Postpartum misoprostol for preventing maternal mortality and morbidity

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Key findings

This updated review found:

- This review focused on safety of use of misoprostol for prevention or treatment, and did not explore effectiveness of misoprostol in terms of blood loss.
- Outcomes of interest were death or severe morbidity (including major surgery, ICU admission, vital organ failure and hyperpyrexia)
- The number of maternal deaths was too small for analysis
- Maternal death/severe morbidity (composite outcome) was increased with misoprostol use, largely due to hyperpyrexia when misoprostol was used in dosages of 600 micrograms or more
- However, two studies contributed most maternal morbidity cases, especially a high incidence of hyperpyrexia in Ecuador. When hyperpyrexia was excluded, there was no evidence of an increase or a reduction in the risk of maternal mortality/severe morbidity when using misoprostol, compared to other uterotonic drugs, placebo or no treatment.

Evidence included in this review

Seventy-eight randomized controlled trials (59,216 women) were included in this review. Trials were mostly of PPH prevention in vaginal birth and compared misoprostol to other uterotonic agents.

Quality assessment

The methodological quality of trials included was variable, although most of the trials reporting data on maternal mortality were at low risk of bias. While results showed high heterogeneity, this was eliminated after the exclusion of two outlier studies in a sensitivity analysis.

Clinical implications

This review assessed safety of misoprostol use. Studies included were of women receiving misoprostol for prevention or treatment of PPH, not for abortion or induction of labour. There was an increased and dose-related risk of pyrexia in misoprostol groups. Authors suggest possible genetic predisposition for high rates of hyperpyrexia in a trial conducted in Ecuador. Maternal deaths occurred in women receiving doses of 600 µg or more.

Further research
If considering misoprostol as an alternative in the prevention of maternal mortality due to PPH at community level, future trials are needed. These trials should be powerful enough to confirm serious adverse events, effectiveness and dosages, especially as misoprostol is currently used prophylactically in healthy women.

**Cochrane review**


**Abstract**

The primary objective of postpartum haemorrhage (PPH) prevention and treatment is to reduce maternal deaths. Misoprostol has the major public health advantage over injectable medication that it can more easily be distributed at community level. Because misoprostol might have adverse effects unrelated to blood loss which might impact on mortality or severe morbidity, it is important to continue surveillance of all relevant evidence from randomised trials. This is particularly important as misoprostol is being introduced on a large scale for PPH prevention in low-income countries, and is commonly used for PPH treatment in well-resourced settings as well.

To review maternal deaths and severe morbidity in all randomised trials of misoprostol for prevention or treatment of PPH.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (11 January 2013).

We included randomised trials including pregnant women who received misoprostol in the postpartum period, versus placebo/no treatment or other uterotonics for prevention or treatment of PPH, and reporting on maternal death, severe morbidity or pyrexia.

We planned to include cluster- and quasi-randomised trials in the analysis, as a very large number of women will be needed to obtain robust estimates of maternal mortality but we did not identify any for this version of the review. In future updates of this review we will include trials reported only as abstracts if sufficient information is available from the abstract or from the authors.

Two review authors independently assessed trials for inclusion and extracted data.

We included 78 studies (59,216 women) and excluded 34 studies. There was no statistically significant difference in maternal mortality for misoprostol compared with control groups overall (31 studies; 11/19,715 versus 4/20,076 deaths; risk ratio (RR) 2.08, 95% confidence interval (CI) 0.82 to 5.28); or for the trials of misoprostol versus placebo: 10 studies, 6/4626 versus 1/4707; RR 2.70; 95% CI 0.72 to 10.11; or for misoprostol versus other uterotonics: 21 studies, 5/15,089 versus 3/15,369 (19/100,000); RR 1.54; 95% CI 0.40 to 5.92. All 11 deaths in the misoprostol arms occurred in studies of misoprostol ? 600 µg.

There was a statistically significant difference in the composite outcome ‘maternal death or severe morbidity’ for the comparison of misoprostol versus placebo (12 studies; average RR 1.70, 95% CI 1.02 to 2.81; $\tau^2 = 0.00, P = 0\%$) but not for the comparison of misoprostol versus other uterotonics (17 studies; average RR 1.50, 95% CI 0.50 to 4.52; $\tau^2 = 1.81, P = 69\%$). When we excluded hyperpyrexia from the composite outcome in exploratory analyses, there was no significant difference in either of these comparisons.
Pyrexia > 38°C was increased with misoprostol compared with controls (56 studies, 2776/25,647 (10.8%) versus 614/26,800 (2.3%); average RR 3.97, 95% CI 3.13 to 5.04; Tau² = 0.47, P = 80%). The effect was greater for trials using misoprostol 600 µg or more (27 studies; 2197/17,864 (12.3%) versus 422/18,161 (2.3%); average RR 4.64; 95% CI 3.33 to 6.46; Tau² = 0.51, P = 86%) than for those using misoprostol 400 µg or less (31 studies; 525/6751 (7.8%) versus 185/7668 (2.4%); average RR 3.07; 95% CI 2.25 to 4.18; Tau² = 0.29, P = 58%).

Misoprostol does not appear to increase or reduce severe morbidity (excluding hyperpyrexia) when used to prevent or treat PPH. Misoprostol did not increase or decrease maternal mortality. However, misoprostol is associated with an increased risk of pyrexia, particularly in dosages of 600 µg or more. Given that misoprostol is used prophylactically in very large numbers of healthy women, the greatest emphasis should be placed on limiting adverse effects. In this context, the findings of this review support the use of the lowest effective dose. As for any new medication being used on a large scale, continued vigilance for adverse effects is essential and there is a need for large randomised trials to further elucidate both the relative effectiveness and the risks of various dosages of misoprostol.

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