of effect reported by the primary studies. As the authors noted, the included studies were small and highly heterogeneous with respect to the dose and regimen of misoprostol and the comparator used. Study findings were inconsistent (such as for evacuation within 24 hours and time to evacuation). There was inconsistency between the text and abstract. In view of the limitations of the evidence base, small sample sizes and heterogeneity between studies, the authors' conclusions may not be reliable.

One of the authors was a principal investigator for a manufacturer of vaginal misoprostol.

Implications of the review for practice and research
**Practice:** The authors stated that misoprostol was an effective alternative to other methods of terminating pregnancy in the second trimester for women with foetal death. There was less evidence about its use for third-trimester terminations. Vaginal misoprostol with oxytocin appeared to be the most effective regimen.

**Research:** The authors stated that more research was needed on the effectiveness, safety, side effects and optimal regimen of misoprostol for termination of pregnancy following foetal death in the second and third trimesters. The optimal intravenous oxytocin regimen needed to be determined.
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