Comparison of sublingual versus vaginal misoprostol for the induction of labour: a systematic review

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Accepted 6 July 2008.

Background The induction of full-term labour in women with a live fetus remains a major challenge in modern obstetrics.

Objectives To determine, using the best level of evidence available, the efficacy and safety of sublingual administration of misoprostol compared with vaginal misoprostol in the third trimester of pregnancy for the induction of labour, according to initial doses, in women with a live, full-term fetus and an unripe cervix.

Search strategy Pubmed/Medline, Lilacs and Scielo databases were consulted, as well as clinical trials registered in the Cochrane Register from January 1996 to February 2008, using the keywords ‘misoprostol’, ‘labour, obstetric’, ‘delivery, obstetric’, ‘induced labour’ and ‘parturition’ with the search limits of ‘clinical trials’ and ‘randomised clinical trials’.

Selection criteria This review contains randomised clinical trials in which the sublingual and vaginal routes of administration of misoprostol were compared. Participants were pregnant women with an indication for induction of labour and a live fetus more than 37 weeks of gestational age.

Data collection and analysis The primary analysis compared sublingual and vaginal routes of administration of misoprostol. Secondary analyses compared different routes and initial doses of misoprostol. Statistical analysis included odds ratios and their respective 95% CI. To evaluate the heterogeneity of the studies, the I-squared test was used, studies being considered heterogeneous when I² was greater than 50%.

Main results Five good quality clinical trials involving a total of 740 women were eligible, and all were included. No statistically significant difference was found between the sublingual and the vaginal misoprostol groups with respect to the rate of vaginal delivery not achieved within 24 hours (OR 1.27, 95% CI 0.87–1.84), uterine hyperstimulation syndrome (OR 1.20, 95% CI 0.61–2.33) or caesarean section (OR 1.33, 95% CI 0.96–1.85). An increased risk of uterine tachysystole was found in the sublingual misoprostol group (OR 1.70, 95% CI 1.02–2.83). When the studies were grouped according to the initial dose of misoprostol, no significant difference was found between sublingual or vaginal groups.

Author’s conclusions The sublingual route of administration is as effective as the vaginal route in inducing labour in full-term pregnancies with live fetuses. However, the safety, adverse effects, optimal dose and perinatal outcome related to this route of administration remain to be established, and it cannot be recommended for routine use in obstetric practice.

Keywords ‘Delivery, obstetric’, induced labour, ‘labour, obstetric’, literature review, meta-analysis, misoprostol, parturition.

Introduction

The induction of labour in women with a live fetus at term remains a major challenge in modern obstetrics. Despite a large body of literature on the subject, the optimal agent for this purpose has yet to be established. Nevertheless, in recent years, labour induction has been frequently performed in maternity hospitals all over the world.

Misoprostol is a prostaglandin E₁ methyl ester that stimulates myometrial contractions in the pregnant uterus by binding to the EP2/EP3 prostaglandin receptors.¹ Its use was originally described for the prevention of gastric ulcers caused by nonsteroidal anti-inflammatory drugs, and it was first used to induce labour with a live fetus in 1991. The initial dose of vaginal misoprostol used was 50 micrograms every 2 hours up to a maximum total dose of 600 micrograms,
resulting in vaginal delivery in 73% of cases and hyperstimulation syndrome in 3.6% of women.2,3 Since then, lower doses have been proposed for the induction of labour in an attempt to reduce adverse effects.4,5

Currently, misoprostol is considered at least as effective as other methods in inducing labour when the cervix is immature.7 A recent systematic review suggested that low-dose misoprostol is more effective than prostaglandin E2 in achieving vaginal delivery within 24 hours without affecting the caesarean section rate.6 The dose of misoprostol usually recommended to reduce the incidence of abnormal uterine contractility and neonatal complications is 25 micrograms administered vaginally every 4–6 hours.7

In Brazil, tablets containing 25 micrograms of misoprostol have been available since 1998 for use exclusively in hospitals. Although the vaginal route of administration appears to be as effective as the oral route, it incurs a greater risk of undesirable adverse effects, such as uterine hyperstimulation syndrome, as well as having the inconvenience of vaginal administration.4 Women prefer to use misoprostol orally, claiming that the oral route is more convenient and offers greater privacy.8

Recent studies have found that sublingual administration of misoprostol is very effective for induction of labour.9–16 Nevertheless, no consensus has yet been reached in the literature regarding the most appropriate route of administration. Meta-analysis have been carried out to compare the effects of the different doses of misoprostol administered vaginally, orally and sublingually and have suggested that there are no statistically significant differences with respect to the efficacy of the different routes of administration. The authors recommend carrying out further randomised studies.4,5,17

Following a literature search carried out in the Cochrane, Pubmed/Medline, Scielo and Lilacs databases, a systematic review17 was found, which included one study comparing buccal and vaginal routes of misoprostol administration18 and two studies comparing sublingual and oral misoprostol for the induction of labour.14,15 However, no studies comparing sublingual and vaginal routes for induction of labour were included.17

Pharmacological studies suggest that sublingual misoprostol might be the optimal route of administration. Tang et al. compared the pharmacological parameters of four different routes of administration in 40 pregnant women: oral, sublingual, vaginal and vaginal with the addition of water. Peak plasma levels were higher in the sublingual group (374.8 ± 250.7 pg/ml) than in the oral group (287.6 ± 144.3 pg/ml), the vaginal group with the addition of water (162.8 ± 57.1 pg/ml) or the group with vaginal misoprostol alone (125 ± 53.8 pg/ml). In addition to the higher peak plasma levels, bioavailability was also found to be greater in the sublingual route than the vaginal route. Nevertheless, plasma levels were sustained for longer periods of time when the vaginal route of administration was used.20

The objectives of this review were to determine, using the best level of evidence available, the efficacy and safety of the sublingual administration of misoprostol compared with vaginal misoprostol in the third trimester of pregnancy for the induction of labour, according to initial doses, in women with a live, full-term fetus and an unripe cervix.

Methods

A literature review was carried out to search for studies in the Pubmed/ Medline, Scielo and Lilacs databases, as well as among the clinical trials registered in the Cochrane Register from January 1996 to February 2008. Studies were identified using the following MeSH descriptors in English, Portuguese and Spanish: ‘misoprostol’, ‘labour, obstetric’, ‘delivery, obstetric’, ‘induced labour’ and ‘parturition’, with the search limits of ‘clinical trials’ and ‘randomised clinical trials’. Additionally, the references of the original articles were manually searched and cross-referenced trying to identify other relevant studies.

This systematic review included randomised clinical trials comparing the sublingual and vaginal routes of administration of misoprostol. Participants were pregnant women with an indication for induction of labour, an unfavourable cervix and a live fetus more than 37 weeks of gestational age. Non-randomised studies were excluded. Because of the lack of detail regarding study methods and results, abstracts and unpublished studies were also excluded.

The validity of each clinical trial included in this review was assessed according to the criteria established in the Jadad scale (Table 1).21 A maximum score of 5 points was possible: 3 points for each positive answer, 1 additional point for an adequate randomisation method and an additional point for an appropriate blinding method. A study is considered to be of poor quality if it achieves a score of 2 points or less. We planned to exclude all poor quality studies from the meta-analysis, but no poor quality study was identified.

Studies were classified according to the blinding technique used for the masking of treatments following randomisation as: double-blind when neither the investigators nor the participants knew which treatment was given, single-blind when either the investigator or the participants knew which treatment was given or the allocation method was not clearly described or unblinded when both the investigator and the participants were aware of the treatment or the subject of blinding was not mentioned in the paper.

With respect to allocation concealment, the studies were classified according to the criteria described in the Cochrane Index22 as adequate (A), unclear (B), inadequate (C) or not performed (D). Studies rated as C or D were excluded from the final analysis.

Loss to follow up or exclusion of women during the study was classified as: less than 5% of participants excluded (A),
5–9.9% of participants excluded (B), 10–19.9% excluded (C), 20% or more excluded (D) or unclear (E). Studies classified as D or E were excluded from the analysis.22

Following identification of the studies, the eligibility criteria were applied and the characteristics of each study were described. Two reviewers (A.S.R.S. and M.M.R.A.) independently extracted relevant data from the studies. Any point of discordance was discussed and settled by consensus. Any disagreements were resolved by consensus after discussion with third reviewer (F.E.L.F.).

The variables analysed were those defined by the authors of the reviews on studies of labour induction in the Cochrane Register, who reached a consensus that was registered in the Cochrane Pregnancy and Childbirth Group.23

The primary variables are the following: vaginal delivery not achieved within 24 hours, uterine hyperstimulation syndrome (tachysystole [more than five contractions in 10 minutes for at least 20 minutes] or hypersystole/hypertonia [a uterine contraction lasting 2 minutes or more] with abnormal fetal heartbeat [persistent decelerations, tachycardia or a decrease in short-term variability]), caesarean section, severe neonatal morbidity (convulsions and neonatal asphyxia) and perinatal death, and severe maternal morbidity (uterine rupture, septicaemia and admission to an intensive care unit) and maternal death. These five primary variables were chosen as being the most representative and clinically significant. However, no studies included data for the latter two outcomes (severe maternal morbidity/perinatal death and severe maternal morbidity/death).

Some secondary variables concerning ineffectiveness, complications and satisfaction were also considered. Ineffectiveness was measured by taking into consideration no change in cervical favourability after 12–24 hours (not reported in any studies), induction failure, the rate of ‘only one dose required to induce the onset of labour’ and need of complementary oxytocin. Complications included uterine tachysystole and hypersystole/hypertonia, epidural analgesia, instrumental vaginal delivery, meconium-stained liquor, 1- and 5-minute Apgar score <7, admission to a neonatal intensive care unit and maternal adverse effects (nausea, vomiting and hyperthermia). The maternal indicator of satisfaction was ‘number of women not satisfied’.

The primary analysis compared sublingual and vaginal routes of administration of misoprostol for all women. A subgroup analyses compared different initial doses of misoprostol. Statistical analysis was carried out using the RevMan 4.2 SE software package (Cochrane Collaboration, Oxford, UK) and included odds ratios and their respective 95% CI for dichotomous variables. Results were considered to be statistically significant if the 95% CI did not included 1.0 for OR or if the P value <0.05. To evaluate the heterogeneity of the studies, the I-squared test was used, studies being considered significantly heterogeneous when I2 was greater than 50%.

**Results**

Five studies were identified and included in the review involving a total of 740 women (see QUOROM flowchart24 in Figure 1). All five studies used a computer-generated randomisation sequence; two were double-blind9,12 and three were unblinded (Table 1).10,13,16 In two of the studies, no participants were excluded following randomisation.10,12 while three participants were excluded in the study conducted by Moraes Filho et al.13 (2005), two participants in the study carried out by Bartusevicius et al.9 (2006) and four participants in the study conducted by Nassar et al.16 (2007). All the studies were considered to be of good quality according to the Jadad scale (Table 1);22 three studies being awarded 3 points10,13,16 and the other two studies receiving 5 points.9,12

The vaginal and sublingual routes of administration of misoprostol were compared in all studies, but the doses used were different (Table 2). Two studies compared a 25 microgram dose used sublingually with a 25 microgram dose used vaginally.12,13 In one of these studies, a maximum of eight doses was permitted,13 while in the other, a maximum of four doses was given.12 Two studies compared 50 micrograms of misoprostol used sublingually with 50 micrograms administered vaginally up to a maximum of five16 and six10 doses,
while the fifth study compared a 50 microgram dose used sublingually with a 25 microgram dose used vaginally up to a maximum of six doses.9

The characteristics of the participants were similar in the two groups in each one of the studies evaluated, and there were few differences between studies. Mean maternal age ranged from 24 to 30 years (Table 2) and gestational age from 38 weeks and 5 days to 41 weeks in the different studies. The main indication for induction of labour was prolonged pregnancy in all studies. The trials of Bartusevicius et al.9 (2006), Caliskan et al.10 (2005), Moraes Filho et al.13 (2005) and Nassar et al.16 (2007) also included women with ruptured membranes who made up 11.4, 10.6, 19.2 and 17.6% of the participants, respectively.

The principal variables from the five studies were analysed for the purposes of this meta-analysis. A total of 740 women were included, 368 of whom received misoprostol sublingually and 372 vaginally.

No statistically significant differences were found, including the subgroup analysis by initial misoprostol doses, between the sublingual and the vaginal misoprostol groups with respect to the rate of vaginal delivery not achieved within 24 hours (OR 1.27, 95% CI 0.87–1.84; Figure 2), uterine hyperstimulation syndrome (OR 1.20, 95% CI 0.61–2.33; Figure 3) or caesarean section (OR 1.33, 95% CI 0.96–1.85; Figure 4).

In comparing the effectiveness of sublingual and vaginal misoprostol, no statistically significant differences were found in the rate of induction failure (OR 1.15, 95% CI 0.58–2.30; Figure 5) or the need of complementary oxytocin (OR 1.11, 95% CI 0.82–1.50; Figure 6) irrespective of the initial doses of misoprostol.

With respect to possible adverse effects induced by misoprostol, an increase was observed in the risk of tachysystole in the sublingual misoprostol group (OR 1.70, 95% CI 1.02–2.83; Figure 7) when compared with the vaginal misoprostol group. There was a borderline statistically significant heterogeneity ($I^2 = 54\%, P = 0.07$), but it did not appear to be related to dosage. No significant difference was found between the groups when subgroup analysis was performed for the outcomes of uterine hypertonia (OR 1.03, 95% CI 0.25–4.18; Figure S1), epidural analgesia (OR 1.12, 95% CI 0.74–1.69; Figure S2) or instrumental vaginal delivery (OR 0.79, 95% CI 0.36–1.73; Figure S3 and Table 3).

With respect to the principal perinatal variables, no statistically significant differences were found between the sublingual and the vaginal misoprostol groups regarding the frequency of meconium (OR 1.10, 95% CI 0.68–1.78; Figure S4), 5-minute Apgar score <7 (OR 0.61, 95% CI 0.19–1.99; Figure S5) or admission to a neonatal intensive care unit (OR 1.21, 95% CI 0.36–4.02; Figure S6), irrespective of the initial dose (Table 3).
Collateral effects were analysed, and no statistically significant difference was found when sublingual and vaginal routes were compared with respect to nausea (OR 0.72, 95% CI 0.34–1.52; Figure S7), vomiting (OR 1.34, 95% CI 0.49–3.67; Figure S8) or hyperthermia (OR 0.81, 95% CI 0.21–3.05; Figure S9 and Table 3).

Women’s satisfaction with vaginal or sublingual routes was evaluated in only one study. A significantly higher proportion of women in the sublingual group thought that the labour experience was better than expected during the second (OR 2.2, 95% CI 1.0–4.7) and third (OR 2.8, 95% CI 1.3–6.2) interviews. The sublingual route was also more appealing to women for induction in a subsequent pregnancy (OR 2.6, 95% CI 1.2–5.2).

An analysis was carried out on other secondary variables in some of the clinical trials. No statistically significant differences were found between the sublingual and the vaginal misoprostol groups with respect to the rate of 1-minute Apgar score <7 (OR 1.19, 95% CI 0.60–2.36; clinical trials = 2, n = 270; heterogeneity chi-squared = 0.19; P = 0.665). There was also no significant difference detected between the groups in the number of women who only needed one dose of misoprostol to induce labour (OR 1.31, 95% CI 0.61–2.80; clinical trials = 3, n = 410).

**Discussion**

The results of this review are based on five clinical trials (n = 740) and must, therefore, be interpreted with caution. It is, however, clear from these studies that misoprostol given sublingually is effective in inducing labour with live, full-term fetuses. The sublingual route of administration is at least as effective as the vaginal route with a similar dose. However,
data are insufficient to allow any comments on related doses, complications, adverse effects and satisfaction. The meta-analysis by subgroups of misoprostol doses must be evaluated with caution because the sample power is very low. Two studies compared 50 micrograms of vaginal and sublingual misoprostol (n = 330), two compared the dose of 25 micrograms by both routes (n = 270) and only one compared 50 micrograms of sublingual misoprostol with 25 micrograms of vaginal misoprostol (n = 140).

With respect to the safety of the sublingual administration of misoprostol, data in the literature are insufficient for this route of administration to be recommended in clinical practice outside of research protocols. However, the rates of vaginal delivery not achieved within 24 hours, uterine hyperstimulation and caesarean section were similar in both routes. These findings are similar to those found in other systematic review published by the Cochrane Collaboration that evaluated buccal/sublingual routes of misoprostol.17 The meta-analysis showed an increased risk of developing tachysystole with sublingual administration of misoprostol, although there was no evidence of any increased risk of uterine hyperstimulation syndrome. It should be emphasised that

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**Figure 3.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of ‘uterine hyperstimulation syndrome’ (subgrouped by initial misoprostol dose).

<table>
<thead>
<tr>
<th>Sublingual</th>
<th>Vaginal</th>
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<tr>
<td>Study or subgroup</td>
<td>Events</td>
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<tr>
<td>Caliskan et al. (2005)</td>
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<td>Nasser et al. (2007)</td>
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<td>Test for overall effect: Z = 0.40 (P = 0.38)</td>
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**Figure 4.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of caesarean section rate (subgrouped by initial misoprostol dose).

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<td>Caliskan et al. (2005)</td>
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<td>Subtotal (95% CI)</td>
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<td>Heterogeneity: χ² = 0.21, df = 1 (P = 0.75); I² = 0%</td>
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<td>Test for overall effect: Z = 0.40 (P = 0.38)</td>
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pharmacokinetic studies suggest that the sublingual route of administration of misoprostol is associated with a rapid initial increase in the blood levels of the drug (similar to that found with the oral route and faster than the vaginal route) and greater bioavailability compared with the vaginal route. Caution should therefore be exercised in its use. The studies in which 50 micrograms of sublingual misoprostol were used showed the highest rates of tachysystole, suggesting that this effect could be dose dependent. Further studies would be useful to compare doses of 25 micrograms of vaginal and sublingual misoprostol and even lower doses of sublingual (12.5 micrograms) with 25 micrograms of vaginal misoprostol.

The doses routinely used by the vaginal route still cannot be considered totally safe for sublingual use in the induction of labour due to the risks of uterine hyperstimulation, an effect that reflects the efficacy of the drug. In the systematic review of Cochrane Library evaluating oral and vaginal misoprostol for induction of labour uterine hyperstimulation was found to be more frequent with vaginal regimens, an effect probably dependent on the dosage. We recommend that pharmacokinetic studies take into consideration not only the efficacy of the various routes of administration of the drug but also the doses.

With respect to perinatal outcome, the data currently available are insufficient to permit any definitive conclusions to be drawn. The published studies show no statistically significant difference between the groups, particularly with respect to the presence of meconium in the amniotic fluid, 5-minute Apgar score <7 and admission to a neonatal intensive care unit. Analysis of the other perinatal variables was carried out in an insufficiently large sample size of participants.

An important benefit of sublingual misoprostol is the satisfaction of women. Nonetheless, satisfaction should be

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<th>Total</th>
<th>Vaginal</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. fixed, 95% CI</th>
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<td>Caliskan et al. (2005)</td>
<td>41</td>
<td>80</td>
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<td>80</td>
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<td>Nasser et al. (2007)</td>
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<td>85</td>
<td>63</td>
<td>85</td>
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<td>97</td>
<td>165</td>
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<td>5.1.2 25 microgram sublingual vs 25 microgram vaginal</td>
<td>Feitoza et al. (2006)</td>
<td>26</td>
<td>75</td>
<td>26</td>
<td>75</td>
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<td>Morcos Filho et al. (2005)</td>
<td>58</td>
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<td>52</td>
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<td>34</td>
<td>70</td>
<td>34</td>
<td>70</td>
<td>22.0%</td>
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<td>Subtotal (95% CI)</td>
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<td>Total (95% CI)</td>
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<td>368</td>
<td>183</td>
<td>372</td>
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analysed with caution in this meta-analysis because it was evaluated in only study, which suggested that women prefer sublingual to vaginal route of misoprostol. Others studies must be conducted before the sublingual route can be recommended for obstetric practice.

Conclusions

In conclusion, the sublingual route of administration is effective in inducing labour with a live, full-term fetus. However, it appears to offer no additional clinical advantages over the vaginal route. Because the safety, adverse effects, dose and perinatal outcome related to this route of administration remain uncertain, it is not recommended for routine use in obstetric practice, and its use should be reserved for clinical research protocols. Future studies should be carried out to test the efficacy of lower doses for sublingual administration with the objective of reducing adverse effects and evaluating patient satisfaction. These studies are important because the sublingual route of administration offers some attractive advantages such as greater ease of use compared with vaginal administration. In certain clinical contexts, such as when premature rupture of the membranes occurs, it is possible that the sublingual route of administration would be preferable to the vaginal route, with the potential benefit of avoiding digital vaginal examination and reducing infection rates. Nevertheless, these possible benefits have yet to be confirmed.

Disclosure of interests

M.M.R.A. and F.E.L.F. have conducted studies on sublingual misoprostol.11,12
**Contribution to authorship**

M.M.R.A. and A.S.R.S. performed review of the literature and extracted independently the data. A.S.R.S. performed meta-analysis. F.E.L.F. contributed to protocol of systematic review and made substantive contributions to final version of the manuscript.

**Details of ethics approval**

This study was approved by Ethical Research Committee of Instituto Materno Infantil Prof Fernando Figueira, Recife, Pernambuco, Brazil.

**Funding**

This study was funded by Instituto Materno Infantil Prof Fernando Figueira.

**Supporting information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of uterine hypertonus/hypertonia (subgrouped by initial misoprostol dose).

**Figure S2.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of epidural analgesia use (subgrouped by initial misoprostol dose).

**Figure S3.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of instrumental vaginal delivery use (subgrouped by initial misoprostol dose).

**Figure S4.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of meconium liquor (subgrouped by initial misoprostol dose).

**Figure S5.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of 5-minute Apgar score <7 (subgrouped by initial misoprostol dose).

**Figure S6.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of maternal nausea (subgrouped by initial misoprostol dose).

**Figure S7.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of instrumental vaginal delivery use (subgrouped by initial misoprostol dose).

**Figure S8.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of maternal hyperthermia (subgrouped by initial misoprostol dose).

**Figure S9.** Meta-analysis of randomised clinical trials comparing the sublingual and vaginal misoprostol routes with an outcome of rate of maternal vomiting (subgrouped by initial misoprostol dose).

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**Acknowledgements**

Thanks to Dr Andrew Weeks who performed a careful review of the manuscript.

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