WHO/RHR/12.29

WHO recommendations for the prevention and treatment of postpartum haemorrhage

Evidence base

World Health Organization

Contents

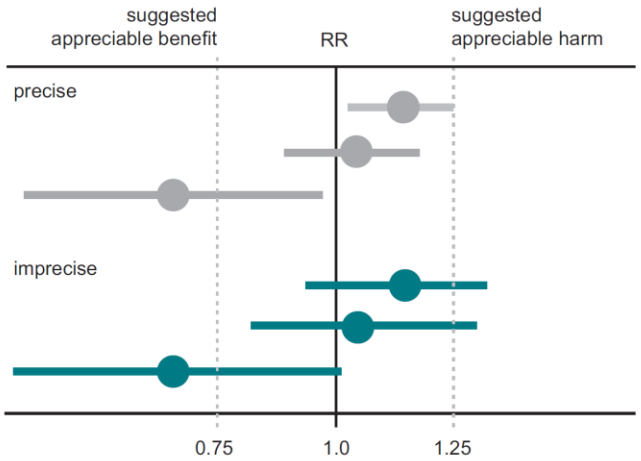
Standard criteria for grading of evidence

Box 1: Standard criteria for grading of evidence 1

Domain	Grade	Characteristic
STUDY DESIGN	0	All randomized controlled trials
	–2	All observational studies
STUDY DESIGN LIMITATIONS	0	Most of the pooled effect provided by studies, with low risk of bias ("A")
	–1	Most of the pooled effect provided by studies with moderate (“B”) or high (“C”) risk of bias. Studies with high risk of bias weighs <40%
	–2	Most of the pooled effect provided by studies with moderate (“B”) or high (“C”) risk of bias. Studies with high risk of bias weighs ≥40%
	Note:	Low risk of bias (no limitations or minor limitations) –“A” Moderate risk of bias (serious limitations or potentially very serious limitations including unclear concealment of allocation or serious limitations, excluding limitations on randomization or concealment of allocation) –“B” High risk of bias (Limitations for randomization, concealment of allocation, including small blocked randomization (<10) or other very serious, crucial methodological limitations) –“C”
INCONSISTENCY	0	No severe heterogeneity (I^2<60% or $\chi^2 \geq 0.1$)
	–1	Severe, non-explained, heterogeneity (I2≥ 60% or χ^2<0.1) If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness should not be downgraded twice)
INDIRECTNESS	0	No indirectness
	–1	Presence of indirect comparison, population, intervention, comparator, or outcome.

1 Adapted from: Schünemann H, Brozek J, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available at: <http://ims.cochrane.org/revman/gradepro>. (This document is contained within the "Help" section of the GRADE profiler software version v.3.2.2.)

Box1 (cont.). Standard criteria for grading of evidence 1

Domain	Grade	Characteristic
IMPRECISION	0	The confidence interval is precise according to the figure below. The total cumulative study population is not very small (i.e. sample size is more than 300 participants) and the total number of events is more than 30. 
	–1	One of the above-mentioned conditions is not fulfilled.
	–2	The two above-mentioned are not fulfilled.
	Note: If the total number of events is less than 30 and the total cumulative sample size is appropriately large (e.g. above 3000 patients, consider not downgrading the evidence). If there are no events in both intervention and control groups, the quality of evidence in the specific outcome should be regarded as very low.	
PUBLICATION BIAS	0	No evident asymmetry in the funnel plot or less than five studies to be plotted.
	–1	Evident asymmetry in funnel plot with at least five studies.

Note: All observational studies will start as low quality evidence but non-controlled studies (e.g. case series) will be further downgraded to very-low quality.

Narrative Summaries of evidence

Recommendation 1: The use of uterotonics during the third stage of labour

Uterotonics in the context of a package of interventions active management of the third stage of labour

- Evidence related to the 'active management of the third stage of labour' consisted of one systematic review of seven RCTs (>8000 women) which compared active management versus expectant (physiological) management.
- All the studies were hospital-based: four were conducted in high-income countries (the UK, Ireland, Sweden and Abu Dhabi) and one was conducted in a low-income country setting (Tunisia).
- The interventions in these studies used different combinations of the 'active management' components, including different types of doses, different routes for the administration of uterotonics, different timings for cord clamping, and the non-standardized use of cord traction.
- The studies in this review did not report any maternal deaths.
- For the priority outcomes, the overall results showed a statistically significant reduction in severe PPH (defined as a blood loss >1000 ml) (RR 0.34; 95% CI 0.14 to 0.87), blood transfusions (RR 0.35; 95% CI 0.22 to 0.55), and the use of additional uterotonics (RR 0.19; 95% CI 0.15 to 0.23).
- The frequency of the following adverse effects increased in the groups that received active management: vomiting (RR 2.47; 95% CI 1.36 to 4.48), abdominal pain (RR 2.53; 95% CI 1.34 to 4.78), requirements for postnatal analgesia RR 2.53 95% CI 1.34 to 4.78), and postnatal diastolic hypertension (RR 4.1; 95% CI 1.63 to 10.3). There was an observed increase in the return of patients to hospital as inpatients or outpatients due to bleeding (RR 2.21; 95% CI 1.29 to 3.79). However, only three trials reported side-effects and these all related to the use of ergometrine or syntometrine as a uterotonic drug.
- There was no significant change in the manual removal of placenta, or the need for surgical evacuation of the retained products of conception.
- In addition to the evidence presented both here and in the associated GRADE tables, evidence related to the role of controlled cord traction (CCT) and uterine massage has also been considered and is presented separately.
- There is a paucity of evidence related to the precise timing of the administration of uterotonics both in relation to the birth of the baby and to cord clamping.

Uterotonics as a single intervention in the third stage of labour

- A systematic review included two randomized trials (1221 women) which reported on the use of oxytocin in the absence of active management. In these trials, oxytocin was either administered by IM injection (5 IU) or IV (10 IU).

- The trials investigated the use of oral misoprostol (>3600 women) and compared a 600 mcg oral dose of misoprostol versus placebo for the prevention of PPH. However, only one trial (India 2006) was conducted in the context of the expectant management of the third stage of labour performed by auxiliary nurse midwives (this trial provides the evidence base for this recommendation).

- Maternal deaths were not reported.

- The use of misoprostol was associated with less blood loss >1000 ml (RR 0.20; 95% CI 0.04 to 0.91), less blood loss >500 ml (RR 0.53; 95% CI 0.39 to 0.74). The use of oxytocin, in contrast, was associated with the reduced use of additional uterotonic drugs (RR 0.66; 95% CI 0.48 to 0.9), and less blood loss >500 ml (RR 0.61; 95% CI 0.51 to 0.73).

- The use of oral misoprostol was associated with adverse outcomes, and increases in the occurrence of shivering and hyperthermia were reported.

Source of evidence

19. Begley CM, Gyte GM, Murphy DJ, Devane D, McDonald SJ, McGuire W. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2011(7):CD007412. In editorial process.

See GRADE Table 1

26. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews.Art. No.: CD001808. In editorial process.

See GRADE Tables 2-3

53. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006 Oct 7;368(9543):1248-53.

Recommendations 2-3: Choice of uterotonic drugs for the prevention of PPH

- All the trials were conducted in settings with skilled attendants.
- Alternative uterotonic drugs were evaluated in two systematic reviews (20 trials, 18 266 women).
- The treatments compared were: ergometrine (or derivatives) versus oxytocin; ergometrine only versus the fixed dose combination of ergometrine and oxytocin; ergometrine-oxytocin versus oxytocin (the doses and routes varied); IV oxytocin versus IV ergometrine; IM oxytocin versus IM ergometrine; IM oxytocin/ergometrine (as a fixed combination) versus IM ergometrine only; and IV oxytocin versus IM oxytocin/ergometrine (as a fixed combination).
- The doses of oxytocin varied in the different trials and ranged between 2 IU and 10 IU, while the doses of ergometrine ranged between 0.2 mg and 4 mg. The fixed drug combination consisted of a 5 IU dose of oxytocin with a 0.5 mg dose of ergometrine.
- None of the trials reported maternal deaths.

Oxytocin versus ergot alkaloids (9 trials, 3960 women)

- There were no observed differences in critical outcomes between the use of oxytocin versus ergot alkaloids.
- A reduction in blood loss >500 ml was observed (RR 0.8; 95% CI 0.65 to 0.99) with the use of oxytocin when compared with the use of ergot alkaloids. However, the data quality was low and there is a high risk of bias for this outcome.
- Among the adverse outcomes rated as important, the comparison of oxytocin versus ergometrine (or derivatives) showed a lower rate of adverse effects in women treated with oxytocin only. These included nausea (RR 0.13; 95% CI 0.08 to 0.21; NNT 5, 95% CI 4 to 6); vomiting (RR 0.08; 95% CI 0.05 to 0.14; NNT 4, 95% CI 3 to 5) and headache (RR 0.03; 95% CI 0.01 to 0.14).
- There was no observed difference in high blood pressure in women treated with oxytocin only (RR 0.53; 95% CI 0.19 to 1.52), though the quality of evidence was low.
- A lower rate for the manual removal of the placenta was reported in women treated with oxytocin (RR 0.60; 95% CI 0.45 to 0.8)

Oxytocin versus fixed drug combination oxytocin-ergometrine (7 trials, >10 000 women)

- The use of the fixed drug combination of oxytocin and ergometrine (IM) was not associated with a reduction in the use of additional uterotonics (RR 1.27; 95% CI 0.91 to 1.76) when compared with the use of IV oxytocin only (two trials, >1600 women). No significant difference was observed between the two groups when blood loss or the need for blood transfusion was compared. Among the adverse outcomes rated as important, the fixed dose of oxytocin-ergometrine was associated with a significant increase in vomiting (RR 3.33; 95% CI 1.21 to 9.2) as well as the elevation of diastolic blood pressure (OR 1.96; 95% CI 1.16 to 3.30)

compared with a dose of IV oxytocin only

- When the fixed drug combination of oxytocin and ergometrine (IM) was compared with IM oxytocin only (five trials, 8341 women) reductions in the use of additional uterotonics (RR 0.78; 95% CI 0.66 to 0.91) and blood loss >500 ml (RR 0.84; 95% CI 0.74 to 0.96) were reported. No differences were found in blood loss >1000 ml, the use of blood transfusion, or the use of the manual removal of the placenta. The side-effects among those receiving oxytocin plus ergometrine, as well as those receiving IV oxytocin, included more frequent nausea, vomiting and hypertension.

Ergometrine versus the fixed drug combination of oxytocin-ergometrine (5 trials, >4200 women)

- A significant reduction in blood loss >500 ml (RR 0.57; 95% CI 0.4 to 0.81) was reported in women who received the fixed dose combination of oxytocin-ergometrine compared with those who received ergometrine only. This finding was not reported for blood loss >1000 ml (RR 1.67; 95% CI 0.4 to 6.94), though the sample size was small and the event rate was noted to be lower. No differences were found in the use of blood transfusion or the manual removal of the placenta.
- Other priority adverse outcomes were not reported for this comparison.
- There is currently no evidence to support the use of either oxytocin or ergometrine for the prevention of PPH by non-skilled attendants. Before recommending the general use of injectable drugs that may have adverse effects, appropriate studies of their use by non-skilled attendants should be conducted.

Source of evidence

130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*
26. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews.Art. No.: CD001808. In editorial process.*

See GRADE Tables 4-6

Oxytocin versus misoprostol

- Evidence for this comparison is based on one systematic review which included seven trials (>22 000 women) which compared the two treatments directly. The oxytocin doses varied between the studies and ranged from 2.5 IU to 10 IU. In the largest trial, which included more than 18 000 women, a dose of 10 IU of oxytocin was used and the misoprostol dose was 600 mcg.
- Among the priority outcomes, two maternal deaths were reported in each arm of the largest trial.
- In six trials (21 977 women), blood loss >1000 ml was reported to have increased with the use of misoprostol compared with the use of 10 IU oxytocin IM (RR 1.36; 95% CI 1.17 to1.58; NNT 105, 95% CI 70 to 200).
- There was no statistically significant difference in the use of blood transfusion when misoprostol was used compared with oxytocin (RR 0.77; 95% CI 0.59–1.02). However, there was a greater use of additional uterotonics when misoprostol was used compared with oxytocin (RR 1.4; 95% CI 1.31 to 1.5; NNT 22, 95% CI 19 to

28)

- Among the important adverse effects reported, misoprostol was associated with an increase in shivering (RR 3.3; 95% CI 3.0 to 3.5; NNH 7, 95% CI 7 to 8), diarrhoea (RR 2.52; 95% CI 1.6 to 3.98; NNH 261, 95% CI 177 to 494), and temperatures higher than 38 °C (RR 6.8; 95% CI 5.5 to 8.3; NNH 18, 95% CI 16 to 19).

- The evidence provided came from studies conducted in hospital settings in which the interventions were provided by skilled attendants.

Source of evidence

209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

See GRADE Table 7

Sublingual misoprostol 600 mcg versus injectable uterotonics

- There was one systematic review of eight relevant trials (>1000 women) that compared the use of sublingual misoprostol versus other uterotonics.

- Only two of these trials (220 women) compared the use of sublingual misoprostol (600 mcg) versus IV syntometrine (one trial) and IV oxytocin (5 IU) (one trial).

- There was no difference in blood loss >1000 ml, although the sample size was insufficiently large to rule out potentially relevant differences. An increased risk of side-effects was reported, namely shivering (RR 27; 95% CI 1.63 to 446.10; NNH 6, 95% CI 4 to11), and pyrexia ≥38 °C (RR 33; 95% CI 2.02 to 540.22; NNH 5, 95% CI 3 to 8).

Sublingual misoprostol (any dose) versus injectable uterotonics

- A further five trials compared a sublingual 400 mcg dose of misoprostol versus injectable uterotonics (0.2 mg methylergometrine IV, and 5 IU and 20 IU of IV oxytocin), one study compared a dose of 200 mcg misoprostol versus 0.2 mg methylergometrine, and another compared a 50 mcg misoprostol dose with either oxytocin 16 IU or methylergometrine 0.2 mg.

- Maternal deaths were not reported.

- There were no observed differences in critical outcomes between the use of sublingual misoprostol (any dose) and injectable uterotonics, except for a significant increase in the use of additional uterotonics among those receiving injectable uterotonics compared with those receiving sublingual misoprostol (RR 0.61; 95% CI 0.44 to 0.85).

- Among the adverse outcomes rated as important, higher incidences of shivering (RR 9.06; 95% CI 4.46 to 19.39) and maternal temperatures above 38 °C were reported among women who received sublingual misoprostol (RR 13.04; 95% CI 4.77 to 35.62) compared with those women who had received injectable

uterotonics. There was no difference between the groups in reported diarrhoea, headache, nausea and vomiting, or the need for the manual removal of the placenta.

Source of evidence

209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

See GRADE Tables 8-9

Rectal misoprostol 400 mcg versus injectable uterotonics

- Lower doses of rectal misoprostol (400 mcg) were used in five studies (>2100 women). In one of these trials, misoprostol was dissolved in 5 ml of saline and administered rectally as a micro-enema. Two trials used IM oxytocin (10 IU and 20 IU) as the comparator, and one used oxytocin 5 IU IV or IM, or 10 IU IM. A combination of ergometrine and oxytocin was used in two trials.
- No difference between the treatments was reported regarding the priority outcomes except with regard to the use of additional uterotonics. This outcome measure was reported in three of the five trials (1210 women) and this was reported to be higher in the groups that received misoprostol (RR 1.64; 95% CI 1.16 to 2.31; NNH 8; 95% CI 5 to 27). The relatively low number of subjects, however, suggests that small differences may not have been detected. Among the important adverse outcomes, rectal misoprostol 400 mcg was associated with more shivering (RR 2.34; 95% CI 1.88 to 2.92), and pyrexia ≥38 °C (RR 2.08; 95% CI 1.21 to 3.57)

Rectal misoprostol 600 mcg versus oxytocin

- Only one study (200 women) in the systematic review compared the use of 600 mcg misoprostol administered rectally versus 10 IU oxytocin IM.
- Maternal deaths, severe PPH (blood loss >1000 ml) and the use of blood transfusions were reported in this trial. There were no differences in blood loss >500 ml, the manual removal of the placenta, or the use of additional uterotonics. Among the important adverse effects, there were no observed differences reported in nausea, shivering, or temperatures above 38 °C, although the sample size was very small.

Rectal misoprostol 800 mcg versus oxytocin

- Two trials (>950 women) compared higher doses of rectal misoprostol (800 mcg) versus oxytocin (5 IU IV or 10 IU IM). There were no significant differences between the groups in terms of the critical outcomes. Among the adverse outcomes reported, there was a significant increase in shivering among women treated with misoprostol (RR 38.6; 95% CI 11.04 to 134.95). However, serious inconsistency between the trial results was noted and there was significant statistical heterogeneity (I2 = 82%).

Source of evidence

209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

See GRADE Tables 10-12

Carboprost versus oxytocin

- Evidence came from one systematic review of 10 trials in which the use of injectable prostaglandins (sulprostone, carboprost, and prostaglandin F2 alpha) was compared versus the use of other injectable uterotonics (>1300 women). Carboprost was compared versus IV ergometrine in four trials (600 women), versus IM syntometrine in one (115 women) and versus IV oxytocin in another (132 women). Sulprostone was compared versus IV oxytocin in one trial (74 women), and versus IV oxytocin and IM ergometrine in another (69 women). Prostaglandin F2 alpha was compared versus IV methergin in two trials (400 women) and versus IV oxytocin in another (60 women). No study was identified in which the use of carboprost/sulprostone was compared versus the use of 10 IU of oxytocin IM.

- Overall, there were no differences in the priority outcomes in the trials of injectable prostaglandins.

- Among the important adverse effects reported, intramuscular prostaglandins were associated with more vomiting (RR 2.33; 95% CI 1.06 to 5.11), more diarrhoea (RR 12.28; 95% CI 4.47 to 33.70), and more abdominal pain (RR 4.99; 95% CI 1.46 to 17.05).

- Maternal high blood pressure and shivering were not assessed.

Source of evidence

209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

See GRADE Table 13

Recommendation 4: The use of misoprostol by community/lay health workers

A Cochrane systematic review found no randomized controlled trials which provided direct evidence about this topic (152). The GDG therefore reviewed the literature using a more inclusive search strategy that included non-randomized and other observational studies (53, 218, 89, 32, 169, 135, 82, 172, 179, 156, 199).

Effectiveness of oral misoprostol only in the reduction of postpartum blood loss

Evidence for the contribution of oral misoprostol only in the reduction of postpartum blood loss came mostly from one randomized controlled trial conducted in rural India (53). In this trial, 600 µg of oral misoprostol was compared with placebo in the context of the expectant management of the third stage of labour. Misoprosotol was administered by auxiliary nurse-midwives who assisted with deliveries at primary health facilities and in homes. An overall reduction was reported in: blood loss (mean difference in total blood loss: -48 ml) (95% CI -63.81 ml to -32.19 ml), PPH (blood loss >500 ml) 149 events (RR 0.53; 95% CI 0.39 to 0.74), and severe PPH (blood loss >1000 ml) 12 events (RR 0.2; 95% CI 0.04 to 0.91). However, firm conclusions cannot be drawn from this evidence as the trial reported too few events related to the impact of misoprostol in severe health outcomes, including severe PPH. (Moderate-quality evidence, see GRADE Table 8a)

As noted, these deliveries were assisted by auxiliary nurse-midwives at primary health facilities or in homes and the use of misoprostol was supervised by these health professionals. Caution should be exercised when extrapolating data provided by this trial to deliveries that are *not* assisted by skilled birth attendants, either at home or when the use of misoprostol is unsupervised. (Very-low-quality evidence, see GRADE Table 8b)

Evidence of a similar very-low quality was provided by other studies (218, 89, 32, 169, 135). In addition, a non-randomized cluster trial evaluated the use, at a community level, of a supervised 400 µg dose of misoprostol during the third stage of labour (82). In this study, a reduced risk of self-reported PPH (RR 0.29, 95% CI 0.18 to 0.48) was found. (Very-low-quality evidence, see GRADE Table 8c).

Feasibility of advanced distribution of misoprostol

Non-randomized and other observational studies (172,179) suggest that the community distribution of misoprostol during pregnancy is strongly associated with an increased use of misoprostol during the third stage of labour. (Moderate-quality evidence, see GRADE Table 8d).

Effect of community distribution of misoprostol on health outcomes

A Cochrane systematic review identified no randomized controlled trials providing direct evidence on the effect of the community distribution of misoprostol on health outcomes (152). Non-randomized trials and other observational studies which evaluated the use of the community distribution of misoprostol did not evaluate the effect on health outcomes or failed to demonstrate any benefit (172,179). Some model-derived data and model-based simulations suggest that the community distribution of misoprostol could potentially contribute to a reduction in the burden of PPH in settings of low coverage of skilled birth attendants (156,199). However, the primary sources of evidence and the assumptions informing the development of this modelling impacted on the quality of the evidence generated. For example, in the models developed by Pagel (156), a trial conducted in rural India (53) is the main source of data regarding the effectiveness of misoprostol for reducing PPH through community distribution. However, in this trial, 25 auxiliary nurse midwives undertook the deliveries, administered the study drug, and measured blood loss. (Overall, the quality of evidence was low or very low, mostly due to indirectness.)

Source of evidence

152. Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. Cochrane Database Syst Rev.2:CD009336.

53. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006 Oct 7;368(9543):1248-53.

218. Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B, et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. BJOG. 2005 Sep; 112(9):1277-83.

89. Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomised double blind clinical trial. BMJ. 2005 Oct 1;331(7519):723.

32. Chandhiok N, Dhillon BS, Datey S, Mathur A, Saxena NC. Oral misoprostol for prevention of postpartum hemorrhage by paramedical workers in India. Int J Gynaecol Obstet. 2006 Feb;92(2):170-5.

169. Prata N, Gessessew A, Abraha AK, Holston M, Potts M. Prevention of postpartum hemorrhage: options for home births in rural Ethiopia. Afr J Reprod Health. 2009 Jun;13(2):87-95.

135. Mobeen N, Durocher J, Zuberi N, Jahan N, Blum J, Wasim S, et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG. Feb;118(3):353-61.

82. Hashima EN, Nahar S, Al Mamun M, Afsana K, Byass P. Oral misoprostol for preventing postpartum haemorrhage in home births in rural Bangladesh: how effective is it? Glob Health Action. 2011;4.

172. Rajbhandari S, Hodgins S, Sanghvi H, McPherson R, Pradhan YV, Baqui AH. Expanding uterotonic protection following childbirth through community-based distribution of misoprostol: operations research study in Nepal. Int J Gynaecol Obstet. Mar;108(3):282-8.

179. Sanghvi H, Ansari N, Prata NJ, Gibson H, Ehsan AT, Smith JM. Prevention of postpartum hemorrhage at home birth in Afghanistan. Int J Gynaecol Obstet. Mar;108(3):276-81.

156. Pagel C, Lewycka S, Colbourn T, Mwansambo C, Meguid T, Chiudzu G, et al. Estimation of potential effects of improved community-based drug provision, to augment health-facility strengthening, on maternal mortality due to post-partum haemorrhage and sepsis in sub-Saharan Africa: an equity-effectiveness model. Lancet. 2009 Oct 24;374(9699):1441-8.

199. Sutherland T, Meyer C, Bishai DM, Geller S, Miller S. Community-based distribution of misoprostol for treatment or prevention of postpartum hemorrhage: cost-effectiveness, mortality, and morbidity reduction analysis. Int J Gynaecol Obstet. Mar;108(3):289-94.

See GRADE Tables 14-17

Recommendations 5-6: Controlled cord traction

- Evidence supporting this recommendation was extracted from two randomized trials (>24 000 women).
- The trials compared CCT in the third stage of labour with a 'hands-off' (i.e. no CCT) approach to the third stage of labour.
- No difference was observed between the groups in terms of severe PPH. No differences were reported for other critical outcomes. CCT was associated with a reduced risk of mild PPH, the overall amount of blood loss, and the duration of the third stage of labour. (High-quality evidence)
- The trial interventions (the active management of the third stage of labour with and without cord traction) were delivered by skilled birth attendants. The quality rating of the evidence was therefore downgraded for indirectness when applied to births not assisted by skilled attendants. (Moderate-quality evidence)
- There is some uncertainty regarding how frequently retained placenta occurs. It is hypothesized that there is an increased risk of retained placenta when CCT is omitted in association with the use of prophylactic ergometrine. As the trials primarily used oxytocin as the prophylactic uterotonic, the quality rating of the evidence was downgraded for indirectness when applied in the context of ergometrine. In the WHO trial, hospitals in Philippines were found to commonly use ergometrine in addition to oxytocin and, in these settings, an increased risk of retained placenta was observed. (Moderate-quality evidence)

Source of evidence

142. Mshweshwe NT, Hofmeyr GJ, Gülmezoglu AM. Controlled cord traction for the third stage of labour. Cochrane Database of Systematic Reviews. 2012(Issue 3.1. Art. No.: CD008020).

See GRADE Table 18

Recommendations 7-8 : The timing of cord clamping

- One systematic review included 13 randomized controlled trials which investigated the effects of different policies for the timing of cord clamping at the delivery of the placenta at term (the sample size was 3600 mothers and their babies). Four of these (>2500 women) included PPH as an outcome.

- Early cord clamping was defined as the clamping of the umbilical cord at 5 seconds after birth in one trial (45 women), at 10 seconds after birth in three trials (980 women), and at 15, 20 and 30 seconds after birth in another three (276, 91, and 64 women respectively). In two trials (433 women), early cord clamping was defined as being "within the first minute" after birth. The remaining four trials defined early cord clamping as "following birth" (963 women), "as soon as possible" (554 women), and "as soon as the baby is born" (two trials, 209 women).

- Late cord clamping was defined as the clamping of the umbilical cord at 1 minute after birth (one trial, 45 women), at 2 minutes after birth (one trial, 476 women), and at 1 and 3 minutes after birth (one trial, 276 women). Four trials (1397 women) defined "late cord clamping" as occurring at 3 minutes after birth. In four trials, early cord clamping was defined as "when the cord stopped pulsating" (two studies, 195 women), "when the cord stopped pulsating or at 3 or 5 minutes, whichever occur first" (two studies, 54 and 963 women, respectively). The remaining two studies conducted in India (209 women) defined late cord clamping as when doctors found evidence that the placenta had descended into the vagina.

- No significant differences were in rates of PPH (>500 ml or >1000 ml) between early and late cord clamping, and no significant effect was observed regarding the use of the manual removal of the placenta, the need for blood transfusion, or the length of the third stage of labour in the trials evaluating this outcome.

- There was a significant reduction in infant jaundice requiring phototherapy (RR 0.59; 95% CI 0.38 to 0.92) in infants who had their cord clamped early. However, the haemoglobin concentration among newborns who received early cord clamping was lower (three trials, 671 babies, WMD -2.17g/dl; 95% CI -4.06g/dl to -0.28g/dl). Their haemoglobin concentration at 24–48 hours of life (three trials, 770 babies, WMD -1.38, 95% CI -1.66 to -1.10), and birth weights were also reported to be lower (10 trials, 1854 babies, WMD -65.57 g, 95% CI -104.22 g to -26.92 g).

- One systematic review of cord clamping in preterm infants was found. This included 15 studies with a total sample size of 734 women and their babies. The definitions of early clamping included "clamping immediately after birth" (seven trials, 313 women), "immediate cord clamping <5 seconds" (two trials, 138 women), "between 5 and 10 seconds" (two trials, 104 women), "at 10 seconds" (one trial, 65 women) "at 20 seconds" (one trial, 40 women), "at less than 30 seconds" (one trial, 37 women) and "at the attendant's discretion" (one trial, 65 women). Definitions of delayed clamping included: "30 seconds after birth" (three trials, 95 women), "between 30 and 45 seconds after birth" (three trials, 137 women), "30–90 seconds after birth" (one trial, 46 women), "45 seconds after birth" (one trial, 40 women), "60 seconds after birth" (two trials, 143 women), "at 60–90 seconds after birth" (one trial, 39 women), "at 60–120 seconds after birth" (one trial, 86 women), and "at >180 seconds after birth" (one trial, 37 women). In two trials, late cord clamping was defined as the "positioning the baby below the introitus or the c-section incision" (one trial, 65 women), and "the time to vigorously milk the cord two or three times" (one trial, 40 women). The position of the infant in these trials also varied, as well as the upper limit of gestational age at delivery (28–36 years).

- This systematic review did not report priority and important maternal outcomes.
- The reported important benefits of delayed clamping included: less infant anaemia requiring transfusion (RR 0.61; 95% CI 0.46 to 0.81), less intraventricular haemorrhage (RR 0.59; 95% CI 0.41 to 0.85), less use of transfusion for low blood pressure (RR 0.52; 95% CI 0.28 to 0.94), less necrotizing enterocolitis (RR 0.62; 95% CI 0.43 to 0.9), and less infant sepsis (RR 0.29; 95% CI 0.09 to 0.99).

Source of evidence

131. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev. 2012; In editorial process.

170. Rabe H, Reynolds GJ, Diaz-Rosello JL, McDonald SJ, Middleton P. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database of Systematic Reviews. 2012;Issue 31. In editorial process.

See GRADE Tables 19-20

Recommendation 9-10: Uterine massage

- The evidence related to the use of uterine massage for the prevention of PPH consisted of one systematic review of two RCTs (1491 women) investigating the effects of uterine massage after birth, before and/or after delivery of the placenta.
- The studies were conducted in Egypt and South Africa.
- The interventions in these studies compared the use of uterine massage both before and after the delivery of the placenta, as well as sustained uterine massage (1–2 hours) and removal of uterine clots. The studies included in the review did not report any maternal deaths.
- Among the critical outcomes reported, there was no difference in uterine blood loss between the group that received uterine massage (irrespective of when the massage was initiated) and the group that did not. Blood loss was not reported in the group who underwent sustained massage and clot expulsion.
- There was a statistically significant reduction in the use of additional uterotonics in the group that received sustained massage and the removal of uterine clots (RR 0.20, 95% CI 0.08 to 0.5). It should be noted that the sample size for this group (200 women) was small.

Source of evidence

88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.

See GRADE Tables 21-23

Recommendations 11: The use of uterotonics in caesarean section

- Part of the evidence supporting this recommendation has been extrapolated (but downgraded for indirectness) from studies investigating the use of oxytocin in vaginal deliveries.

- A systematic review included 39 trials (>7900 women) which addressed the use of different drugs, routes and doses for the prevention of PPH both at elective and emergency caesarean sections. In general, all the sample sizes of the studies were very small, except for the study by Sheehan (2011) which had a sample size of 2069 women.

Oxytocin at different doses and routes (14 trials, 4002 women)

- Two trials compared the use of an oxytocin bolus of 5 IU with the use of a 10 IU oxytocin bolus administered as a 5-minute or 15-minute infusion. Only one trial (102 women) reported clinical outcomes. No differences were found in the use of additional uterotonics. Other outcomes of interest could not be evaluated.

- Three studies (almost 2900 women) compared the use of a bolus of 5 IU oxytocin only followed by an infusion of 30 IU and 40 IU of oxytocin versus a single bolus of 5 IU of oxytocin. The studies found a significant reduction in the use of additional uterotonics (RR 0.54; 95% CI 0.36 to 0.79), but not in blood loss >1000 ml, the use of blood transfusions, or in side-effects.

- Two other studies (217 women) compared the use of a bolus of 5 IU of oxytocin followed by an infusion of 5 IU or 20 IU of oxytocin versus an infusion of 5 IU or 20 IU of oxytocin. No differences were found for any of the priority outcomes. There were fewer cases of hypotension in the group not receiving the bolus (RR 0.44; 95% CI 0.23 to 0.87).

- Oxytocin administered as a bolus was compared at doses of 5 IU versus 10 IU in two trials (137 women). There was an increase in the use of additional uterotonics when a bolus of 5 IU rather than 10 IU was used (RR 17.35; 95% CI 2.18 to 137.83).

- Different doses of oxytocin administered by infusion only were compared in two trials. The first of these (321 women) compared 10 IU versus 80 IU, while the second trial (40 women) compared 5 IU versus 10 IU versus 15 IU versus 20 IU). No conclusions could be drawn for any of the priority outcomes.

- One small study (40 women) compared the use of 20 IU of intramyometrial oxytocin versus a bolus of 5 IU of IV oxytocin. Two other trials (139 women) compared the use of lower doses (1 IU to 3 IU) versus higher doses (5 IU) of oxytocin using a bolus in women also receiving oxytocin administered by IV infusion.

Ergometrine versus oxytocin (3 trials, 239 women)

- A four-arm trial (136 women) compared: (i) a bolus of 10 IU of oxytocin versus (ii) a 10 IU infusion lasting 5 minutes versus (iii) a 10 IU infusion lasting 15 minutes versus (iv) a bolus of 0.2 mg methylergonovine. One small study (55 women) compared the use of an oxytocin bolus of 10 IU IV and methylergonovine maleate 0.2 mg IV bolus followed by 0.125 mg oral methylergonovine repeated at 8-hourly intervals and oxytocin infusion versus oxytocin bolus 10 IU IV and oxytocin

infusion. Another small trial (48 women) compared a 0.25 mg dose of ergometrine and 20 IU oxytocin infusion versus 20 IU oxytocin infusion. The latter reported an increased risk in the use of additional uterotonics in the oxytocin group (RR 2.14; 95% CI1.07 to 4.30) and fewer cases of nausea (RR 0.20; 95% CI 0.05 to 0.82).

Misoprostol versus oxytocin or placebo (11 trials, 1580 women)

- Misoprostol was compared with oxytocin in seven trials (762 women). Misoprostol was given orally, sublingually or rectally in doses ranging from 400 to 800 µg. Oxytocin was administered as a bolus of 10 IU, as an infusion of 10 IU or 20 IU, or as an intramyometrial injection. No additional benefits were found in the misoprostol group for the priority outcomes and an increase in shivering was reported in the vaginal delivery group.

- Four trials (819 women) compared misoprostol and oxytocin versus oxytocin. Misoprostol was given orally, rectally, or as intrauterine tablets in doses of 200 µg, 400 µg, or 800 µg. Oxytocin in the misoprostol group was administered as a bolus or infusion of 5 IU to 20 IU, and in the control group as an IV infusion of 20 IU. Again, no difference was reported for the priority outcomes, but an increase in pyrexia >38 °C and shivering was noted.

- Misoprostol only was compared with misoprostol and 20 IU of intramyometrial oxytocin in a 3-arm trial (124 women) and no differences in priority outcomes were reported.

Injectable prostaglandins versus oxytocin (3 trials, 575 women)

- No differences were found for any of the priority outcomes for the use of carboprost only or combined with oxytocin versus oxytocin [only]. A small trial (60 women) of prostaglandin F2 alpha versus oxytocin did not report any outcomes relevant to this guideline.

Carbetocin versus oxytocin or placebo (6 trials, 1407 women)

- Five trials (nearly 1300 women) compared carbetocin 100 µg IV versus oxytocin (5 IU of IV bolus or IM, 5 IU or 10 IU of IV infusion, or 2.5 IU bolus followed by a 30 IU IV infusion of 16 hours). As stated previously, carbetocin was superior to oxytocin only for reducing the use of additional uterotonics.

- One trial compared carbetocin 100 µg IV versus placebo (119 women) and reported a reduced risk for the additional use of uterotonics.

Other drugs (2 trials, 180 women)

- Oral methergine administered every 6 hours was compared with no methergine (one study, 80 women). A second trial (100 women) compared the use of 1 g of tranexamic acid IV versus no tranexamic acid, with both groups receiving adjunct oxytocin. No differences in the priority outcomes were found.

Haemodynamic effects

- The haemodynamic effects related to the use of oxytocin bolus injections have been evaluated in numerous studies ranging from randomized controlled trials to case reports. The magnitude and clinical significance of haemodynamic effects remain controversial. Generally, randomized studies have reported that the use of oxytocin bolus injection has resulted in milder and transitory haemodynamic effects, while case reports have tended to note more severe effects, including severe hypotension, cardiac arrest, pulmonary oedema, and maternal deaths. The difficulty of interpreting the data derived from case reports is due to the challenge of establishing the causality between the bolus infusion and the reported effects, and in disentangling the role of confounders.

Source of evidence

122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.

106. Kim TS, Bae JS, Park JM, Kang SK. Hemodynamic effects of continuous intravenous injection and bolus plus continuous intravenous injection of oxytocin in cesarean section. Korean J Anesthesiol. Dec;61(6):482-7.

200. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during Caesarean section. Br J Anaesth. 2008 May;100(5):683-9.

202. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. Br J Anaesth. 2007 Jan;98(1):116-9.

166. Pinder AJ, Dresner M, Calow C, Shorten GD, O'Riordan J, Johnson R. Haemodynamic changes caused by oxytocin during caesarean section under spinal anaesthesia. Int J Obstet Anesth. 2002 Jul;11(3):156-9.

50. Davies GA, Tessier JL, Woodman MC, Lipson A, Hahn PM. Maternal hemodynamics after oxytocin bolus compared with infusion in the third stage of labor: a randomized controlled trial. Obstet Gynecol. 2005 Feb;105(2):294-9.

165. Petersson M. Cardiovascular effects of oxytocin. Prog Brain Res. 2002;139:281-8.

43. Cooper GM, Lewis G, Neilson J. Confidential enquiries into maternal deaths, 1997-1999. Br J Anaesth. 2002 Sep;89(3):369-72.

180. Sarna MC, Soni AK, Gomez M, Oriol NE. Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg. 1997 Apr;84(4):753-6.

187. Shahin J, Guharoy SR. Pulmonary edema possibly developing secondary to the intravenous administration of oxytocin. Vet Hum Toxicol. 1991 Dec;33(6):587-8.

86. Heytens L, Camu F. Pulmonary edema during cesarean section related to the use of oxytocic drugs. Acta Anaesthesiol Belg. 1984 Jun;35(2):155-64.

112. Langesaeter E, Rosseland LA, Stubhaug A. Haemodynamic effects of repeated doses of oxytocin during Caesarean delivery in healthy parturients. Br J Anaesth. 2009 Aug;103(2):260-2.

See GRADE Tables 21-30

The use of carbetocin

- One systematic review was found which evaluated 11 trials (2635 women). The trials evaluated the effect of using carbetocin (100 µg as an IV bolus or IM injection) for the prevention of PPH. The trials evaluated the effect of both forms of administration after both vaginal delivery and caesarean section, and compared the results to the use of oxytocin, fixed dose oxytocin-ergometrine, and placebo.

Carbetocin versus placebo

- The systematic review identified one trial (119 women) which compared the use of 100 µg of carbetocin for women undergoing elective caesarean versus saline as a placebo. The use of carbetocin was associated with a statistically significant reduction in the use of therapeutic uterotonicdrugs (RR 0.18; 95% CI 0.09 to

0.35). However, these data came from a single small trial published as an abstract only and the risk of bias was therefore unclear. Critical or important adverse outcomes were not reported.

Carbetocin versus oxytocin

- Five trials were identified (1399 women) which compared the use of carbetocin versus oxytocin for women at high risk of PPH (two trials), low risk of PPH (two trials), and both low and high risk of PPH (one trial). Oxytocin was administered as a single IV bolus of 5 IU (one trial, 377 women), as a 10 IU dose in continuous infusion (two trials, 268 women), and as an initial 2.5 IU and 5 IU bolus followed by a 20 IU infusion (two trials, 754 women). For women who underwent caesarean section, PPH was defined as a blood loss >1000 ml (two trials, 437 women), >500 ml (one trial, 104 women), and was not defined in another (694 women). For vaginal deliveries (one trial, 164 women), PPH was defined as a blood loss >500 ml. Women underwent elective caesarean sections (two trials), elective and emergency caesarean sections (one trial), while the remaining trial[s] did not specify whether the women sampled had had elective or emergency caesareans. The results were presented separately according to the mode of delivery (caesarean or vaginal birth).

- The published systematic review included only three trials that considered the risk of PPH in caesarean section. The results suggests that there is a reduced risk of PPH with the use of carbetocin versus oxytocin (RR 0.55; 95% CI 0.31 to 0.95). However, variation in the definition of PPH was noted in these trials, and the findings were influenced by the trial which had defined PPH as a blood loss of >500 ml – a claim that can be controversial in the context of caesarean section. In addition, when a trial conducted in 2010 by Attilakos , was added to the analysis, the review reported that the results were no longer statistically significant (RR 0.66; 95% CI 0.39 to 1.10). In the context of vaginal deliveries, no difference was noted in the risk of PPH defined as >500 ml (RR 0.95; 95% CI 0.43 to 2.09).

- In comparison to oxytocin, carbetocin was associated with a reduced use of additional uterotonic drugs following caesarean delivery (RR 0.64; 95% CI 0.51 to 0.81) (four trials, >1100 women). This was not found to be the case for vaginal delivery (RR 0.93; 95% CI 0.44 to 1.94) although this was evaluated in only one study (164 women).

- Carbetocin is also associated with a reduced use of uterine massage in both caesarean deliveries (RR 0.54; 95% CI 0.31 to 0.96) and vaginal deliveries (RR 0.70; 95% CI 0.51 to 0.94). There were no other reported differences in important adverse outcomes between the two groups, although it should be noted that the sample sizes in the trials were frequently small, and few conclusions can therefore be drawn.

Carbetocin versus syntometrine

- Four trials were found of women (≥1000) undergoing vaginal delivery. These reported the use of 100 µg of IM carbetocin versus IM syntometrine (a fixed combination of 5 IU of oxytocin and 0.5 mg of methylergonovine). Three of the trials (910 women) were conducted on women with no risk factors for PPH, while one trial (120 women) was conducted on women with risk factors for PPH.

- No difference was noted in the rates of PPH between the groups or in the additional use of uterotonics.

- Among the important adverse outcomes reported, there was a reduction in risk of vomiting (RR 0.21; 95% CI 0.11 to 0.39), nausea (RR 0.24; 95% CI 0.15 to 0.4), and retching (RR 0.14; 95% CI 0.03 to 0.62) in the women receiving carbetocin. Sweating (RR 0.33; 95% CI 0.12 to 0.9) – though the event rate was low – and

uterine/abdominal pain (RR 0.56; 95% CI 0.35 to 0.92) were also reported. No differences were reported for headache, facial flushing or shivering.

- Two randomized controlled trials (>1600 women) observed a reduction in hypertension (blood pressure ≥140/90 mmHg) in women treated with carbetocin versus syntometrine (RR 0.16; 95% CI 0.07 to 0.38)

Source of evidence

197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

14. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG. 2010 Jul;117(8):929-36.

See GRADE Tables 29-31

Recommendation 12: The use of cord traction in caesarean section

- Only one systematic review of 21 randomized controlled trials of women undergoing caesarean section was identified (>5500 women). The review compared the effects of cord traction versus the manual removal of the placenta.

- In three studies (1017 women), the manual removal of the placenta was associated with an increased risk of blood loss >1000 ml (RR 1.84; 95% CI 1.48 to 2.29). Nine studies identified an increased operative blood loss associated with the manual removal of the placenta (2087 patients) (MD 79.46 ml; 95% CI 10.9 ml to 148.01 ml). Lower levels of haematocrit after delivery (two studies, 384 women) (MD -1.55%; 95% CI -3.09 to -0.01) and higher maternal haematocrit fall after delivery (seven studies, 2495 women) (MD 1.96%; 95% CI 0.24% to 3.68%) were also associated with the manual removal of the placenta.

- In addition, the manual removal of the placenta in caesarean deliveries was associated with an increased risk of endometritis (17 studies, 5026 women) (RR 1.75; 95% CI 1.53 to 2.0).

Source of evidence

12. Anorlu RI, Maholwana B, Hofmeyr GJ. Methods of delivering the placenta at caesarean section. Cochrane Database Syst Rev. 2008;2012 - In editorial process for this guideline](3):CD004737.

See GRADE Table 32

Comments

Recommendations 13-14: The use of uterotonics of choice for the treatment of PPH

Misoprostol versus oxytocin

- Evidence related to the effect of misoprostol on the management of PPH is based on a Cochrane systematic review of seven randomized controlled trials (3731 women).

- In one trial (Winikoff 2010), women diagnosed with PPH who had not been exposed to prophylactic oxytocin were randomly assigned to receive 800 µg of misoprostol or 40 IU of intravenous oxytocin. In another trial (Blum 2010), women diagnosed with PPH who had been exposed to prophylactic oxytocin were randomly assigned to receive 800 µg of misoprostol or 40 IU of intravenous oxytocin. One small trial did not specify the previous exposure to prophylactic oxytocin. The other four trials focused on the use of misoprostol as an adjunct treatment for women who had received oxytocin as a primary treatment for PPH, and the review findings where dominated by the trial research conducted by Widmer et al (2010).

- Among those women not exposed to prophylactic oxytocin, the use of misoprostol was associated with an increased risk of blood loss >500 ml (RR 2.66; 95% CI 1.62 to 4.38), the increased use of uterotonics (RR 1.98; 95% CI 1.31 to 2.99), and an increased risk of shivering, hyperthermia and vomiting.

- Among those women exposed to prophylactic oxytocin, and despite the very small number of events (8 in total), an increased risk of blood loss >1000 ml with marginal statistical significance was observed (RR 3.62; 95% CI 1.02 to 12.88) for those women who received misoprostol. In addition, an increase in the risk of shivering was associated with the use of misoprostol (RR 2.54; 95% CI 1.95 to 3.32).

- The use of misoprostol as an adjunct for the treatment of women who received therapeutic oxytocin for PPH added no benefit. An increased risk of hyperthermia, vomiting and shivering was observed.

Source of evidence

140. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

See GRADE Tables 33-34

Various uterotonics (evidence extrapolated from PPH prevention trials)

Evidence was extrapolated from research on the prevention of PPH. Systematic reviews comparing the effects of oxytocin versus ergometrine, a fixed dose combination of oxytocin versus ergometrine, and carbetocin versus prostaglandins for the prevention of PPH were reviewed. The prevention of PPH is more extensively reviewed in the corresponding section of this document.

Oxytocin versus ergometrine (GRADE Table 35)

- Evidence related to the use of oxytocin versus ergometrine for the prevention of PPH was extracted from one Cochrane systematic review which investigated the effects of prophylactic oxytocin versus placebo or no treatment versus ergot alkaloids.

    - Four trials (>2000 women) in the systematic review reported on the critical outcome of blood loss >1000 ml and two of these used the use of blood transfusion as an outcome.
    - There was no observed difference in the incidence of blood loss >1000 ml reported (RR 1.09; 95% CI 0.63 to 1.87). Blood transfusion was given to 2 of the 234 women receiving oxytocin compared with 1 of the 333 women receiving ergometrine (RR 3.74; 95% CI 0.34 to 40.64). No significant difference was observed in the use of additional uterotonics in the four trials included the systematic review.
    - Among the adverse outcomes rated as important, the comparison of oxytocin versus ergometrine (or derivatives) showed a lower rate of adverse effects in women treated with oxytocin only, as well as lower rates of nausea (RR 0.13; 95% CI 0.08 to 0.21), vomiting (RR 0.08; 95% CI 0.05 to 0.14), and headache (RR 0.03; 95% CI 0.01 to 0.14).
    - There was no observed difference reported in high blood pressure in women treated with oxytocin only (RR 0.53; 95% CI 0.19 to1.52), though the quality of evidence was noted to be low.

Oxytocin-ergometrine (fixed dose combination) versus oxytocin (GRADE Tables 35-37)

- Evidence related to the use of oxytocin versus fixed dose combinations of oxytocin-ergometrine for the prevention of PPH was extracted from one Cochrane systematic review which investigated the effects of ergometrine-oxytocin versus oxytocin in reducing the risk of PPH (>8000 women). The doses and routes of administration were IM oxytocin-ergometrine versus IV or IM oxytocin. Doses of oxytocin used ranged from 2 IU to 10 IU, while the fixed drug combination doses consisted of 5 IU of oxytocin and 0.5 mg of ergometrine.

- Of the five identified studies in which IM oxytocin was used as a comparator (8000 women), three of these studies (6000 women) compared the fixed dose combination of oxytocin-ergometrine versus 10 IU of IM oxytocin (see GRADE Table 3)
    - There was no observed difference in the incidence of blood loss >1000 ml between the two groups (RR 0.80; 95% CI 0.60 to 1.07) although there was a reduction in blood loss ≥500 ml (RR 0.85; 95% CI 0.73 to 0.99).
    - In the three studies that reported on the use of blood transfusion, the effect was uncertain as the confidence interval included both benefit and harm (RR 1.25; 95% CI 0.77 to 2.05).
    - Two studies reported a statistically significant lower use of additional uterotonics in the group receiving the fixed dose oxytocin-ergometrine combination (RR 0.78; 95% CI 0.66 to 0.91).
    - Among the adverse outcomes rated as important, higher rates of nausea (RR 4.18; 95% CI 3.51 to 4.99) and vomiting (RR 4.97; 95% CI 4.06 to 6.08) were reported in women treated with the fixed dose combination only (two studies, >4000 women).

- Two studies (6000 women) were identified which compared IV oxytocin versus a fixed dose IM oxytocin-ergometrine combination
    - There was no statistically significant difference between the two groups with regard to blood loss, the use of blood transfusion, or the use of additional uterotonics.
    - Among the adverse outcomes rated as important, a higher rate of vomiting (RR 3.33; 95% CI 1.21 to 9.2) was observed in the group treated with the fixed

dose combination only.

Oxytocin-ergometrine IM (fixed dose combination) versus ergometrine IM (any dose) (GRADE Table 39)

- Evidence was extrapolated from one systematic review of five PPH prevention trials (>4000 women).

- While a significant difference was observed in blood loss ≥500 ml (RR 0.57; 95% CI 0.4 to 0.81) in the group treated with ergometrine only, this difference was not seen for blood loss >1000 ml (RR 1.67; 95% CI 0.4 to 6.94) as it was evaluated in one trial only (1120 women).

- Of the reported critical outcomes, there was no difference in the need for blood transfusion between the groups, or for the manual removal of the placenta. Other important adverse effects were not reported.

Carbetocin versus oxytocin (GRADE Tables 40-41)

- Evidence came from one systematic review of 11 trials (2635 women) which evaluated the effect of carbetocin (100 mcg as an IV bolus or IM injection) for the prevention of PPH after vaginal delivery and caesarean section versus oxytocin, fixed dose oxytocin-ergometrine, and placebo.
    - When compared to oxytocin, carbetocin was associated with a reduced use of additional uterotonic drugs after caesarean delivery (RR 0.64; 95% CI 0.51 to 0.81) in four trials (>1000 women). This association was not apparent for vaginal delivery (RR 0.93; 95% CI 0.44 to 1.94) but this finding was evaluated in only one study (160 women) and the quality of the evidence was very low. The systematic review reported a reduction in the risk of PPH, with the use of carbetocin versus oxytocin for women who underwent caesarean section. However, these results were greatly influenced by the definition of PPH in the trial as blood loss >500 ml, which may have biased the findings significantly. The authors of the systematic review did not include data from one trial (Attilakos 2010, 9/186 versus 9/189) in the meta-analysis. Including this trial in the meta-analysis changes the results (RR 0.60; 95% CI 0.34 to 1.07). No difference in [the risk of] PPH was reported for vaginal delivery (RR 0.95; 95% CI 0.43 to 2.09).

Carbetocin versus oxytocin-ergometrine fixed dose combination (GRADE Table 42)

- Evidence for this comparison was extrapolated from one systematic review which evaluated four trials (>1000 women).
    - No significant difference was observed between the two groups with regard to blood loss, the use of blood transfusion, or the use of additional uterotonics.
    - Among the important adverse maternal outcomes reported, lower rates of nausea (RR 0.24; 95% CI 0.15 to 0.4) and vomiting (RR 0.21; 95% CI 0.11 to 0.39) were observed among the group given carbetocin, compared with the group given fixed dose oxytocin-ergometrine.

Intramuscular prostaglandins versus injectable uterotonics (GRADE Table 43)

- Evidence was extrapolated from one systematic review of 10 trials (>1300 women) which compared intramuscular prostaglandins (sulprostone, carboprost, and prostaglandin F2 alpha) versus injectable uterotonics.

- No difference was observed in the risk of blood loss, the additional use of uterotonics, or the need for blood transfusion.

- Among the important adverse effects reported, IM prostaglandins were associated with a higher risk of vomiting (RR 2.33; 95% CI 1.06 to 5.11), diarrhoea (RR 12.28; 95% CI 4.47 to 33.70), and abdominal pain (RR 4.99; 95% CI 1.46 to 17.05).

Carboprost versus misoprostol (GRADE Table 44)

- One trial within one systematic review (<120 women), reported no difference between those treated with rectal misoprostol (400 mcg) versus intramuscular prostaglandins (prostaglandin F2 alpha), either in terms of blood loss or the use of blood transfusion. Of the 60 patients in the group receiving IM prostaglandin, two required the use of additional uterotonics, compared to 10 of the 60 patients who received rectal misoprostol (RR 0.20; 95% CI 0.05 to 0.87). However, these findings should be viewed with caution due to the low event rate, the small sample, and the very low quality of the evidence

Misoprostol (any route) versus injectable uterotonics (GRADE Tables 45-54)

- Evidence was extrapolated from one systematic review which evaluated a number of routes and doses of misoprostol versus injectable uterotonics for the prevention of PPH.

- There was no difference in the risk of blood loss >1000 ml in women receiving 600 mcg of misoprostol orally or sublingually, 400 mcg rectally, or 800 mcg rectally, compared with those receiving injectable uterotonics. The trials did not report the outcome of invasive or surgical treatment.

Source of evidence

19. Begley CM, Gyte GM, Murphy DJ, Devane D, McDonald SJ, McGuire W. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2011(7):CD007412. In editorial process.

26. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews.Art. No.: CD001808. In editorial process.*

130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

See GRADE Tables 33-54

Recommendation 15: Fluid replacement

Fluid replacement is an important component of resuscitation for women with PPH. However, no RCTs have compared the use of colloids with other replacement fluids for the resuscitation of women with PPH. Indirect evidence though was found in two Cochrane reviews of 95 trials (>20 000 participants) which evaluated the use of colloid versus isotonic versus hypertonic crystalloids in the resuscitation of critically ill patients who required volume replacement secondary to trauma, burns, surgery, sepsis, and other critical conditions. A total of 85 trials reported data on mortality for the following comparisons. Data about the settings were not provided by the review authors.

Albumin versus control

- A higher number of deaths was reported in patients with burns who received albumin (RR 2.93; 95% CI 1.28 to 6.72) than in the control group (small sample size).

Colloid versus crystalloid

- No statistical difference was reported in the incidence of mortality when the following were compared with crystalloids: albumin or plasma protein fraction (23 trials, 7754 patients) (RR 1.01; 95% CI 0.92 to1.10), hydroxyethyl starch (16 trials, 637 patients) (RR 1.05; 95% CI 0.63 to1.75), modified gelatin (11 trials, 506 patients) (RR 0.91; 95% CI 0.49 to 1.72), or dextran (nine trials, 834 patients) (RR 1.24; 95% CI 0.94 to 1.65).

Colloid versus hypertonic crystalloid

- One trial, which compared albumin or plasma protein fraction versus hypertonic crystalloids, reported one death in the colloid group (RR 7.00; 95% CI 0.39 to 126.92).

- Two trials which compared hydroxyethyl starch (16 participants) and modified gelatin versus crystalloids (20 participants) reported that there were no deaths

Colloids in hypertonic crystalloid versus isotonic crystalloid

- The outcome of death was reported in eight trials (1283 patients) which compared dextran in hypertonic crystalloid versus isotonic crystalloid (RR 0.88; 95% CI 0.74 to 1.05) and in one trial with 14 patients (RR 0.5; 95% CI 0.06 to 4.33)

Source of evidence

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See GRADE Tables 55-58

Recommendation 16: The use of tranexamic acid

- No RCTs investigating the use of tranexamic acid for the treatment of PPH following vaginal delivery have addressed priority outcomes. A Cochrane systematic review on tranexamic acid versus no treatment for the prevention of PPH included two small trials – one trial for vaginal births and one for caesarean sections (with a combined total of 453 women) – neither of which evaluated priority outcomes.

- An unpublished systematic review of randomized trials of traxenamic acid for the prevention of PPH identified three relevant trials (460 participants). Although a significant reduction in average postpartum blood loss was reported in women treated with traxenamic acid, the quality of the trials was poor. None of the trials had adequate allocation concealment and, even in aggregate, the trials were too small to assess the effects of traxenamic acid on the clinically important end points.

- A large, pragmatic randomized, placebo controlled trial – currently in the recruitment phase – will examine the effect of the early administration of tranexamic acid on mortality, hysterectomy, and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in women with clinically diagnosed PPH (The WOMAN Trial, ISRCTN76912190). The planned sample size is 15 000 women.

Source of evidence

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See GRADE Table 59

Recommendation 17: The use of uterine massage for the treatment of PPH

- No randomized controlled trials were identified of the use of uterine massage for the treatment of PPH. Evidence for this has therefore been extrapolated from one systematic review of two RCTs set in Egypt and South Africa (1491 women). These investigated the effects of uterine massage after birth, before and/or after delivery of the placenta for the prevention of PPH.

- The interventions in these studies compared uterine massage both before and after the delivery of the placenta. Among the critical outcomes, no difference was reported in uterine blood loss between the uterine massage group and the non uterine massage group, irrespective of the timing of the massage. There was a statistically significant reduction in the use of additional uterotonics in the group who received uterine massage after placental delivery (RR 0.20; 95% CI 0.08 to 0.5). The sample size of this group was small (200 women).

Source of evidence

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See GRADE Tables 60-62

Recommendation 18: The use of balloon tamponade

- No RCTs were identified on the use of uterine tamponade for the treatment of PPH. Twenty-two case series and 18 case reports were identified (278 women), as well as two reviews. The instruments used included Sengstaken-Blakemore and Foley catheters, Bakri and Rusch balloons, and condoms. Case series have reported success rates (indicating that there was no use of hysterectomy or other invasive procedures) that ranged from 60 % to 100 %.

Source of evidence

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No GRADE Table available

Recommendation 19: The use of artery embolization

- No RCTs have examined the use of percutaneous transcatheter arterial embolization for the treatment of PPH. However, institutions equipped with adequate radiological facilities have reported using this intervention for the treatment of PPH.
- Twenty-nine case series and 24 case reports have been published (>600 women) and studies report success rates (indicating that there was no use of hysterectomy or other invasive procedures) ranging from 82 % to 100 %.

Source of evidence

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No GRADE Table available

Recommendation 20: Surgical interventions for the treatment of PPH

- A wide range of surgical interventions has been reported for the control of PPH that is unresponsive to medical or mechanical interventions. These include various forms of compression sutures, ligation of the uterine, ovarian or internal iliac artery, and subtotal or total hysterectomy.
- No RCTs have examined the use of uterine compressive sutures for the treatment of PPH. Twenty-six case series and 12 case reports were identified (425 women). Eight overviews of the use of compression sutures have also been published. The B-Lynch technique appears to be the most commonly reported procedure. Success rates (indicating that there was no use of hysterectomy or other invasive procedures) ranged from 89% to 100 %.
- Similarly, no RCTs were identified on the use of selective artery ligation for the treatment of PPH. Thirty case series and 19 case reports have been published (682 women) and studies report success rates (indicating that there was no use of hysterectomy or other invasive procedures) ranging from 62% to 100 %.

Source of evidence

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No GRADE Table available

Recommendation 21: The use of bimanual uterine compression

- One RCT was identified which examined the use of lower segment uterine compression in addition to standard treatment for the management of PPH (64 women). The technique included the use of both lower segment compression with one hand through the abdominal wall *and* bimanual lower segment and fundal compression through the abdominal wall. The authors reported a decrease in the amount of blood loss in the group in which manual lower segment compression was used together with conventional management.

- Only one case report was found describing the bimanual abdominal/intravaginal technique.

Source of evidence

33. Chantrapitak W, Srijanteok K, Puangsa-art S. Lower uterine segment compression for management of early postpartum hemorrhage after vaginal delivery at Charoenkrung Pracharak Hospital. J Med Assoc Thai. 2009 May;92(5):600-5.

110. Kovavisarch E, Kosolkittiwong S. Bimanual uterine compression as a major technique in controlling severe postpartum hemorrhage from uterine atony. J Med Assoc Thai. 1997 Apr;80(4):266-9.

No GRADE Table available

Recommendation 22: The use of external aortic compression

- A prospective study conducted in Australia examined the haemodynamic effects of external aortic compression in non-bleeding postpartum women. Successful aortic compression, defined as the absence of a femoral pulse and unrecordable blood pressure in a lower limb, was achieved in 11 of the 20 subjects. The authors concluded that the procedure was safe for healthy subjects and may be of benefit as a temporizing measure for the treatment of PPH while resuscitation and management plans are made. Subsequently, one case report from Australia has described the use of internal aortic compression as a temporizing measure to control severe PPH due to placenta percreta at the time of caesarean section. A quasi-randomized study (240 women) conducted in Egypt observed a decrease in the use of additional uterotonics and blood transfusions when a device for external aortic compression was used in addition to conventional treatment compared to conventional treatment only.

Source of evidence

175. Riley DP, Burgess RW. External abdominal aortic compression: a study of a resuscitation manoeuvre for postpartum haemorrhage. Anaesth Intensive Care. 1994 Oct;22(5):571-5.

102. Keogh J, Tsokos N. Aortic compression in massive postpartum haemorrhage--an old but lifesaving technique. Aust N Z J Obstet Gynaecol. 1997 May;37(2):237-8.

196. Soltan MH, Faragallah MF, Mosabah MH, Al-Adawy AR. External aortic compression device: the first aid for postpartum hemorrhage control. J Obstet Gynaecol Res. 2009 Jun;35(3):453-8.

No GRADE Table available

Recommendation 23: The use of anti-shock garments

- No RCTs were identified which reported on the use of pneumatic or non-pneumatic anti-shock garments for the treatment of PPH. Before-and-after studies and case series have, however, been published and summarized. The use of non-pneumatic anti-shock garments (NASGs) has been reported in two before-and-after studies in Egypt (990 women) and Nigeria (169 women). In the first study, uterine atony was present in 40 % of the cases, and in 35% of the cases in the second. Women treated with NASGs in the Egyptian study had a reported total mean measured blood loss significantly lower during the intervention phase than during the pre-intervention phase (253.2 ml versus 378.9 ml; Pb0.01). A similar lower total mean measured blood loss was also observed between the phases in the Nigerian study (73.5 ml versus 253 ml).

- Maternal mortality was significantly lower in the intervention phase than in the pre-intervention phase (7 deaths [8.1%] versus 21 deaths [25.3%]; RR 0.32 [95% CI, 0.14 to 0.72]) in the Egyptian study but not in the Nigerian study (RR 0.46 [95% CI, 0.17 to 1.27]). In both studies, the risk of blood transfusion was not statistically significantly different.

Source of evidence

210. Turan J, Ojengbede O, Fathalla M, Mourad-Youssif M, Morhason-Bello IO, Nsima D, et al. Positive effects of the non-pneumatic anti-shock garment on delays in accessing care for postpartum and postabortion hemorrhage in Egypt and Nigeria. J Women's Health (Larchmt). Jan;20(1):91-8.

138. Mourad-Youssif M, Ojengbede OA, Meyer CD, Fathalla M, Morhason-Bello IO, Galadanci H, et al. Can the Non-pneumatic Anti-Shock Garment (NASG) reduce adverse maternal outcomes from postpartum hemorrhage? Evidence from Egypt and Nigeria. Reprod Health.7:24.

151. Ojengbede OA, Morhason-Bello IO, Galadanci H, Meyer C, Nsima D, Camlin C, et al. Assessing the role of the non-pneumatic anti-shock garment in reducing mortality from postpartum hemorrhage in Nigeria. Gynecol Obstet Invest.71(1):66-72.

83. Hauswald M, Williamson MR, Baty GM, Kerr NL, Edgar-Mied VL. Use of an improvised pneumatic anti-shock garment and a non-pneumatic anti-shock garment to control pelvic blood flow. Int J Emerg Med.3(3):173-5.

132. Miller S, Fathalla MM, Youssif MM, Turan J, Camlin C, Al-Hussaini TK, et al. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Egypt. Int J Gynaecol Obstet. 2010 Apr;109(1):20-4.

134. Miller S, Ojengbede O, Turan JM, Morhason-Bello IO, Martin HB, Nsima D. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Nigeria. Int J Gynaecol Obstet. 2009 Nov;107(2):121-5.

133. Miller S, Martin HB, Morris JL. Anti-shock garment in postpartum haemorrhage. Best Pract Res Clin Obstet Gynaecol. 2008 Dec;22(6):1057-74.

Recommendation 24: The use of uterine packing

- No RCTs were identified which reported on the use of uterine packing for the treatment of PPH. Ten case series and one case report (with a combined total of 208 women) were found, and the largest of these had a sample size of 83 women. One study evaluated patients after caesarean sections undertaken due to placenta previa/accreta. Success rates (indicating that there was no use of hysterectomy or other invasive procedures) in the identified studies ranged from 75% to 100 %.

Source of evidence

149. Nwagha UI, Okaro JM, Nwagha TU. Intraoperative uterine packing with mops: an effective, but under utilized method of controlling post partum haemorrhage-experience from South Eastern Nigeria. Niger J Med. 2005 Jul-Sep;14(3):279-82.

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201. Thapa K, Malla B, Pandey S, Amatya S. Intrauterine condom tamponade in management of post partum haemorrhage. J Nepal Health Res Counc. Apr;8(1):19-22.

80. Hackethal A, Tcharchian G, Ionesi-Pasacica J, Muenstedt K, Tinneberg HR, Oehmke F. Uterine surgery in postpartum hemorrhage. Minerva Ginecol. 2009 Jun;61(3):201-13.

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93. Hsu S, Rodgers B, Lele A, Yeh J. Use of packing in obstetric hemorrhage of uterine origin. J Reprod Med. 2003 Feb;48(2):69-71.

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220. Wax JR, Channell JC, Vandersloot JA. Packing of the lower uterine segment--new approach to an old technique. Int J Gynaecol Obstet. 1993 Nov;43(2):197-8.

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213. Ushakova GA. Use of metrohemostat combined with tight tamponade of the vaginal fornices in the prevention and treatment of hypotonic hemorrhages in the early postnatal period. Akush Ginekol (Mosk). 1974 Nov(11):26-9.

15. Avramov A, Todorov T. Utero-vaginal tamponade as a preventive measure in hypotonic uterine hemorrhage. Akush Ginekol (Sofiia). 1965;4(2):145-6.

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Recommendation 25-27: The use of uterotonics for the treatment of retained placenta

- One double-blind RCT was identified (50 women) which compared sulprostone versus placebo for the treatment of retained placenta (van Beekhuizen 2006). The intended recruitment size was over 100 patients, but the trial was stopped prematurely and sulprostone given to all remaining cases.

- The authors reported a lower risk of the manual removal of the placenta (RR 0.51; 95% CI 0.34 to 0.86) and an increased risk in the use of blood transfusion in the sulprostone group (RR 2.26; 95% CI 1.14 to 4.12). A small, ongoing trial (van Beekhuizen 2009) is investigating the role of misoprostol in the management of retained placenta (the recruitment phase has been completed but no results are as yet available). However, there is no empirical evidence for or against the use of other uterotonics for the treatment of retained placenta.

Source of evidence

214. van Beekhuizen HJ, de Groot AN, De Boo T, Burger D, Jansen N, Lotgering FK. Sulprostone reduces the need for the manual removal of the placenta in patients with retained placenta: a randomized controlled trial. Am J Obstet Gynecol. 2006 Feb;194(2):446-50.

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See GRADE Table 63

Recommendation 28: The use of antibiotics for the manual removal of placenta
• No RCTs of antibiotic prophylaxis after the manual removal of the placenta were identified in a systematic review published in 2012. One retrospective study (550 patients) (Criscuolo JL et al) evaluated prophylactic antibiotic therapy in intrauterine manipulations (such as forceps delivery, manual removal of the placenta, and the exploration of the uterus cavity) during vaginal delivery.
Source of evidence 37. Chongsomchai C, Lumbiganon P, Laopaiboon M. Prophylactic antibiotics for manual removal of retained placenta in vaginal birth. Cochrane Database Syst Rev. 2012; In editorial process. 195. Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2010;20;(1). 44. Criscuolo JL, Kibler MP, Micholet S, Magnin G, Ducroz B, Toullat G, et al. The value of antibiotic prophylaxis during intrauterine procedures during vaginal delivery. A comparative study of 500 patients. J Gynecol Obstet Biol Reprod (Paris). 1990;19(7):909-18.

Recommendation 29: Protocol for the management of PPH

- A literature search revealed a randomized cluster controlled trial of 106 maternity units undertaken in France (146 781 women). The units were randomized to receive a multifaceted intervention (based on the PPH national guidelines) which consisted of a combination of outreach visits, reminders, and a peer review of deliveries with severe PPH. The control group received no intervention. No differences were found in the rates of severe maternal morbidity related to PPH, blood transfusion, or the use of first and second line uterotonics. The results of the before-and-after studies were controversial. But, despite the sparse evidence, those attending the WHO Technical Consultation regarded the management protocols as generally useful and unlikely to be harmful.
  (Quality of evidence: No formal evidence reviewed; consensus. Strength: Strong.)

Source of evidence

52. Deneux-Tharaux C, Dupont C, Colin C, Rabilloud M, Touzet S, Lansac J, et al. Multifaceted intervention to decrease the rate of severe postpartum haemorrhage: the PITHAGORE6 cluster-randomised controlled trial. BJOG. Sep;117(10):1278-87.

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139. Mousa HA, Alfirevic Z. Major postpartum hemorrhage: survey of maternity units in the United Kingdom. Acta Obstet Gynecol Scand. 2002 Aug;81(8):727-30.

69. Foy R, Penney G, Greer I. The impact of national clinical guidelines on obstetricians in Scotland. Health Bull (Edinb). 2001 Nov;59(6):364-72.

Recommendation 30: Formal protocol for the referral of women diagnosed as having PPH
• An update search in 2011 found no additional references and the position adopted in the previous guidelines was therefore maintained by the GDG.
Source of evidence 18. Bagou G. Modalities for maternal transfer in the event of postpartum hemorrhage. J Gynecol Obstet Biol Reprod (Paris). 2004 Dec;33(8 Suppl):4S89-4S92. 57. Donnelly JA, Smith EA, Runcie CJ. Transfer of the critically ill obstetric patient: experience of a specialist team and guidelines for the non-specialist. Int J Obstet Anesth. 1995 Jul;4(3):145-9. 54. Diarra Nama AJ, Angbo O, Koffi MN, Koffi MK, Yao TK, Ekra CW. Morbidity and mortality related to obstetrical transfers in the Bouafle health district of Ivory Coast. Sante Publique. 1999 Jun;11(2):193-201.

Recommendation 31: The use of PPH treatment simulation in training programmes

- A literature search did not reveal any research evidence for or against the use of PPH simulation programmes. Those contributing to the WHO Technical Consultation considered the PPH simulation programmes to be generally useful and unlikely to be harmful.

Source of evidence

11. Andreatta P, Gans-Larty F, Debpuur D, Ofosu A, Perosky J. Evaluation of simulation-based training on the ability of birth attendants to correctly perform bimanual compression as obstetric first aid. Int J Nurs Stud. Oct;48(10):1275-80.

203. Toledo P, McCarthy RJ, Burke CA, Goetz K, Wong CA, Grobman WA. The effect of live and web-based education on the accuracy of blood-loss estimation in simulated obstetric scenarios. Am J Obstet Gynecol. Apr;202(4):400 e1-5.

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97. Johanson RB, Menon V, Burns E, Kargramanya E, Osipov V, Israelyan M, et al. Managing Obstetric Emergencies and Trauma (MOET) structured skills training in Armenia, utilising models and reality based scenarios. BMC Med Educ. 2002 May 20;2:5.

128. Maslovitz S, Barkai G, Lessing JB, Ziv A, Many A. Recurrent obstetric management mistakes identified by simulation. Obstet Gynecol. 2007 Jun;109(6):1295-300.

10. Anderson ER, Black R, Brocklehurst P. Acute obstetric emergency drill in England and Wales: a survey of practice. BJOG. 2005 Mar;112(3):372-5.

99. Jyothi NK, Cox C, Johanson R. Management of obstetric emergencies and trauma (MOET): regional questionnaire survey of obstetric practice among career

obstetricians in the United Kingdom. J Obstet Gynaecol. 2001 Mar;21(2):107-11.

21. Black RS, Brocklehurst P. A systematic review of training in acute obstetric emergencies. BJOG. 2003 Sep;110(9):837-41.

121. Macedonia CR, Gherman RB, Satin AJ. Simulation laboratories for training in obstetrics and gynecology. Obstet Gynecol. 2003 Aug;102(2):388-92.

116. Letterie GS. How virtual reality may enhance training in obstetrics and gynecology. Am J Obstet Gynecol. 2002 Sep;187(3 Suppl):S37-40.

No GRADE Table available

Recommendation 32: Monitoring the use of uterotonics

- The GDG agreed by consensus during the technical consultation to include this recommendation for programmatic monitoring and evaluation based on the experience of other health areas (e.g. child health) that have content-oriented indicators for monitoring.

Statement A: The route of oxytocin for the prevention of PPH

A 2011 Cochrane systematic review found no randomized controlled trials which could support this recommendation.

Source of evidence

153. Oladapo OT, Okusanya BO, Abalos E. Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev.2:CD009332.

Statement B: Recombinant factor VIIa

A recently published Cochrane review found no randomized control trials pertaining to the use of disseminated intravascular coagulation during pregnancy and postpartum. The evidence regarding the use of this treatment for PPH is therefore limited to reviews of case reports and case series (40, 41) and two observational studies (42,43).

Hossain (43) described a retrospective cohort study (34 patients) of blood loss >1500 ml in which 18 patients were treated using rFVIIa. Ahonen (42) compared the outcomes of those who had received rFVIIa for the treatment of PPH (26 women) versus those in the same time period who had not (22 women).

Both studies included women who had had a caesarean section as well as women who had had a vaginal birth. The causes of PPH included uterine atony as well as abnormal placentation, retained placenta, and cervical or vaginal lacerations. The women had received conventional treatments, such as uterotonics, uterine massage, arterial ligation and, in some cases, hysterectomy prior to the administration of rFVIIa.

The risk of maternal death was reported to be lower in women treated with rFVIIa (OR 0.38, 95% CI 0.09 to 1.60), and remained lower following an adjustment for baseline haemoglobin and activated partial thromboplastin time (OR 0.04, 95% CI 0.002 to 0.83) (43). The risk of a subsequent use of hysterectomy is difficult to ascertain as the drug was administered as a 'last resort' treatment. The authors of the study noted that as confidence in the use of rFVIIa increased, there were more instances in which the drug was offered prior to hysterectomy. In Ahonen's report (42), eight women received rFVIIa following a hysterectomy, but none of the remaining 18 women treated with rFVIIa subsequently underwent a hysterectomy. A high rate of thrombotic events (185 events in 165 treated patients) was reported in patients receiving rFVIIa for off-label use (44). Ahonen (42) described one incidence of pulmonary embolus: this woman was subsequently diagnosed with antithrombin deficiency.

A Cochrane review published in 2011 which evaluated the use of Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia was also considered. None of the patients in the systematic review were pregnant.

Source of evidence

127. Marti-Carvajal AJ, Comunian-Carrasco G, Pena-Marti GE. Haematological interventions for treating disseminated intravascular coagulation during pregnancy and postpartum. Cochrane Database Syst Rev. 2012; In editorial review.

192. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev.3:CD005011.

71. Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. BJOG. 2007 Jan;114(1):8-15.

70. Franchini M, Franchi M, Bergamini V, Salvagno GL, Montagnana M, Lippi G. A critical review on the use of recombinant factor VIIa in life-threatening obstetric postpartum hemorrhage. Semin Thromb Hemost. 2008 Feb;34(1):104-12.

2. Ahonen J, Jokela R, Korttila K. An open non-randomized study of recombinant activated factor VII in major postpartum haemorrhage. Acta Anaesthesiol Scand. 2007 Aug;51(7):929-36.

92. Hossain N, Shansi T, Haider S, Soomro N, Khan NH, Memon GU, et al. Use of recombinant activated factor VII for massive postpartum hemorrhage. Acta Obstet Gynecol Scand. 2007 Oct;86(10):1200-6.

150. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA. 2006 Jan 18;295(3):293-8.

Statement C: Intraumbilical vein injection for retained placenta

- The evidence concerning the use of intraumbilical vein injection was summarized in a systematic review which included 15 randomized trials (>1700 women).

- The trials included in the review compared the use of intraumbilical vein injection of saline versus expectant management (four studies, 413 women), intraumbilical vein injection of saline plus oxytocin versus expectant management (five studies, 454 women), intraumbilical vein injection of saline plus oxytocin versus saline (twelve studies, 1276 women), intraumbilical injection of oxytocin versus plasma expander (one RCT, 109 women), and intraumbilical injection of prostaglandin solution versus saline versus oxytocin (two studies, 82 women). Some of the trials compared more than two interventions.

Intraumbilical vein injection of saline versus expectant management

- There were no significant differences in reported rates of the manual removal of the placenta (RR 0.99; 95% CI 0.84 to 1.16), blood loss ≥500 ml (RR 0.98; 95%

CI 0.52 to 1.82), blood loss >1000 ml (RR 0.73; 95% CI 0.17 to3.11), or blood transfusion (RR 0.76; 95% CI 0.41 to1.39)

Intraumbilical vein injection of saline plus oxytocin versus expectant management

- A slightly lower rate of manual removal of the placenta was recorded in the group given saline and oxytocin, although this difference was not statistically significant (RR 0.87; 95% CI 0.74 to 1.03). Rates of blood loss ≥500 ml (RR 1.51; 95% CI 0.87 to 2.60), blood loss >1000 ml (RR 1.29; 95% CI 0.38 to 4.34), and blood transfusion (RR 0.89; 95% CI 0.5 to 1.58) were not statistically significant, and wide confidence intervals were reported.

Intraumbilical vein injection of saline plus oxytocin versus saline

- There was a trend towards a lower risk of manual removal of the placenta in the group given saline and oxytocin (RR 0.91; 95% CI 0.82 to 1.00) up to a confidence interval of 1. No differences were found in rates of blood loss ≥500 ml, blood loss >1000 ml, or the use of blood transfusion.

Intraumbilical injection of oxytocin versus plasma expander

- There were no significant differences in rates of manual removal of the placenta or of blood loss >1000 ml. The sample size was small.

Intraumbilical injection of prostaglandin solution versus saline

- A lower rate of manual removal of the placenta was reported in women who received an intraumbilical vein injection of prostaglandin solution (9 of 31 women) compared with those who received saline (14 of 20 women) (RR 0.42; 95% CI 0.22 to 0.82). These sample numbers were too small to provide any reliable conclusion. Blood loss was not reported, and there was no statistically significant differences reported for the use of additional uterotonics between the groups.

Intraumbilical vein injection of prostaglandin solution versus oxytocin

- A lower rate of the manual removal of the placenta was noted in women who received an intraumbilical vein injection of prostaglandin solution (9 of 31 women) compared with those who received oxytocin (21 of 31 women) (RR 0.43; 95% CI 0.25 to 0.75). Evidence for these conclusions was based on two very small trials with a high risk of detection bias. Blood loss was not reported, and there was no statistically significant difference for the use of additional uterotonics between the groups.

Source of evidence

145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

See GRADE Tables 64-69

Statement D: The distribution of misoprostol for self-administration during the antenatal period

The evidence summary concerning this statement is presented in the Box supporting the recommendation 4.

Statement E: Method of blood loss estimation

Several related studies examining blood loss measurement following childbirth (with the objective of ensuring timely diagnosis of PPH and the improvement of health outcomes) were assessed. Only one large cluster randomized controlled trial published in 2010 reported clinically important outcomes.

Summary of evidence

Quantitative versus visual methods for estimating blood loss after vaginal delivery

One large cluster RCT with 78 clusters (25 381 women) (3), conducted in 13 countries of Europe, compared the measurement of blood collected in a plastic drape with the visual estimation of blood loss. After adjusting for clustering, no differences were found in the incidence of severe maternal complications, blood transfusion, the use of additional uterotonics, the manual removal of the placenta, and surgical procedures or embolisations. Six observational studies (594 participants) (4–9), compared visual estimation with known values in the delivery room or in simulated scenarios. Three studies (10–12) compared visual or quantified estimations versus laboratory measurement of blood loss in 331 vaginal deliveries. Visual methods were reported to have underestimated blood loss when compared with known simulated volumes.

Training courses on the estimation of blood loss after vaginal delivery (GRADE Table 70)

One RCT (13) compared the accuracy of estimation of blood loss by 45 nurses who attended a course on blood loss estimation versus 45 nurses who did not attend the course. In this small RCT (13) which consisted of seven simulated scenarios, blood loss was accurately estimated by 75.55% of the nurses who attend the training course compared with 24.44% of those who did not (RR 3.09; 95% CI 1.80 to 5.30). In three studies (14–16), a total of 486 maternity service staff members visually estimated blood loss in simulated scenarios before and after the training courses. The results of the three uncontrolled studies (14–16) were similar to those of the RCT.

Source of evidence

228. Zhang WH, Deneux-Tharaux C, Brocklehurst P, Juszczak E, Joslin M, Alexander S. Effect of a collector bag for measurement of postpartum blood loss after vaginal delivery: cluster randomised trial in 13 European countries. BMJ.340:c293.

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See GRADE Table 70

GRADE Tables

Table 1: Active vs Expectant management of third stage of labour

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Active management of 3rd stage of labour**	**Expectant management of 3rd stage of labour**	**Relative (95% CI)**	**Absolute**		
Blood loss ≥ 1000 Ml												
3	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	21/2299 (0.91%)	57/2337 (2.4%)	RR 0.34 (0.14 to 0.87)	2 fewer per 100 (from 0 fewer to 2 fewer)	MODERATE	CRITICAL
Blood transfusion												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/2402 (1%)	71/2427 (2.9%)	RR 0.35 (0.22 to 0.55)	2 fewer per 100 (from 1 fewer to 2 fewer)	HIGH	CRITICAL
Additional uterotonics												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	93/2402 (3.9%)	513/2427 (21.1%)	RR 0.19 (0.15 to 0.23)	17 fewer per 100 (from 16 fewer to 18 fewer)	HIGH	IMPORTANT

Vomiting.												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	161/2299 (7%)	72/2337 (3.1%)	RR 2.47 (1.36 to 4.48)	5 more per 100 (from 1 more to 11 more)	HIGH	IMPORTANT
Abdominal pain												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/705 (4.5%)	13/724 (1.8%)	RR 2.53 (1.34 to 4.78)	3 more per 100 (from 1 more to 7 more)	HIGH	IMPORTANT
High blood pressure												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/2299 (2.5%)	14/2337 (0.6%)	RR 4.1 (1.63 to 10.3)	19 more per 1000 (from 4 more to 56 more)	HIGH	IMPORTANT
Maternal Hb < 9 g/dL 24-72 hours postpartum												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/788 (3.6%)	56/784 (7.1%)	-	-	HIGH	IMPORTANT
Admission to neonatal special/intensive care												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/1594 (4.3%)	84/1613 (5.2%)	RR 0.81 (0.6 to 1.11)	1 fewer per 100 (from 2 fewer to 1 more)	HIGH	NOT IMPORTANT[7]

Neonatal jaundice requiring phototherapy or exchange transfusion												
2	randomized trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	71/1562 (4.5%)	78/1580 (4.9%)	RR 0.96 (0.55 to 1.68)	0 fewer per 100 (from 2 fewer to 3 more)	LOW	NOT IMPORTANT[7]
Manual removal of placenta												
4	randomized trials	no serious risk of bias	serious[4]	no serious indirectness	serious[3]	none	51/2402 (2.1%)	36/2427 (1.5%)	RR 1.78 (0.57 to 5.56)	1 more per 100 (from 1 fewer to 7 more)	LOW	IMPORTANT
Any analgesia between birth of the baby and discharge from labour ward												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/705 (4.5%)	13/724 (1.8%)	RR 2.53 (1.34 to 4.78)	3 more per 100 (from 1 more to 7 more)	HIGH	NOT IMPORTANT[7]
Secondary blood loss/any vaginal bleeding needing treatment (after 24 hours and up to 6 weeks)												
3	randomized trials	no serious risk of bias	serious[5]	no serious indirectness	serious[3]	none	89/2299 (3.9%)	73/2337 (3.1%)	RR 1.1 (0.4 to 2.99)	0 more per 100 (from 2 fewer to 6 more)	LOW	NOT IMPORTANT[7]
Surgical evacuation of retained products of conception												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	22/2299 (0.96%)	30/2337 (1.3%)	RR 0.74 (0.32 to 1.71)	0 fewer per 100 (from 1 fewer to 1 more)	MODERATE	NOT IMPORTANT[7]

Apgar score < 7 at 5 minutes												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3,6]	none	8/846 (0.95%)	8/849 (0.94%)	RR 1 (0.38 to 2.66)	0 fewer per 100 (from 1 fewer to 2 more)	MODERATE	NOT IMPORTANT[7]
Exclusive breastfeeding at discharge from hospital												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	637/846 (75.3%)	632/849 (74.4%)	RR 1.01 (0.96 to 1.07)	7 more per 1000 (from 30 fewer to 52 more)	HIGH	IMPORTANT
Return to hospital as in- or outpatient because of bleeding (not pre-specified)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/1453 (2.8%)	19/1488 (1.3%)	RR 2.21 (1.29 to 3.79)	2 more per 100 (from 0 more to 4 more)	HIGH	NOT IMPORTANT[7]

[1] Statistical heterogeneity (I^2=60 %)

[2] Statistical Heterogeneity (I^2=66%).

[3] Wide confidence interval crossing the line of no effect.

[4] Statistical Heterogeneity (I^2=73%).

[5] Statistical Heterogeneity (I^2= 87%).

[6] Few events.

[7] Was not in the proposed outcomes.

Source of evidence: 19. Begley CM, Gyte GM, Murphy DJ, Devane D, McDonald SJ, McGuire W. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2011(7):CD007412. In editorial process.

Table 2. Oxytocin without active management of third stage of labour prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin without active management	Control	Relative (95% CI)	Absolute		
Blood loss >1000ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/591 (6.6%)	59/630 (9.4%)	RR 0.73 (0.49 to 1.07)	3 fewer per 100 (from 5 fewer to 1 more) -	HIGH	CRITICAL
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	9/591 (1.5%)	8/630 (1.3%)	RR 1.30 (0.5 to 3.39)	0 more per 100 (from 1 fewer to 3 more) -	LOW	CRITICAL
Additional uterotonics												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/591 (9.1%)0	93/630 (14.8%)	RR 0.66 (0.48 to 0.9)	5 fewer per 100 (from 1 fewer to 8 fewer) -	HIGH	CRITICAL

Blood loss > 500ml												
2	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	129/591 (21.8%)	230/630 (36.5%)	RR 0.61 (0.51 to 0.73)	14 fewer per 100 (from 10 fewer to 18 fewer) -	MODERATE	IMPORTANT
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/591 (3.2%)	11/630 (1.7%)	RR 1.67 (0.82 to 3.41)	1 more per 100 (from 0 fewer to 4 more) -	MODERATE	IMPORTANT

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Statistical Heterogeneity (I^2: 67%).

Source of evidence: 26. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews.Art. No.: CD001808. In editorial process.*

Table 3. Misoprostol for preventing PPH (unsupervised administration)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Placebo	Relative (95% CI)	Absolute		
Blood loss > 1000 ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	serious [2]	none	2/812 (0.25%)	10/808 (1.2%)	RR 0.2 (0.04 to 0.91)	10 fewer per 1000 (from 1 fewer to 12 fewer)	VERY LOW	CRITICAL
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,4]	none	1/812 (0.1%)	7/808 (0.9%)	RR 0.14 (0.02 to 1.15)	7 fewer per 1000 (from 8 fewer to 1 more)	VERY LOW	CRITICAL
Blood loss > 500ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	52/812 (6.4%)	97/808 (12%)	RR 0.53 (0.39 to 0.74)	56 fewer per 1000 (from 31 fewer to 73 fewer)	LOW	IMPORTANT
Total blood loss (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	812	808	-	MD 48 lower (63.81 to 32.19 lower)	LOW	IMPORTANT

ICU admission												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	Very serious[2,3]	none	2/812 (0.2%)	2/808 (0.2%)	RR 1 (0.14 to 7.05)	0 fewer per 1000 (from 2 fewer to 15 more)	VERY LOW	IMPORTANT
Additional uterotonics												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	Very serious[2,3]	none	3/812 (0.37%)	6/808 (0.74%)	RR 0.50 (0.12 to 1.98)	0 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT
Shivering												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	no serious imprecision	none	419/812 (51.6%)	140/808 (17.3%)	RR 2.98 (2.53 to 3.51)	35 more per 100 (from 27 more to 44 more)	LOW	IMPORTANT
Maternal temperature > 38°C												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	no serious imprecision	none	34/812 (4.2%)	9/808 (1.1%)	RR 3.76 (1.81 to 7.79)	3 more per 100 (from 1 more to 8 more)	LOW	IMPORTANT
Maternal Transfer												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious[1]	Very serious[2,4]	none	4/812 (0.5%)	12/808 (1.5%)	RR 0.33 (0.11 to 1.02)	10 fewer per 1000 (from 13 fewer to 0 more)	VERY LOW	NOT IMPORTANT

Medical procedures undertaken												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,3]	none	0/812 (0 %)	1/808 (0.1%)	RR 0.33 (0.01 to 8.13)	1 fewer per 1000 (from 1 fewer to 9 more)	VERY LOW	NOT IMPORTANT
Surgical interventions												
1	randomised trials	no serious risk of bias	no serious inconsistency	Very serious [1]	serious [2]	none	1/812 (0.1%)	8/808 (1%)	RR 0.12 (0.02 to 0.99)	9 fewer per 1000 (from 0 fewer to 10 fewer)	VERY LOW	NOT IMPORTANT

[1] In this trial, deliveries were assisted by auxiliary nurse midwives at primary health facilities or at home and the use of misoprostol was supervised by these health professionals. Caution should be exercised when extrapolating data provided by this trial to deliveries not assisted by skilled birth attendants, at home, with unsupervised use of misoprostol.

[2] Very few events

[3] Confidence interval ranging from appreciable benefit to appreciable harm

[4] Confidence interval ranging from appreciable benefit to negligible harm

Source of evidence: 53. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006 Oct 7;368(9543):1248-53.

Table 4. Oxytocin vs Ergot alcaloids for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergot alcaloids	Relative (95% CI)	Absolute		
Blood loss >1000ml (assessed with: objectively by weighting pads[1])												
4	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23/1064 (2.2%)	28/1025 (2.7%)	RR 1.09 (0.63 to 1.87)	0 more per 100 (from 1 fewer to 2 more) -	VERY LOW	CRITICAL
Blood transfusion												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5,6]	none	2/234 (0.85%)	1/333 (0.3%)	RR 3.74 (0.34 to 40.64)	1 more per 100 (from 0 fewer to 12 more) -	VERY LOW	CRITICAL
Additional uterotonics												
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/1010 (6%)	99/1141 (8.7%)	RR 0.74 (0.55 to 1.01)	2 fewer per 100 (from 4 fewer to 0 more) -	MODERATE	CRITICAL
Nausea												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/523 (3.3%)	140/568 (24.6%)	RR 0.13 (0.08 to 0.21)	21 fewer per 100 (from 19 fewer to 23 fewer) -	LOW	IMPORTANT

Vomiting												
3	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/523 (2.3%)	163/568 (28.7%)	RR 0.08 (0.05 to 0.14)	26 fewer per 100 (from 25 fewer to 27 fewer) -	LOW	IMPORTANT
Headache												
2	randomised trials	very serious	serious[8]	no serious indirectness	no serious imprecision	none	1/453 (0.22%)	56/490 (11.4%)	RR 0.03 (0.01 to 0.14)	11 fewer per 100 (from 10 fewer to 11 fewer) -	VERY LOW	IMPORTANT
High blood pressure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,6]	none	4/50 (8%)	15/100 (15%)	RR 0.53 (0.19 to 1.52)	7 fewer per 100 (from 12 fewer to 8 more) -	LOW	IMPORTANT
Blood loss > 500ml (assessed with: objectively estimated[1])												
7	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/1836 (6.4%)	183/1826 (1 0 %)	RR 0.80 (0.65 to 0.99)	2 fewer per 100 (from 0 fewer to 4 fewer) -	LOW	IMPORTANT
Manual removal of the placenta												
5	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/1361 (6%)	93/1328 (7%)	RR 0.60 (0.45 to 0.8)	3 fewer per 100 (from 1 fewer to 4 fewer) -	MODERATE	IMPORTANT

[1] Only one study (De Groot 1996) reported method of blood loss estimation
[2] Two studies (Saito 2007, Sorbe 1978) at high risk of bias.
[3] Wide confidence interval crossing the line of no effect.
[4] One study (Saito 2007) at high risk of bias.
[5] Very wide confidence interval crossing the line of no effect.
[6] Small sample size.
[7] Two studies (Saito 2007, Orji 2007) at high risk of bias.
[8] Statistical Heterogeneity (I^2= 85%).
[9] Three studies (Saito2007, Sorbe1978, Orji 2008) at high risk of bias.

Source of evidence: 26. Brass E, Cotter AM, Ness A, Tolosa JE, Westhoff G. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews.Art. No.: CD001808. In editorial process.*

Table 5. Oxytocin- Ergometrine IM (fixed dose combination) vs Oxytocin IV (any dose) for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Oxytocin IV (any dose)	Relative (95% CI)	Absolute		
Blood loss > 500ml (assessed with: not mentioned)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31/840 (3.7%)	35/837 (4.2%)	RR 0.88 (0.55 to 1.41)	1 fewer per 100 (from 2 fewer to 2 more)	MODERATE	CRITICAL
										-		
Blood loss > 1000ml (assessed with: not mentioned)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/840 (1.1%)	14/837 (1.7%)	RR 0.65 (0.28 to 1.47)	1 fewer per 100 (from 1 fewer to 1 more)	MODERATE	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/840 (2.3%)	9/837 (1.1%)	RR 2.05 (0.97 to 4.33)	11 more per 1000 (from 0 fewer to 36 more)	MODERATE	CRITICAL

										-		
Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	87/840 (10.4%)	70/837 (8.4%)	RR 1.27 (0.91 to 1.76)	2 more per 100 (from 1 fewer to 6 more)	MODERATE	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	210/840 (25%)	196/837 (23.4%)	RR 1.09 (0.85 to 1.39)	2 more per 100 (from 4 fewer to 9 more)	MODERATE	IMPORTANT
										-		
Vomiting												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/840 (1.4%)	7/837 (0.84%)	RR 3.33 (1.21 to 9.2)	2 more per 100 (from 0 more to 7 more)	MODERATE	IMPORTANT
										-		
Manual removal of the placenta												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	3/840 (0.36%)	7/837 (0.84%)	RR 0.44 (0.13 to 1.53)	0 fewer per 100 (from 1 fewer to 0 more)	MODERATE	IMPORTANT

[1] Wide confidence interval crossing the line of no effect.
[2] Few events

Source of evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 6. Oxytocin- Ergometrine IM (fixed dose combination) vs Oxytocin IM (any dose) in Management of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Oxytocin IM (any dose)	Relative (95% CI)	Absolute		
Blood loss > 500ml												
5	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	369/4161 (8.9%)	443/4180 (10.6%)	RR 0.84 (0.74 to 0.96)	2 fewer per 100 (from 0 fewer to 3 fewer)	MODERATE	CRITICAL
										-		
Blood loss 1000ml												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/3472 (2.4%)	105/3491 (3%)	RR 0.79 (0.59 to 1.06)	1 fewer per 100 (from 1 fewer to 0 more)	HIGH	CRITICAL
										-		
Blood transfusion												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	36/3242 (1.1%)	29/3260 (0.89%)	RR 1.25 (0.77 to 2.05)	0 more per 100 (from 0 fewer to 1 more)	MODERATE	CRITICAL

										-		
Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/2226 (15.5%)	430/2248 (19.1%)	RR 0.78 (0.66 to 0.91)	4 fewer per 100 (from 2 fewer to 7 fewer)	HIGH	CRITICAL
Nausea												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	476/2221 (21.4%)	122/2246 (5.4%)	RR 4.18 (3.51 to 4.99)	17 more per 100 (from 14 more to 22 more)	MODERATE	IMPORTANT
										-		
Vomiting												
2	randomised trials	no serious risk of bias	serious[4,5]	no serious indirectness	no serious imprecision	none	365/2221 (16.4%)	64/2246 (2.8%)	RR 4.97 (4.06 to 6.08)	11 more per 100 (from 9 more to 14 more)	MODERATE	IMPORTANT
										-		
Manual removal of the placenta												
5	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	122/4161 (2.9%)	119/4180 (2.8%)	RR 1.04 (0.8 to 1.34)	0 more per 100 (from 1 fewer to 1 more)	MODERATE	CRITICAL
High blood pressure												

3	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	48/3237 (1.5%)	19/3258 (0.58%)	RR 2.44 (1.50 to 3.96)	1 more per 100 (from 0 more to 2 more)	MODERATE	IMPORTANT
										-		

[1] Nieminem 1963, unclear risk of bias but likely to be high. Women were divided into 3 groups.

[2] Asymmetrical Funnel Plot.

[3] Wide confidence interval crossing the line of no effect.

[4] Heterogeneity (I^2 = 61%).

[5] Heterogeneity (I^2 = 79%).

[6] Heterogeneity (I^2 = 75%)

Source of evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 7. Oxytocin- Ergometrine IM (fixed dose combination) vs Ergometrine IM (any dose) for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Ergometrine IM (any dose)	Relative (95% CI)	Absolute		
Blood loss >500ml (assessed with: not mentioned)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	44/2048 (2.1%)	90/2240 (4%)	RR 0.57 (0.4 to 0.81)	2 fewer per 100 (from 1 fewer to 2 fewer)	LOW	CRITICAL
										-		
Blood loss > 1000ml (assessed with: not mentioned)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	5/560 (0.89%)	3/560 (0.54%)	RR 1.67 (0.4 to 6.94)	4 more per 1000 (from 3 fewer to 32 more)	LOW	CRITICAL
										-		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	5/560 (0.89%)	7/560 (1.3%)	RR 0.71 (0.23 to 2.24)	0 fewer per 100 (from 1 fewer to 2 more)	LOW	CRITICAL

										-		
Manual removal of the placenta												
5	randomised trials	serious[1]	serious[5]	no serious indirectness	serious[3]	reporting bias[2]	46/2018 (2.3%)	61/2240 (2.7%)	RR 0.81 (0.56 to 1.18)	1 fewer per 100 (from 1 fewer to 0 more)	VERY LOW	IMPORTANT

[1] Two studies (Chuckudebelu 1963 and Kemp 1963) at high risk of bias.

[2] Asymmetrical Funnel Plot.

[3] Wide confidence interval crossing the line of no effect.

[4] Few events

[5] Heterogeneity (I^2:74%).

Source of evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 8. Misoprostol 600mcg (oral) vs injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (oral)	Injectable uterotonics	Relative (95% CI)	Absolute		
Maternal death												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/9463 (0.02%)	2/9366 (0.02%)	RR 1 (0.14 to 7.1)	0 fewer per 1000 (from 0 fewer to 1 more)	MODERATE	CRITICAL
										-		
Blood loss > 500ml												
7	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	1969/11067 (17.8%)	1384/11097 (12.5%)	RR 1.42 (1.3 to 1.52)	5 more per 100 (from 4 more to 6 more)	MODERATE	CRITICAL
										-		
Blood loss > 1000ml												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	396/10972 (3.6%)	292/11005 (2.7%)	RR 1.36 (1.17 to 1.58)	10 more per 1000 (from 5 more to 15 more)	HIGH	CRITICAL
										-		

Blood transfusion												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/10793 (0.82%)	114/10807 (1.1%)	RR 0.77 (0.59 to 1.02)	2 fewer per 1000 (from 4 fewer to 0 more)	HIGH	CRITICAL
										-		
Additional uterotonics												
6	randomised trials	no serious risk of bias[3]	serious[2]	no serious indirectness	no serious imprecision	none	1701/10885 (15.6%)	1212/10900 (11.1%)	RR 1.4 (1.31 to 1.5)	4 more per 100 (from 3 more to 6 more)	MODERATE	CRITICAL
										-		
Nausea												
6	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	146/10886 (1.3%)	132/10907 (1.2%)	RR 1.1 (0.8 to 1.4)	1 more per 1000 (from 2 fewer to 5 more)	LOW	IMPORTANT
										-		
Vomiting												
7	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	130/11072 (1.2%)	107/11103 (0.96%)	RR 1.21 (0.94 to 1.57)	0 more per 100 (from 0 fewer to 1 more)	LOW	IMPORTANT
										-		

Diarrhoea												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/10161 (0.63%)	25/10165 (0.25%)	RR 2.52 (1.6 to 3.98)	0 more per 100 (from 0 more to 1 more)	HIGH	IMPORTANT
										-		
Headache												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/1113 (8.2%)	95/1126 (8.4%)	RR 0.97 (0.74 to 1.28)	0 fewer per 100 (from 2 fewer to 2 more)	HIGH	IMPORTANT
										-		
Shivering												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2229/11071 (20.1%)	676/11103 (6.1%)	RR 3.3 (3 to 3.5)	14 more per 100 (from 12 more to 15 more)	HIGH	IMPORTANT
										-		
Maternal temperature > 38°C												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	733/11056 (69.4%)	108/11081 (0.97%)	RR 6.8 (5.5 to 8.3)	6 more per 100 (from 4 more to 7 more)	HIGH	IMPORTANT
										-		

[1] Very wide confidence interval crossing the line of no effect

[2] Visual Heterogeneity.

[3] Although India 2005a has unclear risk of bias

[4] Wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 9. Misoprostol any dose (sublingual) vs injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol any dose (sublingual)	Injectable uterotonics	Relative (95% CI)	Absolute		
Blood loss > 500ml												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[1]	68/331 (20.5%)	68/332 (20.5%)	RR 1.00 (0.83 to 1.21)	0 fewer per 100 (from 3 fewer to 4 more)	MODERATE	CRITICAL
										-		
Blood loss > 1000ml												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/135 (5.2%)	13/135 (9.6%)	RR 0.54 (0.23 to 1.27)	4 fewer per 100 (from 7 fewer to 3 more)	LOW	CRITICAL
										-		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/60 (0 %)	0/60 (0 %)	-	-	LOW	CRITICAL
										-		

Additional uterotonics												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/506 (9.1%)	76/507 (15%)	RR 0.61 (0.44 to 0.85)	6 fewer per 100 (from 2 fewer to 8 fewer)	HIGH	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[5]	none	14/166 (8.4%)	17/167 (10.2%)	RR 0.83 (0.42 to 1.62)	2 fewer per 100 (from 6 fewer to 6 more)	LOW	IMPORTANT
										-		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	20/241 (8.3%)	16/242 (6.6%)	RR 1.25 (0.67 to 2.32)	2 more per 100 (from 2 fewer to 9 more)	MODERATE	IMPORTANT
										-		
Diarrhoea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/66 (1.5%)	0/67 (0 %)	RR 3.04 (0.13 to 73.42)	-	LOW	IMPORTANT
Headache												

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,5]	none	12/150 (8%)	16/150 (10.7%)	RR 0.75 (0.37 to 1.52)	3 fewer per 100 (from 7 fewer to 6 more)	LOW	IMPORTANT
Shivering												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/391 (17.9%)	6/392 (1.5%)	RR 9.06 (4.46 to 19.39)	12 more per 100 (from 5 more to 28 more)	HIGH	IMPORTANT
										-		
Maternal temperature > 38°C												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/326 (15.3%)	2/327 (0.61%)	RR 13.04 (4.77 to 35.62)	7 more per 100 (from 2 more to 21 more)	HIGH	IMPORTANT
										-		
Manual removal of the placenta												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,5]	none	0/60 (0 %)	1/61 (1.6%)	RR 0.33 (0.01 to 8.02)	1 fewer per 100 (from 2 fewer to 12 more)	LOW	IMPORTANT

[1] Asymmetrical Funnel Plot.

[2] Wide confidence interval crossing de line of no effect.

[3] Small sample size.

[4] Statistical heterogeneity (I^2 = 8 0 %).

[5] Wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 10a. Misoprostol 600mcg (sublingual) vs no uterotonics or placebo for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (sublingual)	No uterotonics or placebo	Relative (95% CI)	Absolute		
Maternal death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/330 (0.3%)	0/331 (0 %)	RR 3.01 (0.12 to 73.6)	-	LOW	CRITICAL
										-		
Blood loss > 500ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/330 (45.5%)	170/331 (51.4%)	RR 0.89 (0.76 to 1.04)	6 fewer per 100 (from 12 fewer to 2 more)	HIGH	CRITICAL
										-		
Blood loss > 1000ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/330 (11.2%)	56/331 (16.9%)	RR 0.66 (0.45 to 0.98)	6 fewer per 100 (from 0 fewer to 9 fewer)	HIGH	CRITICAL
										-		
Nausea												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	2/330 (0.61%)	4/331 (1.2%)	RR 0.5 (0.09 to 2.72)	1 fewer per 100 (from 1 fewer to 2 more)	LOW	IMPORTANT
										-		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	10/330 (3%)	4/331 (1.2%)	RR 2.51 (0.79 to 7.92)	2 more per 100 (from 0 fewer to 8 more)	LOW	IMPORTANT
										-		
Diarrhoea												
1	Randomised trial					none	10/330 (3%)	4/331 (1.2%)	RR 2.51 (0.79 to 7.92)	2 more per 100 (from 0 fewer to 8 more)		IMPORTANT
Shivering												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/330 (57.3%)	78/331 (23.6%)	RR 2.43 (1.96 to 3.01)	34 more per 100 (from 23 more to 47 more)	HIGH	IMPORTANT
										-		
Maternal temperature > 38°C												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	78/330 (23.6%)	11/331 (3.3%)	RR 7.11 (3.85 to	20 more per 100 (from 9	HIGH	IMPORTANT

		risk of bias							13.12)	more to 40 more)		
										-		

[1] Small sample size.

[2] Wide confidence interval crossing the line of no effect.

[3] Few events.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 10b. Misoprostol 400mcg (rectal) vs injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 400mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Maternal death												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/466 (0 %)	0/477 (0 %)	-	-	LOW	CRITICAL
										-		
Blood loss > 500ml												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	121/1104 (11%)	110/1140 (9.6%)	RR 1.14 (0.92 to 1.43)	1 more per 100 (from 1 fewer to 4 more)	MODERATE	CRITICAL
										-		
Blood loss > 1000ml												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32/873 (3.7%)	29/907 (3.2%)	RR 1.14 (0.7 to 1.85)	0 more per 100 (from 1 fewer to 3 more)	LOW	CRITICAL
										-		

Blood transfusion												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	16/1058 (1.5%)	16/1095 (1.5%)	RR 1.03 (0.52 to 2.04)	0 more per 100 (from 1 fewer to 2 more)	MODERATE	CRITICAL
										-		
Additional uterotonics												
3	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	71/592 (12%)	45/618 (7.3%)	RR 1.64 (1.16 to 2.31)	5 more per 100 (from 1 more to 10 more)	MODERATE	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[5]	none	8/175 (4.6%)	8/180 (4.4%)	RR 1.04 (0.41 to 2.16)	0 more per 100 (from 3 fewer to 5 more)	LOW	IMPORTANT
										-		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5,6]	none	10/894 (1.1%)	8/924 (0.87%)	RR 1.28 (0.53 to 3.12)	0 more per 100 (from 0 fewer to 2 more)	MODERATE	IMPORTANT
										-		

Diarrhoea												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,6]	none	11/719 (1.5%)	0/745 (0 %)	RR 1.03 (0.46 to 2.31)	-	MODERATE	IMPORTANT
Headache												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,7]	none	9/105 (8.6%)	4/110 (3.6%)	RR 2.36 (0.75 to 7.42)	5 more per 100 (from 1 fewer to 23 more)	LOW	IMPORTANT
Shivering												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	214/1053 (20.3%)	95/1090 (8.7%)	RR 2.34 (1.88 to 2.92)	12 more per 100 (from 8 more to 17 more)	MODERATE	CRITICAL
										-		
Maternal temperature >38°C												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/503 (7.2%)	18/519 (3.5%)	RR 2.08 (1.21 to 3.57)	4 more per 100 (from 1 more to 9 more)	HIGH	IMPORTANT
										-		
Manual removal of the placenta												
2	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[7]	none	1/180 (0.56%)	7/183 (3.8%)	RR 0.20 (0.04 to	3 fewer per 100 (from 4	MODERATE	IMPORTANT

		risk of bias							1.16)	fewer to 1 more)		

[1] Small sample size.

[2] Wide confidence interval crossing the line of no effect.

[3] Asymmetrical Funnel Plot.

[4] Statystical Heterogenity (I^2: 60 %).

[5] Wide confidence interval crossing the line of no effect,

[6] Few events.

[7] Small saple size.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 11. Misoprostol 600mcg (rectal) vs Injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Blood loss > 500ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/100 (1%)	0/100 (0 %)	RR 3 (0.12 to 72.77)	-	LOW	CRITICAL
										-		
Additional uterotonics												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	5/100 (5%)	1/100 (1%)	RR 5 (0.59 to 42.04)	4 more per 100 (from 0 fewer to 41 more)	LOW	CRITICAL
										-		
Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	2/100 (2%)	0/100 (0 %)	RR 5 (0.24 to 102.85)	-	LOW	IMPORTANT
										-		
Shivering												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2,3]	none	16/100 (16%)	13/100 (13%)	RR 1.23 (0.63 to	3 more per 100 (from 5 fewer	LOW	IMPORTANT

		risk of bias							2.42)	to 18 more) -		
Maternal temperature > 38°C												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	2/100 (2%)	0/100 (0 %)	RR 5 (0.24 to 102.85)		LOW	IMPORTANT
Manual removal of the placenta												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	3/100 (3%)	1/100 (1%)	RR 3 (0.32 to 28.35)	2 more per 100 (from 1 fewer to 27 more)	LOW	IMPORTANT

[1] Very wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 12. Misoprostol 800mcg (rectal) vs Injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 800mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Maternal death												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	0/224 (0 %)	1/226 (0.44%)	RR 0.34 (0.37 to 8.2)	0 fewer per 100 (from 0 fewer to 3 more)	LOW	CRITICAL
										-		
Blood loss > 500ml												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/474 (4.2%)	18/481 (3.7%)	RR 1.12 (0.6 to 2.09)	0 more per 100 (from 1 fewer to 4 more)	MODERATE	CRITICAL
										-		
Blood loss > 1000ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/217 (0 %)	1/224 (0.45%)	RR 0.34 (0.01 to 8.4)	0 fewer per 100 (from 0 fewer to 3 more)	LOW	CRITICAL
										-		

Blood transfusion												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[1,2]	none	9/474 (1.9%)	9/478 (1.9%)	RR 1.01 (0.4 to 2.52)	0 more per 100 (from 1 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/480 (3.1%)	23/481 (4.8%)	RR 0.65 (0.35 to 1.24)	2 fewer per 100 (from 3 fewer to 1 more)	HIGH	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/469 (0.21%)	5/473 (1.1%)	RR 0.40 (0.08 to 2.08)	1 fewer per 100 (from 1 fewer to 1 more)	LOW	IMPORTANT
										-		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	7/471 (1.5%)	7/470 (1.5%)	RR 1 (0.35 to 2.82)	0 fewer per 100 (from 1 fewer to 3 more)	LOW	IMPORTANT
										-		

Diarrhoea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	6/257 (2.3%)	5/257 (1.9%)	RR 1.20 (0.37 to 3.88)	0 more per 100 (from 1 fewer to 6 more)	LOW	IMPORTANT
Shivering												
2	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	none	96/470 (20.4%)	2/470 (0.43%)	RR 38.6 (11.04 to 134.95)	16 more per 100 (from 4 more to 57 more)	MODERATE	IMPORTANT
										-		

[1] Wide confidence interval crossing the line of no effect.

[2] Few events.

[3] Very wide confidence interval crossing the line of no effect.

[4] Statistical Heterogeneity (I^2: 71%).

[5] Statistical Heterogeneity (I^2: 82%).

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

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Table 13. Intramuscular prostaglandins vs Injectable uterotonics for Prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular prostaglandins	Injectable uterotonics	Relative (95% CI)	Absolute		
Blood loss > 500ml (assessed with: objectively assessed[1])												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	30/276 (10.9%)	31/288 (10.8%)	RR 1.06 (0.7 to 1.61)	1 more per 100 (from 3 fewer to 7 more)	MODERATE	CRITICAL
										-		
Blood loss > or = 1000ml												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	4/55 (7.3%)	11/64 (17.2%)	RR 0.41 (0.14 to 1.2)	10 fewer per 100 (from 15 fewer to 3 more)	LOW	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	7/63 (11.1%)	7/66 (10.6%)	RR 1.05 (0.39 to 2.86)	1 more per 100 (from 6 fewer to 20 more)	LOW	CRITICAL
										-		

Additional uterotonics												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	4/206 (1.9%)	4/216 (1.9%)	RR 1.02 (0.28 to 3.68)	0 more per 100 (from 1 fewer to 5 more)	LOW	CRITICAL
										-		
Nausea												
3	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[3,4]	none	3/135 (2.2%)	1/145 (0.69%)	RR 2.39 (0.36 to 16.09)	1 more per 100 (from 0 fewer to 10 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
3	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[2,7]	none	19/211 (9%)	8/214 (3.7%)	RR 2.33 (1.06 to 5.11)	5 more per 100 (from 0 more to 15 more)	LOW	IMPORTANT
										-		
Diarrhoea												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/305 (15.1%)	2/312 (0.64%)	RR 12.28 (4.47 to 33.7)	7 more per 100 (from 2 more to 21 more)	HIGH	IMPORTANT
Headache												

2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,7]	none	4/148 (2.7%)	4/147 (2.7%)	RR 1 (0.28 to 3.57)	0 fewer per 100 (from 2 fewer to 7 more)	LOW	IMPORTANT
Abdominal pain												
0	no evidence available					none	13/160 (8.1%)	2/171 (1.2%)	RR 4.99 (1.46 to 17.05)	5 more per 100 (from 1 more to 19 more)		IMPORTANT
Maternal temperature > 38°C												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	0/54 (0 %)	0/54 (0 %)	-	-	LOW	IMPORTANT
										-		
Manual removal of the placenta												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,7]	none	4/309 (1.3%)	4/322 (1.2%)	RR 1.09 (0.31 to 3.81)	0 more per 100 (from 1 fewer to 3 more)	LOW	IMPORTANT

[1] Amount of blood loss was quantified by noting the increment in weight of standardized tampons (India 2008).

[2] Wide confidence interval crossing the line of no effect

[3] Very wide confidence interval crossing the line of no effect

[4] Small sample size.

[5] Egypt 1993 inadequate support of judgment

[6] Statistical Heterogeneity (I^2: 77%).

[7] Few events.

[8] No events in both intervention and control group.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

~~Table 15~~ (28)R2

Author(s):
Date: 2011-09-01
Question: Should Injectable prostaglandins vs no uterotonics or placebo be used for Prevention of PPH?
Settings: High, low and middle income countries

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Injectable prostaglandins**	**No uterotonics or placebo**	**Relative (95% CI)**	**Absolute**		
Blood loss >1000ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/22 (4.5%)	3/24 (12.5%)	RR 0.3 (0.04 to 3.24)	9 fewer per 100 (from 12 fewer to 28 more)	LOW	CRITICAL
										-		
Additional uterotonics												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/22 (0 %)	2/24 (8.3%)	RR 0.22 (0.01 to 4.29)	6 fewer per 100 (from 8 fewer to 27 more)	LOW	CRITICAL
										-		
Adverse effects												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	0/22 (0 %)	1/24 (4.2%)	RR 0.36 (0.02 to 8.46)	3 fewer per 100 (from 4 fewer to 31 more)	LOW	CRITICAL
										-		
Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	0/22 (0 %)	1/24 (4.2%)	RR 0.34 (0.02 to 8.46)	3 fewer per 100 (from 4 fewer to 31 more)	LOW	IMPORTANT
										-		

[1] Very wide confidence interval crossing the line of no effect.

[2] Small sample size.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 14. Misprostol vs placebo for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Placebo	Relative (95% CI)	Absolute		
Blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	serious[2]	none	2/812 (0.25%)	10/808 (1.2%)	RR 0.2 (0.04 to 0.91)	10 fewer per 1000 (from 1 fewer to 12 fewer)	MODERATE	CRITICAL
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	Very serious[2,4]	none	1/812 (0.1%)	7/808 (0.9%)	RR 0.14 (0.02 to 1.15)	7 fewer per 1000 (from 8 fewer to 1 more)	LOW	CRITICAL
Blood loss > 500ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	no serious imprecision	none	52/812 (6.4%)	97/808 (12%)	RR 0.53 (0.39 to 0.74)	56 fewer per 1000 (from 31 fewer to 73 fewer)	HIGH	IMPORTANT
Total blood loss (Better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	no serious imprecision	none	812	808	-	MD 48 lower (63.81 to 32.19 lower)	HIGH	IMPORTANT

ICU admission												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	Very serious[2,3]	none	2/812 (0.2%)	2/808 (0.2%)	RR 1 (0.14 to 7.05)	0 fewer per 1000 (from 2 fewer to 15 more)	LOW	IMPORTANT
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	Very serious[2,3]	none	3/812 (0.37%)	6/808 (0.74%)	RR 0.50 (0.12 to 1.98)	0 fewer per 100 (from 1 fewer to 1 more)	LOW	IMPORTANT
Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	no serious imprecision	none	419/812 (51.6%)	140/808 (17.3%)	RR 2.98 (2.53 to 3.51)	35 more per 100 (from 27 more to 44 more)	HIGH	IMPORTANT
Maternal temperature > 38°C												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	no serious imprecision	none	34/812 (4.2%)	9/808 (1.1%)	RR 3.76 (1.81 to 7.79)	3 more per 100 (from 1 more to 8 more)	HIGH	IMPORTANT
Maternal Transfer												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	Very serious[2,4]	none	4/812 (0.5%)	12/808 (1.5%)	RR 0.33 (0.11 to 1.02)	10 fewer per 1000 (from 13 fewer to 0 more)	LOW	NOT IMPORTANT

Medical procedures undertaken											
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	Very serious[2,3]	none	0/812 (0 %)	1/808 (0.1%)	RR 0.33 (0.01 to 8.13)	1 fewer per 1000 (from 1 fewer to 9 more)	LOW	NOT IMPORTANT
Surgical interventions											
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness [1]	serious[2]	none	1/812 (0.1%)	8/808 (1%)	RR 0.12 (0.02 to 0.99)	9 fewer per 1000 (from 0 fewer to 10 fewer)	MODERATE	NOT IMPORTANT

[1] This grading of evidence only applies for supervised administration of misoprostol in a mixed setting of primary health facilities and homes

[2] Very few events

[3] Confidence interval ranging from appreciable benefit to appreciable harm

[4] Confidence interval ranging from appreciable benefit to negligible harm

Source of evidence: 53. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006 Oct 7;368(9543):1248-53

Table 15. Misprostol vs placebo for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Placebo	Relative (95% CI)	Absolute		
Blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	serious [2]	none	2/812 (0.25%)	10/808 (1.2%)	RR 0.2 (0.04 to 0.91)	10 fewer per 1000 (from 1 fewer to 12 fewer)	VERY LOW	CRITICAL
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,4]	none	1/812 (0.1%)	7/808 (0.9%)	RR 0.14 (0.02 to 1.15)	7 fewer per 1000 (from 8 fewer to 1 more)	VERY LOW	CRITICAL
Blood loss > 500ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	52/812 (6.4%)	97/808 (12%)	RR 0.53 (0.39 to 0.74)	56 fewer per 1000 (from 31 fewer to 73 fewer)	LOW	IMPORTANT
Total blood loss (Better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	812	808	-	MD 48 lower (63.81 to 32.19 lower)	LOW	IMPORTANT

ICU admission												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,3]	none	2/812 (0.2%)	2/808 (0.2%)	RR 1 (0.14 to 7.05)	0 fewer per 1000 (from 2 fewer to 15 more)	VERY LOW	IMPORTANT
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,3]	none	3/812 (0.37%)	6/808 (0.74%)	RR 0.50 (0.12 to 1.98)	0 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT
Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	419/812 (51.6%)	140/808 (17.3%)	RR 2.98 (2.53 to 3.51)	35 more per 100 (from 27 more to 44 more)	LOW	IMPORTANT
Maternal temperature > 38°C												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	no serious imprecision	none	34/812 (4.2%)	9/808 (1.1%)	RR 3.76 (1.81 to 7.79)	3 more per 100 (from 1 more to 8 more)	LOW	IMPORTANT
Maternal Transfer												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,4]	none	4/812 (0.5%)	12/808 (1.5%)	RR 0.33 (0.11 to 1.02)	10 fewer per 1000 (from 13 fewer to 0 more)	VERY LOW	NOT IMPORTANT

Medical procedures undertaken												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	Very serious [2,3]	none	0/812 (0 %)	1/808 (0.1%)	RR 0.33 (0.01 to 8.13)	1 fewer per 1000 (from 1 fewer to 9 more)	VERY LOW	NOT IMPORTANT
Surgical interventions												
1	randomized trials	no serious risk of bias	no serious inconsistency	Very serious [1]	serious [2]	none	1/812 (0.1%)	8/808 (1%)	RR 0.12 (0.02 to 0.99)	9 fewer per 1000 (from 0 fewer to 10 fewer)	VERY LOW	NOT IMPORTANT

[1] In this trial, deliveries were assisted by auxiliary nurse midwives at primary health facilities or at home and the use of misoprostol was supervised by these health professionals. Caution should be exercised when extrapolating data provided by this trial to deliveries not assisted by skilled birth attendants, at home, with unsupervised use of misoprostol.

[2] Very few events

[3] Confidence interval ranging from appreciable benefit to appreciable harm

[4] Confidence interval ranging from appreciable benefit to negligible harm

Source of evidence: 53. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006 Oct 7;368(9543):1248-53

Table 16. Misoprostol for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol (400µg)	No intervention	Relative (95% CI)	Absolute		
Postpartum haemorrhage (assessed with: self-reported)												
1	observational studies (Quasi-experimental)	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none[3,4]	19/1009 (1.9%)	65/1008 (6.4%)	RR 0.29 (0.18 to 0.48)	46 fewer per 1000 (from 34 fewer to 53 fewer)	VERY LOW	IMPORTANT
Retained placenta (interval between delivery of the baby and placenta > 30min)												
1	observational studies (Quasi-experimental)	no serious risk of bias[1]	no serious inconsistency	serious[2]	serious[5]	none	31/884 (3.5%)	52/1008 (5.2%)	RR 0.68 (0.44 to 1.05)	17 fewer per 1000 (from 29 fewer to 3 more)	VERY LOW	NOT IMPORTANT
Manual removal of the placenta												
1	observational studies (Quasi-experimental)	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	none	26/884 (2.9%)	68/1008 (6.7%)	RR 0.44 (0.28 to 0.68)	38 fewer per 1000 (from 22 fewer to 49 fewer)	VERY LOW	NOT IMPORTANT

[1] Unblinded study, no use of placebo in the control group
[2] Misoprostol administered under direct supervision
[3] Over 70 % of risk reduction
[4] Multinomial logistic regression analysis found that after adjustment for possible risk factors, the Relative Risk would be further reduced (RR0.19, CI 0.08 to 0.48)
[5] Estimated effect ranging from appreciable benefit to negligible harm

Source of evidence: 82. Hashima EN, Nahar S, Al Mamun M, Afsana K, Byass P. Oral misoprostol for preventing postpartum haemorrhage in home births in rural Bangladesh: how effective is it? Glob Health Action. 2011;4.

Table 17. Misoprostol for prevention of PPH (unsupervised community distribution)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol (Unsupervised community distribution)	No intervention	Relative (95% CI)	Absolute		
Use of any uterotonic (non-randomized controlled trial)												
1	observational studies	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	1960/2039 (96.1%)	295/1148 (25.7%) 25.7%	RR 3.74 (3.39 to 4.13)	704 more per 1000 (from 614 more to 804 more)	MODERATE	NOT IMPORTANT
Use of any uterotonic (before and after study)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	609/816 (74.6%)	87/813 (10.7%)	RR 6.97 (5.7 to 8.54)	639 more per 1000 (from 503 more to 807 more)	MODERATE	NOT IMPORTANT

[1] Unblinded trial, with no use of placebo in the control group

[2] Large effect (RR>2.0), consistent evidence from at least 2 studies.

Source of evidence: 179. Sanghvi H, Ansari N, Prata NJ, Gibson H, Ehsan AT, Smith JM. Prevention of postpartum hemorrhage at home birth in Afghanistan. Int J Gynaecol Obstet. Mar;108(3):276-81.

Table 18. Controlled cord traction for prevention of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Controlled cord traction	No controlled cord traction	Relative (95% CI)	Absolute		
Blood loss > 1000 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	242/11722 (2.1%)	224/11719 (1.9%)	RR 1.08 (0.9 to 1.29)	0 more per 100 (from 0 fewer to 1 more)	HIGH	CRITICAL
Blood loss > 500 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	1615/11722 (13.8%)	1515/11719 (12.9%)	RR 1.07 (1 to 1.14)	9 more per 1000 (from 0 more to 18 more)	HIGH	IMPORTANT
Manual removal of the placenta - Routine uterotonics given												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	153/11814 (1.3%)	105/11794 (0.89%)	RR 1.45 (1.14 to 1.86)	0 more per 100 (from 0 more to 1 more)	HIGH	IMPORTANT
Manual removal of the placenta - Excluding Philippines												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	62/9483 (0.65%)	64/9470 (0.68%)	RR 0.97 (0.68 to 1.37)	0 fewer per 100 (from 0 fewer to 0 more)	HIGH	IMPORTANT

Uterine inversion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	0/11962 (0 %)	1/11918 (0.008%)	RR 0.33 (0.01 to 8.15)	0 fewer per 100 (from 0 fewer to 0 more)	MODERATE	NOT IMPORTANT[2]
Additional Uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	2434/11802 (20.6%)	2390/11783 (20.3%)	RR 1.02 (0.97 to 1.07)	0 more per 100 (from 1 fewer to 1 more)	HIGH	IMPORTANT
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	62/11814 (0.52%)	55/11790 (0.47%)	RR 1.12 (0.78 to 1.62)	0 more per 100 (from 0 fewer to 0 more)	HIGH	CRITICAL
Maternal death												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	2/11818 (0.02%)	1/11798 (0.008%)	RR 2 (0.18 to 22.02)	0 more per 100 (from 0 fewer to 0 more)	MODERATE	CRITICAL
Additional surgical procedures												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/11814 (0.02%)	9/11790 (0.08%)	RR 0.22 (0.05 to 1.03)	0 fewer per 100 (from 0 fewer to 0 more)	MODERATE	NOT IMPORTANT[2]

Maternal death or Severe Maternal Morbidity												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	20/11616 (0.17%)	31/11616 (0.27%)	RR 0.65 (0.37 to 1.13)	0 fewer per 100 (from 0 fewer to 0 more)	MODERATE	CRITICAL

[1] Wide confidence interval crossing the line of no effect.

[2] Was not in the proposed outcomes.

Source of evidence: 142. Mshweshwe NT, Hofmeyr GJ, Gülmezoglu AM. Controlled cord traction for the third stage of labour. Cochrane Database of Systematic Reviews. 2012(Issue 3.1. Art. No.: CD008020).

Table 19. Early cord clamping for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early cord clamping**	**Late cord clamping**	**Relative (95% CI)**	**Absolute**		
Blood loss > 1000 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/786 (2.5%)	28/898 (3.1%)	RR 0.84 (0.48 to 1.49)	0 fewer per 100 (from 2 fewer to 2 more)	MODERATE	CRITICAL
Blood loss > 500 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	115/871 (13.2%)	117/1007 (11.6%)	RR 1.22 (0.96 to 1.55)	3 more per 100 (from 0 fewer to 6 more)	MODERATE	IMPORTANT
Manual removal of placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/736 (2.4%)	12/779 (1.5%)	RR 1.59 (0.78 to 3.26)	1 more per 100 (from 0 fewer to 3 more)	MODERATE	IMPORTANT
Length of third stage > 30 min												
1	randomized	no	no serious	no serious	serious[1,2]	none	5/480	5/483	RR 1 (0.29	0 fewer per		NOT

	trials	serious risk of bias	inconsistency	indirectness			(1%)	(1%)	to 3.41)	100 (from 1 fewer to 2 more)	MODERATE	IMPORTANT[5]
Length of third stage > 60 min												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	8/480 (1.7%)	10/483 (2.1%)	RR 0.81 (0.32 to 2.04)	0 fewer per 100 (from 1 fewer to 2 more)	MODERATE	NOT IMPORTANT[5]
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1,3]	none	3/480 (0.63%)	4/483 (0.83%)	RR 0.79 (0.2 to 3.15)	0 fewer per 100 (from 1 fewer to 2 more)	LOW	CRITICAL
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/480 (20.8%)	107/483 (22.2%)	RR 0.94 (0.74 to 1.2)	1 fewer per 100 (from 6 fewer to 4 more)	HIGH	IMPORTANT
Admission to SCN or NICU												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/599 (3.2%)	24/694 (3.5%)	RR 1.03 (0.56 to 1.9)	0 more per 100 (from 2 fewer to 3 more)	MODERATE	NOT IMPORTANT[5]

Jaundice requiring phototherapy												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/852 (3.3%)	50/910 (5.5%)	RR 0.59 (0.38 to 0.92)	2 fewer per 100 (from 0 fewer to 3 fewer)	HIGH	NOT IMPORTANT[5]
Apgar score < 7 at 5 min												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30/672 (4.5%)	24/670 (3.6%)	RR 1.23 (0.73 to 2.07)	1 more per 100 (from 1 fewer to 4 more)	MODERATE	NOT IMPORTANT[5]
Not Breastfeeding on Discharge												
9	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	483/1386 (34.8%)	587/1564 (37.5%)	RR 1.01 (0.94 to 1.09)	0 more per 100 (from 2 fewer to 3 more)	HIGH	IMPORTANT
Newborn haemoglobin (g/dL) (Better indicated by higher values)												
3	randomized trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	276	395	-	MD 2.17 lower (4.06 to 0.28 lower)	MODERATE	IMPORTANT
Infant haemoglobin at 24-48 hours (g/dL) (Better indicated by higher values)												

3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	328	442	-	MD 1.38 lower (1.66 to 1.1 lower)	HIGH	IMPORTANT
Birth weight (g) (Better indicated by higher values)												
10	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	844	1010	-	MD 65.57 lower (104.22 to 26.92 lower)	HIGH	NOT IMPORTANT[5]

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Few events.

[4] Statistical heterogeneity. I^2: 96%

[5] Was not in the proposed outcomes.

Source of evidence: 131. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev. 2012; In editorial process.*

Table20. Early cord clamping for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early cord clamping	Delayed cord clamping	Relative (95% CI)	Absolute		
Infant death (up to discharge/ variable)												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	10/319 (3.1%)	17/349 (4.9%)	RR 0.63 (0.31 to 1.28)	2 fewer per 100 (from 3 fewer to 1 more)	LOW	NOT IMPORTANT[4]
Survival to discharge												
13	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	309/319 (96.9%)	332/349 (95.1%)	RR 1.02 (0.99 to 1.06)	2 more per 100 (from 1 fewer to 6 more)	HIGH	NOT IMPORTANT[4]
Severe intraventricular haemorrhage												
6	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	5/154 (3.2%)	7/151 (4.6%)	RR 0.68 (0.23 to 1.96)	1 fewer per 100 (from 4 fewer to 4 more)	LOW	NOT IMPORTANT[4]
Periventricular leukomalacia												
2	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	very serious[1,3]	none	2/35 (5.7%)	2/36 (5.6%)	RR 1.02 (0.19 to 5.56)	0 more per 100 (from 4 fewer to 25 more)	LOW	NOT IMPORTANT[4]

		bias										
Respiratory distress syndrome												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	36/56 (64.3%)	33/59 (55.9%)	RR 1.16 (0.89 to 1.5)	9 more per 100 (from 6 fewer to 28 more)	MODERATE	NOT IMPORTANT[4]
Severe respiratory distress syndrome												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	3/19 (15.8%)	4/20 (2 0 %)	RR 0.79 (0.2 to 3.07)	4 fewer per 100 (from 16 fewer to 41 more)	LOW	NOT IMPORTANT[4]
Surfactant treatment												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,3]	none	10/42 (23.8%)	8/43 (18.6%)	RR 1.28 (0.56 to 2.93)	5 more per 100 (from 8 fewer to 36 more)	MODERATE	NOT IMPORTANT[4]
Ventilated for respiratory distress syndrome												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	40/119 (33.6%)	49/146 (33.6%)	RR 0.97 (0.71 to 1.31)	1 fewer per 100 (from 10 fewer to 10 more)	MODERATE	NOT IMPORTANT[4]
Oxygen supplementation at 28 days												

2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[3]	none	3/37 (8.1%)	7/39 (17.9%)	RR 0.48 (0.15 to 1.59)	9 fewer per 100 (from 15 fewer to 11 more)	LOW	NOT IMPORTANT[4]
Oxygen supplementation at 36 weeks												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	19/104 (18.3%)	28/105 (26.7%)	RR 0.69 (0.42 to 1.13)	8 fewer per 100 (from 15 fewer to 3 more)	MODERATE	NOT IMPORTANT[4]
Transfused for low blood pressure												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	11/66 (16.7%)	20/64 (31.3%)	RR 0.52 (0.28 to 0.94)	15 fewer per 100 (from 2 fewer to 22 fewer)	MODERATE	NOT IMPORTANT[4]
Patent ductus arteriosus												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	19/108 (17.6%)	19/115 (16.5%)	RR 1.04 (0.6 to 1.81)	1 more per 100 (from 7 fewer to 13 more)	LOW	NOT IMPORTANT[4]
Intraventricular haemorrhage												
10	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/260 (13.5%)	56/279 (20.1%)	RR 0.59 (0.41 to 0.85)	8 fewer per 100 (from 3 fewer to 12 fewer)	HIGH	NOT IMPORTANT[4]
Necrotizing enterocolitis												

5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	24/117 (20.5%)	39/124 (31.5%)	RR 0.62 (0.43 to 0.9)	12 fewer per 100 (from 3 fewer to 18 fewer)	MODERATE	NOT IMPORTANT[4]
Transfused for anaemia												
7	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/186 (23.7%)	75/206 (36.4%)	RR 0.61 (0.46 to 0.81)	14 fewer per 100 (from 7 fewer to 20 fewer)	HIGH	IMPORTANT
Hyperbilirubinemia (treated)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	51/82 (62.2%)	51/98 (52%)	RR 1.21 (0.94 to 1.55)	11 more per 100 (from 3 fewer to 29 more)	MODERATE	NOT IMPORTANT[4]
Sepsis												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	3/66 (4.5%)	11/71 (15.5%)	RR 0.29 (0.09 to 0.99)	11 fewer per 100 (from 0 fewer to 14 fewer)	MODERATE	NOT IMPORTANT[4]
Retinopathy of prematurity												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,3]	none	10/36 (27.8%)	13/36 (36.1%)	RR 0.77 (0.39 to 1.52)	8 fewer per 100 (from 22 fewer to 19 more)	LOW	NOT IMPORTANT[4]

[1] Wide confidence interval crossing the line of no effect.
[2] Few events.
[3] Small sample size.

[4] Was not in the proposed outcomes.

Source of evidence: 170. Rabe H, Reynolds GJ, Diaz-Rosello JL, McDonald SJ, Middleton P. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database of Systematic Reviews. 2012;Issue 31; In editorial process.*

Table 21. Uterine massage (before placental delivery) for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage before placental delivery	No uterine massage	Relative (95% CI)	Absolute		
Blood loss > 1000ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	3/652 (0.46%)	1/639 (0.16%)	RR 2.96 (0.31 to 28.35)	0 more per 100 (from 0 fewer to 4 more)	LOW	CRITICAL
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	4/637 (0.63%)	4/620 (0.65%)	RR 0.97 (0.26 to 3.58)	0 fewer per 100 (from 0 fewer to 2 more)	LOW	CRITICAL
Additional uterotonics												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	21/638 (3.3%)	20/622 (3.2%)	RR 1.02 (0.56 to 1.85)	0 more per 100 (from 1 fewer to 3 more)	MODERATE	IMPORTANT

[1] Very wide confidence interval crossing the line of no effect.

[2] Few events.

[3] Wide confidence interval crossing the line of no effect.

Source of evidence: 88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.*

Table 22. Uterine massage (before or after placental delivery) for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage before or after placental delivery	No uterine massage	Relative (95% CI)	Absolute		
Blood loss > 1000ml												
2[1]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	3/652 (0.46%)	1/639 (0.16%)	RR 2.96 (0.31 to 28.35)	0 more per 100 (from 0 fewer to 4 more)	LOW	CRITICAL
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,4]	none	4/735 (0.54%)	4/722 (0.55%)	RR 0.97 (0.26 to 3.58)	0 fewer per 100 (from 0 fewer to 1 more)	LOW	CRITICAL
Additional uterotonics												
3	randomized trials	no serious risk of bias	very serious[5]	no serious indirectness	serious[4]	none	26/736 (3.5%)	46/724 (6.4%)	RR 0.52 (0.15 to 1.81)	3 fewer per 100 (from 5 fewer to 5 more)	VERY LOW	IMPORTANT

[1] One study with no events.

[2] Very wide confidence interval crossing the line of no effect.

[3] Few events.

[4] Wide confidence interval crossing the line of no effect.

[5] Heterogeneity (I^2=78%)

Source of evidence: 88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.*

Table 23. Uterine massage (after delivery of the placenta for 1-2 hours and empty the clots) for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage after delivery of the placenta for 1-2 hours and empty the clots	No uterine massage	Relative (95% CI)	Absolute		
Maternal death												
1	randomized trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/98 (0 %)	0/102 (0 %)	-Not pooled	-	LOWVERY LOW[3]	CRITICAL
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/98 (0 %)	0/102 (0 %)	-Not pooled	-	LOWVERY LOW[3]	CRITICAL
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecisionserious[2]	none	5/98 (5.1%)	26/102 (25.5%)	RR 0.20 (0.08 to 0.5)	20 fewer per 100 (from 13 fewer to 23 fewer)	HIGH MODERATE	IMPORTANT

[1] There is only one study that evaluates uterine massage for 1h.
[2] Small sample size.

[3]No events

Table 24. Oxytocin (bolus and infusion) for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxytocin bolus and infusion**	**Oxytocin infusion only**	**Relative (95% CI)**	**Absolute**		
Blood loss > 500 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	562/1063 (52.9%)	551/1048 (52.6%)	RR 1.01 (0.93 to 1.09)	1 more per 100 (from 4 fewer to 5 more)	HIGH	IMPORTANT
Blood loss > 1000 ml												
3	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	184/1423 (12.9%)	214/1408 (15.2%)	RR 0.7 (0.36 to 1.33)	5 fewer per 100 (from 10 fewer to 5 more)	LOW	CRITICAL
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19/1449 (1.3%)	15/1439 (1%)	RR 1.26 (0.64 to 2.47)	0 more per 100 (from 0 fewer to 2 more)	MODERATE	CRITICAL
Additional uterotonic												

3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/1449 (10.8%)	264/1439 (18.3%)	RR 0.54 (0.36 to 0.79)	8 fewer per 100 (from 4 fewer to 12 fewer)	HIGH	IMPORTANT
Side effects - not reported												
3	-	-	-	-	-[2]	none	239/1449 (16.5%)	208/1439 (14.5%)	-	-	MODERATE	IMPORTANT[4]
Estimated mean blood loss (Better indicated by lower values)												
3	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	serious[2]	none	1423	1408	-	MD 41.19 lower (107.01 lower to 24.63 higher)	LOW	IMPORTANT

[1] Statistical Heterogeneity (I^2: 81%).

[2] Wide confidence interval crossing the line of no effect.

[3] Statistical Heterogeneity (I^2: 77%).

[4] Considered as any side effect of intervention.

Source of evidence: 122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.*

Table 25. Oxytocin (infusion only) for prevention of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin infusion only	Oxytocin bolus and infusion	Relative (95% CI)	Absolute		
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	3/73 (4.1%)	1/70 (1.4%)	RR 2.88 (0.31 to 27)	3 more per 100 (from 1 fewer to 37 more)	LOW	CRITICAL
Additional uterotonic (24 hours)												
2	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1,2]	none	36/88 (40.9%)	28/129 (21.7%)	RR 2.04 (0.85 to 4.92)	23 more per 100 (from 3 fewer to 85 more)	VERY LOW	IMPORTANT
Additional uterotonic (1st hour)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	15/73 (20.5%)	12/70 (17.1%)	RR 1.2 (0.6 to 2.38)	3 more per 100 (from 7 fewer to 24 more)	LOW	IMPORTANT
Nausea												

2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	2/88 (2.3%)	0/129 (0 %)	RR 5.32 (0.63 to 44.82)	-	LOW	IMPORTANT
Vomiting												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/88 (0 %)	0/129 (0 %)	not pooled	not pooled	VERY LOW	IMPORTANT
Headache												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	0/73 (0 %)	1/70 (1.4%)	RR 0.32 (0.01 to 7.72)	10 fewer per 1000 (from 14 fewer to 96 more)	LOW	IMPORTANT
Hypotension												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/88 (12.5%)	36/129 (27.9%)	RR 0.44 (0.23 to 0.87)	16 fewer per 100 (from 4 fewer to 21 fewer)	MODERATE	NOT IMPORTANT[5]
Tachycardia												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/88 (1.1%)	2/129 (1.6%)	RR 1.07 (0.13 to 8.48)	0 more per 100 (from 1 fewer to 12 more)	LOW	IMPORTANT[4]

Flushing												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	8/88 (9.1%)	6/129 (4.7%)	RR 1.28 (0.47 to 3.5)	1 more per 100 (from 2 fewer to 12 more)	LOW	IMPORTANT[4]
Light-headed												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	0/73 (0 %)	1/70 (1.4%)	RR 0.32 (0.01 to 7.72)	1 fewer per 100 (from 1 fewer to 10 more)	LOW	IMPORTANT[4]
Estimated mean blood loss (Better indicated by lower values)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	88	129	-	MD 90 higher (0.54 to 179.46 higher)	MODERATE	IMPORTANT

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Statistical Heterogeneity (I^2: 71%).

[4] Considered as any side effect of intervention.

[5] Was not in the proposed outcomes.

Source of evidence: 122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.*

Table 26. Oxytocin (low dose bolus) for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose oxytocin bolus	High dose oxytocin bolus	Relative (95% CI)	Absolute		
Additional uterotonic												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13/69 (18.8%)	0/68 (0 %)	OR 17.35 (2.18 to 137.83)	-	MODERATE	IMPORTANT
Estimated mean blood loss (Better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	52	51	-	MD 45 higher (109.4 lower to 199.4 higher)	MODERATE	IMPORTANT

[1] Small sample size.

[2] Wide confidence interval crossing the line of no effect.,

Source of evidence: 122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.*

Table 27. Oxytocin (low dose infusion) for prevention of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose oxytocin infusion	High dose oxytocin infusion	Relative (95% CI)	Absolute		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/163 (39.3%)	30/158 (19%)	RR 2.07 (1.42 to 3.01)	20 more per 100 (from 8 more to 38 more)	HIGH	IMPORTANT
Estimated mean blood loss (Better indicated by lower values)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	183	168	-	MD 20 higher (13.63 lower to 53.63 higher)	MODERATE	IMPORTANT

[1] Wide confidence interval crossing the line of no effect,

Source of evidence: 122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.*

Table 28. Oxytocin (very low dose bolus and infusion) for prevention of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Very Low dose oxytocin bolus and infusion	Higher dose oxytocin bolus and infusion	Relative (95% CI)	Absolute		
Additional uterotonic												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	13/84 (15.5%)	9/55 (16.4%)	RR 1.01 (0.45 to 2.25)	0 more per 100 (from 9 fewer to 20 more)	LOW	CRITICAL
Nausea												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2/84 (2.4%)	13/55 (23.6%)	RR 0.15 (0.04 to 0.64)	20 fewer per 100 (from 9 fewer to 23 fewer)	MODERATE	IMPORTANT
Vomiting												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/84 (1.2%)	6/55 (10.9%)	RR 0.17 (0.02 to 1.32)	9 fewer per 100 (from 11 fewer to 3 more)	LOW	IMPORTANT

Flushing - not reported												
1	-	-	-	-	-[2]	none	0/44 (0 %)	0/15 (0 %)	-	-	VERY LOW	IMPORTANT[3]
Shortness of breath												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/44 (0 %)	0/15 (0 %)	not pooled	not pooled	VERY LOW	IMPORTANT[3]
Arrhythmia												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/44 (0 %)	0/15 (0 %)	not pooled	not pooled	VERY LOW	IMPORTANT[3]

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Considered as any side effect of intervention.

Source of evidence: 122. Mahomed K, Sheehan S, Murphy DJ, Heatley E, Middleton P. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2011; In editorial process.*

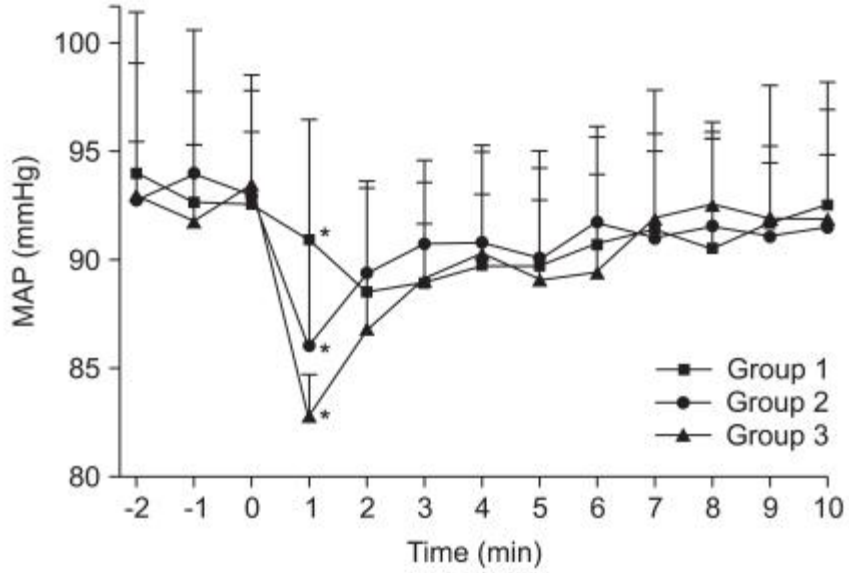

Fig. 1 Example of hemodynamic effect reported in a randomized controlled trial (Kim 2011)

Change of maternal mean arterial pressure (MAP) after oxytocin injection during Cesarean delivery. Oxytocin was injected in the following doses; Group 1: 0.5 IU/min continuous injection, Group 2: 2 IU bolus-continuous injection, Group 3: 5 IU bolus continuous injection. $^{*}P < 0.05$ compared with each group after oxytocin injection.

Table 29. Carbetocin for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterotonics alone (Carbetocin)	Control	Relative (95% CI)	Absolute		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious imprecision[2]	none	8/62 (12.9%)	41/57 (71.9%)	RR 0.18 (0.09 to 0.35)	59 fewer per 100 (from 47 fewer to 65 fewer)	LOW	IMPORTANT

[1] The study evaluates the use of additional uterotonics after caesarean section.

[2] Small sample size.

Source of evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.*

Table 30. Carbetocin for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Carbetocin versus oxytocin**	**Control**	**Relative (95% CI)**	**Absolute**		
Postpartum haemorrhage (mixed definition, without Attilakos trial)- Caesarean delivery												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/411 (3.4%)	26/409 (6.4%)	RR 0.55 (0.31 to 0.95)	3 fewer per 100 (from 0 fewer to 4 fewer)	HIGH	IMPORTANT[6]
Postpartum haemorrhage (mixed definition, with Attilakos trial)- Caesarean delivery												
4[1]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23/597 (3.9%)	35/598 (5.9%)	RR 0.60 (0.34 to 1.07)	2 fewer per 100 (from 4 fewer to 0 more)	MODERATE	IMPORTANT[6]
Postpartum haemorrhage - Vaginal delivery												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	10/64 (15.6%)	11/67 (16.4%)	RR 0.95 (0.43 to 2.09)	1 fewer per 100 (from 9 fewer to 18 more)	LOW	IMPORTANT[6]
Additional uterotonic - Caesarean delivery												

4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	80/586 (13.7%)	126/587 (21.5%)	RR 0.64 (0.51 to 0.81)	8 fewer per 100 (from 4 fewer to 11 fewer)	HIGH	IMPORTANT
Additional uterotonic - Vaginal delivery												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	12/83 (14.5%)	12/77 (15.6%)	RR 0.93 (0.44 to 1.94)	1 fewer per 100 (from 9 fewer to 15 more)	LOW	IMPORTANT
Blood transfusion - Caesarean delivery												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,4]	none	4/188 (2.1%)	5/189 (2.6%)	RR 0.8 (0.22 to 2.95)	1 fewer per 100 (from 2 fewer to 5 more)	MODERATE	CRITICAL
Maternal adverse drug reactions for caesarean delivery - Headache												
3	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/411 (12.4%)	61/409 (14.9%)	RR 0.83 (0.59 to 1.18)	3 fewer per 100 (from 6 fewer to 3 more)	LOW	IMPORTANT
Maternal adverse drug reactions for caesarean delivery - Chills												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/29 (3.4%)	0/28 (0 %)	RR 2.9 (0.12 to 68.33)	-	LOW	IMPORTANT

Maternal adverse drug reactions for caesarean delivery - Abdominal pain/pain												
2	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	132/358 (36.9%)	129/358 (36%)	RR 1.03 (0.85 to 1.24)	1 more per 100 (from 5 fewer to 9 more)	VERY LOW	IMPORTANT
Maternal adverse drug reactions for caesarean delivery - Dizziness												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/29 (3.4%)	1/28 (3.6%)	RR 0.97 (0.06 to 14.7)	0 fewer per 100 (from 3 fewer to 49 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Tremor												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/329 (11.2%)	49/330 (14.8%)	RR 0.76 (0.51 to 1.13)	4 fewer per 100 (from 7 fewer to 2 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Nausea												
2	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94/358 (26.3%)	103/358 (28.8%)	RR 0.91 (0.72 to 1.16)	3 fewer per 100 (from 8 fewer to 5 more)	LOW	IMPORTANT
Maternal adverse drug reactions for caesarean delivery - Vomiting												
2	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	32/358 (8.9%)	34/358 (9.5%)	RR 0.94 (0.59 to 1.49)	1 fewer per 100 (from 4 fewer to 5	VERY LOW	IMPORTANT

										more)		
Maternal adverse drug reactions for caesarean delivery - Back pain												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	13/329 (4%)	16/330 (4.8%)	RR 0.81 (0.4 to 1.67)	1 fewer per 100 (from 3 fewer to 3 more)	VERY LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Pruritus/itching												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	3/29 (10.3%)	3/28 (10.7%)	RR 0.97 (0.21 to 4.39)	0 fewer per 100 (from 8 fewer to 36 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Feeling of warmth												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2,3]	none	65/329 (19.8%)	56/330 (17%)	RR 1.16 (0.84 to 1.61)	3 more per 100 (from 3 fewer to 10 more)	VERY LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Metallic taste												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	20/329 (6.1%)	21/330 (6.4%)	RR 0.96 (0.53 to 1.73)	3 fewer per 1000 (from 30 fewer to 46 more)	VERY LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Flushing												
1	randomized	very	no serious	no serious	no serious	none	86/329	76/330	RR 1.14 (0.87 to	3 more per 100 (from 3 fewer		IMPORTANT[7]

	trials	serious[5]	inconsistency	indirectness	imprecision		(26.1%)	(23%)	1.48)	to 11 more)	LOW	
Maternal adverse drug reactions for caesarean delivery - Sweating												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	10/329 (3%)	10/330 (3%)	RR 1 (0.42 to 2.38)	0 fewer per 100 (from 2 fewer to 4 more)	VERY LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Shortness of breath												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	3/29 (10.3%)	0/28 (0 %)	RR 6.77 (0.37 to 125.32)	-	LOW	IMPORTANT[7]
Maternal adverse drug reactions for caesarean delivery - Premature ventricular contractions												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/29 (0 %)	1/28 (3.6%)	RR 0.32 (0.01 to 7.59)	2 fewer per 100 (from 4 fewer to 24 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Headache												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	6/83 (7.2%)	11/77 (14.3%)	RR 0.51 (0.2 to 1.3)	7 fewer per 100 (from 11 fewer to 4 more)	MODERATE	IMPORTANT
Maternal adverse drug reactions for vaginal delivery - Chills												
1	randomized	no serious risk of	no serious	no serious	very	none	8/83	7/77	RR 1.06 (0.4 to	1 more per 100 (from 5 fewer		IMPORTANT

	trials	bias	inconsistency	indirectness	serious[2,3]		(9.6%)	(9.1%)	2.79)	to 16 more)	LOW	
Maternal adverse drug reactions for vaginal delivery - Abdominal pain/pain												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	5/83 (6%)	0/77 (0 %)	RR 10.21 (0.57 to 181.71)	-	LOW	IMPORTANT
Maternal adverse drug reactions for vaginal delivery - Dizziness												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/83 (8.4%)	6/77 (7.8%)	RR 1.08 (0.38 to 3.08)	1 more per 100 (from 5 fewer to 16 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Tremor												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	none	5/83 (6%)	4/77 (5.2%)	RR 1.16 (0.32 to 4.16)	1 more per 100 (from 4 fewer to 16 more)	MODERATE	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Nausea												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	5/83 (6%)	7/77 (9.1%)	RR 0.66 (0.22 to 2)	3 fewer per 100 (from 7 fewer to 9 more)	LOW	IMPORTANT
Maternal adverse drug reactions for vaginal delivery - Vomiting												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/83 (0 %)	6/77 (7.8%)	RR 0.07 (0 to 1.25)	7 fewer per 100 (from 8 fewer to 2	MODERATE	IMPORTANT

										more)		
Maternal adverse drug reactions for vaginal delivery - Pruritus/itching												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/83 (0 %)	4/77 (5.2%)	RR 0.1 (0.01 to 1.89)	5 fewer per 100 (from 5 fewer to 5 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Nervous												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	12/83 (14.5%)	9/77 (11.7%)	RR 1.24 (0.55 to 2.77)	3 more per 100 (from 5 fewer to 21 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Cardiovascular												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	8/83 (9.6%)	11/77 (14.3%)	RR 0.67 (0.29 to 1.59)	5 fewer per 100 (from 10 fewer to 8 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Vasodilatation												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	6/83 (7.2%)	5/77 (6.5%)	RR 1.11 (0.35 to 3.5)	1 more per 100 (from 4 fewer to 16 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Haemic/lymphatic												
1	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	very serious[2,3]	none	9/83 (10.8%)	10/77 (13%)	RR 0.83 (0.36 to	2 fewer per 100 (from 8 fewer to 12	LOW	IMPORTANT[7]

		bias							1.94)	more)		
Maternal adverse drug reactions for vaginal delivery - Leukocytosis												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	6/83 (7.2%)	8/77 (10.4%)	RR 0.7 (0.25 to 1.91)	3 fewer per 100 (from 8 fewer to 9 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Digestive												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	none	7/83 (8.4%)	10/77 (13%)	RR 0.65 (0.26 to 1.62)	5 fewer per 100 (from 10 fewer to 8 more)	MODERATE	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Urogenital												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/83 (8.4%)	5/77 (6.5%)	RR 1.3 (0.43 to 3.92)	2 more per 100 (from 4 fewer to 19 more)	LOW	IMPORTANT[7]
Maternal adverse drug reactions for vaginal delivery - Skin/appendages												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/83 (0 %)	5/77 (6.5%)	RR 0.08 (0 to 1.5)	6 fewer per 100 (from 6 fewer to 3 more)	MODERATE	IMPORTANT[7]
Headache in caesarean/vaginal delivery - Caesarean												
3	randomized	serious[5]	no serious	no serious	serious[2]	none	54/410	58/410	RR 0.83 (0.41 to	2 fewer per 100 (from 8		IMPORTANT

	trials		inconsistency	indirectness			(13.2%)	(14.1%)	1.67)	fewer to 9 more)	LOW	
Headache in caesarean/vaginal delivery - Vaginal												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	6/83 (7.2%)	11/77 (14.3%)	RR 0.51 (0.2 to 1.3)	7 fewer per 100 (from 11 fewer to 4 more)	LOW	IMPORTANT
Nausea for caesarean/vaginal delivery - Caesarean												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	94/358 (26.3%)	103/358 (28.8%)	RR 0.91 (0.72 to 1.16)	3 fewer per 100 (from 8 fewer to 5 more)	MODERATE	IMPORTANT
Nausea for caesarean/vaginal delivery - Vaginal												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	5/83 (6%)	7/77 (9.1%)	RR 0.66 (0.22 to 2)	3 fewer per 100 (from 7 fewer to 9 more)	LOW	IMPORTANT
Vomiting for caesarean/vaginal delivery - Caesarean												
2	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	32/358 (8.9%)	34/358 (9.5%)	RR 0.94 (0.59 to 1.49)	1 fewer per 100 (from 4 fewer to 5 more)	VERY LOW	IMPORTANT
Vomiting for caesarean/vaginal delivery - Vaginal												

1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0/83 (0 %)	6/77 (7.8%)	RR 0.07 (0 to 1.25)	7 fewer per 100 (from 8 fewer to 2 more)	LOW	IMPORTANT
Tremor for caesarean/vaginal delivery - Caesarean												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/329 (11.2%)	49/330 (14.8%)	RR 0.76 (0.51 to 1.13)	4 fewer per 100 (from 7 fewer to 2 more)	LOW	IMPORTANT[7]
Tremor for caesarean/vaginal delivery - Vaginal												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	5/83 (6%)	4/77 (5.2%)	RR 1.16 (0.32 to 4.16)	1 more per 100 (from 4 fewer to 16 more)	LOW	IMPORTANT[7]
Chills in caesarean/vaginal delivery - Caesarean												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/29 (3.4%)	0/28 (0 %)	RR 2.9 (0.12 to 68.33)	-	LOW	IMPORTANT
Chills in caesarean/vaginal delivery - Vaginal												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	8/83 (9.6%)	7/77 (9.1%)			LOW	IMPORTANT
At least one adverse event - Vaginal delivery												

1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	43/83 (51.8%)	42/77 (54.5%)	RR 0.95 (0.71 to 1.27)	3 fewer per 100 (from 16 fewer to 15 more)	LOW	IMPORTANT[7]
Uterine massage												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/452 (14.4%)	102/447 (22.8%)	RR 0.64 (0.49 to 0.84)	8 fewer per 100 (from 4 fewer to 12 fewer)	HIGH	NOT IMPORTANT[8]
Uterine massage - Caesarean delivery												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/369 (7.9%)	54/370 (14.6%)	RR 0.54 (0.31 to 0.96)	7 fewer per 100 (from 1 fewer to 10 fewer)	HIGH	NOT IMPORTANT[8]
Uterine massage - Vaginal delivery												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	36/83 (43.4%)	48/77 (62.3%)	RR 0.7 (0.51 to 0.94)	19 fewer per 100 (from 4 fewer to 31 fewer)	MODERATE	NOT IMPORTANT[8]

[1] Including Attilakos 2010.

[2] Wide confidence interval crossing the line of no effect.

[3] Small sample size.

[4] Few events.

[5] Danserau 1999 at high risk of bias.

[6] PPH could be blood loss > 500ml of >1,000 ml. Thus, we considered it as important.

[7] Considered as side effects of intervention.

[8] Was not in the proposed outcomes

Source of evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.*

Table 31. Carbetocin for prevention of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Syntometrine	Relative (95% CI)	Absolute		
Additional uterotonic												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/515 (11.5%)	71/515 (13.8%)	RR 0.83 (0.6 to 1.15)	2 fewer per 100 (from 6 fewer to 2 more)	HIGH	IMPORTANT
Blood loss > 500 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14/515 (2.7%)	14/515 (2.7%)	RR 1 (0.48 to 2.07)	0 fewer per 100 (from 1 fewer to 3 more)	MODERATE	IMPORTANT
Blood loss> 1000 ml												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/455 (0.22%)	3/455 (0.66%)	RR 0.5 (0.09 to 2.72)	0 fewer per 100 (from 1 fewer to 1 more)	LOW	CRITICAL
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	6/455 (1.3%)	3/455 (0.66%)	RR 1.75 (0.52 to 5.93)	0 more per 100 (from 0 fewer to 3 more)	LOW	CRITICAL
Vomiting												

4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/515 (2.1%)	54/515 (10.5%)	RR 0.21 (0.11 to 0.39)	8 fewer per 100 (from 6 fewer to 9 fewer)	HIGH	IMPORTANT
Nausea												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/515 (3.3%)	71/515 (13.8%)	RR 0.24 (0.15 to 0.4)	10 fewer per 100 (from 8 fewer to 12 fewer)	HIGH	IMPORTANT
Tremor												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/245 (4.5%)	26/245 (10.6%)	RR 0.42 (0.22 to 0.83)	6 fewer per 100 (from 2 fewer to 8 fewer)	HIGH	IMPORTANT[3]
Retching												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2/185 (1.1%)	14/185 (7.6%)	RR 0.14 (0.03 to 0.62)	7 fewer per 100 (from 3 fewer to 7 fewer)	MODERATE	IMPORTANT[3]
Headache												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/515 (3.7%)	23/515 (4.5%)	RR 0.83 (0.46 to 1.48)	1 fewer per 100 (from 2 fewer to 2 more)	MODERATE	IMPORTANT
Sweating												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/185 (2.7%)	15/185 (8.1%)	RR 0.33 (0.12 to 0.9)	5 fewer per 100 (from 1 fewer to 7 fewer)	MODERATE	IMPORTANT[3]
Uterine or abdominal pain												

2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/305 (7.2%)	39/305 (12.8%)	RR 0.56 (0.35 to 0.92)	6 fewer per 100 (from 1 fewer to 8 fewer)	HIGH	IMPORTANT
Facial flushing												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	8/455 (1.8%)	17/455 (3.7%)	RR 0.49 (0.22 to 1.09)	2 fewer per 100 (from 3 fewer to 0 more)	MODERATE	IMPORTANT[3]
Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	2/150 (1.3%)	6/150 (4%)	RR 0.33 (0.07 to 1.63)	27 fewer per 1000 (from 37 fewer to 25 more)	LOW	IMPORTANT
								4%		27 fewer per 1000 (from 37 fewer to 25 more)		
Hypertension												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/810 (0.49%)	37/840 (4.4%)	RR 0.16 (0.07 to 0.38)	4 fewer per 100 (from 3 fewer to 4 fewer)	HIGH	IMPORTANT

[1] Wide confidence interval crossing the line of no effect.

[2] Few events

[3] Considered as side effects of intervention.

Source of evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.*

Table 32. Manual removal of placenta for prevention of PPH at caesarean section.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual placental removal	Cord traction	Relative (95% CI)	Absolute		
Blood loss > 1000 ml												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	167/504 (33.1%)	92/513 (17.9%)	RR 1.84 (1.48 to 2.29)	151 more per 1000 (from 86 more to 231 more)	HIGH	CRITICAL
Operative blood loss (ml) (Better indicated by lower values)												
9	randomized trials	no serious risk of bias	serious	no serious indirectness	no serious imprecision	none	1051	1036	-	MD 79.46 higher (10.9 to 148.01 higher)	MODERATE	IMPORTANT
Haematocrit levels after delivery (Better indicated by lower values)												
2	randomized trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	192	192	-	MD 1.55 lower (3.09 to 0.01 lower)	MODERATE	IMPORTANT
Maternal haematocrit fall after delivery (Better indicated by lower values)												

7	randomized trials	no serious risk of bias	very serious[3,4]	no serious indirectness	no serious imprecision	none	1246	1249	-	MD 1.96 higher (0.24 to 3.68 higher)	LOW	IMPORTANT
Endometritis												
17	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	468/2523 (18.5%)	265/2503 (10.6%)	RR 1.75 (1.53 to 2)	79 more per 1000 (from 56 more to 106 more)	HIGH	NOT IMPORTANT[5]
Puerperal fever												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	none	19/290 (6.6%)	17/290 (5.9%)	RR 1.14 (0.63 to 2.08)	8 more per 1000 (from 22 fewer to 63 more)	MODERATE	NOT IMPORTANT[5]
Feto-maternal haemorrhage												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	18/269 (6.7%)	11/265 (4.2%)	RR 1.58 (0.78 to 3.18)	24 more per 1000 (from 9 fewer to 90 more)	LOW	NOT IMPORTANT[5]
Duration of operation (minutes) (Better indicated by lower values)												
10	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	serious[1]	none	1128	1124	-	MD 0.56 lower (2.9 lower to 1.79 higher)	LOW	NOT IMPORTANT[5]

Haemoglobin levels after delivery (Better indicated by lower values)												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[1]	none	300	300	-	MD 0.36 lower (1.24 lower to 0.52 higher)	LOW	IMPORTANT
Maternal haemoglobin fall after delivery (Better indicated by lower values)												
6	randomized trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	950	927	-	MD 0.39 higher (0 to 0.78 higher)	MODERATE	IMPORTANT
Blood transfusion												
7	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36/1017 (3.5%)	35/1029 (3.4%)	RR 1.04 (0.66 to 1.64)	1 more per 1000 (from 12 fewer to 22 more)	MODERATE	CRITICAL
Length of postoperative hospital stay for the mother (Better indicated by lower values)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	273	273	-	MD 0.39 higher (0.17 to 0.61 higher)	MODERATE	NOT IMPORTANT[5]

[1] From appreciable benefit to appreciable harm

[2] Very small number of events

[3] I^2=98%

[4] High statistical heterogeneity

[5] Was not in the proposed outcomes.

Source of evidence: 12. Anorlu RI, Maholwana B, Hofmeyr GJ. Methods of delivering the placenta at caesarean section. Cochrane Database Syst Rev. 2008; 2012 - In editorial process for this guideline (3):CD004737.*

Table 33. Misoprostol for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin / ergometrine	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
2	randomized trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	111/895 (12.4%)	73/892 (8.2%)	RR 1.51 (1.14 to 2)	4 more per 100 (from 1 more to 8 more)	MODERATE	CRITICAL
Additional blood loss > 500 ml - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/488 (10.9%)	20/490 (4.1%)	RR 2.66 (1.62 to 4.38)	7 more per 100 (from 3 more to 14 more)	HIGH	CRITICAL
Additional blood loss > 500 ml - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	58/407 (14.3%)	53/402 (13.2%)	RR 1.08 (0.76 to 1.53)	1 more per 100 (from 3 fewer to 7 more)	MODERATE	CRITICAL
Additional blood loss > 1000 ml - Women not exposed to prophylactic oxytocin												
1	randomized	no	no serious	no serious	very	none	5/488	3/490	RR 1.67	0 more per		CRITICAL

	trials	serious risk of bias	inconsistency	indirectness	serious[2,3]		(1%)	(0.61%)	(0.4 to 6.96)	100 (from 0 fewer to 4 more)	LOW	
Additional blood loss > 1000 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/895 (1.8%)	6/892 (0.67%)	RR 2.65 (1.04 to 6.75)	1 more per 100 (from 0 more to 4 more)	HIGH	CRITICAL
Additional blood loss > 1000 ml - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	11/407 (2.7%)	3/402 (0.75%)	RR 3.62 (1.02 to 12.88)	2 more per 100 (from 0 more to 9 more)	MODERATE	CRITICAL
Additional uterotonics												
3	randomized trials	no serious risk of bias	serious[4]	no serious indirectness	serious[2]	none	103/927 (11.1%)	88/924 (9.5%)	RR 1.17 (0.89 to 1.53)	2 more per 100 (from 1 fewer to 5 more)	LOW	CRITICAL
Additional uterotonics - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/488 (12.5%)	31/490 (6.3%)	RR 1.98 (1.31 to 2.99)	6 more per 100 (from 2 more to 13 more)	HIGH	CRITICAL

Additional uterotonics - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40/407 (9.8%)	46/402 (11.4%)	RR 0.86 (0.58 to 1.28)	2 fewer per 100 (from 5 fewer to 3 more)	MODERATE	CRITICAL
Additional uterotonics - Women exposure to oxytocin not stated/mixed												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	2/32 (6.3%)	11/32 (34.4%)	RR 0.18 (0.04 to 0.76)	28 fewer per 100 (from 8 fewer to 33 fewer)	MODERATE	CRITICAL
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/895 (7.3%)	44/892 (4.9%)	RR 1.47 (1.02 to 2.14)	2 more per 100 (from 0 more to 6 more)	HIGH	CRITICAL
Blood transfusion - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	41/488 (8.4%)	26/490 (5.3%)	RR 1.58 (0.98 to 2.55)	3 more per 100 (from 0 fewer to 8 more)	MODERATE	CRITICAL
Blood transfusion - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	none	24/407 (5.9%)	18/402 (4.5%)	RR 1.32 (0.73 to	1 more per 100 (from 1 fewer to 6	MODERATE	CRITICAL

		bias							2.39)	more)		
Hysterectomy												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	4/927 (0.43%)	3/923 (0.33%)	RR 1.26 (0.32 to 5.06)	0 more per 100 (from 0 fewer to 1 more)	LOW	CRITICAL
Hysterectomy - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/488 (0 %)	0/490 (0 %)	not pooled	not pooled	LOW	CRITICAL
Hysterectomy - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	4/407 (0.98%)	2/402 (0.5%)	RR 1.98 (0.36 to 10.72)	0 more per 100 (from 0 fewer to 5 more)	LOW	CRITICAL
Hysterectomy - Women exposure to oxytocin not stated/mixed												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/32 (0 %)	1/31 (3.2%)	RR 0.32 (0.01 to 7.65)	2 fewer per 100 (from 3 fewer to 21 more)	MODERATE	CRITICAL
Maternal temperature > 38°C												

2	randomized trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	305/895 (34.1%)	86/892 (9.6%)	RR 3.53 (2.83 to 4.42)	24 more per 100 (from 18 more to 33 more)	MODERATE	IMPORTANT
Maternal temperature > 38°C - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	217/488 (44.5%)	27/490 (5.5%)	RR 8.07 (5.52 to 11.8)	39 more per 100 (from 25 more to 60 more)	HIGH	IMPORTANT
Maternal temperature > 38°C - Women exposed to prophylactic oxytocin - not reported												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/407 (21.6%)	59/402 (14.7%)	RR 1.47 (1.09 to 1.99)	7 more per 100 (from 1 more to 15 more)	HIGH	IMPORTANT
Maternal temperature > 40°C												
2	randomized trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	71/895 (7.9%)	1/892 (0.11%)	RR 47.57 (9.5 to 238.3)	5 more per 100 (from 1 more to 27 more)	MODERATE	CRITICAL
Maternal temperature > 40°C - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/488 (13.5%)	0/490 (0 %)	RR 133.54 (8.29 to 2151.28)	-	HIGH	CRITICAL

Maternal temperature > 40°C - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	5/407 (1.2%)	1/402 (0.25%)	RR 4.94 (0.58 to 42.08)	1 more per 100 (from 0 fewer to 10 more)	LOW	CRITICAL
Nausea												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/895 (12.1%)	110/892 (12.3%)	RR 0.98 (0.76 to 1.25)	0 fewer per 100 (from 3 fewer to 3 more)	HIGH	IMPORTANT
Nausea - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	49/488 (1 0 %)	41/490 (8.4%)	RR 1.2 (0.81 to 1.78)	2 more per 100 (from 2 fewer to 7 more)	MODERATE	IMPORTANT
Nausea - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	59/407 (14.5%)	69/402 (17.2%)	RR 0.84 (0.61 to 1.16)	3 fewer per 100 (from 7 fewer to 3 more)	MODERATE	IMPORTANT
Vomiting												
2	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/895 (4.8%)	17/892 (1.9%)	RR 2.52 (1.45 to	3 more per 100 (from 1 more to 6	HIGH	IMPORTANT

		bias							4.38)	more)		
Vomiting - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/488 (4.9%)	7/490 (1.4%)	RR 3.44 (1.5 to 7.92)	3 more per 100 (from 1 more to 10 more)	HIGH	IMPORTANT
Vomiting - Women exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	19/407 (4.7%)	10/402 (2.5%)	RR 1.88 (0.88 to 3.99)	2 more per 100 (from 0 fewer to 7 more)	LOW	IMPORTANT
Shivering												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	381/895 (42.6%)	141/892 (15.8%)	RR 2.7 (2.28 to 3.19)	27 more per 100 (from 20 more to 35 more)	HIGH	IMPORTANT
Shivering - Women not exposed to prophylactic oxytocin												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	229/488 (46.9%)	82/490 (16.7%)	RR 2.8 (2.25 to 3.49)	30 more per 100 (from 21 more to 42 more)	HIGH	IMPORTANT
Shivering - Women exposed to prophylactic oxytocin												

1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/407 (37.3%)	59/402 (14.7%)	RR 2.54 (1.95 to 3.32)	23 more per 100 (from 14 more to 34 more)	HIGH	IMPORTANT
Surgical co-interventions (excluding hysterectomy)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,5]	none	2/32 (6.3%)	2/32 (6.3%)	RR 1 (0.15 to 6.67)	0 fewer per 100 (from 5 fewer to 35 more)	LOW	CRITICAL
Persistent haemorrhage												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	2/32 (6.3%)	11/32 (34.4%)	RR 0.18 (0.04 to 0.76)	28 fewer per 100 (from 8 fewer to 33 fewer)	MODERATE	NOT IMPORTANT[8]

[1] Statistical Heterogeneity (I^2:88%).

[2] Wide confidence interval crossing the line of no effect.

[3] Few events.

[4] Statistical Heterogeneity (I^2: 87%).

[5] Small sample sizes.

[6] Statistical Heterogeneity (I^2: 97.9%).

[7] Statistical Heterogeneity (I^2: 70.5%).

[8] Was not in the proposed outcomes.

Source of evidence: 140. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.*

Table 34. Misoprostol for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjunct Misoprostol versus placebo	Control	Relative (95% CI)	Absolute		
Maternal death												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	5/901 (0.55%)	0/919 (0 %)	RR 6.16 (0.75 to 50.85)	-	LOW	CRITICAL
Maternal death - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	2/784 (0.26%)	0/798 (0 %)	RR 5.08 (0.24 to 105.73)	-	MODERATE	CRITICAL
Maternal death - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	3/117 (2.6%)	0/121 (0 %)	RR 7.24 (0.38 to 138.6)	-	MODERATE	CRITICAL
Additional blood loss > 500 ml												

4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	121/930 (13%)	138/950 (14.5%)	RR 0.89 (0.71 to 1.12)	2 fewer per 100 (from 4 fewer to 2 more)	MODERATE	CRITICAL
Additional blood loss > 500 ml - Misoprostol 600 µg (any route)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	115/813 (14.1%)	127/830 (15.3%)	RR 0.92 (0.73 to 1.17)	1 fewer per 100 (from 4 fewer to 3 more)	MODERATE	CRITICAL
Additional blood loss > 500 ml - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	6/117 (5.1%)	11/120 (9.2%)	RR 0.56 (0.21 to 1.46)	4 fewer per 100 (from 7 fewer to 4 more)	LOW	CRITICAL
Additional blood loss > 1000 ml												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/901 (2.2%)	27/918 (2.9%)	RR 0.76 (0.43 to 1.33)	1 fewer per 100 (from 2 fewer to 1 more)	MODERATE	CRITICAL
Additional blood loss > 1000 ml - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/784 (2.4%)	27/798 (3.4%)	RR 0.72 (0.4 to 1.28)	1 fewer per 100 (from 2 fewer to 1 more)	MODERATE	CRITICAL

Additional blood loss > 1000 ml - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	1/117 (0.85%)	0/120 (0 %)	RR 3.08 (0.13 to 74.76)	-	LOW	CRITICAL
Blood transfusion												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	139/928 (15%)	147/949 (15.5%)	RR 0.97 (0.78 to 1.2)	0 fewer per 100 (from 3 fewer to 3 more)	HIGH	CRITICAL
Blood transfusion - Misoprostol 600 µg (any route)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	120/813 (14.8%)	132/830 (15.9%)	RR 0.93 (0.74 to 1.17)	1 fewer per 100 (from 4 fewer to 3 more)	MODERATE	CRITICAL
Blood transfusion - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/115 (16.5%)	15/119 (12.6%)	RR 1.31 (0.7 to 2.45)	4 more per 100 (from 4 fewer to 18 more)	MODERATE	CRITICAL
Additional uterotonics												
3	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	no serious imprecision	none	254/895 (28.4%)	271/910 (29.8%)	RR 0.95 (0.83 to	1 fewer per 100 (from 5 fewer to 3	HIGH	CRITICAL

		bias							1.09)	more)		
Additional uterotonics - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	191/784 (24.4%)	208/798 (26.1%)	RR 0.93 (0.79 to 1.1)	2 fewer per 100 (from 5 fewer to 3 more)	HIGH	CRITICAL
Additional uterotonics - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	63/111 (56.8%)	63/112 (56.3%)	RR 1.01 (0.8 to 1.27)	1 more per 100 (from 11 fewer to 15 more)	MODERATE	CRITICAL
Invasive (non surgical) interventions												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/29 (6.9%)	7/32 (21.9%)	RR 0.32 (0.07 to 1.4)	15 fewer per 100 (from 20 fewer to 9 more)	HIGH	CRITICAL
Invasive (non surgical) interventions - Misoprostol 600 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	2/29 (6.9%)	7/32 (21.9%)	RR 0.32 (0.07 to 1.4)	15 fewer per 100 (from 20 fewer to 9 more)	LOW	CRITICAL
Hysterectomy												

3	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1,2]	none	3/225 (1.3%)	2/234 (0.85%)	RR 1.24 (0.04 to 40.78)	0 more per 100 (from 1 fewer to 34 more)	VERY LOW	CRITICAL
Hysterectomy - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,4]	none	0/108 (0 %)	2/113 (1.8%)	RR 0.20 (0.01 to 4.20)	1 fewer per 100 (from 2 fewer to 6 more)	LOW	CRITICAL
Hysterectomy - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,4]	none	3/117 (2.6%)	0/121 (0 %)	RR 7.24 (0.38 to 138.6)	-	MODERATE	CRITICAL
Maternal temperature > 38°C												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	436/926 (47.1%)	142/948 (15%)	RR 3.13 (2.66 to 3.67)	32 more per 100 (from 25 more to 40 more)	HIGH	IMPORTANT
Maternal temperature > 38°C- Misoprostol 600 µg (any route)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	425/812 (52.3%)	140/830 (16.9%)	RR 3.09 (2.63 to 3.63)	35 more per 100 (from 27 more to 44 more)	HIGH	IMPORTANT

Maternal temperature > 38°C - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	11/114 (9.6%)	2/118 (1.7%)	RR 5.69 (1.29 to 25.12)	8 more per 100 (from 0 more to 41 more)	MODERATE	IMPORTANT
Maternal temperature > 40 °C												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	8/850 (0.94%)	3/870 (0.34%)	RR 2.33 (0.72 to 7.5)	0 more per 100 (from 0 fewer to 2 more)	MODERATE	CRITICAL
Maternal temperature > 40 °C - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	5/733 (0.68%)	3/749 (0.4%)	RR 1.63 (0.43 to 6.15)	0 more per 100 (from 0 fewer to 2 more)	MODERATE	CRITICAL
Maternal temperature > 40 °C - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,4]	none	3/117 (2.6%)	0/121 (0 %)	RR 7.24 (0.38 to 138.6)	-	Low	CRITICAL
Maternal severe morbidity - not reported												
1	-	-	-	-	-[1,2]	none	8/705 (1.1%)	10/717 (1.4%)	-	-	MODERATE	CRITICAL

Maternal severe morbidity - Misoprostol 600 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	none	8/705 (1.1%)	10/717 (1.4%)	RR 0.81 (0.32 to 2.05)	0 fewer per 100 (from 1 fewer to 1 more)	MODERATE	CRITICAL
Maternal transfer												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,4]	none	1/29 (3.4%)	1/32 (3.1%)	RR 1.1 (0.07 to 16.85)	0 more per 100 (from 3 fewer to 50 more)	MODERATE	CRITICAL
Maternal transfer - Misoprostol 600 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,4]	none	1/29 (3.4%)	1/32 (3.1%)	RR 1.1 (0.07 to 16.85)	0 more per 100 (from 3 fewer to 50 more)	MODERATE	CRITICAL
Nausea												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	65/812 (8%)	56/830 (6.7%)	RR 1.19 (0.84 to 1.67)	1 more per 100 (from 1 fewer to 5 more)	MODERATE	IMPORTANT
Nausea - Misoprostol 600 µg (any route)												
3	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[1]	none	65/812 (8%)	56/830 (6.7%)	RR 1.19 (0.84 to	1 more per 100 (from 1 fewer to 5	MODERATE	IMPORTANT

		bias							1.67)	more)		
Vomiting												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/733 (6.4%)	26/749 (3.5%)	RR 1.85 (1.16 to 2.95)	3 more per 100 (from 1 more to 7 more)	HIGH	IMPORTANT
Vomiting - Misoprostol 600 µg (any route)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/733 (6.4%)	26/749 (3.5%)	RR 1.85 (1.16 to 2.95)	3 more per 100 (from 1 more to 7 more)	HIGH	IMPORTANT
Shivering												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	615/928 (66.3%)	292/948 (30.8%)	RR 2.15 (1.94 to 2.38)	35 more per 100 (from 29 more to 43 more)	HIGH	IMPORTANT
Shivering - Misoprostol 600 µg (any route)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	552/812 (68%)	262/830 (31.6%)	RR 2.15 (1.93 to 2.4)	36 more per 100 (from 29 more to 44 more)	HIGH	IMPORTANT
Shivering - Misoprostol 1000 µg (any route)												

1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/116 (54.3%)	30/118 (25.4%)	RR 2.14 (1.5 to 3.04)	29 more per 100 (from 13 more to 52 more)	HIGH	IMPORTANT
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	4/196 (2%)	7/202 (3.5%)	RR 0.59 (0.17 to 1.98)	1 fewer per 100 (from 3 fewer to 3 more)	LOW	NOT IMPORTANT[5]
Manual removal of the placenta - Misoprostol 600 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,4]	none	3/79 (3.8%)	3/81 (3.7%)	RR 1.03 (0.21 to 4.93)	0 more per 100 (from 3 fewer to 15 more)	MODERATE	NOT IMPORTANT[5]
Manual removal of the placenta - Misoprostol 1000 µg (any route)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,4]	none	1/117 (0.85%)	4/121 (3.3%)	RR 0.26 (0.03 to 2.28)	2 fewer per 100 (from 3 fewer to 4 more)	LOW	NOT IMPORTANT[5]

[1] Wide confidence interval crossing the line of no effect.

[2] Few events.

[3] Statistical Heterogeneity (I^2: 63.4%)

[4] Small sample size.

[5] Was not in the proposed outcomes.

Source of evidence: 140. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.*

Table 35. Oxytocin for treatment of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergometrine	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: objectively by weighting pads[1])												
7	randomized trials	very serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	117/1836 (6.4%)	183/1826 (1 0 %)	RR 0.80 (0.65 to 0.99)	2 fewer per 100 (from 0 fewer to 4 fewer)	VERY LOW	CRITICAL
										-		
Additional blood loss > 1000 ml (assessed with: objectively by weighting pads[1])												
4	randomized trials	very serious[4]	no serious inconsistency	serious[3]	serious[5]	reporting bias	23/1064 (2.2%)	28/1025 (2.7%)	RR 1.09 (0.63 to 1.87)	0 more per 100 (from 1 fewer to 2 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
2	randomized trials	no serious risk of bias[6]	no serious inconsistency	serious[3]	very serious[7,8]	None	2/234 (0.85%)	1/333 (0.3%)	RR 3.74 (0.34 to 40.64)	8 more per 1000 (from 2 fewer to 119 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
4	randomized trials	very serious[9]	no serious inconsistency	serious[3]	no serious imprecision[5]	None	66/1010 (6.5%)	99/1141 (8.7%)	RR 0.74 (0.55 to	2 fewer per 100 (from 4 fewer to	VERY	CRITICAL

									1.01)	0 more)	LOW	
										-		
Nausea												
3	randomized trials	very serious[9]	no serious inconsistency	serious[3]	no serious imprecision	None	17/523 (3.3%)	140/568 (24.6%)	RR 0.13 (0.08 to 0.21)	21 fewer per 100 (from 19 fewer to 23 fewer)	VERY LOW	IMPORTANT
										-		
Vomiting												
3	randomized trials	very serious[9]	no serious inconsistency	serious[3]	no serious imprecision	None	12/523 (2.3%)	163/568 (28.7%)	RR 0.08 (0.05 to 0.14)	26 fewer per 100 (from 25 fewer to 27 fewer)	VERY LOW	IMPORTANT
										-		
Manual removal of the placenta												
5	randomized trials	very serious[2]	no serious inconsistency	serious[3]	serious[5]	None	122/4161 (2.9%)	119/4180 (2.8%)	RR 1.04 (0.8 to 1.34)	0 more per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT

[1] Only one study (De Groot 1996) reported method of blood loss estimation

[2] Three studies (Orji 2008- Saito 2007, Sorbe 1978) at high risk of bias.

[3] SR for prevention of PPH

[4] Two studies (Saito 2007, Sorbe 1978) at high risk of bias.

[5] Wide confidence interval crossing the line of no effect.

[6] One study (Saito 2007) at high risk of bias.

[7] Very wide confidence interval crossing the line of no effect.

[8] Small sample size.

[9] Two studies (Orji 2008, Saito 2007) at high risk of bias.

Source of the evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

Table 36. Oxytocin- Ergometrine IM (fixed dose combination) for treatment of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Oxytocin IM (any dose)	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
5	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	reporting bias[3]	369/4161 (8.9%)	443/4180 (10.6%)	RR 0.84 (0.74 to 0.96)	2 fewer per 100 (from 0 fewer to 3 fewer)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	83/3472 (2.4%)	105/3491 (3%)	RR 0.79 (0.59 to 1.06)	1 fewer per 100 (from 1 fewer to 0 more)	MODERATE	CRITICAL
										-		
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	36/3242 (1.1%)	29/3260 (0.89%)	RR 1.25 (0.77 to 2.05)	0 more per 100 (from 0 fewer to 1 more)	LOW	CRITICAL

										-		
Additional uterotonics												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	345/2226 (15.5%)	430/2248 (19.1%)	RR 0.78 (0.66 to 0.91)	4 fewer per 100 (from 2 fewer to 7 fewer)	MODERATE	CRITICAL
Nausea												
2	randomized trials	no serious risk of bias	serious[5]	serious[2]	no serious imprecision	none	476/2221 (21.4%)	122/2246 (5.4%)	RR 4.18 (3.51 to 4.99)	17 more per 100 (from 14 more to 22 more)	LOW	IMPORTANT
										-		
Vomiting												
2	randomized trials	no serious risk of bias	serious[5,6]	serious[2]	no serious imprecision	none	365/2221 (16.4%)	64/2246 (2.8%)	RR 4.97 (4.06 to 6.08)	11 more per 100 (from 9 more to 14 more)	LOW	IMPORTANT
										-		
Manual removal of the placenta												
5	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	no serious imprecision	reporting bias[3]	122/4161 (2.9%)	119/4180 (2.8%)	RR 1.04 (0.8 to 1.34)	0 more per 100 (from 1 fewer to 1 more)	LOW	CRITICAL

[1] Nieminem 1963, unclear risk of bias but likely to be high. Women were divided into 3 groups.

[2] The RS is for prevention of PPH.

[3] Asymmetrical Funnel Plot.
[4] Wide confidence interval crossing the line of no effect.
[5] Heterogeneity (I^2: 61%).
[6] Heterogeneity (I^2 79%).

Source of the evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 37. Oxytocin- Ergometrine IM (fixed dose combination) for treatment of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Oxytocin 10IU IM	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: not mentioned)												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	349/3242 (10.8%)	406/3260 (12.5%)	RR 0.85 (0.73 to 0.99)	2 fewer per 100 (from 0 fewer to 3 fewer)	MODERATE	CRITICAL
										-		
Additional blood loss > 1000 ml												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	83/3242 (2.6%)	104/3260 (3.2%)	RR 0.80 (0.6 to 1.07)	1 fewer per 100 (from 1 fewer to 0 more)	MODERATE	CRITICAL
										-		
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	36/3242 (1.1%)	29/3260 (0.89%)	RR 1.25 (0.77 to 2.05)	0 more per 100 (from 0 fewer to 1 more)	LOW	CRITICAL

										-		
Additional uterotonics												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	345/2226 (15.5%)	430/2248 (19.1%)	RR 0.78 (0.66 to 0.91)	4 fewer per 100 (from 2 fewer to 7 fewer)	MODERATE	CRITICAL
										-		
Nausea												
2	randomized trials	no serious risk of bias	serious[3]	serious[1]	no serious imprecision	none	476/2221 (21.4%)	122/2246 (5.4%)	RR 4.18 (3.51 to 4.99)	17 more per 100 (from 14 more to 22 more)	LOW	IMPORTANT
										-		
Vomiting												
2	randomized trials	no serious risk of bias	serious[4,5]	serious[1]	no serious imprecision	none	365/2221 (16.4%)	64/2246 (2.8%)	RR 4.97 (4.06 to 6.08)	11 more per 100 (from 9 more to 14 more)	LOW	IMPORTANT
										-		
Manual removal of the placenta												
3	randomized trials	no serious risk of bias	serious[4]	serious[1]	serious[2]	reporting bias[6]	99/3242 (3.1%)	104/3260 (3.2%)	RR 0.96 (0.73 to 1.27)	0 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT

[1] The SR is for prevention PPH.
[2] Wide confidence interval crossing the line of no effect.
[3] Heterogeneity (I^2= 61%).
[4] Heterogeneity (I^2= 63%).
[5] Heterogeneity (I^2= 79%).
[6] Asymmetrical Funnel Plot.

Source of the evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 38. Oxytocin- Ergometrine IM (fixed dose combination) for treatment of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Oxytocin IV (any dose)	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: not mentioned)												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	31/840 (3.7%)	35/837 (4.2%)	RR 0.88 (0.55 to 1.41)	1 fewer per 100 (from 2 fewer to 2 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml (assessed with: not mentioned)												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	9/840 (1.1%)	14/837 (1.7%)	RR 0.65 (0.28 to 1.47)	1 fewer per 100 (from 1 fewer to 1 more)	LOW	CRITICAL
										-		
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[2]	none	19/840 (2.3%)	9/837 (1.1%)	RR 2.05 (0.97 to 4.33)	11 more per 1000 (from 0 fewer to 36 more)	LOW	CRITICAL

										-		
Additional uterotonics												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	87/840 (10.4%)	70/837 (8.4%)	RR 1.27 (0.91 to 1.76)	2 more per 100 (from 1 fewer to 6 more)	LOW	CRITICAL
										-		
Nausea												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	210/840 (25%)	196/837 (23.4%)	RR 1.09 (0.85 to 1.39)	2 more per 100 (from 4 fewer to 9 more)	LOW	IMPORTANT
										-		
Vomiting												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	12/840 (1.4%)	7/837 (0.84%)	RR 3.33 (1.21 to 9.2)	2 more per 100 (from 0 more to 7 more)	MODERATE	IMPORTANT
										-		
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[1]	none	3/840 (0.36%)	7/837 (0.84%)	RR 0.44 (0.13 to 1.53)	0 fewer per 100 (from 1 fewer to 0 more)	LOW	IMPORTANT

[1] The SR is for prevention of PPH.

[2] Wide confidence interval crossing the line of no effect.

Source of the evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 39. Oxytocin- Ergometrine IM (fixed dose combination) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin-Ergometrine IM (fixed dose combination)	Ergometrine IM (any dose)	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: not mentioned)												
5	randomized trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	reporting bias[3]	44/2048 (2.1%)	90/2240 (4%)	RR 0.57 (0.4 to 0.81)	2 fewer per 100 (from 1 fewer to 2 fewer)	VERY LOW	CRITICAL
										-		
Additional blood loss > 1000 ml (assessed with: not mentioned)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	5/560 (0.89%)	3/560 (0.54%)	RR 1.67 (0.4 to 6.94)	4 more per 1000 (from 3 fewer to 32 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	5/560 (0.89%)	7/560 (1.3%)	RR 0.71 (0.23 to 2.24)	0 fewer per 100 (from 1 fewer to 2 more)	VERY LOW	CRITICAL

										-		
Manual removal of the placenta												
5	randomized trials	serious[1]	serious[6]	serious[2]	serious[4]	reporting bias[3]	46/2018 (2.3%)	61/2240 (2.7%)	RR 0.81 (0.56 to 1.18)	1 fewer per 100 (from 1 fewer to 0 more)	VERY LOW	IMPORTANT

[1] Two studies (Chuckudebelu 1963 and Kemp 1963) at high risk of bias.

[2] SR is from prevention studies.

[3] Asymmetrical Funnel Plot.

[4] Wide confidence interval crossing the line of no effect.

[5] Few events

[6] Heterogeneity (I^2: 74%).

Source of the evidence: 130. McDonald S, Murphy D, Sheehan S. Prophylactic ergometrine-oxytocin versus other uterotonics for active management of the third stage of labour. Cochrane Database Of Systematic Reviews. In editorial process.*

Table 40. Carbetocin for treatment of of PPH after vaginal birth

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Oxytocin	Relative (95% CI)	Absolute		
Additional blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	10/64 (15.6%)	11/67 (16.4%)	RR 0.95 (0.43 to 2.09)	1 fewer per 100 (from 9 fewer to 18 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	12/83 (14.5%)	12/77 (15.6%)	RR 0.93 (0.44 to 1.94)	1 fewer per 100 (from 9 fewer to 15 more)	VERY LOW	CRITICAL
										-		
Nausea												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	5/83 (6%)	7/77 (9.1%)	RR 0.66 (0.22 to 2)	3 fewer per 100 (from 7 fewer to 9 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	0/83 (0 %)	6/77 (7.8%)	RR 0.07 (0 to 1.25)	7 fewer per 100 (from 8 fewer to 2 more)	LOW	IMPORTANT
										-		

Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	8/83 (9.6%)	7/77 (9.1%)	RR 1.06 (0.4 to 2.79)	1 more per 100 (from 5 fewer to 16 more)	VERY LOW	IMPORTANT
										-		

[1] SR is from prevention studies.

[2] Wide confidence interval crossing the line of no effect.

[3] Small sample size

Source of the evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

Table 41. Carbetocin for treatment of PPH after caesarean delivery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Carbetocin**	**Oxytocin**	**Relative (95% CI)**	**Absolute**		
Additional blood loss > 1000 ml (assessed with: measure objectively[1])												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	23/597 (3.9%)	35/598 (5.9%)	RR 0.60 (0.34 to 1.07)	2 fewer per 100 (from 4 fewer to 0 more)	MODERATE	CRITICAL
								3.6%		1 fewer per 100 (from 2 fewer to 0 more)		
Blood transfusion												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	4/188 (2.1%)	5/189 (2.6%)	RR 0.80 (0.22 to 2.95)	1 fewer per 100 (from 2 fewer to 5 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	80/586 (13.7%)	126/587 (21.5%)	RR 0.64 (0.51 to 0.81)	8 fewer per 100 (from 4 fewer to 11 fewer)	MODERATE	CRITICAL
										-		
Nausea												
2	randomized trials	very serious[5]	no serious inconsistency	serious[2]	serious[3]	none	94/358 (26.3%)	103/358 (28.8%)	RR 0.91 (2 to 1.16)	3 fewer per 100 (from 5 more to 29 more)	VERY LOW	IMPORTANT
										-		

Vomiting												
2	randomized trials	very serious[5]	no serious inconsistency	serious[2]	serious[3]	none	32/358 (8.9%)	34/358 (9.5%)	RR 0.94 (0.59 to 1.49)	1 fewer per 100 (from 4 fewer to 5 more)	VERY LOW	IMPORTANT
										-		
Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,6]	none	1/29 (3.4%)	0/28 (0 %)	RR 2.9 (0.12 to 68.33)	-	VERY LOW	IMPORTANT
										-		

[1] Danserau 1999 measured drop in haemoglobin level by postoperative day 2, Includes Attilakos 2010, One study (Borruto 2009) defines PPH as blood loss > 500 ml.

[2] SR is from prevention studies.

[3] Wide confidence interval crossing the line of no effect,

[4] Small sample size.

[5] One study (Danserau 1999) with high risk of bias. Randomization block size of two made allocation concealment less effective.

[6] Very wide confidence interval crossing the line of no effect.

Source of the evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

Table 42. Carbetocin for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Oxytocin-Ergometrine (fixed dose combination)	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	14/515 (2.7%)	14/515 (2.7%)	RR 1 (0.48 to 2.07)	0 fewer per 100 (from 1 fewer to 3 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	1/455 (0.22%)	3/455 (0.66%)	RR 0.5 (0.09 to 2.72)	0 fewer per 100 (from 1 fewer to 1 more)	LOW	CRITICAL
										-		
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3]	none	6/455 (1.3%)	3/455 (0.66%)	RR 1.75 (0.52 to 5.93No)	0 more per 100 (from 0 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
4	randomized trials	no serious	no serious inconsistency	serious[1]	serious[2]	reporting bias[4]	59/515 (11.5%)	71/515 (13.8%)	RR 0.83 (0.6 to 1.15)	2 fewer per 100 (from 6 fewer to 2 more)	VERY LOW	CRITICAL

		risk of bias								-		
Nausea												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	17/515 (3.3%)	71/515 (13.8%)	RR 0.24 (0.15 to 0.4)	10 fewer per 100 (from 8 fewer to 12 fewer)	MODERATE	IMPORTANT
										-		
Vomiting												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	11/515 (2.1%)	54/515 (10.5%)	RR 0.21 (0.11 to 0.39)	8 fewer per 100 (from 6 fewer to 9 fewer)	MODERATE	IMPORTANT
										-		
Shivering												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,5]	none	2/150 (1.3%)	6/150 (4%)	RR 0.33 (0.07 to 1.63)	3 fewer per 100 (from 4 fewer to 3 more)	VERY LOW	IMPORTANT
										-		
										-		

[1] SR is from prevention studies.

[2] Wide confidence interval crossing the line of no effect.

[3] Very wide confidence interval crossing the line of no effect.

[4] Asymmetrical Funnel Plot.

[5] Small sample size

Source of the evidence: 197. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012; In editorial process.

Table 43. Intramuscular prostaglandins for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular prostaglandins	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: objectively assessed[1])												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	30/276 (10.9%)	31/288 (10.8%)	RR 1.06 (0.7 to 1.61)	1 more per 100 (from 3 fewer to 7 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	4/55 (7.3%)	11/64 (17.2%)	RR 0.41 (0.14 to 1.2)	10 fewer per 100 (from 15 fewer to 3 more)	LOW	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	7/63 (11.1%)	7/66 (10.6%)	RR 1.05 (0.39 to 2.86)	1 more per 100 (from 6 fewer to 20 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
4	randomised	no serious	no serious	serious[2]	very	none	4/206	4/216	RR 1.02	0 more per 100		CRITICAL

	trials	risk of bias	inconsistency		serious[5,6]		(1.9%)	(1.9%)	(0.28 to 3.68)	(from 1 fewer to 5 more)	VERY LOW	
										-		
Nausea												
3	randomised trials	very serious[7]	no serious inconsistency	serious[2]	very serious[4,5]	none	3/135 (2.2%)	1/145 (0.69%)	RR 2.39 (0.36 to 16.09)	1 more per 100 (from 0 fewer to 10 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
3	randomised trials	no serious risk of bias	very serious[8]	serious[2]	serious[6]	none	19/211 (9%)	8/214 (3.7%)	RR 2.33 (1.06 to 5.11)	5 more per 100 (from 0 more to 15 more)	VERY LOW	IMPORTANT
										-		
Maternal temperature > 38°C												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,9]	none	0/54 (0 %)	0/54 (0 %)	-	-	VERY LOW	IMPORTANT
										-		

[1] Amount of blood loss was quantified by noting the increment in weight of standardized tampons (India 2008).

[2] SR is from prevention studies

[3] Wide confidence interval crossing the line of no effect

[4] Small sample size.

[5] Very wide confidence interval crossing the line of no effect

[6] Few events.

[7] Egypt 1993 inadequate support of judgment

[8] Statistical Heterogenity (I^2= 77%).

[9] No events in both intervention and control group.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 44. Carboprost for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboprost	Misoprostol (rectal)	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: objectively assessed[3])												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[5,6]	none	3/60 (5%)	4/60 (6.7%)	RR 0.75 (0.18 to 3.21)	2 fewer per 100 (from 5 fewer to 15 more)	LOW	CRITICAL
										-		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[6,7]	none	0/60 (0 %)	1/60 (1.7%)	RR 0.33 (0.01 to 8.02)	1 fewer per 100 (from 2 fewer to 12 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[6]	none	2/60 (3.3%)	10/60 (16.7%)	RR 0.20 (0.05 to 0.87)	13 fewer per 100 (from 2 fewer to 16 fewer)	LOW	CRITICAL
										-		

[1] The comparison of the studies is PG IM (Carboprost, Sulprostone and PGF2 alpha). The only study included used PF2Alpha

[2] The comparison is rectal misoprostol 400 mcg

[3] Clinical estimation.

[4] SR is from prevention studies.

[5] Wide confidence interval crossing the line of no effect.

[6] Small sample size.

[7] Very wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 45. Misoprostol 600mcg (oral) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (oral)	No uterotonics or placebo	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: objectively assessed)												
5	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	260/2172 (12%)	356/2219 (16%)	RR 0.74 (0.64 to 0.86)	4 fewer per 100 (from 2 fewer to 6 fewer)	MODERATE	CRITICAL
										-		
Additional blood loss > 1000 ml (assessed with: objectively assessed[2])												
6	randomized trials	no serious risk of bias	serious[3]	serious[1]	serious[4]	none	74/2641 (2.8%)	81/2684 (3%)	RR 0.92 (0.68 to 1.26)	0 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
3	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	2/1311 (0.15%)	10/1308 (0.76%)	RR 0.24 (0.06 to 0.94)	1 fewer per 100 (from 0 fewer to 1 fewer)	LOW	CRITICAL
										-		

Severe morbidity (coagulopathy, organ failure, ICU admission)												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	6/1441 (0.42%)	5/1407 (0.36%)	RR 1.16 (0.36 to 3.8)	0 more per 100 (from 0 fewer to 1 more)	LOW	CRITICAL
										-		
Nausea												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	none	20/1662 (1.2%)	21/1681 (1.2%)	RR 0.9 (0.52 to 1.77)	0 fewer per 100 (from 1 fewer to 1 more)	LOW	IMPORTANT
										-		
Vomiting												
5	randomized trials	no serious risk of bias	serious[3]	serious[1]	serious[4]	reporting bias[6]	33/1848 (1.8%)	41/1901 (2.2%)	RR 0.82 (0.52 to 1.3)	0 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT
										-		
Shivering												
7	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[6]	720/2691 (26.8%)	297/2743 (10.8%)	RR 2.47 (2.18 to 2.79)	16 more per 100 (from 13 more to 19 more)	LOW	IMPORTANT
										-		

Maternal temperature > 38°C												
5	randomized trials	no serious risk of bias	serious[7]	serious[1]	no serious imprecision	reporting bias[6]	183/2030 (9%)	34/2110 (1.6%)	RR 5.39 (3.78 to 7.69)	7 more per 100 (from 4 more to 11 more)	VERY LOW	IMPORTANT
										-		
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4,5]	none	4/500 (0.8%)	3/500 (0.6%)	RR 1.33 (0.3 to 5.93)	2 more per 1000 (from 4 fewer to 30 more)	LOW	IMPORTANT
Additional uterotonics												
4	randomized trials	no serious risk of bias	serious[3]	serious[1]	serious[4]	none	82/1343 (6.1%)	96/1342 (7.2%)	RR 0.85 (0.64 to 1.13)	1 fewer per 100 (from 3 fewer to 1 more)	VERY LOW	CRITICAL
										-		

[1] SR is from prevention studies.

[2] Drop in Hb level (Pakistan 1999).

[3] Visual Heterogeneity.

[4] Wide confidence interval crossing the line of no effect.

[5] Few events.

[6] Asymmetrical Funnel Plot.

[7] Statistical Heterogeneity (I^2: 75%).

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 46. Misoprostol 600mcg (sublingual) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (sublingual)	No uterotonics or placebo	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	150/330 (45.5%)	170/331 (51.4%)	RR 0.89 (0.76 to 1.04)	6 fewer per 100 (from 12 fewer to 2 more)	MODERATE	CRITICAL
										-		
Additional blood loss > 1000 ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	37/330 (11.2%)	56/331 (16.9%)	RR 0.66 (0.45 to 0.98)	6 fewer per 100 (from 0 fewer to 9 fewer)	MODERATE	CRITICAL
										-		
Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	2/330 (0.61%)	4/331 (1.2%)	RR 0.5 (0.09 to 2.72)	1 fewer per 100 (from 1 fewer to 2 more)	VERY LOW	IMPORTANT
										-		

Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	10/330 (3%)	4/331 (1.2%)	RR 2.51 (0.79 to 7.92)	2 more per 100 (from 0 fewer to 8 more)	VERY LOW	IMPORTANT
										-		
Shivering												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	189/330 (57.3%)	78/331 (23.6%)	RR 2.43 (1.96 to 3.01)	34 more per 100 (from 23 more to 47 more)	MODERATE	IMPORTANT
										-		
Maternal temperature > 38°C												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	78/330 (23.6%)	11/331 (3.3%)	RR 7.11 (3.85 to 13.12)	20 more per 100 (from 9 more to 40 more)	MODERATE	IMPORTANT
										-		

[1] SR is from prevention studies.

[2] Wide confidence interval crossing the line of no effect.

[3] Few events.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 47. Misoprostol 400mcg (rectal) for treatment of PPH due to uterine atony.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 400mcg (rectal)	No uterotonics or placebo	Relative (95% CI)	Absolute		
Additional blood loss > 1000 ml												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	13/270 (4.8%)	19/272 (7%)	RR 0.69 (0.35 to 1.37)	2 fewer per 100 (from 5 fewer to 3 more)	LOW	CRITICAL
										-		
Additional uterotonics												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	9/271 (3.3%)	13/275 (4.7%)	RR 0.70 (0.31 to 1.62)	1 fewer per 100 (from 3 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	1/271 (0.37%)	1/275 (0.36%)	RR 1.01 (0.06 to 16.41)	0 more per 100 (from 0 fewer to 6 more)	VERY LOW	IMPORTANT
										-		
Shivering												
1	randomised	no	no serious	serious[2]	very	none	1/34	4/36	RR 0.26	8 fewer per 100		IMPORTANT

	trials	serious risk of bias	inconsistency		serious[3,6]		(2.9%)	(11.1%)	(0.03 to 2.25)	(from 11 fewer to 14 more)	VERY LOW	
										-		

[1] Dose: 400 mcg of rectal misoprostol.

[2] Data from prevention studies.

[3] Wide confidence interval crossing the line of no effect.

[4] Few events.

[5] Very wide confidence interval crossing the line of no effect.

[6] Small sample size.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 48. Misoprostol (200mcg buccal) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 200mcg (buccal)	No uterotonics or placebo	Relative (95% CI)	Absolute		
Additional blood loss > 1000 ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	24/173 (13.9%)	22/179 (12.3%)	RR 1.13 (0.66 to 1.94)	2 more per 100 (from 4 fewer to 12 more)	LOW	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	6/550 (1.1%)	9/558 (1.6%)	RR 0.68 (0.24 to 1.89)	1 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	55/550 (1 0 %)	76/558 (13.6%)	RR 0.64 (0.48 to 0.85)	5 fewer per 100 (from 2 fewer to 7 fewer)	MODERATE	CRITICAL
										-		

[1] Dose: 200mcg of misoprostol.
[2] SR is from prevention studies
[3] Wide confidence interval crossing the line of no effect.
[4] Few events.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 49. Misoprostol 600mcg (oral) treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (oral)	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
7	randomized trials	no serious risk of bias	serious[1]	serious[2]	no serious imprecision	none	1969/11067 (17.8%)	1384/11097 (12.5%)	RR 1.42 (1.3 to 1.52)	5 more per 100 (from 4 more to 6 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml												
6	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	396/10972 (3.6%)	292/11005 (2.7%)	RR 1.36 (1.17 to 1.58)	10 more per 1000 (from 5 more to 15 more)	MODERATE	CRITICAL
										-		
Blood transfusion												
5	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	88/10793 (0.82%)	114/10807 (1.1%)	RR 0.77 (0.59 to 1.02)	2 fewer per 1000 (from 4 fewer to 0 more)	LOW	CRITICAL
										-		
Additional uterotonics												

6	randomized trials	no serious risk of bias[4]	serious[1]	serious[2]	no serious imprecision	none	1701/10885 (15.6%)	1212/10900 (11.1%)	RR 1.4 (1.31 to 1.5)	4 more per 100 (from 3 more to 6 more)	LOW	CRITICAL
										-		
Nausea												
6	randomized trials	no serious risk of bias	serious[1]	serious[2]	serious[3]	none	146/10886 (1.3%)	132/10907 (1.2%)	RR 1.1 (0.8 to 1.4)	1 more per 1000 (from 2 fewer to 5 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
7	randomized trials	no serious risk of bias	serious[1]	serious[2]	serious[3]	none	130/11072 (1.2%)	107/11103 (0.96%)	RR 1.21 (0.94 to 1.57)	0 more per 100 (from 0 fewer to 1 more)	VERY LOW	IMPORTANT
										-		
Shivering												
7	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	2229/11071 (20.1%)	676/11103 (6.1%)	RR 3.3 (3 to 3.5)	14 more per 100 (from 12 more to 15 more)	MODERATE	IMPORTANT
										-		
Maternal temperature > 38°C												
7	randomized	no	no serious	serious[2]	no serious	none	733/1056	108/11081	RR 6.8	6 more per		IMPORTANT

	trials	serious risk of bias	inconsistency		imprecision		(69.4%)	(0.97%)	(5.5 to 8.3)	100 (from 4 more to 7 more)	MODERATE	
										-		

[1] Visual Heterogeneity.

[2] SR is from prevention studies

[3] Wide confidence interval crossing the line of no effect.

[4] Although India 2005a has unclear risk of bias

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 50. Misoprostol 400mcg (rectal) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 400mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	121/1104 (11%)	110/1140 (9.6%)	RR 1.14 (0.92 to 1.43)	1 more per 100 (from 1 fewer to 4 more)	MODERATE	CRITICAL
										-		
Additional blood loss > 1000 ml												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	reporting bias[4]	32/873 (3.7%)	29/907 (3.2%)	RR 1.14 (0.7 to 1.85)	0 more per 100 (from 1 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	16/1058 (1.5%)	16/1095 (1.5%)	RR 1.03 (0.52 to 2.04)	0 more per 100 (from 1 fewer to 2 more)	LOW	CRITICAL
										-		

Additional uterotonics												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	71/592 (12%)	45/618 (7.3%)	RR 1.64 (1.16 to 2.31)	5 more per 100 (from 1 more to 10 more)	MODERATE	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	serious[5]	serious[2]	very serious[6,7]	none	8/175 (4.6%)	8/180 (4.4%)	RR 1.04 (0.41 to 2.16)	0 more per 100 (from 3 fewer to 5 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[6,7]	none	10/894 (1.1%)	8/924 (0.87%)	RR 1.28 (0.53 to 3.12)	0 more per 100 (from 0 fewer to 2 more)	VERY LOW	IMPORTANT
										-		
Shivering												
8	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	reporting bias[4]	214/1053 (20.3%)	95/1090 (8.7%)	RR 2.34 (1.88 to 2.92)	12 more per 100 (from 8 more to 17 more)	LOW	CRITICAL
										-		

Maternal temperature > 38°C												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	36/503 (7.2%)	18/519 (3.5%)	RR 2.08 (1.21 to 3.57)	4 more per 100 (from 1 more to 9 more)	MODERATE	IMPORTANT
										-		
Manual removal of the placenta												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[8]	none	1/180 (0.56%)	7/183 (3.8%)	RR 0.20 (0.04 to 1.16)	3 fewer per 100 (from 4 fewer to 1 more)	LOW	IMPORTANT

[1] Dose: 400mcg of rectal misoprostol.

[2] SR is from prevention studies.

[3] Wide confidence interval crossing the line of no effect.

[4] Asymmetrical Funnel Plot.

[5] Statistical Heterogeneity (I^2: 60 %).

[6] Wide confidence interval crossing the line of no effect,

[7] Few events.

[8] Small sample size.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 51. Misoprostol 600mcg (rectal) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 600mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	1/100 (1%)	0/100 (0 %)	RR 3 (0.12 to 72.77)	-	VERY LOW	CRITICAL
										-		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	5/100 (5%)	1/100 (1%)	RR 5 (0.59 to 42.04)	4 more per 100 (from 0 fewer to 41 more)	VERY LOW	CRITICAL
										-		
Nausea												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	2/100 (2%)	0/100 (0 %)	RR 5 (0.24 to 102.85)	-	VERY LOW	IMPORTANT
										-		
Shivering												
1	randomized trials	no serious risk of	no serious inconsistency	serious[2]	very serious[4,5]	none	16/100 (16%)	13/100 (13%)	RR 1.23 (0.63 to 2.42)	3 more per 100 (from 5 fewer to 18 more)	VERY LOW	IMPORTANT

		bias								-		
Maternal temperature > 38°C												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	2/100 (2%)	0/100 (0 %)	RR 5 (0.24 to 102.85)	-	VERY LOW	IMPORTANT
										-		
Manual removal of the placenta												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	3/100 (3%)	1/100 (1%)	RR 3 (0.32 to 28.35)	2 more per 100 (from 1 fewer to 27 more)	VERY LOW	IMPORTANT

[1] Dose: 600mcg of rectal misoprostol.
[2] SR is from prevention studies.
[3] Very wide confidence interval crossing the line of no effect.
[4] Small sample size.
[5] Wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 52. Misoprostol 800mcg (rectal) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 800mcg (rectal)	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500ml												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	20/474 (4.2%)	18/481 (3.7%)	RR 1.12 (0.6 to 2.09)	0 more per 100 (from 1 fewer to 4 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000ml												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	none	0/217 (0 %)	1/224 (0.45%)	RR 0.34 (0.01 to 8.4)	0 fewer per 100 (from 0 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	serious[6]	serious[2]	very serious[3,5]	none	9/474 (1.9%)	9/478 (1.9%)	RR 1.01 (0.4 to 2.52)	0 more per 100 (from 1 fewer to 3 more)	VERY LOW	CRITICAL
										-		

Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	15/480 (3.1%)	23/481 (4.8%)	RR 0.65 (0.35 to 1.24)	2 fewer per 100 (from 3 fewer to 1 more)	MODERATE	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,5]	none	2/469 (0.43%)	5/473 (1.1%)	RR 0.40 (0.08 to 2.08)	1 fewer per 100 (from 1 fewer to 1 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,5]	none	7/471 (1.5%)	7/470 (1.5%)	RR 1 (0.35 to 2.82)	0 fewer per 100 (from 1 fewer to 3 more)	VERY LOW	IMPORTANT
										-		
Shivering												
2	randomised trials	no serious risk of bias	serious[7]	serious[2]	no serious imprecision	none	96/470 (20.4%)	2/470 (0.43%)	RR 38.6 (11.04 to 134.95)	16 more per 100 (from 4 more to 57 more)	LOW	IMPORTANT
										-		

[1] Dose: 800mcg of rectal misoprostol.
[2] SR is from prevention studies.
[3] Wide confidence interval crossing the line of no effect.
[4] Very wide confidence interval crossing the line of no effect.
[5] Few events.
[6] Statistical Heterogeneity (I^2: 71%).
[7] Statistical Heterogeneity (I^2: 82%).

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 53. Misoprostol for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol any dose (sublingual)	Injectable uterotonics	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	reporting bias[2]	68/331 (20.5%)	68/332 (20.5%)	RR 1.00 (0.83 to 1.21)	0 fewer per 100 (from 3 fewer to 4 more)	LOW	CRITICAL
										-		
Additional blood loss > 1000 ml												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3,4]	none	7/135 (5.2%)	13/135 (9.6%)	RR 0.54 (0.23 to 1.27)	4 fewer per 100 (from 7 fewer to 3 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4]	none	0/60 (0 %)	0/60 (0 %)	-	-	VERY LOW	CRITICAL
										-		
Additional uterotonics												

8	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	46/506 (9.1%)	76/507 (15%)	RR 0.61 (0.44 to 0.85)	6 fewer per 100 (from 2 fewer to 8 fewer)	MODERATE	CRITICAL
										-		
Nausea												
2	randomised trials	no serious risk of bias	serious[5]	serious[6]	serious[7]	none	14/166 (8.4%)	17/167 (10.2%)	RR 0.83 (0.42 to 1.62)	2 fewer per 100 (from 6 fewer to 6 more)	VERY LOW	IMPORTANT
										-		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[7]	none	20/241 (8.3%)	16/242 (6.6%)	RR 1.25 (0.67 to 2.32)	2 more per 100 (from 2 fewer to 9 more)	LOW	IMPORTANT
										-		
Shivering												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	70/391 (17.9%)	6/392 (1.5%)	RR 9.06 (4.46 to 19.39)	12 more per 100 (from 5 more to 28 more)	MODERATE	IMPORTANT
										-		
Maternal temperature > 38°C												

5	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	50/326 (15.3%)	2/327 (0.61%)	RR 13.04 (4.77 to 35.62)	7 more per 100 (from 2 more to 21 more)	MODERATE	IMPORTANT
										-		
Manual removal of the placenta												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[4,7]	none	0/60 (0 %)	1/61 (1.6%)	RR 0.33 (0.01 to 8.02)	1 fewer per 100 (from 2 fewer to 12 more)	VERY LOW	IMPORTANT

[1] Data from prevention studies.
[2] Asymmetrical Funnel Plot.
[3] Wide confidence interval crossing de line of no effect.
[4] Small sample size.
[5] Statistical heterogeneity (I^2: 80 %).
[6] SR is from prevention studies.
[7] Wide confidence interval crossing the line of no effect.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 54. Misoprostol 400mcg (rectal) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol 400mcg (rectal)	Intramuscular prostaglandins	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	4/60 (6.7%)	3/60 (5%)	RR 1.33 (0.31 to 5.7)	2 more per 100 (from 3 fewer to 23 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	none	10/60 (16.7%)	2/60 (3.3%)	RR 5 (1.14 to 21.86)	133 more per 1000 (from 5 more to 695 more)	VERY LOW	CRITICAL
										-		

[1] Dose: 400mcg of rectal misoprostol.

[2] SR is from prevention studies.

[3] Very wide confidence interval crossing the line of no effect.

[4] Small sample size.

Source of evidence: 209. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2011(Issue 3. Art. No.: CD000494.).

Table 55. Colloid and hypertonic crystalloid for fluid resuscitation in critically ill patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colloid and hypertonic crystalloid	isotonic crystalloid	Relative (95% CI)	Absolute		
Deaths - albumin or PPF												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	none	1/7 (14.3%)	2/7 (28.6%)	RR 0.5 (0.06 to 4.33)	14 fewer per 100 (from 27 fewer to 95 more)	VERY LOW	CRITICAL
								28.6%		14 fewer per 100 (from 27 fewer to 95 more)		
Deaths – dextran												
8	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	182/667 (27.3%)	179/616 (29.1%)	RR 0.88 (0.74 to 1.05)	3 fewer per 100 (from 8 fewer to 1 more)	MODERATE	CRITICAL
								29.5%		4 fewer per 100 (from 8 fewer to 1 more)		

[1] None of the studies included in this SR involve women in third stage of labour.

[2] Wide confidence interval crossing the line of no effect.

[3] Small sample size.

Source of evidence: 164. Perel P, Roberts I, Pearson M. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2011; In editorial process..

Table 56. Supplemental albumin for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supplemental albumin	Control	Relative (95% CI)	Absolute		
Deaths												
38	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	997/5413 (18.4%)	961/5429 (17.7%)	OR 1.05 (0.95 to 1.16)	1 more per 100 (from 1 fewer to 2 more)	LOW	CRITICAL
Deaths – hypovolaemia												
22	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	909/4929 (18.4%)	897/4951 (18.1%)	OR 1.02 (0.92 to 1.13)	0 more per 100 (from 1 fewer to 2 more)	LOW	CRITICAL
Deaths – burns												
4	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	22/100 (22%)	9/105 (8.6%)	OR 2.93 (1.28 to 6.72)	130 more per 1000 (from 21 more to 301 more)	LOW	CRITICAL
Deaths – hypoalbuminaemia												
12	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	66/384 (17.2%)	55/373 (14.7%)	OR 1.26 (0.84 to 1.88)	3 more per 100 (from 2 fewer to 10 more)	LOW	CRITICAL

[1] None of the studies included in this SR involve women in third stage of labour.

[2] Wide confidence interval crossing the line of no effect.

[3] Small sample size.

Source of evidence: 7. Alderson P, Bunn F, Li WP, Li LP, M., Roberts I, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011; In review process.

Table 57. Colloid for fluid resuscitation in critically ill patients I

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colloid	crystalloid (add-on colloid)	Relative (95% CI)	Absolute		
Deaths - albumin or PPF												
23	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	None	782/3870 (20.2%)	778/3884 (2 0 %)	RR 1.01 (0.92 to 1.1)	0 more per 100 (from 2 fewer to 2 more)	MODERATE	CRITICAL
								6.7%		0 more per 100 (from 1 fewer to 1 more)		
Deaths - hydroxyethyl starch												
17	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	None	131/636 (20.6%)	111/536 (20.7%)	RR 1.18 (0.96 to 1.44)	4 more per 100 (from 1 fewer to 9 more)	LOW	CRITICAL
										-		
Deaths - modified gelatine												
11	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	None	13/224 (5.8%)	15/282 (5.3%)	RR 0.91 (0.49 to 1.72)	0 fewer per 100 (from 3 fewer to 4 more)	LOW	CRITICAL
										-		

Deaths – dextran												
9	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	None	96/412 (23.3%)	57/422 (13.5%)	RR 1.24 (0.94 to 1.65)	3 more per 100 (from 1 fewer to 9 more)	LOW	CRITICAL

[1] None of the studies included in this SR involve women in third stage of labour.

[2] Wide confidence interval crossing the line of no effect.

Source of evidence: 164. Perel P, Roberts I, Pearson M. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2011; In editorial process.

Table 58. Colloid for fluid resuscitation in critically ill patients II

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colloid**	**hypertonic crystalloid**	**Relative (95% CI)**	**Absolute**		
Deaths - albumin or PPF												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2,3]	None	3/19 (15.8%)	0/19 (0 %)	RR 7 (0.39 to 126.92)	-	LOW	CRITICAL
										-		
Deaths - hydroxyethyl starch												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3]	None	0/8 (0 %)	0/8 (0 %)	not pooled	not pooled	VERY LOW	CRITICAL

Deaths - modified gelatin												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3]	None	0/10 (0 %)	0/10 (0 %)	not pooled	not pooled	VERY LOW	CRITICAL

[1] None of the studies included in this SR involve women in third stage of labour.

[2] Wide confidence interval crossing the line of no effect.

[3] Small sample size.

Source of evidence: 164. Perel P, Roberts I, Pearson M. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2011; In editorial process.

Table 59. Tranexamic acid for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tranexamic acid**	**Placebo or no treatment**	**Relative (95% CI)**	**Absolute**		
Blood loss > 400ml												
2[1]	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	40/277 (14.4%)	57/176 (32.4%)	RR 0.51 (0.36 to 0.72)	16 fewer per 100 (from 9 fewer to 21 fewer)	MODERATE	NOT IMPORTANT

										-		

[1] One for vaginal birth and one for caesarean section.

[2] Data from prevention studies.

Source of evidence: 148. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2010(7):CD007872.

Table 60. Uterine massage (before placental delivery) for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage before placental delivery	No uterine massage	Relative (95% CI)	Absolute		
Additional blood loss 1000 ml (assessed with: not mentioned)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2,3]	None	3/652 (0.46%)	1/639 (0.16%)	RR 2.96 (0.31 to 28.35)	0 more per 100 (from 0 fewer to 4 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[3,4]	None	4/637 (0.63%)	4/620 (0.65%)	RR 0.97 (0.26 to 3.58)	0 fewer per 1000 (from 5 fewer to 17 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[4]	None	21/638 (3.3%)	20/622 (3.2%)	RR 1.02 (0.56 to 1.85)	0 more per 100 (from 1 fewer to 3 more)	LOW	CRITICAL
										-		

Manual removal of the placenta												
2	randomised trials	no serious risk of bias	serious[5]	serious[1]	very serious[3,4]	None	13/655 (2%)	11/634 (1.7%)	RR 1.13 (0.52 to 2.46)	0 more per 100 (from 1 fewer to 3 more)	VERY LOW	IMPORTANT

[1] SR is from prevention studies.

[2] Very wide confidence interval crossing the line of no effect.

[3] Few events.

[4] Wide confidence interval crossing the line of no effect.

[5] Statistical heterogeneity (I^2: 61%).

Source of evidence: 88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.

Table 61. Uterine massage (after placental delivery) for treatment of PPH.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage after placental delivery	No uterine massage	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml (assessed with: objectively meassured[1])												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	None	4/98 (4.1%)	8/102 (7.8%)	RR 0.52 (0.16 to 1.67)	4 fewer per 100 (from 7 fewer to 5 more)	VERY LOW	CRITICAL
Blood transfusion												
1[5]	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4]	None	0/98 (0 %)	0/102 (0 %)	-	-	VERY LOW	CRITICAL
										-		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	None	5/98 (5.1%)	26/102 (25.5%)	RR 0.20 (0.08 to 0.5)	20 fewer per 100 (from 13 fewer to 23 fewer)	LOW	CRITICAL
										-		
Severe morbidity (coagulopathy, organ failure and ICU admission)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4]	None	0/98 (0 %)	0/102 (0 %)	-	-	VERY LOW	CRITICAL

[1] Plastic drape placed under the woman's buttocks after birth of the baby.
[2] SR is from prevention studies.
[3] Wide confidence interval crossing the line of no effect.
[4] Small sample size.
[5] One study with no events.

Source of evidence: 88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.

Table 62. Uterine massage before or after placental delivery for treatment of PPH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage before and after placental delivery	No uterine massage	Relative (95% CI)	Absolute		
Additional blood loss > 1000 ml (assessed with: not mentioned)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3,4]	None	3/652 (0.46%)	1/639 (0.16%)	RR 2.96 (0.31 to 28.35)	0 more per 100 (from 0 fewer to 4 more)	VERY LOW	CRITICAL
										-		
Blood transfusion												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[4,5]	None	4/735 (0.54%)	4/722 (0.55%)	RR 0.97 (0.26 to 3.58)	0 fewer per 1000 (from 4 fewer to 14 more)	VERY LOW	CRITICAL
										-		
Additional uterotonics												
3	randomised trials	no serious risk of bias	serious[6]	serious[2]	serious[5]	None	26/736 (3.5%)	46/724 (6.4%)	RR 0.52 (0.15 to 1.81)	3 fewer per 100 (from 5 fewer to 5 more)	VERY LOW	CRITICAL
										-		

[1] One study with no events.

[2] SR is from prevention studies.

[3] Very wide confidence interval crossing the line of no effect.
[4] Few events.
[5] Wide confidence interval crossing the line of no effect.
[6] Statistical Heterogeneity (I^2: 78%).

Source of evidence: 88. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews. 2012; In review process.

Table 63. Uterotonics for treatment of retained placenta

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Uterotonics	Control	Relative (95% CI)	Absolute		
Manual removal of placenta												
1	Randomised trial	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11/24 (45.8%)	22/26 (84.6%)	RR 0.54 (0.34-0.86)	34 fewer per 1000 (195 fewer to 161 more)-	Very Low	CRITICAL
Blood transfusion												
1	Randomised trial	Very serious [1]	No serious inconsistency	No serious indirectness	Serious[2]	None	16/24 (66.7%)	8/26 (3 0 %)	RR 2.26 (1.14-4.12)	378 more per 1000	Very Low	CRITICAL
1	-	-	-	-	-	None	-	-	-	-		CRITICAL

1 The study was stopped prematurely after "the null hypothesis of equal effectiveness of both treatments was rejected" (Interim analyses were made after each 5 consecutive patients. Small sample size. 15% of women excluded from analyses.

2 Very small sample size

Source of evidence: 214. van Beekhuizen HJ, de Groot AN, De Boo T, Burger D, Jansen N, Lotgering FK. Sulprostone reduces the need for the manual removal of the placenta in patients with retained placenta: a randomized controlled trial. Am J Obstet Gynecol. 2006 Feb;194(2):446-50.

Table 64. Intraumbilical vein injection of saline solution for treatment of retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intraumbilical injection of saline solution**	**Expectant management**	**Relative (95% CI)**	**Absolute**		
Additional blood loss > 500 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	15/88 (17%)	15/89 (16.9%)	RR 0.98 (0.52 to 1.82)	3 fewer per 1000 (from 81 fewer to 138 more)	LOW	CRITICAL
Additional blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	None	3/62 (4.8%)	4/60 (6.7%)	RR 0.73 (0.17 to 3.11)	2 fewer per 100 (from 6 fewer to 14 more)	LOW	CRITICAL
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	None	15/118 (12.7%)	19/117 (16.2%)	RR 0.76 (0.41 to 1.39)	4 fewer per 100 (from 10 fewer to 6 more)	LOW	CRITICAL
Surgical evacuation of retained products of conception												
1	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	None	25/90 (27.8%)	31/88 (35.2%)	RR 0.79 (0.51 to	7 fewer per 100 (from 17 fewer to 8	MODERATE	NOT IMPORTANT[4]

		bias							1.22)	more)		
Infection												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2,3]	None	2/90 (2.2%)	4/86 (4.7%)	RR 0.48 (0.09 to 2.54)	2 fewer per 100 (from 4 fewer to 7 more)	MODERATE	CRITICAL
Serious maternal morbidity												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	None	0/42 (0 %)	0/45 (0 %)	not pooled	not pooled	VERY LOW	CRITICAL
Manual removal of the placenta												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	None	114/206 (55.3%)	113/197 (57.4%)	RR 0.99 (0.84 to 1.16)	1 fewer per 100 (from 9 fewer to 9 more)	MODERATE	NOT IMPORTANT[4]
Maternal mortality												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	None	0/42 (0 %)	0/45 (0 %)	not pooled	not pooled	VERY LOW	CRITICAL

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Wide confidence interval crossing the line of no events.

[4] Was not in the proposed outcomes.

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table65. Intraumbilical injection of oxytocin for retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intraumbilical injection of oxytocin**	**Expectant management**	**Relative (95% CI)**	**Absolute**		
Additional blood loss > 500 ml												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	26/96 (27.1%)	15/89 (16.9%)	RR 1.51 (0.87 to 2.6)	9 more per 100 (from 2 fewer to 27 more)	LOW	CRITICAL
Additional blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	6/70 (8.6%)	4/60 (6.7%)	RR 1.29 (0.38 to 4.34)	2 more per 100 (from 4 fewer to 22 more)	LOW	CRITICAL
Blood transfusion												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	18/120 (15%)	19/117 (16.2%)	RR 0.89 (0.5 to 1.58)	18 fewer per 1000 (from 81 fewer to 94 more)	LOW	CRITICAL
Surgical evacuation of retained products of conception												

1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	None	23/94 (24.5%)	31/88 (35.2%)	RR 0.69 (0.44 to 1.09)	11 fewer per 100 (from 20 fewer to 3 more)	MODERATE	NOT IMPORTANT[3]
Infection												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	None	5/93 (5.4%)	4/86 (4.7%)	RR 1.16 (0.32 to 4.16)	1 more per 100 (from 3 fewer to 15 more)	MODERATE	CRITICAL
Serious maternal morbidity												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	0/45 (0 %)	0/45 (0 %)	not pooled	not pooled	LOW	CRITICAL
Manual removal of the placenta												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	117/234 (5 0 %)	123/210 (58.6%)	RR 0.87 (0.74 to 1.03)	8 fewer per 100 (from 15 fewer to 2 more)	MODERATE	NOT IMPORTANT[3]

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Was not in the proposed outcomes.

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table 66 Intraumbilical injection of oxytocin for retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical injection of oxytocin	Saline solution	Relative (95% CI)	Absolute		
Additional blood loss > 500 ml												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	131/424 (30.9%)	124/405 (30.6%)	RR 1.01 (0.83 to 1.24)	0 more per 100 (from 5 fewer to 7 more)	MODERATE	CRITICAL
Additional blood loss > 1000 ml												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	37/391 (9.5%)	33/375 (8.8%)	RR 1.08 (0.7 to 1.68)	1 more per 100 (from 3 fewer to 6 more)	MODERATE	CRITICAL
Blood transfusion												
5	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	63/446 (14.1%)	52/434 (12%)	RR 1.18 (0.84 to 1.65)	2 more per 100 (from 2 fewer to 8 more)	HIGH	CRITICAL
Additional uterotonics												
4	randomized trials	no serious risk of	no serious inconsistency	no serious indirectness	no serious imprecision	None	43/346 (12.4%)	46/332 (13.9%)	RR 0.85 (0.59 to	2 fewer per 100 (from 6 fewer to 3	HIGH	CRITICAL

		bias							1.23)	more)		
Surgical evacuation of retained products of conception												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	27/420 (6.4%)	29/406 (7.1%)	RR 0.89 (0.56 to 1.4)	1 fewer per 100 (from 3 fewer to 3 more)	MODERATE	CRITICAL
Infection												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	43/417 (10.3%)	31/403 (7.7%)	RR 1.35 (0.87 to 2.09)	3 more per 100 (from 1 fewer to 8 more)	HIGH	CRITICAL
Severe morbidity (including coagulopathy organ failure and ICU admission)												
4	randomized trials	serious	no serious inconsistency	no serious indirectness	very serious[3]	None	0/369 (0 %)	1/355 (0.28%)	RR 0.33 (0.01 to 7.95)	0 fewer per 100 (from 0 fewer to 2 more)	VERY LOW	CRITICAL
Nausea												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	None	0/32 (0 %)	0/28 (0 %)	not pooled	not pooled	MODERATE	IMPORTANT
Shivering												
1	randomized trials	no serious	no serious inconsistency	no serious indirectness	serious[4]	None	0/32 (0 %)	0/28 (0 %)	not pooled	not pooled	MODERATE	IMPORTANT

		risk of bias										
Fever												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,4]	None	1/43 (2.3%)	0/35 (0 %)	RR 2 (0.09 to 43.22)	-	MODERATE	NOT IMPORTANT[5]
Manual removal of the placenta												
12	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	355/655 (54.2%)	371/621 (59.7%)	RR 0.91 (0.82 to 1)	5 fewer per 100 (from 11 fewer to 0 more)	HIGH	NOT IMPORTANT[5]

[1] Wide confidence interval crossing the line of no effect.

[2] Authors of the SR collected data on fever

[3] Very wide confidence interval crossing the line of no effect.

[4] Small sample size.

[5] Was not in the proposed outcomes.

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table 67. Intraumbilical injection of prostaglandin solution for retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical injection of prostaglandin solution	Saline solution	Relative (95% CI)	Absolute		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	6/10 (6 0 %)	4/7 (57.1%)	RR 1.05 (0.46 to 2.38)	3 more per 100 (from 31 fewer to 79 more)	LOW	CRITICAL
Fever[5]												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1,2]	None	1/10 (1 0 %)	0/7 (0 %)	RR 2.18 (0.1 to 46.92)	-	MODERATE	NOT IMPORTANT[4]
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1]	None	9/31 (29%)	14/20 (7 0 %)	RR 0.42 (0.22 to 0.82)	41 fewer per 100 (from 13 fewer to 55 fewer)	VERY LOW	NOT IMPORTANT[4]

[1] Small sample size.

[2] Wide confidence interval crossing the line of no effect.

[3] Statistical Heterogeneity (I^2: 82%).

[4] Was not in the proposed outcomes.

[5]Authors of the SR collected data on fever

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table 68. Intraumbilical injection of prostaglandin solution for retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical injection of prostaglandin solution	Oxytocin solution	Relative (95% CI)	Absolute		
Additional uterotonics												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	6/10 (6 0 %)	5/11 (45.5%)	RR 1.32 (0.58 to 3)	15 more per 100 (from 19 fewer to 91 more)	LOW	CRITICAL
Fever[4]												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	1/10 (1 0 %)	1/11 (9.1%)	RR 1.1 (0.08 to 15.36)	1 more per 100 (from 8 fewer to 100 more)	LOW	NOT IMPORTANT[3]
Manual removal of the placenta												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	9/31 (29%)	21/31 (67.7%)	RR 0.43 (0.25 to 0.75)	39 fewer per 100 (from 17 fewer to 51 fewer)	MODERATE	NOT IMPORTANT[3]

[1] Small sample size.

[2] Wide confidence interval crossing the line of no effect.

[3] Was not in the proposed outcomes.

[4]Authors of the SR collected data on fever

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table 69. Intraumbilical injection of oxytocin for retained placenta.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin solution	Plasma expander	Relative (95% CI)	Absolute		
Manual removal of the placenta												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	49/68 (72.1%)	22/41 (53.7%)	RR 1.34 (0.97 to 1.85)	18 more per 100 (from 2 fewer to 46 more)	LOW	NOT IMPORTANT[3]
Additional blood loss > 1000 ml												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	None	8/68 (11.8%)	5/41 (12.2%)	RR 0.96 (0.34 to 2.75)	5 fewer per 1000 (from 80 fewer to 213 more)	LOW	CRITICAL

[1] Wide confidence interval crossing the line of no effect.

[2] Small sample size.

[3] Was not in the proposed outcomes.

Source of evidence: 145. Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev. (5):CD001337.

Table 70. Blood loss quantitative estimation for diagnosis of PPH:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quantitative estimation	Visual estimation	Relative (95% CI)	Absolute		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	86/11037 (0.78%)	135/14344 (0.94%)	OR 0.83 (0.35 to 1.96)[2]	2 fewer per 1000 (from 6 fewer to 9 more)	⨁⨁⨁◯ MODERATE	CRITICAL
										-		
Additional uterotonics (Prostaglandins after birth)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	501/11037 (4.5%)	766/14344 (5.3%)	OR 0.84 (0.4 to 1.77)[3]	8 fewer per 1000 (from 31 fewer to 37 more)	⨁⨁⨁◯ MODERATE	CRITICAL
										-		
Severe maternal morbidity												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	189/11037 (1.7%)	295/14344 (2.1%)	OR 0.83 (0.27 to 2.6)[4]	0 fewer per 100 (from 1 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
										-		

Manual removal of the placenta												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	326/11037 (3%)	366/14344 (2.6%)	OR 1.16 (0.76 to 1.77)[5]	4 more per 1000 (from 6 fewer to 19 more)	⨁⨁⨁◯ MODERATE	CRITICAL
										-		
Surgical procedures or embolization												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	None	50/11037 (0.45%)	76/14344 (0.53%)	OR 0.85 (0.2 to 3.63)[6]	1 fewer per 1000 (from 4 fewer to 14 more)	⨁⨁⨁◯ MODERATE	CRITICAL
										-		

[1] Wide confidence interval crossing the line of no effect,

[2] Adjusted for clustering (ICC: 0.011).

[3] Adjusted for clustering (ICC: 0.129).

[4] Adjusted for clustering (ICC: 0.023)

[5] Adjusted for clustering (ICC: 0.016)

[6] Adjusted for clustering (ICC: 0.012).

Source of the evidence: Diaz V, Abalos E. Methods for blood loss estimation after vaginal delivery. Cochrane Review in preparation.

Box 2: Activities prioritized by the GDG for Dissemination and implementation of the guideline

- **Promote discussion, dissemination and uptake during the FIGO meeting in Rome 2012;**
- **Prepare the translation of WHO Executive Summary: three to five pages into six official United Nations languages;**
- **Prepare guideline derivatives for policy-makers, consumers, clinicians and other groups (e.g. a two-page policy brief, a press release for engaging the public via the media, Managing Complications in Pregnancy and Childbirth update);**
- **Maximize the dissemination of these guidelines across WHO (regional and country offices);**
- **Increase the visibility and availability of WHO guidelines;**
- **Prepare WHO–UNFPA Joint Statements related to the main recommendations of these guidelines;**
- **Seek endorsement by national and international professional societies, including International Federation of Gynecology and Obstetrics, International Confederation of Midwives, and others (e.g. American Congress of Obstetricians and Gynecologists, Royal College of Obstetricians and Gynaecologists);**
- **Disseminate WHO guidelines in Health Sector Review meetings;**
- **Foster agreement between guidelines (e.g. FIGO) for unified recommendations;**
- **Promote the development of local guidelines/protocols based on these guidelines;**
- **Disseminate these guidelines using WHO guidance community and Knowledge Gateway to virtual community;**
- **Promote active engagement and dialogue rather than passive distribution and action plans;**
- **Foster availability of injectable uterotonics;**
- **Promote the development of tools to facilitate the formulation of health policies based on evidence-based guidelines.**
- **Promote task shifting (including independent use by all care providers skilled in the use of injectable uterotonics).**

Statement on misoprostol use for prevention of postpartum haemorrage

WHO recommends misoprostol use for the prevention of postpartum haemorrhage in settings where the use of oxytocin is not feasible

September 2012

The World Health Organization added orally administered misoprostol at 600 mcg dose to its Essential Medicines List in 2011 for prevention of postpartum haemorrhage (PPH) in settings where the use of oxytocin is not feasible. This action was based on evidence-informed recommendations for prevention of postpartum haemorrhage (1). These recommendations were developed following standard procedures including systematic reviews of the evidence, critical appraisal and grading of evidence quality. An international, multi-stakeholder panel was convened to review these findings and consider applicability and implementation of the recommendations. Development of the recommendations involved a thorough assessment of whether interventions are more likely to be beneficial than harmful. Based on the recommendations and supporting evidence, an application for inclusion of misoprostol in the WHO Essential Medicines List for prevention of PPH was prepared, and then reviewed and approved by the Expert Committee of the WHO on "Selection and Use of Essential Medicines".

In view of recent public debate related to the use of misoprostol in the prevention of postpartum haemorrhage, WHO considers parenterally administered oxytocin 10 IU more effective than orally administered misoprostol at 600 mcg in preventing PPH. At the same time, WHO considers the use of misoprostol by health workers (including lay health workers trained in this practice) an alternative in settings where the use of oxytocin is not possible. The use of misoprostol as an alternative uterotonic for PPH prevention should not detract from the objective of making oxytocin widely accessible.

Finally, WHO considers that there is still insufficient evidence to recommend the advance distribution of misoprostol at the community level for PPH prevention (i.e. distribution of misoprostol to pregnant women during the antenatal period for self-administration after childbirth). The current recommendations are reinforced in the new, updated guidelines published and available on the WHO website in September 2012 (2). WHO will continue to monitor studies in this area with a view to provide updates, as and when necessary.

References

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2. World Health Organization recommendations for the prevention and treatment of postpartum haemorrhage. Geneva, World Health Organization, 2012 (available at http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf)

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