Comparison of sublingual versus vaginal misoprostol for the induction of labour: a systematic review
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CRD summary
This review concluded that sublingual administration of misoprostol was comparable to vaginal administration for inducing labour in full-term pregnancies, but it appeared to offer no additional clinical advantages. The authors’ conclusions reflected the evidence shown, but the possibility of bias and errors during the review process means that caution is required when interpreting these findings.

Authors’ objectives
To compare the efficacy and safety of sublingual versus vaginal administration of misoprostol in the third trimester of pregnancy for the induction of labour in women with a live, full-term foetus and an unripe cervix.

Searching
PubMed, LILACS, SciELO, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1996 to February 2008 for studies in English, Portuguese and Spanish. Search terms were reported. Reference lists of retrieved papers were reviewed.

Study selection
Randomised controlled trials (RCTs) that compared sublingual and vaginal routes of administration of misoprostol in pregnant women were eligible for inclusion. Eligible women had to have an indication for induction of labour, an unfavourable cervix and a live foetus more than 37 weeks of gestational age. Abstracts and unpublished data were excluded.

The primary outcomes were: vaginal delivery not achieved within 24 hours; uterine hyperstimulation syndrome classified as tachysystole (more than five contractions in 10 minutes for at least 20 minutes) or hypersystole/hypertonia (a uterine contraction lasting two minutes or more) with abnormal foetal heartbeat; caesarean section; severe neonatal morbidity (defined as convulsions and neonatal asphyxia); perinatal death; severe maternal morbidity (defined as uterine rupture, sepsicaemia or admission to an intensive care unit); and maternal death. Secondary outcomes on ineffectiveness, complications (as defined in the review), and maternal satisfaction were also measured. Unfavourable cervix was defined according to the Bishop score using different cut-off scores.

Mean maternal age in the included trials ranged from 24 to 30 years; gestational age ranged from 38 weeks and five days to 41 weeks. Prolonged pregnancy was the main indication for induction of labour in all the included trials. Four trials included up to 19.2% of women with ruptured membrane. Misoprostol was administered at 25 to 50mcg every four or six hours for up to a maximum of four to eight doses. The included trials were conducted in Brazil, Lebanon, Lithuania and Turkey.

The authors did not state how studies were selected for the review.

Assessment of study quality
The quality of the included trials was assessed using the Jadad scale for allocation concealment, blinding, and withdrawal/drop-out. The score for a trial could range from 0 to 5, with 5 indicating the highest quality. Allocation concealment and loss to follow-up were classified according to the Cochrane criteria. Trials that reported inadequate concealment or that did not performing concealment, and trials with losses of 20% or more or in which losses were unclear, were excluded from the review. Trials scoring 2 points or less on the Jadad scale were excluded.

The authors did not state how many reviewers assessed the quality of the included studies.
Data extraction
Two reviewers independently extracted odds ratio (OR) and 95% confidence interval (CI). Disagreements were resolved by consensus with a third reviewer.

Methods of synthesis
Odd ratios and 95% confidence intervals were combined in a meta-analysis using a fixed-effect model. Statistical heterogeneity between trials was assessed by the $I^2$ statistic and $X^2$ test.

The impact of initial dose of misoprostol was assessed in subgroup analyses.

Results of the review
Five RCTs met the inclusion criteria and were included in the review (n=740 women). All five trials used adequate methods for concealment of allocation; two trials were double-blind; five trials described loss to follow-up and exclusions.

Misoprostol administered sublingually was not statistically significantly different from vaginal administration for: vaginal delivery not achieved within 24 hours (four trials, n=620 women); hyperstimulation syndrome (five trials, n=740 women); caesarean section (five trials, n=740 women); rate of induction of labour failure (three trials, n=440 women); or complementary oxytocin requirements (five trials, n=740 women). Comparisons for vaginal delivery not achieved, hyperstimulation, caesarean section, rate of induction of labour failure and complementary oxytocin showed no evidence of statistical heterogeneity.

Subgroup analyses by initial dose did not change the results. However, there was a statistically significantly increased risk of tachysystole with sublingual compared to vaginal misoprostol (OR 1.70, 95% CI 1.02 to 2.83; five trials, n=740 women), but there was evidence of moderate heterogeneity between the trials ($I^2= 54\%$).

There were no statistically significant differences between administration routes for other outcomes.

The only trial that evaluated satisfaction found that a higher proportion of women were satisfied with sublingual misoprostol compared with the vaginal route.

Authors’ conclusions
Sublingual route of administration was as effective as the vaginal route in inducing labour in full-term pregnancies with a live full-term foetus, but it did not appear that sublingual administration offered additional clinical advantages over vaginal administration; further research is needed.

CRD commentary
This review addressed a well-defined question in terms of participants, interventions, outcomes, and study design. The search included appropriate databases, but the restriction to studies in English, Portuguese and Spanish meant that the possibility of language bias could not be ruled out. Abstracts and unpublished studies were excluded from the review, so all the relevant data might not have been included. The authors reported using appropriate methods to minimise reviewer bias and errors in extracting data, but it was unclear how selection of studies was performed and how many reviewers assessed quality of the included trials.

Quality was assessed using appropriate criteria. The characteristics of the individual trials were presented. Potential sources of heterogeneity were explored. There were only a small number of included trials which the authors acknowledged and advised cautious interpretation of the findings.

The authors’ conclusions reflected the evidence shown, but methodological heterogeneity, and the potential for bias and errors during the review process, means that caution is required when interpreting these findings.

Implications of the review for practice and research
Practice: The authors stated that the safety, dose and perinatal outcomes related to sublingual misoprostol remain
uncertain, so it is not recommended for routine use in obstetric practice.

**Research:** The authors stated that future studies are warranted to evaluate patient satisfaction, adverse events, and the efficacy of lower sublingual doses.

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