

Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects

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Objective To review maternal deaths and the dose-related effects of misoprostol on blood loss and pyrexia in randomized trials of misoprostol use for the prevention or treatment of postpartum haemorrhage.

Methods We searched the Cochrane Controlled Trials Register and PubMed, without language restrictions, for "(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)", and we evaluated reports identified through the Cochrane Pregnancy and Childbirth Group search strategy. Randomized trials comparing misoprostol with either placebo or another uterotonic to prevent or treat postpartum haemorrhage were checked for eligibility. Data were extracted, tabulated and analysed with Reviewer Manager (RevMan) 4.3 software.

Findings We included 46 trials with more than 40 000 participants in the final analysis. Of 11 deaths reported in 5 trials, 8 occurred in women receiving ≥ 600 μg of misoprostol (Peto odds ratio, OR: 2.49; 95% confidence interval, CI: 0.76–8.13). Severe morbidity, defined as the need for major surgery, admission to intensive care, organ failure or body temperature ≥ 40 °C, was relatively infrequent. In prevention trials, severe morbidity was experienced by 16 of 10 281 women on misoprostol and by 16 of 10 292 women on conventional uterotonics; in treatment trials, it was experienced by 1 of 32 women on misoprostol and by 1 of 32 women on conventional uterotonics. Misoprostol recipients experienced more adverse events than placebo recipients: 8 of 2070 versus 5 of 2032, respectively, in prevention trials, and 5 of 196 versus 2 of 202, respectively, in treatment trials. Meta-analysis of direct and adjusted indirect comparisons of the results of randomized trials showed no evidence that 600 μg are more effective than 400 μg for preventing blood loss ≥ 1000 ml (relative risk, RR: 1.02; 95% CI: 0.71–1.48). Pyrexia was more than twice as common among women who received ≥ 600 μg rather than 400 μg of misoprostol (RR: 2.53; 95% CI: 1.78–3.60).

Conclusion Further research is needed to more accurately assess the potential beneficial and harmful effects of misoprostol and to determine the smallest dose that is effective and safe. In this review, 400 μg of misoprostol were found to be safer than ≥ 600 μg and just as effective.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

In low-income countries, postpartum haemorrhage is a major cause of maternal death¹ and arguably the most preventable. Attempts to reduce deaths from postpartum haemorrhage have been complicated by the fact that many deaths occur in out-of-hospital settings or too quickly for the patient to be transferred to a health facility. Furthermore, prevention and treatment have depended primarily on injectable uterotonics, which are seldom available for births outside the health system. For these reasons, the use of misoprostol to prevent or treat postpartum haemorrhage has attracted considerable attention. Misoprostol, an inexpensive and stable prostaglandin E1 analogue, has been shown to stimulate uterine contractility in early pregnancy² and at term.³ Administered orally or vaginally, it is effective for inducing abortion^{4,5} and labour,^{6–8} though it poses certain risks.^{9,10}

Administration of this drug on a wide scale at the community level to prevent and treat postpartum haemorrhage is of major public health importance. The first of many randomized trials of the use of misoprostol in the third stage of labour was conducted in 1995.¹¹ When administered in

various doses and via various routes for the prevention of postpartum haemorrhage, misoprostol has been less effective than conventional injectable uterotonics.^{12,13} Initial reports of placebo-controlled trials have shown variable results,¹² but in more recent studies misoprostol has proved better than placebo, in terms of measured blood loss, for both the prevention^{14,15} and treatment¹⁶ of postpartum haemorrhage. The main side effects reported have been chills and pyrexia, both of which have been dose-dependent.¹⁷

We have reviewed the pharmacological, physiological and clinical evidence surrounding the use of misoprostol for the treatment of postpartum haemorrhage.¹⁶ The oral route of administration is the fastest but also the one associated with the shortest duration of action. The rectal route has slow uptake but a prolonged duration of action. The buccal and sublingual routes have rapid intake, prolonged duration of action and the greatest total bioavailability. We concluded from the data reviewed that the most promising route of administration was the sublingual route.

Misoprostol has been widely recommended to prevent postpartum haemorrhage when other methods are not available,¹⁸ and large-scale implementation projects are currently

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in progress. Caution has been urged, however, because side-effects may occasionally be life-threatening.¹⁹ In a recent placebo-controlled trial in rural India in which babies were delivered by auxiliary nurse midwives at home or in village subcentres, a significant reduction in postpartum haemorrhage and other complications was obtained with misoprostol, 600 µg orally used alone (i.e. without other components of the active management of the third stage of labour – umbilical cord clamping and controlled cord traction).¹⁵ WHO has developed guidelines supporting the use of a uterotonic when the full package of active management of the third stage of labour is not practised, which can be either oxytocin, 10 IU administered parenterally, or misoprostol, 600 µg administered orally.²⁰

Apart from its uterotonic effects, misoprostol has known pharmacologic effects on several organ systems. It inhibits platelet-activating factor²¹ and affects metabolic and physiological processes, including thermoregulation. Life-threatening hyperpyrexia has been reported following the use of misoprostol, 800 µg orally, after childbirth.²²

Whenever a new medical intervention is promoted, one must take into account not only its clinical benefits and risks, but also the collateral benefits and risks from both use and potential misuse in the community. Before distributing misoprostol at the community level, it is important to consider its possible misuse, an example being its administration before delivery, which could lead to uterine rupture. Because of its enormous potential benefits as an effective, oral uterotonic during the third stage of labour and its likely use on a large scale worldwide, it is important to monitor misoprostol's benefits as well as its potential risks, both direct and indirect.

In September 2005, the *BMJ* published the first placebo-controlled trial to suggest a clear effect of misoprostol for preventing postpartum haemorrhage.¹⁴ The study elicited several responses, however. One of them was the suggestion to regard the single maternal death in the misoprostol group as an adverse event potentially related to misoprostol use.²³ This is plausible because a drug with ubiquitous pharmacologic effects might have unanticipated adverse effects when used in the

third stage of labour. Another response was a call for a trial of misoprostol as a treatment for postpartum haemorrhage, with maternal death as the primary endpoint.²⁴

In this paper we hypothesized that women on misoprostol in the third stage of labour were at increased risk of death or severe morbidity because of an as yet unexplained adverse effect of the drug on maternal homeostatic functions.²⁵ Thus, the primary objectives of this review was to investigate maternal deaths and severe morbidity in connection with the use of misoprostol for preventing or treating postpartum haemorrhage during the third stage of labour, as well as to see whether side effects were dose-related. A secondary objective was to determine the relative effectiveness of ≥ 600 µg of misoprostol versus smaller doses, since to justify the use of the larger dose in large numbers of women, particularly in light of potential side effects, would require evidence that it is considerably more effective than the smaller dose.

Methods

Systematic review

Types of studies: We performed a systematic review of randomized controlled trials in which misoprostol versus either placebo or another uterotonic were given to women after delivery to prevent or treat postpartum haemorrhage. We looked for the following primary outcome measures: (i) maternal death, or (ii) maternal death or severe morbidity, defined as either major surgery, admission to the intensive care unit (ICU), vital organ failure or body temperature ≥ 40 °C. For dose comparisons, the outcomes selected were a blood loss of ≥ 1000 ml or of ≥ 500 ml after the diagnosis of postpartum haemorrhage, and pyrexia (i.e. a body temperature ≥ 38 °C or as defined by trial authors).

Search strategy

We followed the search strategy used by the Cochrane Collaboration's Pregnancy and Childbirth Group. Briefly, potentially eligible trials were identified from: (i) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); (ii) monthly searches of Medline; (iii) hand searches of 30 journals and the proceedings of major conferences; and (iv) weekly

current awareness searches of a further 37 journals. We also searched the Cochrane Controlled Trials Register and Pubmed, without language restrictions, for "(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)" (last search February 2007). We tried to contact authors to obtain further details about any maternal deaths reported and, if no maternal death was mentioned in a paper, we asked the authors to confirm that no death had occurred.

All studies identified through the search strategy were assessed for inclusion in the analysis. We designed a data extraction form that was used by two of the authors, and any disagreements were resolved through discussion. We used Review Manager (RevMan) 4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to enter the data and check it for accuracy.

Assessment of methodological quality

For each trial we classified allocation concealment as follows: (i) adequate if a method such as telephone randomization or consecutively numbered sealed opaque envelopes was used; (ii) unclear if the concealment method was not described; or (iii) inadequate if an open list of random numbers, case record numbers, dates of birth, days of the week or another such method was used.

Measures of treatment effect and assessment of heterogeneity

We used fixed effects meta-analysis for combining data in the absence of significant heterogeneity. For dichotomous data, we presented the results as summary relative risks (RRs) with 95% confidence intervals (CIs). For the outcome maternal mortality, we used both RRs and Peto odds ratios (ORs) to check for discrepancies between the two summary statistics. Peto ORs are recommended when events are very infrequent. We applied tests of heterogeneity between trials using the I^2 statistic, a variation of the χ^2 statistic.

Subgroup analyses

We classified whole trials according to interaction tests as described by Deeks et al.²⁶ and carried out the following subgroup analyses: (i) misoprostol versus placebo and versus other utero-

tonics; (ii) misoprostol to prevent or treat postpartum haemorrhage; and (iii) misoprostol at a dose of $\geq 600 \mu\text{g}$ or more; 400 to $< 600 \mu\text{g}$; or $< 400 \mu\text{g}$.

In the analysis tables we ranked the trials by route of administration and dose of misoprostol to check for route- or dose-related trends in effects. We coded the trial identifiers to indicate the route of administration and dose used.

Comparisons of dose-related effectiveness and side-effects

In view of inadequate data from direct randomized comparisons of different doses of misoprostol, we supplemented the direct data with adjusted indirect comparisons. In most cases, the results of adjusted indirect comparisons have proved similar to those of direct comparisons in 44 previous meta-analyses.²⁷ Thus, to estimate the relative effectiveness of two different doses of misoprostol we combined the results

of trials in which each dose of the drug was tested against the same type of control (either placebo or a uterotonic other than misoprostol).²⁸ Three-way comparisons of $600 \mu\text{g}$ versus $400 \mu\text{g}$ of misoprostol versus placebo or another uterotonic were included only in the direct comparisons. Studies of rectally-administered misoprostol were excluded because of uncertain absorption via the rectal route.

For direct and indirect comparisons the primary outcome measures were blood loss ≥ 1000 ml and pyrexia $\geq 38^\circ\text{C}$. As the effectiveness outcome was blood loss measured within 1 hour of drug administration, doses of misoprostol given 1 hour or more after the initial dose were not taken into account.

Most of the trials in the review were conducted in settings with routine active management of the third stage of labour. To determine if such management affected the results, we performed

a sensitivity analysis from which we excluded the one trial in which active management was not practiced.¹⁵

Prospective adverse-event surveillance studies

We report on adverse events from misoprostol use as recorded in the WHO Adverse Reaction Database, maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. The UMC collects reports of suspected adverse drug reactions from 70 participating countries. We ranked adverse events by frequency of reporting.

Results

Systematic review

We found 46 randomized controlled trials with more than 40 000 participants. They are summarily described in Table 1.

Table 1. Studies included in a systematic review and meta-analysis of randomized controlled trials of misoprostol for preventing or treating postpartum haemorrhage

Study ^a [Allocation concealment ^b]	Intervention	Notes
<i>Australia 1999: 400 PO vs U¹³</i> : Not blinded. Randomization by table, in balanced blocks. [A]	M 400 μg PO vs oxytocin (10 IU) or vs oxytocin (5 IU) + ergometrine 0.5 mg IM	3rd stage of labour management not mentioned. Blood loss both estimated and measured.
<i>Belgium 1999: 600 PO vs U¹⁵</i> : Outcome blinded. Randomization generated by computer; blocks allocation from computer-generated list of study numbers. [A]	M 600 μg PO vs methylergometrine 200 μg IV	Active management of 3rd stage of labour. Blood loss assessment not described.
<i>Canada 2002: 400 PR vs U²⁹</i> : Not blinded. Central centre statistician performed block randomization for participating centres. [A]	M 400 μg PR after delivery vs oxytocin 5 IU IV or IM, or 10 IU IM	3rd stage management and blood loss measurement not described.
<i>Canada 2007: 400 PO vs U³⁰</i> : Not blinded. Randomization generated by computer. [A]	M 400 μg PO vs oxytocin 5 IU IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
<i>China 2001: 600 PO vs U³¹</i> : Outcome not blinded. Randomization generated by computer. [A]	M 600 μg PO vs oxytocin 5 IU + ergometrine 0.5 mg IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
<i>China 2004a: 600 SL vs U³²</i> : Not blinded. Randomization by random numbers table. [C]	M 600 μg SL vs syntocinon 5 IU + ergometrine 0.5 mg IV	Active management of 3rd stage of labour. Blood loss estimated visually and measured.
<i>China 2004b: 400 PO vs P³³</i> : Double blinded. Randomization generated by computer. [A]	M 400 μg PO vs syntometrine 1 ampoule IM	Management of 3rd stage of labour and blood loss assessment not described.
<i>China 2007: 400 PO vs U³⁴</i> : Double blinded. Randomization generated by computer. [A]	M 400 μg PO after delivery vs syntometrine 1 ampoule IM	Active management of 3rd stage of labour. Blood loss estimated clinically.
<i>Colombia 2002: 50 SL vs U³⁵</i> : Not blinded. Randomization method not stated. [B]	M 50 μg SL vs oxytocin 16 mIU/min IV vs methylergometrine 0.2 mg IM	Active management of 3rd stage of labour. Blood loss measured.
<i>France 2001: 600 PO vs P vs U³⁶</i> : Not blinded. Randomization by drawn envelopes containing treatment codes. [A]	M 600 μg PO vs oxytocin 2.5 IU IV vs no uterotonic	Management of 3rd stage of labour not described. Blood loss measured.
<i>Gambia 2004: 600 PO/SL vs P³⁷</i> : Blinded. Randomization generated by computer. [A]	M 600 μg PO & SL vs placebo	Active management of 3rd stage of labour. Blood loss measured.

(Table 1, cont.)

Study ^a [Allocation concealment ^b]	Intervention	Notes
<i>Gambia 2005: 600 PO vs P³⁸</i> : Blinded. Randomization generated by computer. [A]	M 600 µg PO vs placebo	Active management of 3rd stage of labour. Blood loss measured.
<i>Ghana 2000: 400 PO vs U³⁹</i> : Double blinded. Randomization generated by computer. [A]	M 400 µg in powdered form PO (in 50 ml of water) and 1 ml IM injection of normal saline (placebo) vs powdered lactose placebo PO (in 50 ml of water) and 1 ml IM 10 IU oxytocin	Active management of 3rd stage of labour. Blood loss assessment not described.
<i>Ghana 2006: 800 PR vs U⁴⁰</i> : Not blinded. Randomization generated by computer. [A]	M 800 µg PR vs oxytocin 10 IU IM	Management of 3rd stage of labour and blood loss assessment not described.
<i>Guinea-Bissau 2005: 600 SL vs P^{14,41}</i> : Outcome not blinded. Randomization by random numbers list. [A]	M 600 µg SL vs identical placebo	Active management of 3rd stage of labour. Blood loss measured.
<i>India 2004a: 400 SL vs U⁴²</i> : Unclear if outcome assessments were blinded. Randomization by sealed, consecutively numbered envelopes. [A]	M 400 µg SL vs methylethergometrine 0.2 mg IV	Active management of 3rd stage of labour. Blood loss measured.
<i>India 2005: 600 PO vs U⁴³</i> : Unclear if outcome assessments were blinded. Random allocation, no further details. [B]	M 600 µg PO vs methylethergometrine 0.2 mg IV	Active management of 3rd stage of labour. Blood loss assessment not mentioned.
<i>India 2006a: CS 400 vs SL vs U⁴⁴</i> : Unclear if outcome assessments were blinded. Randomization generated by computer. [B]	M 400 µg SL vs 20 IU oxytocin in 1 L lactated Ringer's solution at 125 ml/h.	Management of 3rd stage of labour and blood loss assessment not described. All women had Caesarean section with spinal anaesthesia.
<i>India 2006b: 400 PO vs U⁴⁵</i> : No mention of blinding. Randomization generated by computer. [B]	M 400 µg PO vs oxytocin 10 IU IM vs ergometrine 0.2 mg IV	Management of 3rd stage of labour not described. Blood loss measured.
<i>India 2006c: 600 PO vs P⁴⁶</i> : Blinded. Randomization generated by computer. [A]	M 600 µg PO vs identical placebos	Management of 3rd stage of labour not described. Blood loss measured.
<i>India 2006d: 400 PR vs U⁴⁷</i> : Interventions administered "randomly". [B]	M 400 µg PR vs carboprost 125 µg IM	Management of 3rd stage of labour not described. Blood loss assessed clinically.
<i>India 2006e: 400 SL vs U⁴⁸</i> : Double blinded. Randomization method not described. [A]	M 400 µg SL vs ergometrine 0.2 mg IM	Management of 3rd stage of labour not described. Blood loss measured.
<i>India 2006f: 600 PR vs U⁴⁹</i> : Double blinded. Randomization generated by computer. [A]	M 600 µg PR vs oxytocin 10 IU IM	Management of 3rd stage of labour not described. Blood loss measured.
<i>Indonesia 2002: 600 PO vs U⁵⁰</i> : Randomization method not described. [B]	M 600 µg PO vs oxytocin 10 IU IM	Management of 3rd stage of labour not described. Blood loss measured, method not described.
<i>Mozambique 2001: 400 PR vs U⁵¹</i> : Double blinded. Randomization generation unclear. Double placebos prepared daily by pharmacist independent of the trial and provided to the researchers upon request. [B]	M 400 µg dissolved in 5 ml saline PR as a microenema + 1 ml saline placebo IM vs oxytocin 10 IU IM + 5 ml saline microenema (placebo)	Management of 3rd stage of labour not described. Blood loss measured.
<i>Nigeria 2003: 600 PO vs U⁵²</i> : Double blinded. Randomization by random number table. [A]	M 600 µg in powder form dissolved in 50 ml water PO vs oxytocin 10 IU IM	Active management of 3rd stage of labour. Blood loss assessed clinically.
<i>South Africa 1998a: 400 PR vs U⁵³</i> : Not blinded. Randomization generated by computer. [A]	M 400 µg PR vs ergometrine-oxytocin 1 ampoule IM	Management of 3rd stage of labour not described. Blood loss measured.
<i>South Africa 1998b: 400 PO vs P¹¹</i> : Double blinded. Randomization generated by computer. [A]	M 400 µg PO vs placebo	Active management of 3rd stage of labour. Blood loss measured.
<i>South Africa 1998c: 400 PR vs P⁵⁴</i> : Blinded. Randomization generated by computer. [A]	M 400 µg PR vs placebo	Active or expectant management of 3rd stage of labour. Blood loss measured.
<i>South Africa 1998d: 600/400 PO vs P^{55,56}</i> : Blinded. Randomization generated by computer. [A]	M 600 µg PO vs M 400 µg PO vs placebo	Management of 3rd stage of labour not described. Blood loss measured.
<i>South Africa 2001a: 600 PO vs P⁵⁵</i> : Blinded. Randomization generated by computer. [A]	M 600 µg PO vs placebo	Management of 3rd stage of labour not described. Blood loss measured.
<i>South Africa 2001b: 800 PR vs U⁵⁷</i> : Blinded. Randomization generated by computer. [A]	M 800 µg PR vs oxytocin 5 IU IM vs ergometrine 0.5 mg IM	Women with postpartum haemorrhage after vaginal delivery or Caesarean section. Blood loss assessed clinically.

(Table 1, cont.)

Study ^a [Allocation concealment ^b]	Intervention	Notes
<i>South Africa 2004: 1000 PO/SL/PR vs P</i> ⁵⁸ : Double blinded. Randomization generated by computer. [A]	M 200 µg PO + 400 µg SL + 400 PR vs placebo	Active management of 3rd stage of labour. Blood loss measured.
<i>Switzerland 1999: 600 PO vs P</i> ⁵⁹ : Double blinded. Randomization by random number table. [A]	M 600 µg PO vs placebo	Active management of 3rd stage of labour. Blood loss estimated by pre- and post-delivery haemoglobin and haematocrit.
<i>Switzerland 2006: CS 800 PO vs U</i> ⁶⁰ : Double blinded. Randomization generated by computer. [A]	oxytocin 5 IU IV + M 800 mg vs oxytocin 5 IU IV + oxytocin 20 IU in 1000 ml normal saline over 8 hours.	All patients had Caesarean section. Blood loss measured.
<i>Turkey 2002: 400 PR vs P/U</i> ⁶¹ : Outcome blinded. Randomization generated by computer. [A]	4 groups, all received corresponding placebos. Group 1: oxytocin 10 IU IV + M 400 µg PR, followed by 2 doses, 4 and 8 hours after delivery, of M 100 µg. Group 2: M as above. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus methylergometrine 1 ml IM	Management of 3rd stage of labour and blood loss assessment not described.
<i>Turkey 2003: 400 PO vs P/U</i> ⁶² : Outcome blinded. Randomization generated by computer. [A]	Group 1: oxytocin 10 IU IV + M 400 µg PO, followed by 2 doses, 4 and 8 hours after delivery, of M 100 µg PO. Group 2: M as above. Group 3: oxytocin 10 IU IV. Group 4: oxytocin 10 IU IV plus methylergometrine 1 ml IM	Active management of 3rd stage of labour. Blood loss measured.
<i>Turkey 2005: 400 V/R vs P</i> ⁶³ : Randomization generated by computer. [B]	M 400 µg PV or PR vs placebo	Expectant management of 3rd stage of labour. Blood loss measured. Women with profuse haemorrhage or placental separation for > 30 min were excluded.
<i>United Kingdom 2000: 500 PO vs U</i> ⁶⁴ : Not blinded. Randomization by sealed, opaque, consecutively numbered envelopes. [A]	M 500 µg PO vs ergometrine for women (2%) at high risk of haemorrhage; women with hypertension (18%) received oxytocin. All others (80%) received ergometrine-oxytocin.	Management of 3rd stage of labour not described. Blood loss assessed clinically.
<i>United Kingdom 2001: 500 PO vs U</i> ⁶⁵ : Blinded. Randomization generated by computer. [B]	M 500 µg PO + normal saline 2 ml IV bolus vs oxytocin 10 IU IV bolus + 2 placebo tablets	All women underwent elective or emergency Caesarean section. Blood loss assessed clinically.
<i>United States 2001: 400 PR vs U</i> ⁶⁶ : Not blinded. Random allocation sequence concealed until enrolment. [B]	M 400 µg PR + placebo (2 ml saline) vs oxytocin 20 IU IV infusion in 1 L of Ringer's lactate solution + placebo PR (lactose tablets)	Management of 3rd stage of labour not described. Blood loss measured.
<i>United States 2004: 200 B vs P</i> ⁶⁷ : Not blinded. Randomization by random number table. [B]	M 200 µg B vs placebo. All women received oxytocin 20 IU IV infusion in 1 L of normal saline at 10 ml/min for 30 minutes (i.e. received oxytocin, approximately 6 IU IV)	Active management of 3rd stage of labour. Blood loss measured.
<i>United States 2005: CS 200 B vs P</i> ⁶⁸ : Outcome blinded. No mention of random number generation scheme. Allocation concealment by pharmacy-assigned numbers to opaque vials containing either misoprostol tablets or oxytocin ampoules. [A]	M 200 µg B vs placebo. All women received oxytocin 20 IU IV in 1000 ml normal saline	All women underwent Caesarean section. Blood loss estimated following "standard" procedures.
<i>WHO 1999: 400/600 PO vs U</i> ¹⁷ : Double blinded. Randomization sequence generated centrally. [A]	M 600 µg PO vs M 400 µg PO vs oxytocin 10 IU IV	Active management of 3rd stage of labour. Blood loss measured.
<i>WHO 2001: 600 PO vs U</i> ^{69,70} : Double blinded. Random allocation sequence generated centrally. [A]	M 600 µg PO + placebo IV/IM, vs oxytocin 10 IU IV/IM + placebo tablets	Active management of 3rd stage of labour. Blood loss measured.
<i>Zimbabwe 2001: 400 PO vs U</i> ⁷¹ : Randomization generated by computer. Blinding not mentioned. [A]	M 400 µg PO + 1 ml saline (placebo) vs oxytocin 10 IU IM + 2 placebo tablets	Management of 3rd stage of labour not described. Blood loss measured.

^a The format used for study identifiers was as follows: country, year, misoprostol (M) dose in micrograms (µ), route of administration (B = buccal; IM = intramuscular; IV = intravenous; PO = oral; PR = rectal; SL = sublingual), misoprostol compared with (vs) placebo (P) or another uterotonic (U).

^b Concealment allocation code: A: adequate; B: unclear; C: inadequate.

Table 2. Maternal deaths and severe morbidity reported in randomized controlled trials of misoprostol to prevent or treat postpartum haemorrhage

Study ^a	Misoprostol group	Control group
China 2001: 600 PO vs U ³¹	No cases	1 hysterectomy in multiparous woman with PPH (5 L) due to uterine atony
China 2004a: 600 PO vs U ³²	PPH (4 L) due to uterine atony in primiparous woman	No cases
Gambia 2004 ³⁷ : 600 PO/SL vs P	No cases	2 hysterectomies, no details reported
Gambia 2005 ³⁸ : 600 PO vs P	1 maternal death from PPH (2.2 L) in gravida 7, para 6, delivered at home 1 maternal death from disseminated intravascular coagulation due to malaria 2 hospital admissions from severe postpartum anaemia	1 hospital admission for PPH and clinical anaemia 2 hospital admissions for severe postpartum anaemia
Guinea-Bissau 2005 ^{14,41} : 600 SL vs P	1 maternal death, PPH (1.4 L), cause of death not established on autopsy	No cases
India 2006c ⁴⁶ : 600 PO vs P	2 ICU admissions	2 ICU admissions
South Africa 2001a ⁵⁵ : 600 PO vs P	1 case of fever > 40 °C	No cases
South Africa 2001b ⁵⁷ : 80 PO vs U	1 internal iliac artery ligation for severe PPH	1 hysterectomy for severe PPH
South Africa 2004 ⁵⁸ : 1000 PO/SL/PR vs P	1 maternal death from severe PPH, coagulopathy, had hysterectomy, died on day 2 postpartum 1 maternal death from severe PPH (3 L) secondary to cervical tear, coagulopathy 1 maternal death from PPH (1 L), hypotension and cardiac arrest, possibly had internal bleeding from dehiscence Caesarean section scar 2 hysterectomies for PPH	No cases
WHO 2001 ^{69,70} : 600 PO vs U	2 maternal deaths 4 hysterectomies 4 ICU admissions 5 cases of fever > 40 °C	2 maternal deaths 8 hysterectomies 5 ICU admissions

ICU, intensive care unit; IV, intravascular; PPH, postpartum haemorrhage.

^a The format used for study identifiers was as follows: country, year, misoprostol (M) dose in micrograms (μ), route of administration (IM = intramuscular; IV = intravenous; PO = oral; PR = rectal; SL = sublingual), misoprostol compared with (vs) placebo (P) or another uterotonic (U).

Maternal deaths

Maternal deaths were reported in five trials.^{14,15,38,58,69} Three other trials specified that there were no maternal deaths.^{30,39,71} No additional maternal deaths were identified through communication with the authors of the included trials.

Fig. 1 (available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>) shows only the five trials in which maternal deaths were reported. Of 11 deaths reported in these trials,^{14,15,38,58,69} 8 occurred in women receiving misoprostol (RR: 2.0; 95% CI: 0.68–5.83; Peto OR: 2.49; 95% CI: 0.76–8.13). Of 8 maternal deaths reported in the misoprostol group, 6 were associated with postpartum haemorrhage.^{14,38,58}

Severe maternal morbidity

Fig. 2 (available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>) shows the data on maternal deaths and severe morbidity as reported in the randomized controlled trials of misoprostol compared with placebo or other uterotonics to prevent or treat postpartum haemorrhage. When misoprostol was compared with other uterotonics, a similar number of adverse events was reported in both prevention and treatment trials: in prevention trials, 16 of 10281 versus 16 of 10292 women, respectively (RR: 1.0; 95% CI: 0.51–1.96); in treatment trials, 1 of 32 women in the treatment as well as the control group (RR: 1.0; 95% CI: 0.07–15.30). When misoprostol was compared with placebo,

slightly more adverse events were reported in the misoprostol group in both prevention and treatment trials: in prevention trials, 8 of 2070 versus 5 of 2032 women, respectively (RR: 1.46; 95% CI: 0.52–4.09); in treatment trials, 5 of 196 versus 2 of 202 women, respectively (RR: 2.06; 95% CI: 0.52–8.17). Events were too few to draw any conclusions.

Table 2 presents descriptions of cases of maternal death and morbidity reported in the trials. In a study from India,¹⁵ one maternal death in the placebo group was not related to haemorrhage. In the WHO (2001) study,⁶⁹ the causes of two deaths in the injectable uterotonic group were not mentioned. A few studies reported admission of the participants to the ICU. One of them was the WHO

(2001) study, in which 9 women were admitted to the ICU: 4 of 9224 in the misoprostol group and 5 of 9231 in the injectable uterotonic group (RR: 0.80; 95% CI: 0.22–2.98).⁶⁹ In a recent study from India, 4 participants were admitted to the ICU: 2 of 812 in the misoprostol group and 2 of 808 in the placebo group.¹⁵

Blood loss ≥ 1000 ml

In the initial analysis of misoprostol versus placebo (Fig. 3, available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>), significant heterogeneity (I^2 : $> 50\%$) was noted in the results for 600 μg (4914 women; RR: 0.92; 95% CI: 0.54–1.57; I^2 : 66%) and for 400 μg (3039 women; RR: 0.80; 95% CI: 0.47–1.37, random effects model; I^2 : 58%). The heterogeneity could not be accounted for by route of administration or trial quality. Rather, it appeared to be related to a single outlier study that contributed data to both subgroups. Removal of this study from the meta-analysis eliminated the significant heterogeneity (I^2 : $< 50\%$). After exclusion of the outlier, less blood loss ≥ 1000 ml was noted with 600 μg of misoprostol (4514 women; RR: 0.77; 95% CI: 0.59–1.00, trend, fixed effects model) and with 400 μg of misoprostol (2642 women; RR: 0.63; 95% CI: 0.44–0.91) than with placebo.

In one small trial in which 200 μg of misoprostol were compared with placebo (in addition to an oxytocin

Table 3. Meta-analysis of direct comparisons and adjusted indirect comparisons of misoprostol, another uterotonic or placebo for risk of PPH

PPH (≥ 1000 ml of blood)	RR	95% CI
Direct comparison, M, 600 μg vs 400 μg	0.841	0.501–1.411
Indirect adjusted comparison, M, 600 μg or 400 μg , vs P	1.420	0.790–2.555
Indirect adjusted comparison, M, 600 μg or 400 μg , vs U	0.931	0.599–1.446
All	1.023	0.707–1.481

CI, confidence interval; M, misoprostol; P, placebo; PPH, postpartum haemorrhage; RR, relative risk; U, uterotonic besides misoprostol.

infusion in both groups) at Caesarean section, no statistically significant difference in blood loss ≥ 1000 ml was found (misoprostol versus placebo: 352 women; RR: 1.13; 95% CI: 0.66–1.94).

When misoprostol was compared with other uterotonics (Fig. 4, available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>), results showed no heterogeneity (I^2 : 0%). Misoprostol, at a dose of 600 to 800 μg , was less effective than other uterotonics (22 827 women; RR: 1.36; 95% CI: 1.17–1.58). Furthermore, the results obtained with 400–500 μg of misoprostol did not differ significantly from those obtained with 600 μg (9772 women; RR: 1.23; 95% CI: 0.96–1.58), even though the sample size was smaller than for the 600–800 μg doses, the direction of the trend was the same.

In one small trial in which misoprostol at a dose of 50 μg administered sublingually was compared with inject-

able uterotonics, no significant difference was found (75 women; RR: 0.33; 95% CI: 0.04–2.62).

When given in addition to routine methods of treatment (Fig. 5, available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>), 600–1000 μg of misoprostol in split doses orally, sublingually and/or rectally was more effective than placebo at reducing an additional blood loss ≥ 500 ml after postpartum haemorrhage (397 women; RR: 0.57; 95% CI: 0.34–0.96).

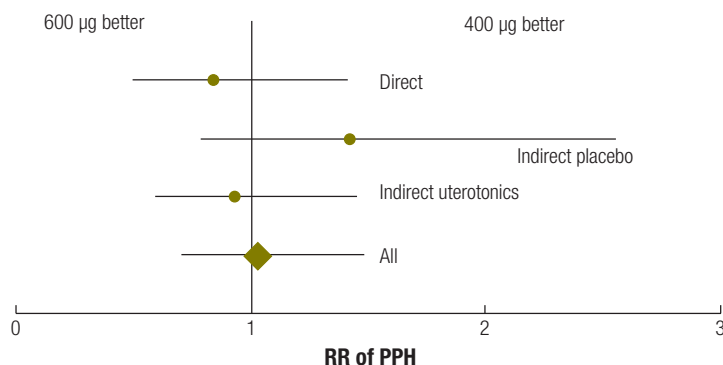
Meta-analysis of direct and adjusted indirect data from randomized trials showed no evidence of a benefit of 600 μg over 400 μg of misoprostol for reducing blood loss ≥ 1000 ml (RR: 1.02; 95% CI: 0.71–1.48; Table 3 and Fig. 6, available at: <http://www.who.int/bulletin/volumes/87/9/08-055715/en/index.html>). A sensitivity analysis excluding the one trial in which active management was not practised¹⁵ produced similar results (data not shown).

Pyrexia

Pyrexia (body temperature ≥ 38 °C or as defined by authors) was higher among women who were given misoprostol in all subgroups (Fig. 7). There was quantitative but not qualitative heterogeneity in the subgroup in which misoprostol, at a dose of 400–500 μg , was compared with other uterotonics (I^2 = 65%). Such heterogeneity could not be explained by route of administration or trial quality.

In comparisons with both placebo and other uterotonics, 600 μg of misoprostol produced pyrexia more often than 400–500 μg : misoprostol, 600 μg versus placebo: 3685 women; RR: 6.71; 95% CI: 4.83–9.32; misoprostol, 400 μg versus placebo: 1996 women; RR: 3.90; 95% CI: 2.27–6.69; misoprostol, 600 μg versus other uterotonics: 22 337 women; RR: 6.76; 95% CI: 5.54–8.25; misoprostol, 400–500 μg versus other

Fig. 7. Meta-analysis^a of direct comparisons (misoprostol, 600 μg vs 400 μg) and adjusted indirect comparisons (misoprostol, 600 μg or 400 μg versus another uterotonic or placebo) for risk of PPH



PPH, postpartum haemorrhage; RR, relative risk.

^a Each horizontal bar represents the 95% confidence interval.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

uterotonics: 8135 women; RR: 3.05; 95% CI: 2.45–3.81. In the two treatment trials, pyrexia was more common in the misoprostol group (392 women; RR: 2.78; 95% CI: 1.39–5.53).

In meta-analysis of direct and adjusted indirect data from randomized trials, pyrexia was more common in the group given 600 µg of misoprostol rather than 400 µg (RR: 2.53; 95% CI: 1.78–3.60; Table 4 and Fig. 8). There was consistency between the estimates derived from the direct and the adjusted indirect comparisons.

Prospective surveillance of adverse events

The 14 most frequent adverse events associated with misoprostol use in the WHO Adverse Reaction Database were as follows (an association does not imply causality): diarrhoea (1001), abdominal pain (687), nausea (394), haemorrhage (294), abortion (209), vomiting (209), dyspepsia (162), flatulence (154), dizziness (152), menorrhagia (125), vaginal haemorrhage (153) and fever (98). Death (53) was the 23rd most common adverse event. Without details of the clinical situations in which these complications occurred, it is not possible to draw conclusions from the data.

Discussion

Misoprostol is used in the third stage of labour primarily to prevent maternal death. Because this is such a rare outcome, no trials to date have been designed to assess the effect on mortality. However, the occurrence of several deaths in misoprostol trials has raised some concern.

It is difficult to evaluate rare adverse outcomes in randomized trials. However, the systematic review of misoprostol trials included in this study provides data on more than 40 000 women. In addition, we complemented our search with adverse events reported to an international centre for such events. To our knowledge, there are no other large population-based datasets or observational studies of maternal deaths or severe adverse outcomes potentially associated with misoprostol use.

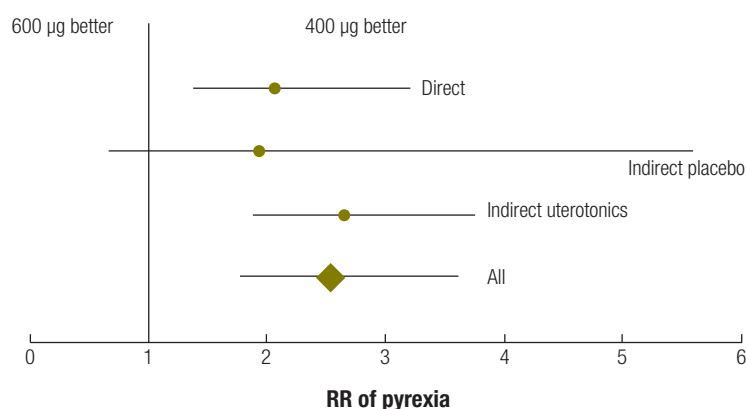
Our systematic review of maternal mortality is limited, first, by the small number of deaths associated with misoprostol use and the wide 95% con-

Table 4. Meta-analysis of direct comparisons and adjusted indirect comparisons of misoprostol, another uterotonic, or placebo for risk of pyrexia

Pyrexia (body temperature ≥ 38 °C)	RR	95% CI
Direct comparison, M, 600 µg vs 400 µg	2.059	1.399–3.031
Indirect adjusted comparison, M, 600 µg or 400 µg, vs P	1.944	0.676–5.596
Indirect adjusted comparison, 600 µg or 400 µg, vs U	2.656	1.878–3.758
All	2.532	1.779–3.604

CI, confidence interval; M, misoprostol; P, placebo; RR, relative risk; U, uterotonic besides misoprostol.

Fig. 8. Meta-analysis^a of direct comparisons (misoprostol, 600 µg vs 400 µg) and adjusted indirect comparisons (misoprostol, 600 µg or 400 µg versus another uterotonic or placebo) for risk of pyrexia (body temperature [t] ≥ 38 °C or as defined by trial authors)



RR, relative risk.

^a Each horizontal bar represents the 95% confidence interval.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

fidence intervals, which are consistent with anything from a modest reduction to a large increase in maternal deaths. Second, this was a post-hoc analysis in response to an observed clustering of maternal deaths, and the statistical calculations need to be interpreted with caution. We recommend prospective surveillance of all randomized trials for further evidence for or against our working hypothesis.

The idea that a drug may have proven benefits against a life-threatening condition yet increase mortality is counterintuitive, but such a thing is plausible. For example, class 1 antiarrhythmics were routinely administered to patients after myocardial infarction because of their proven suppression of ventricular premature depolarizations, a common cause of death after infarction. However, in a double-blind, placebo-controlled trial in 3549 patients who had suffered myocardial infarction and had left ventricular dysfunction, 1 year after randomization

to blinded therapy mortality among drug-treated patients was 10%, compared with 5% in the placebo-treated group ($P = 0.0006$).⁷² Monitoring for unexpected adverse effects is critical before any new medical intervention is introduced.

The cause of death was given for some of the deaths reported in the trials. Some deaths were due to severe haemorrhage, while others did not seem to be directly related to haemorrhage. In addition, deaths were too few to allow for any meaningful interpretation of the role misoprostol or other therapeutic interventions may have played in them.

Although they do not prove our working hypothesis, these results do suggest that misoprostol may have as yet unexplained adverse effects on maternal homeostatic functions in the third stage of labour. The potential for serious side effects is particularly worrisome in connection with the use of misoprostol for preventing, rather than treating, postpartum haemorrhage,

because to prevent a single case of postpartum haemorrhage one would need to treat very large numbers of women.

In estimating the relative effect of 600 µg versus 400 µg of misoprostol on postpartum haemorrhage, we used meta-analysis of direct and adjusted indirect comparisons of randomized trial data to improve the precision of the findings from direct comparisons alone. This method proved useful in an empirical study of 44 meta-analyses.²⁷ We further validated the method by applying it to the same trials for the outcome pyrexia, for which direct data were reasonably precise because pyrexia was more common than haemorrhage. We found that the findings from adjusted indirect comparisons were consistent with those of direct comparisons.

In all studies in which maternal

deaths were reported, misoprostol was given at a dose of ≥ 600 µg. Physiological studies have shown uterotonic effects with doses as low as 200 µg. Our direct and indirect comparisons of data from randomized trials showed no difference in effect size between 600 µg and 400 µg doses. Since misoprostol sometimes produces dose-related side effects such as pyrexia and chills, we suggest that research be undertaken to establish the smallest dose of the drug that is effective and safe.

Because of the enormous benefits of using an effective oral uterotonic in the third stage of labour and since misoprostol could be used in this manner on a large scale worldwide, further research is essential to better assess the potential beneficial and harmful effects of the drug. However, the use of misoprostol should not detract from

international efforts to ensure that all childbearing women have access to conventional uterotonics that have been proven safe and effective. ■

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Résumé

Administration de misoprostol pour prévenir et traiter les hémorragies postpartum : revue systématique et méta-analyse de la mortalité maternelle et des effets dose-dépendants

Objectif Étudier la mortalité maternelle et les effets dose-dépendants du misoprostol sur la perte de sang et la pyrexie dans le cadre d'essais randomisés portant sur l'utilisation de ce médicament pour prévenir et traiter les hémorragies postpartum.

Méthodes Nous avons fait des recherches dans le registre Cochrane des essais contrôlés et dans Pubmed sans émettre de restriction concernant la langue et en utilisant l'expression « (misoprostol AND postpartum) » OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage), puis nous avons évalué les rapports identifiés avec la stratégie de recherche du Groupe Cochrane Pregnancy and Childbirth. Nous avons vérifié la conformité avec les critères d'admissibilité dans l'étude des essais randomisés comparant le misoprostol à un placebo ou à un autre utérotonique dans la prévention ou le traitement des hémorragies postpartum. Nous avons extrait et tabulé des données, puis nous les avons analysées avec le logiciel Reviewer Manager (RevMan) 4.3.

Résultats Dans l'analyse finale, nous avons pris en compte 46 essais portant sur plus de 40 000 participantes. Sur 11 décès rapportés dans 5 essais, 8 sont survenus chez des femmes ayant reçu ≥ 600 µg de misoprostol (Odds ratio de Peto, OR : 2,49 ; intervalle de confiance à 95 %, IC : 0,76-8,13). La morbidité grave, définie comme la nécessité d'une intervention chirurgicale importante, l'admission en soins intensifs, la défaillance d'un organe ou une

température corporelle ≥ 40 °C, était relativement rare. Dans les essais de prévention, nous avons relevé une morbidité grave chez 16 des 10281 femmes sous misoprostol et chez 16 des 10292 parturientes recevant un utérotonique classique et, dans les essais thérapeutiques, chez une des 32 femmes sous misoprostol et chez une des 32 femmes sous utérotonique classique. Les femmes recevant du misoprostol ont manifesté plus d'effets indésirables que celles recevant un placebo : 8 sur 2070 contre 5 sur 2032 respectivement dans les essais de prévention et 5 sur 196 contre 2 sur 202 dans les essais thérapeutiques. La méta-analyse des comparaisons directes et indirectes ajustées des résultats d'essais randomisés n'a fait apparaître aucune preuve d'une efficacité supérieure de la dose de 600 µg de misoprostol par rapport à la dose de 400 µg, dans la prévention d'une perte de sang ≥ 1000 ml (risque relatif, RR : 1,02 ; IC à 95 % : 0,71-1,48). La pyrexie était plus de deux fois plus fréquente chez les femmes ayant reçu ≥ 600 µg de misoprostol que chez celles ayant reçu une dose de 400 µg (RR : 2,53 ; IC à 95 % : 1,78-3,60).

Conclusion Des recherches supplémentaires sont nécessaires pour évaluer plus précisément les effets bénéfiques et nocifs potentiels du misoprostol et pour identifier la plus faible dose de ce médicament à la fois efficace et sans risque. La présente étude a trouvé qu'une dose de 400 µg de misoprostol était plus sûre qu'une dose ≥ 600 µg et tout aussi efficace.

Resumen

Prevención y tratamiento de la hemorragia posparto con misoprostol: revisión sistemática y metanálisis de la mortalidad materna y los efectos dosis-dependientes

Objetivo Analizar la mortalidad materna y los efectos dosis-dependientes del misoprostol sobre la pérdida de sangre y en forma de fiebre en los ensayos aleatorizados realizados sobre su uso con fines de prevención o tratamiento de la hemorragia posparto.

Métodos Utilizamos el Registro de Ensayos Controlados de Cochrane y Pubmed para realizar una búsqueda en todos los idiomas planteada en los siguientes términos: «(misoprostol AND postpartum) OR (misoprostol AND haemorrhage) OR (misoprostol AND hemorrhage)». Se procedió a evaluar los trabajos identificados mediante la estrategia de búsqueda del Grupo Cochrane de Embarazo y Parto, y se determinó la elegibilidad de los ensayos aleatorizados en que se comparó el misoprostol ya fuera con un placebo o con otro uterotónico como forma de prevención o tratamiento de la hemorragia posparto. Los datos extraídos fueron tabulados y analizados con el software Reviewer Manager (RevMan) 4.3.

Resultados Incluimos en el análisis final 46 ensayos que abarcaron a más de 40 000 participantes. De las 11 defunciones notificadas en 5 ensayos, 8 correspondían a mujeres que habían recibido $\geq 600 \mu\text{g}$ de misoprostol (oportunidad relativa [OR] de Peto: 2,49; intervalo de confianza [IC] del 95%: 0,76–8,13). La morbilidad grave, definida como la necesidad de cirugía mayor, el ingreso en cuidados intensivos, la aparición de insuficiencia orgánica o una temperatura corporal $\geq 40^\circ\text{C}$, fue

relativamente poco frecuente. En los ensayos de prevención, sufrieron morbilidad grave 16 de las 10 281 mujeres a las que se administró misoprostol, y 16 de las 10 292 mujeres sometidas a uterotónicos convencionales; en los ensayos de tratamiento, sufrieron cuadros graves 1 de 32 mujeres sometidas a misoprostol y 1 de 32 mujeres tratadas con uterotónicos convencionales. Quienes recibieron misoprostol sufrieron más eventos adversos que quienes recibieron placebo: 8 de 2070 frente a 5 de 2032, respectivamente, en los ensayos de prevención, y 5 de 196 frente a 2 de 202, respectivamente, en los ensayos de tratamiento. El metanálisis de las comparaciones directas e indirectas ajustadas de los resultados de los ensayos aleatorizados no aportó ningún indicio de que la dosis de $600 \mu\text{g}$ sea más eficaz que la de $400 \mu\text{g}$ para prevenir las hemorragias $\geq 1000 \text{ ml}$ (riesgo relativo, RR: 1,02; IC95%: 0,71–1,48). La frecuencia de fiebre entre las mujeres que recibieron $\geq 600 \mu\text{g}$ de misoprostol fue más del doble que en las tratadas con $400 \mu\text{g}$ (RR: 2,53; IC95%: 1,78–3,60).

Conclusión Es necesario realizar nuevas investigaciones para evaluar con más precisión los posibles efectos beneficiosos y nocivos del misoprostol y para determinar la dosis más baja eficaz y segura. Según los resultados de este análisis, las dosis de $400 \mu\text{g}$ de misoprostol son más seguras que las dosis $\geq 600 \mu\text{g}$ y tienen la misma eficacia.

ملخص

الميزوبروستول للوقاية من النزف التالي للولادة ومعالجته: مراجعة منهجية وتحليل تلوي لوفيات الأمهات وللتأثيرات المتعلقة بالجرعة

الهدف: لمراجعة وفيات الأمهات والتأثيرات المتعلقة بجرعة الميزوبروستول على فقدان الدم وعلى الحمى في التجارب المعشاة حول استخدام الميزوبروستول للوقاية من النزف التالي للولادة ومعالجته. **الطريقة:** بحث الباحثون في سجل كوكران للتجارب المعشاة PubMed، دون أي قيود لغوية، عن كلمات (ميزوبروستول وتال للولادة) أو (ميزوبروستول ونزف) أو (ميزوبروستول ونزف دموي)، وأجروا تقييماً للتقارير التي تعرفوا عليها من خلال استراتيجية البحث في مجموعة كوكران للحمل والولادة. وتحقق الباحثون من التجارب المعشاة التي تقارن بين الميزوبروستول مع دواء غفل أو دواء آخر موثّر للرحم بهدف الوقاية من النزف التالي للولادة أو معالجته، من حيث الملاءمة. وقد استخدم الباحثون برنامج إدارة المراجعة (RevMan) بإخراجه الرابعة لاستخلاص المعطيات، وجَدولتها وتحليلها. **الموجودات:** ضم التحليل النهائي 46 دراسة شارك فيها ما يزيد على 40 000 مشاركة، ومن بين 11 وفاة أبلغ عنها في 5 تجارب، حدثت 8 وفيات لدى نسوة تلقين ما يزيد على 600 ميكروغرام من الميزوبروستول (نسبة الأرجحية لبيتو 2.49، وفاصلة الثقة 95%: 0.76 – 8.13). وكان من النادر نسبياً حصول مراضة وخيمة تعرّف بأنها تستدعي إجراء جراحة كبرى أو إدخال إلى الرعاية المركزة، أو فشل أحد الأعضاء، أو ارتفاع درجة حرارة الجسم لأكثر من 40° سيلزيوس. وفي التجارب الخاصة بالوقاية، عانت من مراضة وخيمة، 16 امرأة من بين 10 281 امرأة ممن تلقين الميزوبروستول، و16 امرأة من بين 10 292 تلقين المعالجة التقليدية الموثرة للرحم. أما في التجارب الخاصة بالمعالجة، فقد عانت من مراضة وخيمة، امرأة واحدة من

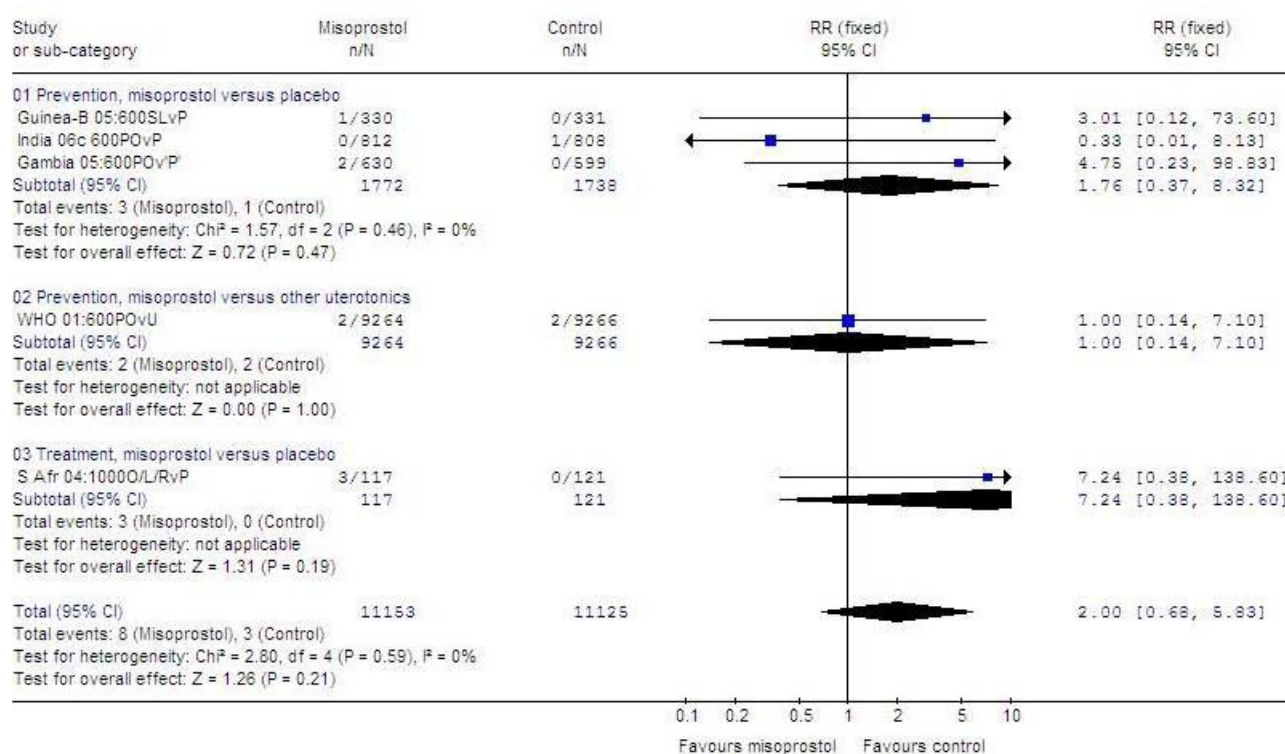
بين 32 امرأة ممن تلقين الميزوبروستول، وامرأة واحدة من بين 32 امرأة تلقين المعالجة التقليدية. وهكذا عانت النسوة اللاتي تلقين الميزوبروستول من أحداث ضائرة أكثر مما عانت منها النسوة اللاتي تلقين الدواء الغفل: حيث عانت 8 من بين 2070 من النسوة اللاتي تلقين الميزوبروستول من أحداث ضائرة، وهو أكثر مما عانت منه النساء اللاتي تلقين دواءً غفلاً وهن 5 من أصل 2032؛ وذلك في التجارب الوقائية، أما في تجارب المعالجة، فقد عانت 5 من أصل 196 ممن تلقين الميزوبروستول، من أحداث ضائرة، فيما عانت 2 من أصل 202 ممن تلقين المعالجة بالدواء الغفل. وقد أوضح التحليل التلوي للمقارنات المباشرة والمقارنات غير المباشرة المعدلة لنتائج التجارب المعشاة عدم وجود بينة على أن إعطاء 600 ميكروغرام هو أكثر فعالية من إعطاء 400 ميكروغرام للوقاية من فقدان 1000 ميلي لتر أو أكثر من الدم (فالاختطار النسبي 1.02 بفاصلة ثقة 95%: 0.71 – 1.48). وقد كانت الحمى أكثر شيوعاً لدى من تلقين أكثر من 600 ميكروغرام من الميزوبروستول، بمقدار الضعف مما كانت عليه لدى اللاتي تلقين 400 ميكروغرام منه (الاختطار النسبي 2.53، وفاصلة الثقة 95%: 1.78 – 3.60). **الاستنتاج:** تمس الحاجة إلى المزيد من البحوث للحصول على تقييم أكثر دقة للتأثيرات المفيدة والمحتملة وللتأثيرات الضائرة لاستخدام الميزوبروستول، وللتعرف على الجرعة الأصغر التي تتمتع بالفعالية (النجاعة) والمأمونية. وقد وجد الباحثون في هذه الدراسة أن جرعة مقدارها 400 ميكروغرام من الميزوبروستول تعد أكثر مأمونية من جرعة مقدارها 600 ميكروغرام منه، رغم أنها تتمتع بنفس القدر من الفعالية (النجاعة).

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Fig. 1. Maternal deaths^a reported in randomized trials of misoprostol^b versus placebo or another uterotonic to prevent or treat PPH



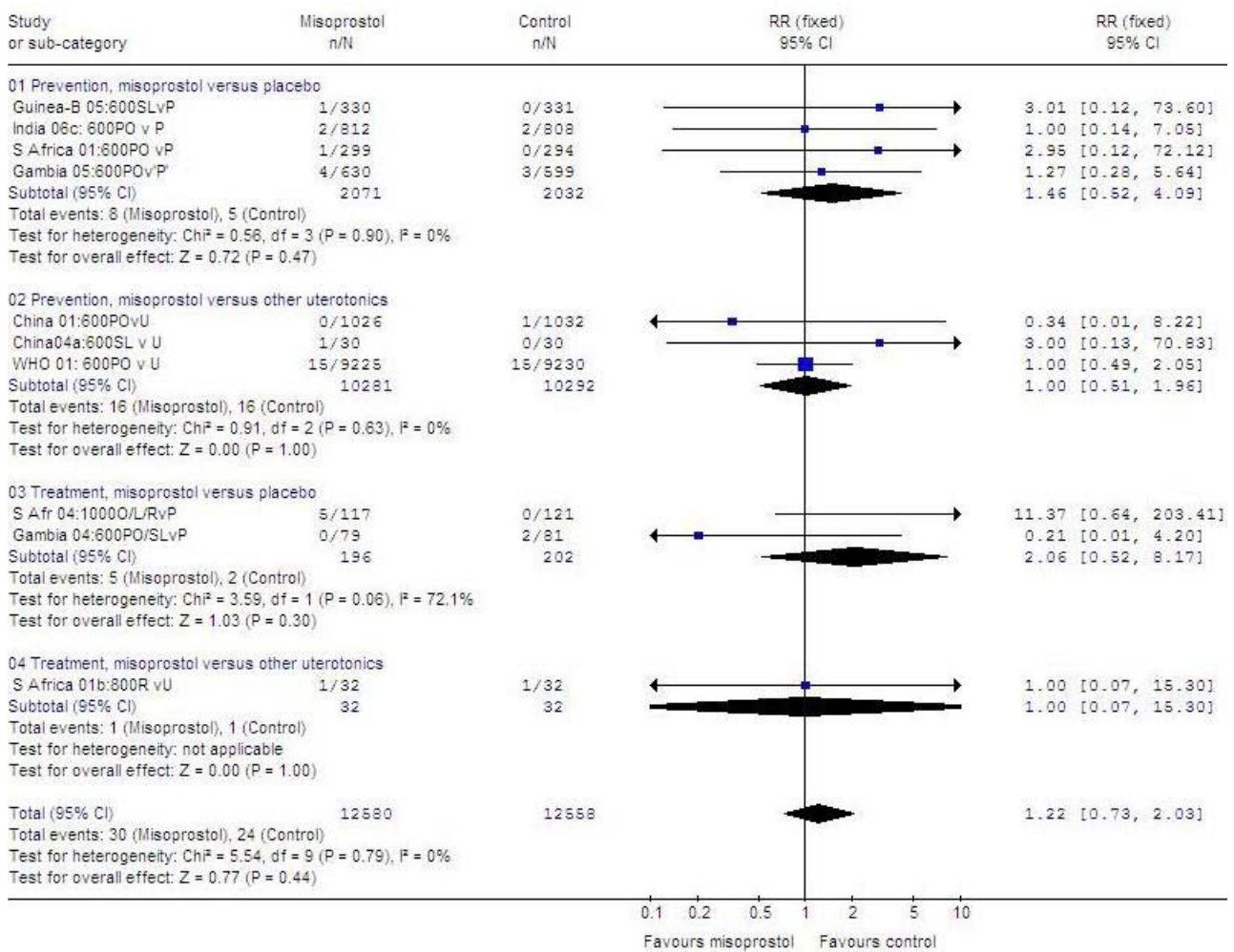
CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual; O or PO, oral; P, placebo; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Afr, South Africa; U, uterotonic other than misoprostol.

^a Trials that did not report maternal deaths are not shown. The denominators for all trials are 21 814 for misoprostol groups and 22 526 for control groups. Meta-analysis with all trials included yielded the same RR and 95% CI.

^b Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 2. Randomized trials^a of misoprostol^b versus placebo or another uterotonic to prevent or treat PPH



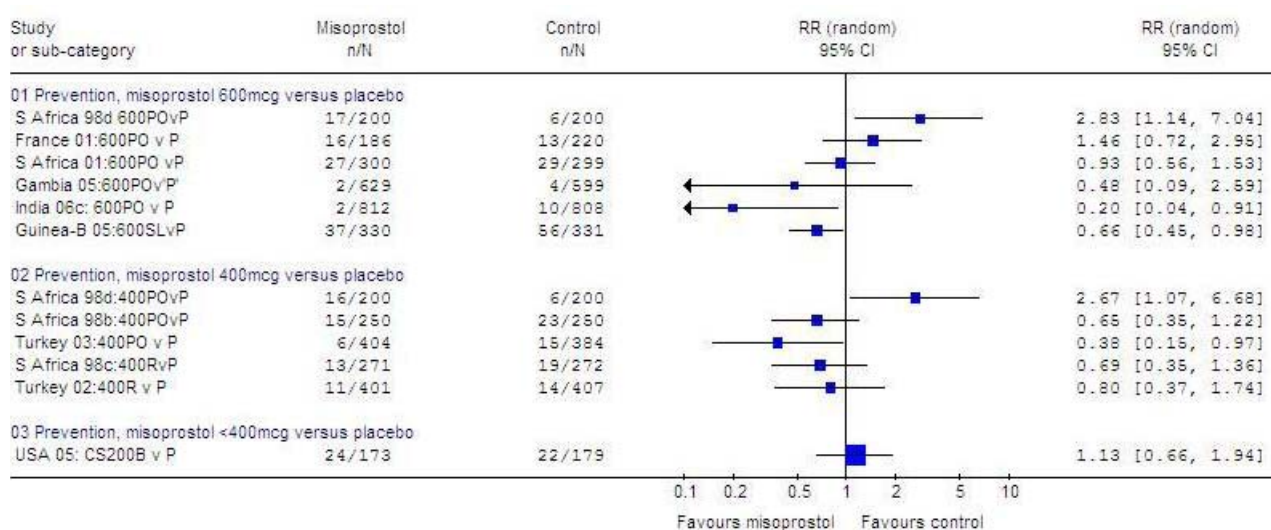
CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual, O or PO, oral; P, placebo; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa; U, uterotonic other than misoprostol.

^a Outcome variables: maternal death or severe morbidity.

^b Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 3. Randomized trials of misoprostol^a versus placebo to prevent PPH, effect on blood loss ≥ 1000 ml

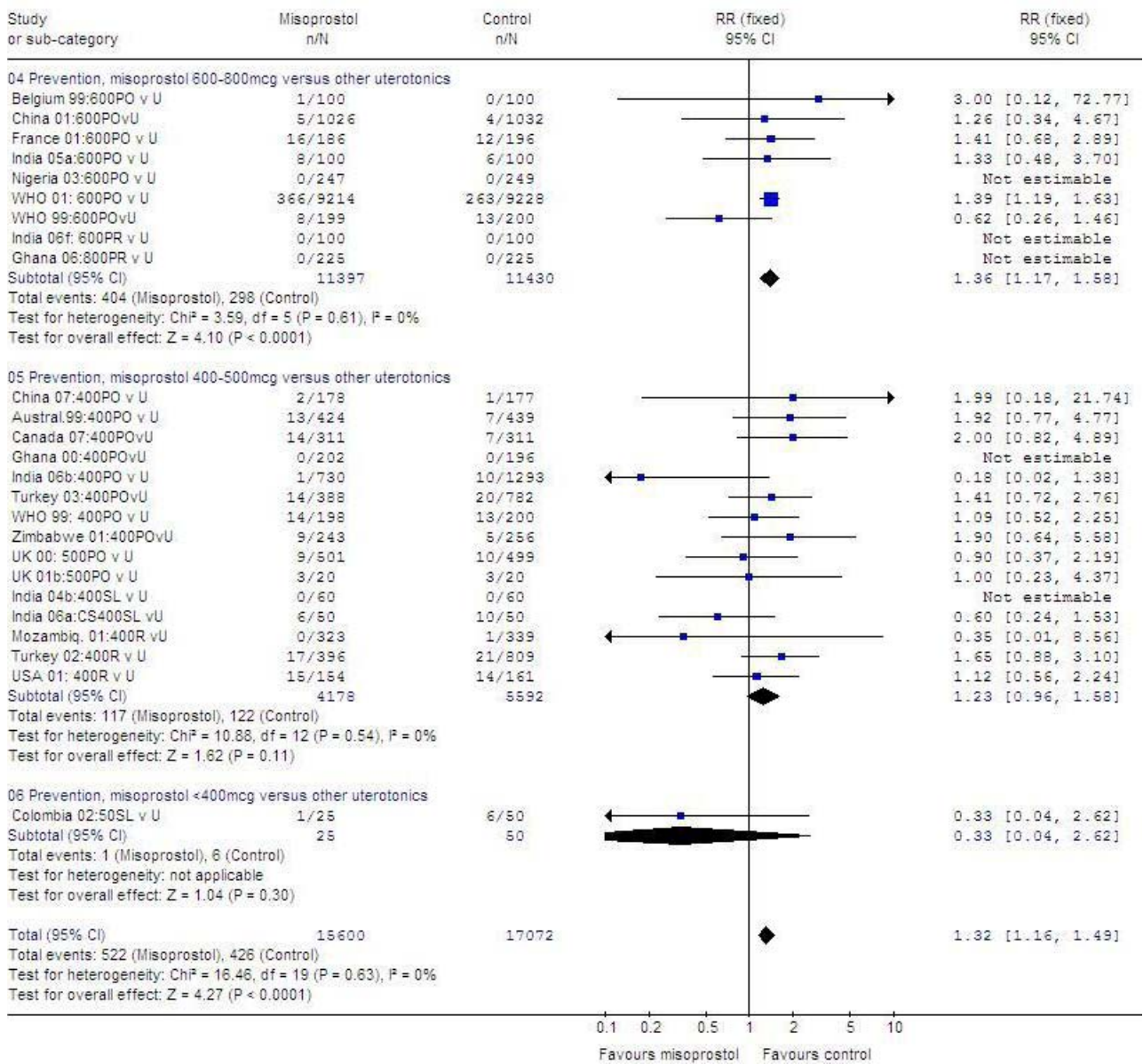


CB, buccal; CI, confidence interval; CS, Caesarean section; SL, sublingual; P, placebo; PO, oral; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa; USA, United States of America.

^a Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

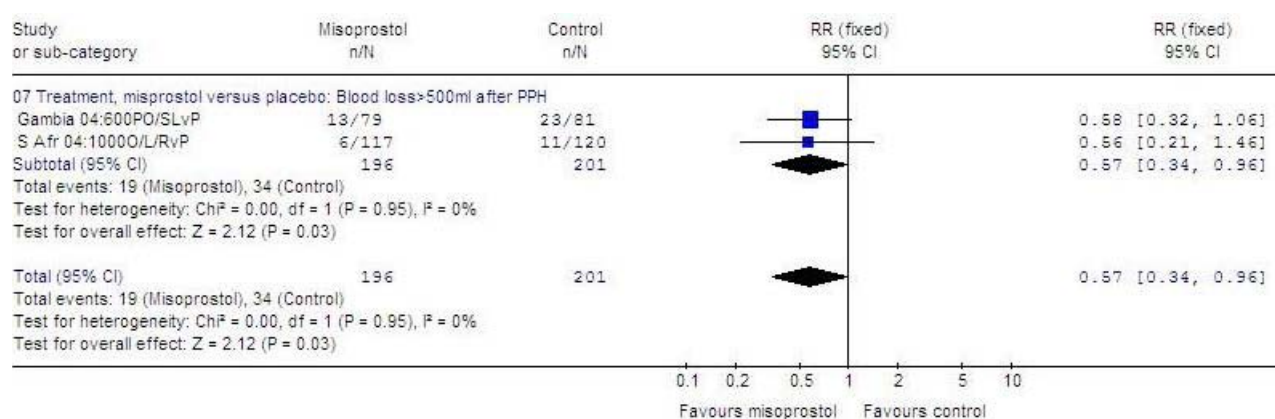
Fig. 4. Randomized trials of misoprostol^a versus another uterotonic to prevent PPH, effect on blood loss ≥ 1000 ml



CI, confidence interval; CS, Caesarean section; PO, oral; PPH, postpartum haemorrhage; R or PR, rectal; RR, relative risk; S Africa, South Africa; SL, sublingual; U, uterotonic other than misoprostol; UK, United Kingdom; USA, United States of America.

^a Misoprostol dose always in micrograms.

Fig. 5. Randomized trials of misoprostol^a versus placebo to treat PPH, effect on additional blood loss \geq 500 ml following postpartum haemorrhage

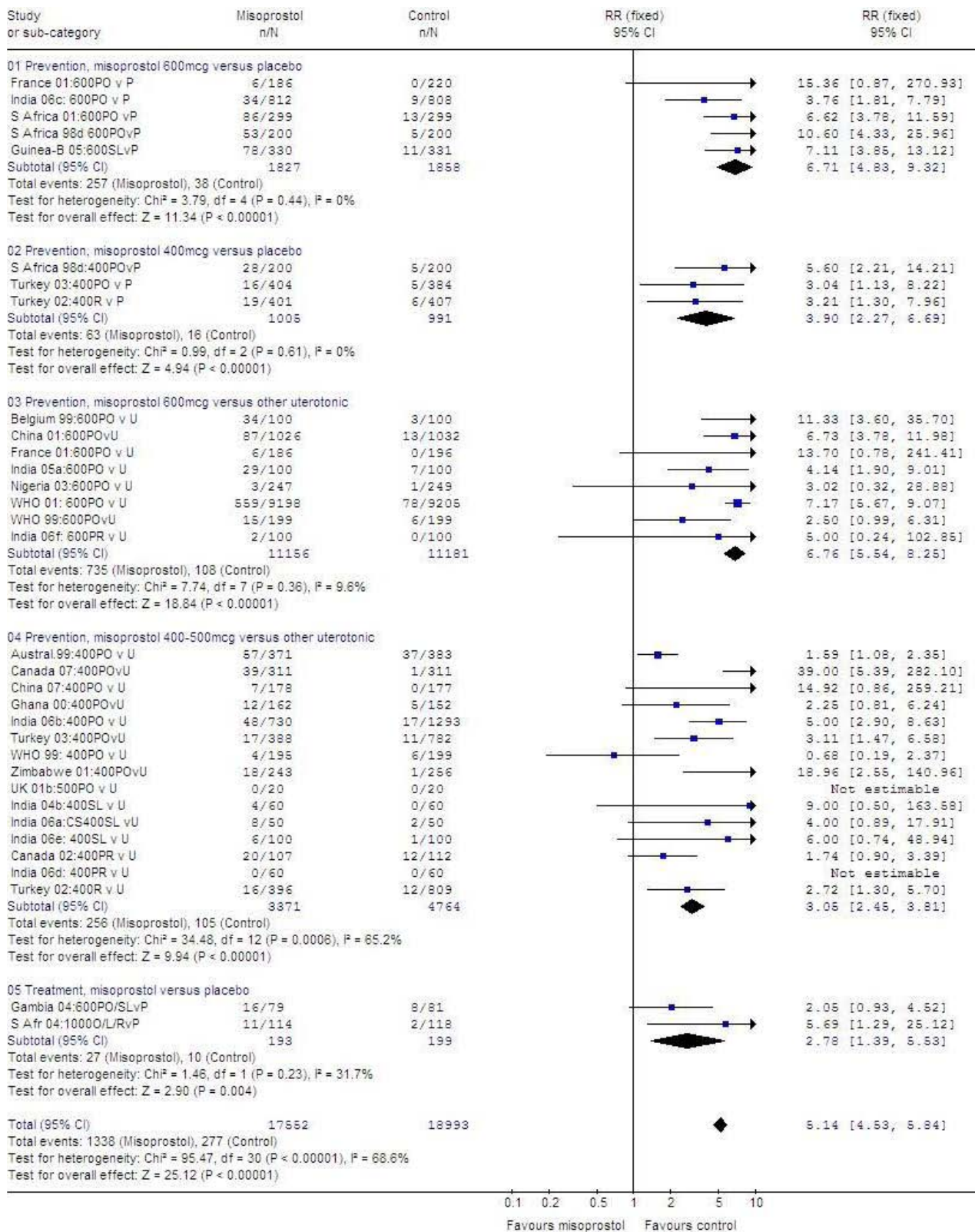


CI, confidence interval; L or SL, sublingual; PO, oral; PPH, postpartum haemorrhage; R, rectal; RR, relative risk; S Africa, South Africa.

^a Misoprostol dose always in micrograms.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Fig. 6. Randomized trials of misoprostol^a versus placebo or another uterotonic to prevent or treat PPH, effect on pyrexia (body temperature [t] ≥ 38 °C or as defined by trial authors^b)



CI, confidence interval; Guinea-B, Guinea-Bissau; L or SL, sublingual, O or PO, oral; P, placebo; PPH, postpartum haemorrhage; PR or R, rectal; S Afr or S Africa, South Africa; U, uterotonic other than misoprostol; UK, United Kingdom.

^a Misoprostol dose always in micrograms.

^b t > 37.1 °C in India 06b; t ≥ 37.3 °C in Australia 99; t ≥ 37.5 °C in Gambia 04 and Ghana 04; t ≥ 37.8 °C in S Africa 98d, 01; t > 37.9 °C in Canada 02; t > 38 °C in Canada 07, Turkey 02, Turkey 03, WHO 99, WHO 01 and Zimbabwe 01; t ≥ 38 °C in Belgium 99, China 01, China 07, France 01, India 04b, India 06f, Guinea-B 05 and Nigeria 03; t ≥ 38.5 °C in S Africa 04; t > 39 °C in France 01; t undefined in India 05a, India 06a, India 06c, India 06d and India 06e.

Graph generated by Review Manager (RevMan) 4.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).