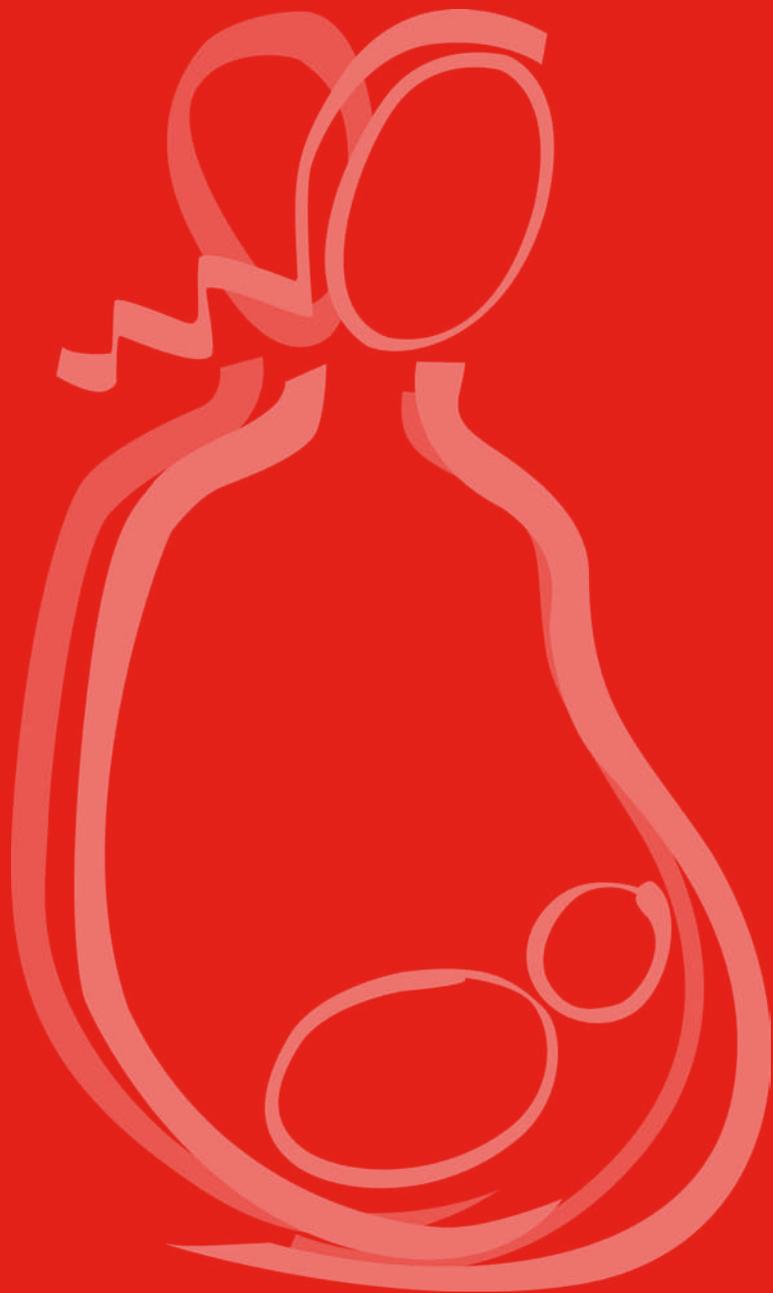


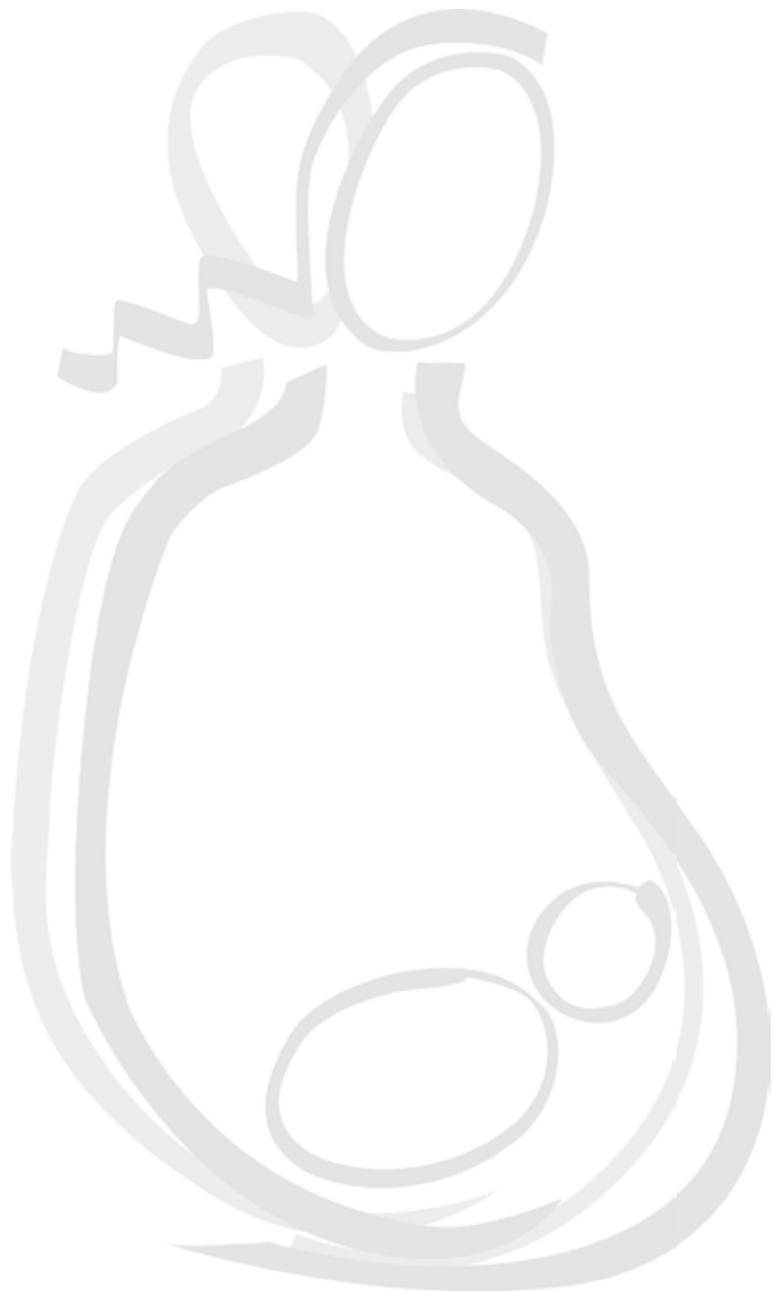
WHO Recommendations for the Prevention of Postpartum Haemorrhage



**World Health
Organization**

Department of Making Pregnancy Safer

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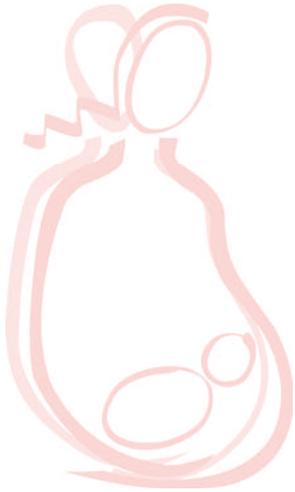
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BACKGROUND

Bleeding after childbirth (postpartum haemorrhage) is an important cause of maternal mortality, accounting for nearly one quarter of all maternal deaths worldwide. Common causes for postpartum haemorrhage (PPH) include failure of the uterus to contract adequately after birth leading to atonic PPH, tears of the genital tract leading to traumatic PPH and bleeding due to retention of placental tissue. Atonic PPH is the most common cause of PPH and the leading cause of maternal death.

Attempts have been made to identify women at risk of atonic PPH based on historical or clinical factors and steps are planned to prevent it in this allegedly high-risk group of women. Unfortunately, atonic PPH can occur even in women without identifiable risk factors. Numerically, more women without risk factors have atonic PPH compared to those with risk factors. To prevent atonic PPH, interventions should therefore be targeted at all women during childbirth.

One intervention that has been promoted as an effective intervention in preventing atonic PPH is the active management of the third stage of labour. This intervention was described in the Cochrane review as a package comprising the following interlocking interventions: administration of a prophylactic uterotonic after delivery of the baby, and usually also early cord clamping and cutting, and controlled traction of the umbilical cord.¹ According to the International Confederation of Midwives (ICM) and the International Federation of Gynecology & Obstetrics (FIGO), the usual components of active management include administration of uterotonic agents, controlled cord traction and uterine massage after delivery of the placenta, as appropriate;² while in WHO's Integrated Management of Pregnancy and Childbirth guidelines, the steps in active management of third stage of labour involve giving oxytocin immediately, delivery of the placenta by controlled cord traction and uterine massage.³ In the two latter definitions, the word "early" was left out because of evidence suggesting benefits of delayed cord clamping for the baby. It is also known that the timing of "early" cord clamping has not been consistent in the active management arms of the trials.

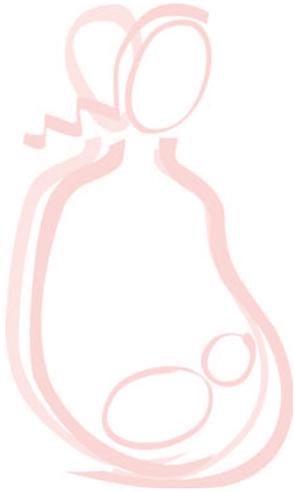
In contrast to active management, expectant management involves waiting for signs of separation and allowing the placenta to deliver spontaneously, or aided by gravity or nipple stimulation.¹ Expectant management is also known as conservative or physiological management.

While there is general agreement on the beneficial effects of active management of the third stage of labour, there are several issues which are yet to be resolved, such as clear definitions on the individual components of the intervention, the best methods and the requirements for the safe administration of this intervention under conditions of limited resources. For example, how soon after birth should the uterotonic be administered? Which drug should be recommended for different settings? What is the best route of administration? Is early clamping of the cord necessary and if so, what does "early" mean? Traction on the cord before separation of the placenta from the uterus may increase the risk of maternal complications. Is it a procedure that can be carried out safely by "non-skilled" providers?

Injectable oxytocin has been recommended for routine use in the active management of the third stage of labour;³ however, administration of an injection requires skills and sterile equipment for safe administration. Oxytocin may be inactivated if exposed to high ambient temperatures.⁴

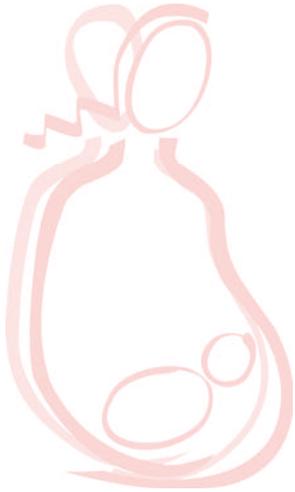
Misoprostol, a prostaglandin analogue with uterotonic effects, is reportedly more stable than oxytocin and has been administered by oral, sublingual and rectal routes in several studies.⁵ Suggestions have been made to provide misoprostol tablets where oxytocin is not available⁶ to non-skilled providers⁷ and to women themselves for the prevention of PPH;⁸ however, there are concerns that misuse of misoprostol can lead to significant maternal morbidity and even death.

In the light of these issues, the World Health Organization held a Technical Consultation on the Prevention of Postpartum Haemorrhage in Geneva on 18–20 October 2006 to discuss the various issues related to prevention of PPH and to develop recommendations.



METHODS

- WHO staff from the departments of Making Pregnancy Safer, Reproductive Health and Research, and Medicines, Policies and Standards drafted questions on various interventions described for prevention of atonic postpartum haemorrhage (active management of third stage of labour and its components). Each question was subdivided to address issues related to the type of health-care provider – skilled or non-skilled. For this discussion, the term "skilled attendant" refers exclusively to people with midwifery skills (for example, midwives, doctors and nurses) who have been trained to proficiency in the skills necessary to manage normal deliveries and diagnose, manage or refer complications.^{9,10} Skilled attendants must be able to manage normal labour and delivery, recognize the onset of complications, perform essential interventions, start treatment and supervise the referral of mother and baby for the interventions that are beyond the attendants' competence or not possible in the particular setting. Depending on the setting, other health-care providers, such as auxiliary nurse/midwives, community midwives, village midwives and health visitors, may also have acquired appropriate skills if they have been specially trained. Non-skilled attendants are those care providers who do not satisfy the above conditions. In making recommendations, participants of the Technical Consultation also considered making a distinction regarding the skills needed as defined above and the skills needed to make a safe intramuscular injection. A set of key beneficial and harmful outcomes of interventions was also drafted by WHO staff (Annexes 1 & 2), based mainly on published systematic reviews.
- These questions and proposed outcomes to consider were sent by e-mail to an international panel of experts (midwives, obstetricians, neonatologists, researchers, programme experts). Members of the panel were invited to comment on the relevance of these questions, to modify them if required and to add additional relevant questions. Panel members were also asked to rate each beneficial and harmful outcome on a scale of 1-9. A critical outcome was defined as an outcome that scored on average between 7 and 9. Those outcomes that scored between 4 and 6 on average were considered "important but not critical", while those scoring less than 4 were considered "not important".
- All responses were reviewed by the WHO core team. Where necessary, reminders were sent to members of the expert panel.
- An external organization, Centro per la Valutazione della Efficacia della Assistenza Sanitaria (Centre for the Evaluation of Effectiveness of Health Care) (CeVEAS), Modena, Italy, founded by the Public Health Service, was commissioned to review and grade the evidence to answer the questions asked using the GRADE methodology (Annexe 3). Draft evidence tables prepared by CeVEAS were reviewed by the WHO core team along with staff from CeVEAS. Evidence-based recommendations in response to the questions asked were then drafted.
- A draft of the methodology, results and recommendations was sent for review to a sub-group of experts prior to their participation in the WHO Technical Consultation on Prevention of Postpartum Haemorrhage.
- This draft and the supporting evidence were reviewed at the Technical Consultation in Geneva on 18–20 October 2006 and changes were made based on the recommendations of the expert panel.



RESULTS

- The draft questions related to prevention of PPH and the scoring grid for beneficial and harmful outcomes of interventions were sent to 58 experts from all six WHO regions.
- Responses were received from 37 of these experts. Questions were modified based on feedback received. The table below shows the average scores assigned to beneficial and harmful outcomes by this group.
- Based on this ranking, the **critical beneficial outcomes** for making a recommendation were:
 - reduction in maternal mortality and
 - reduction in maternal morbidity as indicated by
 - > measured blood loss of 1 l or more, and
 - > use of blood transfusion.
- Adverse effects of the drugs, including manual removal of the placenta, were considered **important harms** of the intervention, but not considered critical for decision-making.

Table 1 : Average scores

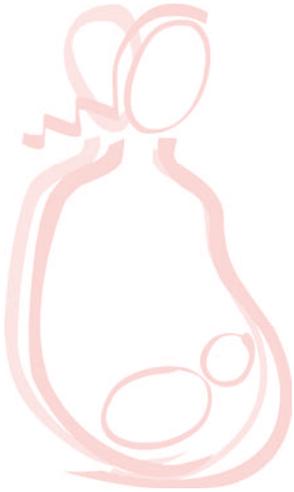
What are the most important beneficial outcomes of interventions to prevent PPH?

| | |
|---|------------|
| Fewer maternal deaths | 8.5 |
| Fewer admissions to intensive care unit | 6.4 |
| Less blood loss > 500 ml | 6.3 |
| Less blood loss > 1000 ml | 7.7 |
| Less use of blood transfusion | 7.8 |
| Less use of additional uterotonics | 5.9 |
| Decreased mean blood loss | 5.6 |
| Less postpartum anaemia | 6.1 |
| Earlier establishment of breastfeeding | 5.1 |
| Less anaemia in infancy | 4.8 |
| Other (please specify) | |

What are the most significant risks in interventions to prevent PPH?

| | |
|---|-----|
| Any side effect of intervention | 4.9 |
| Any side effect requiring treatment (e.g. manual removal of placenta) | 6.2 |
| Nausea | 4.0 |
| Vomiting | 4.7 |
| Diarrhoea | 4.6 |
| Headache | 4.8 |
| Abdominal pain | 4.8 |
| High blood pressure | 6.5 |
| Shivering | 4.7 |
| Temp > 38° C | 5.4 |
| Temp > 40° C | 6.8 |
| Maternal death | 6.7 |
| Anaemia in infancy | 4.6 |

Members of the panel who met for the Technical Consultation reviewed the overall ratings. It was agreed that "critical outcomes" should be referred to as "priority outcomes". In addition to the outcomes identified above, it was also agreed that "less use of additional uterotonics" should be considered as a priority beneficial outcome because it informs the interpretation of blood-loss data and has cost implications for implementation.



EVIDENCE & RECOMMENDATIONS

1. Should active management of the third stage of labour be offered by skilled attendants for all women to prevent postpartum haemorrhage? Should active management of the third stage be offered by non-skilled attendants to prevent PPH?

The evidence related to active management of the third stage consists of one systematic review of five RCTs comparing active and expectant (physiological) management in over 6000 women.¹ The studies were carried out in the United Kingdom, Ireland and the United Arab Emirates in hospital settings. The interventions in these studies used different combinations of the components of "active management", including different timings of cord clamping, different types, dosages and routes of administration of uterotonics, and non-standardized use of cord traction.

The studies in this review do not report any maternal deaths.

For the other priority outcomes, the overall results were a statistically significant reduction in blood loss of 1 l or more (RR 0.33; 95% CI 0.21, 0.51) (NNT Min 41 to Max 73), the use of blood transfusion (RR 0.34; 95% CI 0.22, 0.53) (NNT 28; 95% CI 18.7, 59.1) and the use of additional uterotonics (RR 0.20; 95% CI 0.17, 0.25) (NNT Min 4 Max 35.5).

The frequency of important adverse effects was increased in groups receiving active management when ergometrine was the drug used, but not in the group receiving oxytocin: nausea (RR 1.83; 95% CI 1.51, 2.23) (NNH Min 7 Max 18) and vomiting (RR 2.19, 95% CI 1.68, 2.86) (NNH Min 10 Max 18) were increased. However, there was no overall increase in manual delivery of placenta.

There is no evidence on the use of active management of the third stage of labour by non-skilled attendants.

Recommendation:

- Active management of the third stage of labour should be offered by skilled attendants to all women (Strong recommendation, moderate quality evidence).
 - > Recommendations on the individual components of active management are discussed below.
- The panel does not recommend active management by non-skilled attendants.

Remarks:

Although no evidence was found for or against the use of active management by non-skilled providers, the group placed high value on the potential risks – such as uterine inversion – that may result from inappropriate cord traction.

NOTE: Questions 2–6 are related to the selection of the uterotonic and summary tables, including evidence derived from trials comparing different uterotonics within the context of active management of the third stage of labour, assuming that there is no interaction between the other components of active management and the uterotonic.

2. Should oxytocin (10 IU parenterally) or ergometrine/methylergometrine (0.25 mg parenterally) be offered to all women by skilled attendants to prevent PPH?

The evidence for this comparison is based on two systematic reviews^{11 12} that include trials in over 9000 women. All trials were conducted in settings with skilled attendants. The treatments compared were ergometrine (or derivatives) and oxytocin, or ergometrine alone versus the fixed dose combination of ergometrine and oxytocin. The doses and routes of administration are different: IV oxytocin versus IV ergometrine and IM oxytocin/ergometrine (as a fixed combination) versus IM ergometrine alone. Doses of oxytocin used ranged from 2 to 10 IU; doses of ergometrine used ranged from 0.2 mg to 4 mg; and the fixed drug combination doses had 5 IU oxytocin with 0.5 mg ergometrine. Information on the co-interventions for management of the third stage in these trials is limited. There is only one trial (which included 1049 women) that directly compared the 10 IU dose of oxytocin with the 0.2 mg dose of ergometrine, but both were given by the IV route.¹³ For this reason, the overall quality of the evidence for this question is downgraded.

None of the trials report maternal deaths. For the priority outcomes related to blood loss and transfusion, the results of the trials do not show a difference between lower doses of oxytocin and the recommended dose of ergometrine. The fixed drug combination of oxytocin and ergometrine was associated with less use of additional uterotonics (RR 0.86; 95% CI 0.76, 0.97) (NNT Min 19, Max 31) but there was insufficient evidence on the other priority outcomes. The available comparisons are limited, but a major difference in the benefits of oxytocin and ergometrine appears unlikely.

Among the adverse outcomes that were rated as important, the comparison of oxytocin versus the fixed drug combination (5 IU oxytocin + 0.5 mg ergometrine) showed a higher rate of adverse effects in women treated with the combination drug: nausea (RR 3.85; 95% CI 3.2, 4.63) (NNH 5; 95% CI 4.4, 5.6); vomiting (RR 5.72; 95% CI 4.44, 7.38) (NNH 6; 95% CI 5.2, 6.6); high blood pressure (RR 2.47; 95% CI 1.58, 3.86) (NNH Min 51 Max 144). A lower rate of manual removal of placenta was seen in women treated with oxytocin (RR 0.57; 95% CI 0.41, 0.79) (NNH Max -26; 95% CI -62.8, -16.0).

Overall, ergometrine alone or in combination with oxytocin is associated with more adverse effects, especially with regard to causing high blood pressure. This is likely to be a particularly important consideration in women with hypertension or heart disease.

There is currently no evidence to support the use of either oxytocin or ergometrine for prevention of PPH by non-skilled attendants. Before recommending general use of injectable drugs that may have adverse effects, appropriate studies of their use by non-skilled attendants should be conducted.

The acquisition costs of the drugs are essentially the same.¹⁴ Administration costs are likely to be generally equivalent. Ergometrine (and the fixed drug combination of oxytocin and ergometrine) requires temperature-controlled transport and storage and protection from light; storage costs may be higher. Oxytocin is more stable.⁴

Recommendation:

In the context of active management of the third stage of labour, if all injectable uterotonic drugs are available:

- Skilled attendants should offer oxytocin to all women for prevention of PPH in preference to ergometrine/methylegometrine. (Strong recommendation, low quality evidence)

If oxytocin is not available:

- Skilled attendants should offer ergometrine/methylegometrine or the fixed drug combination of oxytocin and ergometrine to women without hypertension or heart disease for prevention of PPH. (Strong recommendation, low quality evidence)

Remarks:

These recommendations place a high value on avoiding adverse effects of ergometrine and assume similar benefit for oxytocin and ergometrine for preventing PPH.

3. Should oral misoprostol (600 mcg) be offered to all women by skilled attendants to prevent PPH instead of oxytocin (10 IU IM)?

The evidence for this comparison is based on one systematic review¹⁵ that includes seven trials directly comparing the two treatments in the dosages for misoprostol stated here. For oxytocin, the doses range from 2.5 IU to 10 IU. The largest trial, which included over 18 000 women, used 600mcg and 10 IU.

Among the priority outcomes, two maternal deaths were reported in each arm of the trial that included over 18 000 women. Blood loss of 1000 ml or more was increased with misoprostol when compared to oxytocin 10 IU IM (RR 1.34; 95% CI 1.16, 1.55) (NNT -89; 95% CI -167.1, -60.8) in three trials of over 18 000 women. There was no statistically significant difference in the use of blood transfusion with misoprostol compared with oxytocin (RR 0.80; 95% CI 0.62, 1.04) but there was more use of additional uterotonics with misoprostol (RR 1.41; 95% CI 1.31, 1.5) (NNT -23.3; 95% CI -5.3, -3.3).

Among important adverse effects, misoprostol was associated with an increase in shivering (RR 3.29; 95% CI 3.03, 3.56) (NNH 8; 95% CI 7.5, 8.6), diarrhoea (RR 2.52; 95% CI 1.6, 3.98) (NNH 342; 95% CI 231.6, 651) and temperature higher than 38° C (RR 6.62; 95% CI 5.45, 8.05) (NNH 19; 95% CI 17.4, 21.2).

The current acquisition cost of misoprostol (600 mcg) is more than the acquisition cost of oxytocin.¹⁴ Misoprostol is more stable.¹⁶

Recommendation:

In the context of active management of the third stage of labour:

- Skilled attendants should offer oxytocin for prevention of PPH in preference to oral misoprostol (600 mcg). (Strong recommendation, high quality evidence)

Remarks:

This recommendation places a high value on the relative benefits of oxytocin in preventing blood loss compared to misoprostol, as well as the increased adverse effects of misoprostol compared to oxytocin.

4. Should sublingual misoprostol (600 mcg) be offered to all women by skilled attendants to prevent PPH instead of oxytocin (10 IU IM)?

One systematic review¹⁵ has two relevant trials that compared sublingual misoprostol with other uterotonics in less than 200 women. Only one trial on 60 women compared sublingual misoprostol with IV syntometrine. There was no difference in blood loss over 1 l or in any other outcome, although the sample size was not large enough to rule out potentially relevant differences.

Recommendation:

In the context of active management of the third stage of labour :

- Skilled attendants should not offer sublingual misoprostol for prevention of PPH in preference to oxytocin. (Strong recommendation, very low quality evidence)
- Further research is needed to define the role of sublingual misoprostol administration for prevention of PPH.

5. Should rectal misoprostol (600 mcg) be offered to all women by skilled attendants to prevent PPH instead of oxytocin (10 IU IM)?

There is only one study in the systematic review¹⁵ that compared 600 mcg misoprostol administered rectally with 10 IU oxytocin IM in 803 women. This was part of a larger study of 1633 women, which included two sub-groups within the intervention group. One received 10 IU oxytocin IV plus misoprostol 400 mcg rectally and followed by two 100 mcg doses of misoprostol 4 and 8 hours later. The other sub-group received 400 mcg misoprostol rectally followed by two 100 mcg doses 4 and 8 hours later. The control arm received IV oxytocin 10 IU or IV oxytocin 10 IU plus ergometrine.

No deaths were reported in this trial. There were no differences in the blood loss of ≥ 1 l and blood transfusions. The use of additional uterotonics was not reported in this trial. Among the important adverse effects, there was increased shivering (RR 3.02; 95% CI 1.74, 5.23) (NNH 13; 95% CI 9, 24) and temperature of over 38° C (RR 2.74; 95% CI 1.08, 6.93) (NNH 39; 95% CI 21, 336) with rectal misoprostol.

In this systematic review, there were three studies of over 1400 women that used lower doses of rectal misoprostol (400 mcg). 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 and 20 IU) as the comparator while the third used a combination of ergometrine and oxytocin. For the priority outcomes, there was no evidence of difference between treatments except for the use of additional uterotonics, which was higher in the group receiving misoprostol (RR 1.64; 95% CI 1.16, 2.31) (NNT -8; 95% CI -27, -5). However, the small number of subjects included means that small differences would not have been detected. Among the important adverse outcomes, rectal misoprostol 400 mcg was associated with more shivering (RR 2.23; 95% CI 1.74, 2.86) (NNH 4; 95% CI 3, 6).

Rectal administration of drugs may not be acceptable to some women.

Recommendation:

In the context of active management of the third stage of labour:

- Skilled attendants should not offer rectal misoprostol for prevention of PPH in preference to oxytocin. (Strong recommendation, low quality evidence)

Remarks:

This recommendation places a high value on the known benefits of oxytocin and notes the significant uncertainty about whether rectal misoprostol is equivalent. Misoprostol has more adverse effects and a higher purchase cost.

6. Should carboprost 0.25 mg/sulprostone 0.5 mg be offered to all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

There is one systematic review¹⁵ of eight trials comparing injectable prostaglandins with other injectable uterotonics, but no study has compared carboprost/sulprostone with 10 units oxytocin IM.

Overall, there were no differences in priority outcomes in the trials of injectable prostaglandins. However, among the important outcomes, there was more vomiting (RR 10.74, 95% CI 2.06, 53.02) (NNH Max 7; 95% CI 4.2, 16.1), and abdominal pain (RR 5.33; 95% CI 1.4, 20.3) (NNH Min 12; 95% CI 6.9, 53.3) in low-risk women and more diarrhoea in all women (RR 6.65; 95% CI 2.03, 21.85 for low risk and 15; 95% CI 0.89, 254.13 for high risk) (NNH Min 12 (95% CI 6.9, 53.3) for low risk, 6 (95% CI 3.4, 17.9) for high risk) receiving injectable prostaglandins.

Injectable prostaglandins require refrigerated storage and are more expensive than oxytocin.

Recommendation:

In the context of active management of the third stage of labour:

- Skilled attendants should not offer carboprost/sulprostone for prevention of PPH in preference to oxytocin. (Strong recommendation, very low quality evidence)

Remarks:

This recommendation is based on the paucity of the evidence comparing the two treatments and the known effectiveness of oxytocin.

7. In the absence of active management, should uterotonics be used alone for prevention of PPH?

There are two randomized trials included in a systematic review¹² that report the use of oxytocin in the absence of active management and one trial with misoprostol.¹⁷

Oxytocin was used either as IM injection (5 IU) or IV (10 IU) in two trials on 1221 women. The trial of oral misoprostol included 1620 women and compared oral misoprostol 600 mcg given after delivery of the baby and within five minutes of clamping and cutting of the umbilical cord, with placebo in the context of expectant management of the third stage of labour conducted by auxiliary nurse midwives.

There was no significant difference in maternal deaths between the groups. Use of misoprostol was associated with less blood loss ≥ 1 l (RR 0.20; 95% CI 0.04, 0.91) and less blood transfusion (RR 0.14; 95% CI 0.02, 0.85) (NNT 135; 95% CI 70.1, 1674), while the use of oxytocin was associated with less use of additional uterotonic drugs (RR 0.66; 95% CI 0.48, 0.9).

Among important adverse outcomes, oral misoprostol was associated with more shivering (RR 3.01; 95% CI 2.56, 3.55) (NNH 3; 95% CI 2.6, 3.3) and temperature $> 38^{\circ}$ C (RR 3.76; 95% CI 1.81, 7.79).

Recommendation:

- In the absence of active management of the third stage of labour, a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH. (Strong recommendation, moderate quality evidence)

Remarks:

For misoprostol, this recommendation places a high value on the potential benefits of avoiding PPH and ease of administration of an oral drug in settings where other care is not available, but notes there is only one study.

The only trial relevant to this recommendation used 600 mcg of misoprostol. The efficacy of lower doses has not been evaluated. There is still uncertainty about the lowest effective dose and optimal route of administration.

8. When should the cord be clamped to maximize benefits for mother and baby?

One systematic review on cord clamping at term births is available,¹⁸ although the studies included were not randomized controlled trials. In addition, there are three trials on over 500 women that compared early with delayed clamping.¹⁹⁻²¹ Definitions of early clamping varied: "10 seconds after birth", "within the first 15 seconds" and "at 1 minute". Delayed clamping varied from "2 minutes after delivery of the shoulder" to "3 minutes" and "after the cord stopped pulsating". None of the priority outcomes were reported in these trials. There is very little evidence to suggest that the timing of cord clamping has an impact on the incidence of PPH.

However, among the important outcomes, delayed cord clamping was associated with less anaemia in the newborn 24-48 hours after birth (defined by a haematocrit level of >45%) (RR 0.2; 95% CI 0.06, 0.6) (NNT 7, 95% CI 4.5, 20.8). There were no differences in priority or important adverse effects. One study (179 women) reported no significant difference in postpartum haemorrhage associated with timing of cord clamping.²¹

One systematic review on cord clamping in preterm infants is available.²² This includes eight studies covering less than 300 women. The definitions of early clamping included "clamping immediately after birth", "immediate cord clamping < 5 seconds", "at 20 seconds", and "at the attendant's discretion". Delayed clamping included "30 seconds after birth", "45 seconds after birth", "60 seconds after birth" and "60-120 seconds after birth". The position of the infant in these trials also varied. Among the important benefits of delayed clamping reported were less infant anaemia (RR 0.49; 95% CI 0.3, 0.81) (Max NNT 3; 95% CI 1.6, 29.6) and less intraventricular haemorrhage (RR 0.59; 95% CI 0.35, 0.92) (Max NNT -2 (-1.4, -9.8).

A more recent randomized controlled trial²³ on 72 women having preterm births compared cord clamping before 10 seconds with clamping 30-45 seconds after birth with the infant held lower than the introitus at vaginal delivery or below the incision at Caesarean section. Intraventricular haemorrhage (RR 0.28; 95% CI 0.09, 0.9) (NNT -4; 95% CI -2.4, -38.3) and late onset sepsis (RR 0.12; 95% CI 0.03, 0.95) (NNT -5; 95% CI -2.9, -21.6) were less in preterm infants whose cords were clamped late.

Neither the systematic review nor the RCT reported on priority and important maternal outcomes.

To evaluate the haematological benefits of late cord clamping, infants need to be followed to at least two months of age, when a nadir occurs for mean haemoglobin concentration in healthy term infants. Preterm infants are also at risk for development of anaemia in infancy. However, anaemia after the newborn period was not among the outcomes considered in this review.

Note: In physiological management of the third stage, the cord is not clamped immediately.

Recommendation:

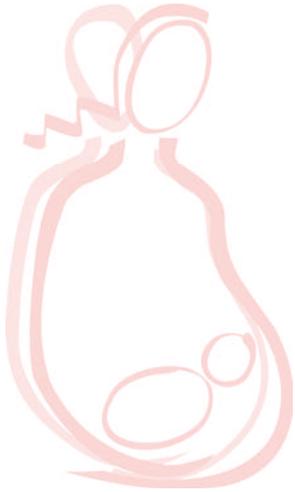
- Because of the benefits to the baby, the cord should not be clamped earlier than is necessary for applying cord traction in the active management of the third stage of labour. (Weak recommendation, low quality evidence)
 - > For the sake of clarity, it is estimated that this will normally take around 3 minutes.
 - > Early clamping may be required if the baby is asphyxiated and requires immediate resuscitation.

9. Should the placenta be delivered by controlled traction in all women?

There is no evidence that directly answers this question. Studies have compared cord drainage with none, cord traction and drainage with cord traction and uterotonic (given various ways).

Recommendation:

Given the current evidence for active management includes cord traction, the panel does not recommend any change in the current practice. Further research is needed. (Strong recommendation, very low quality evidence)



KEY DISCUSSION POINTS

1. What is active management of the third stage of labour?

There are various definitions of active management of the third stage of labour. Based on the review of evidence and discussions related to the individual components of the intervention, the panel agreed that the term "active management of third stage of labour" should include administration of an uterotonic soon after birth of the baby, delayed cord clamping and delivery of the placenta by controlled cord traction, followed by uterine massage.

2. Who should practise active management?

Evidence on active management of the third stage is derived from studies in hospital settings. There is no evidence from studies about the benefits or harmful effects of active management of the third stage of labour by non-skilled attendants. The risks of cord traction in the absence of uterotonics have to be considered. In the absence of evidence, the panel agreed that active management should not be performed by the non-skilled attendants.

3. Who is a skilled attendant?

Definitions of skilled and unskilled attendants were discussed extensively in the context of components of active management of labour. In these recommendations, the panel agreed to use a modification of the definition recommended by WHO, FIGO and ICM in 2004¹⁰, incorporating some parts of an earlier definition agreed by WHO, UNFPA, UNICEF and the World Bank.⁹ This revised definition is broader and considers the variable conditions in many low- and middle-income developing countries. For these recommendations, skilled attendants are health professionals who have been educated and trained to proficiency in skills needed to manage normal labour and delivery, recognize the onset of complications, perform essential interventions, start treatment and supervise the referral of mother and baby for interventions that are beyond their competence or are not possible in the particular setting. Depending on the setting, health-care providers such as auxiliary nurse-midwives, community midwives, village midwives and health visitors may also have acquired appropriate skills, if they have been specially trained.

4. What are beneficial and harmful outcomes?

Beneficial and harmful outcomes were identified prior to the consultation based on the feedback received from an international panel of experts. Outcomes that scored on average between 7 and 9 were considered "critical" while those which scored on average between 4 and 6 were considered "important". Based on these scores, three critical beneficial outcomes – maternal death, blood loss of ≥ 1 l and blood transfusion – were identified as "critical" outcomes. However, the panel meeting in Geneva agreed to refer to "critical outcomes" as "priority outcomes".

5. Use of additional uterotonics in PPH

Additional uterotonics are used on the basis of clinical judgement and will influence the interpretation of data on blood transfusion. If included in priority outcomes, recommendations would be made stronger. The panel agreed to include "use of additional uterotonics" as a priority outcome, thus upgrading it from "important outcome".

6. Choice and dosage of uterotonics

Although oxytocin is recommended as the drug of choice, ergometrine has similar efficacy but more side effects. However, ergometrine is a time-tested drug and should be used when oxytocin is not available. The recommendation that oxytocin should be used by skilled attendants should not prevent attendants who are skilled in administering uterotonics (but not skilled in active management) from using the drug. This is also applicable to misoprostol. However, because of the potential side effects, the panel agreed that training and experience in the use of the drug is mandatory.

Misoprostol has unpleasant side effects that are dose related. A dose of 400 mcg has been shown to be effective in preventing PPH but has not been compared directly with 600 mcg. Most trials have used 600 mcg because the largest trial by WHO has used that dosage. It may be prudent to use the lowest effective dose to avoid undesirable side effects but this has to be determined based on further trials.

7. Study designs providing evidence for these recommendations

The evidence profiles include only randomized trials. Assessment of quality of evidence was also based on study design where randomized trials were given greater weightage. Evidence of harm from observational studies and case reports has also been considered. Fatal adverse effects are generally obtained only from case reports.

8. Timing of cord clamping

Studies on timing of cord clamping have assessed mostly infant outcomes. The beneficial or harmful effects of early or delayed cord clamping on the mother are not known. The early recommendation to clamp the cord as soon as the uterotonic was administered was possibly due to fear that over-transfusion to the baby may occur when the uterus contracts following administration of the uterotonic. Current evidence shows that delayed cord clamping is beneficial for the baby. Therefore, delayed cord clamping must be recommended as a component of active management. Though there is controversy regarding the time at which the cord should be clamped, the panel agreed that by the time the baby is dried and wrapped and passed to the mother to breastfeed, the placenta usually separates and it is time to apply cord traction. The cord may therefore be clamped at that time.

9. Other issue

The panel agreed that these recommendations are applicable to developing and developed countries. Informed decision-making by women should be taken into consideration. The panel agreed to use the term "offer" in preference to "use" in the recommendations.

10. Implementation of recommendations

The panel agreed that these recommendations should be disseminated and implemented through:

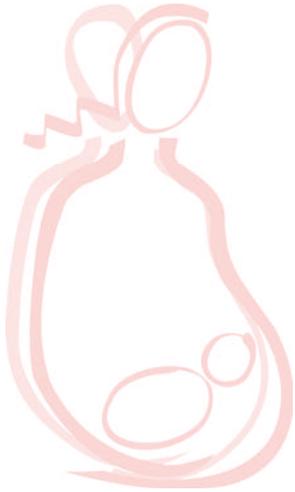
- support from international professional organizations and partner agencies;
- working through regional and country offices (WHO and partners) for changes in policy and regulations;
- working towards including PPH prevention as an indication for use of misoprostol in the WHO essential medicines list;
- working on a press release and co-publication in several journals;
- translation into official languages one by one and disseminating recommendations in the available languages immediately;
- dissemination and implementation of the recommendations by professional associations, partner agencies, institutions and individuals;
- developing a feedback mechanism including obtaining information on dissemination and impact of the recommendations; and
- developing a "PPH virtual network" to monitor evidence and develop a mechanism to determine appropriate time for update/development of new recommendations.

11. Research priorities

According to the GRADE methodology, "low" and "very low" quality evidence indicates situations where future research is likely to have an impact on the recommendation. Therefore recommended practices based on such quality of evidence indicate the need for more research in these areas. However, those may not necessarily be high-priority research questions for various reasons. As a general principle, all research recommended here should be preceded by systematic reviews.

The panel agreed that future research on prevention of PPH should focus on addressing the following (in no order of priority):

- What dose and route of administration of misoprostol are preferred for the best risk-benefit ratio?
 - a. in active management?
 - b. in expectant management?
- Can oxytocin be administered safely by unskilled attendants?
- What is the role of buccal and sublingual use of oxytocin?
- What is the effect of uterotonics on breastfeeding?
- With active management, should misoprostol be used in addition to oxytocin?
- What is the optimal time for cord clamping in the context of physiologic and active management?
- What is the optimum time for oxytocin administration in active management to optimize the timing of cord clamping?
- What is the role of individual components of active management?



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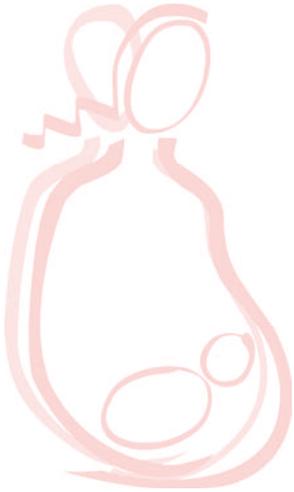
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ANNEXES

Annex 1. Questions for Panel 21 June 2006

A: Active Management

- 1a. Should active management of the third stage of labour be used by skilled providers for all women to prevent PPH?
- 1b. Should active management of the third stage of labour be used for all women to prevent PPH when there is no skilled provider?

B. Choice of uterotonic for use as part of active management

- 1a. Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?
- 1b. Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?
- 2a. Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of oral misoprostol (600 mcg)?
- 2b. Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of oral misoprostol (600 mcg)?
- 3a. Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of sublingual misoprostol (600 mcg)?
- 3b. Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of sublingual misoprostol (600 mcg)?
- 4a. Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of rectal misoprostol (600 mcg)?
- 4b. Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of rectal misoprostol (600 mcg)?
- 5a. Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of carboprost 0.25 mg IM/sulprostone 0.5 mg IM?
- 5b. Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of carboprost 0.25 mg IM/sulprostone 0.5 mg IM?

C. Other questions

- 1a.** Should uterotonics be used alone for all women rather than together with other components (controlled cord traction, early cord clamping, uterine massage) of active management by skilled providers?
- 1b.** Should uterotonics be used alone for all women rather than together with other components (controlled cord traction, early cord clamping, uterine massage) of active management by non-skilled providers?
- 2a.** Should the cord be clamped early (within 1 minute) or later (after 1 minute) for all babies during active management of the third stage of labour by skilled providers?
- 2b.** Should the cord be clamped early (within 1 minute) or later (after 1 minute) for all babies during active management of the third stage of labour by non-skilled providers?
- 2c.** Should the cord be clamped early (within 1 minute) or later (after 1 minute) for preterm babies during active management of the third stage of labour by skilled providers?
- 2d.** Should the cord be clamped early (within 1 minute) or later (after 1 minute) for preterm babies during active management of the third stage of labour by non-skilled providers?
- 3a.** Should the placenta be delivered in all women by skilled providers through controlled cord traction with or without other components of active management?
- 3b.** Should the placenta be delivered in all women by non-skilled providers through controlled cord traction with or without other components of active management?

Annex 2. List of outcomes

Recommendations for the Prevention of Postpartum Haemorrhage Provisional list of outcomes for inclusion

Please enter your initials in the box

**Do not attempt to rank the outcomes
– score each one individually from 1– 9.**

| Score | Relative importance |
|-------|----------------------------|
| 1–3 | Not important |
| 4–6 | Important but not critical |
| 7–9 | Critical |

What are the most important beneficial outcomes of interventions to prevent postpartum haemorrhage?

| Outcome | Relative Importance |
|---|---------------------|
| Fewer maternal deaths | |
| Fewer admissions to intensive care unit | |
| Less blood loss \geq 500 ml | |
| Less blood loss \geq 1000 ml | |
| Less use of blood transfusion | |
| Less use of additional uterotonics | |
| Decreased mean blood loss | |
| Less postpartum anaemia | |
| Earlier establishment of breastfeeding | |
| Less anaemia in infancy | |
| Other (please specify) | |

What are the most significant risks in interventions to prevent postpartum haemorrhage?

| Outcome | Relative Importance |
|-------------------------------------|---------------------|
| Any side effect of intervention | |
| Any side effect requiring treatment | |
| Nausea | |
| Vomiting | |
| Diarrhoea | |
| Headache | |
| Abdominal pain | |
| High blood pressure | |
| Shivering | |
| Temp $>$ 38° C | |
| Temp $>$ 40° C | |
| Maternal death | |
| Anaemia in infancy | |
| Other (please specify) | |

Annex 3. Methods used for developing guidelines

Preparation of the background documentation

Summaries of the best available evidence were prepared to answer nine primary questions regarding the treatment and prophylaxis of postpartum haemorrhage:

Should active management of the third stage of labour be used by skilled providers for all women to prevent postpartum haemorrhage? Should active management of the third stage be used by non-skilled providers to prevent PPH?

Should oxytocin (10 IU IM) or ergometrine/methylergometrine (0.2 mg IM) be used for all women by skilled providers to prevent PPH? Should non-skilled providers use either drug?

Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of oral misoprostol (600 mcg)? Should either drug be used by non-skilled providers?

Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of sublingual misoprostol (600 mcg)? Should either drug be used by non-skilled providers?

Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of rectal misoprostol (600 mcg)? Should either drug be used by non-skilled providers?

Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of carboprost 0.25 mg/sulprostone 0.5 mg)? Should either drug be used by non-skilled providers?

In the absence of active management, should uterotonics be used alone for prevention of PPH?

When should the cord be clamped to maximize benefits for mother and baby?

Should the placenta be delivered in all women by controlled traction?

Identification of important outcomes

A list of potential outcomes to be considered by the panel was initially developed by the WHO team and sent electronically to an international panel comprising midwives, obstetricians, neonatologists, researchers and programme experts. Members of the panel independently scored the relative importance of each outcome from 1–9, where 7–9 indicated the outcome was critical for a decision, 4–6 indicated it was important and 1–3 indicated it was not important. The average of scores for each outcome was used for determining the relative importance of each outcome. The panel was also asked to identify additional important outcomes not included in the list of potential outcomes identified by the team that prepared the background documentation.

Search strategy

The search strategy aimed to identify for systematic reviews and recent randomized trials for the prevention of PPH.

For systematic reviews, the Cochrane Library (Issue 3, 2006) was searched for records with the following terms

- labour
- third stage
- active management
- oxytocin
- ergometrine
- methylergometrine
- syntometrine
- misoprostol
- carboprost
- sulprostone
- uterotonics
- cord clamping
- cord traction

PubMed-Medline, Embase, Lilacs and IMEMR were also searched for records using the following terms

- labour OR labor
- third stage
- active management
- oxytocin
- ergometrine
- methylergometrine
- syntometrine
- misoprostol
- carboprost
- sulprostone
- uterotonics
- cord clamp*
- cord traction
- skilled providers
- non-skilled providers

Limits used were

- a. Type of studies
 - Randomized controlled trial
 - Meta-analysis
 - Reviews

- b. Time limits

Whenever a SR from the Cochrane Library was identified, the publication year of the more recent study included in the SR was used as a time limit. No time limit was used when a SR from the Cochrane was not identified.

Draft summaries of the evidence were sent to the members of the Technical Consultation Group prior to the meeting and they were asked to identify any important evidence that had not been included.

Selection criteria, data collection and judgements

Systematic reviews were used to summarize the evidence from randomized trials related to interventions for prevention of PPH. Titles identified from the searches for reviews and assessed for the quality of relevant reviews were screened by two reviewers using checklists.^{24,26} For each question, data were extracted for all of the outcomes that were judged to be important, beginning with the most recent review of good quality and supplementing that with additional data from other good quality reviews that addressed the same question.

Evidence profiles were created using the GRADE approach.²⁷ Using this approach, assessments of the quality of evidence for each important outcome take into account the study design, limitations of the studies, consistency of the evidence across studies, the directness of the evidence and the precision of the estimate. A liberal approach to assessment of study limitations was taken. Three main criteria were used for assessing trial limitations: concealment of allocation, blinding and follow-up. If most of the evidence for an outcome (based on the weight given to each study in the meta-analysis) came from trials that did not have serious limitations, the overall assessment for that outcome was that there were no important limitations.

If data were available as continuous outcomes, such as mean blood loss, absolute differences were presented as weighted mean difference (WMD). All estimates of effect size were expressed as relative risk if it was possible to calculate it from the data provided, with absolute risk estimates included where appropriate. In order to provide the panel with a broad and informative set of measures of effect, the NNTs and NNHs were calculated for each outcome. In systematic reviews, for each outcome, the lowest and highest baseline risks were extrapolated from control groups across the studies. The minimum and maximum NNTs and NNHs were therefore calculated, providing a range of values for these measures.

One reviewer extracted data from the reviews and prepared drafts of the evidence profiles with detailed footnotes explaining the judgements that were made. These were checked by at least one other member of the team and discussed with the team that prepared the background documentation.

All of the evidence profiles and additional tables were sent to the members of the Technical Consultation Group for review prior to the technical consultation.

Summary of findings tables

The key findings for each question were summarized in tables with the most important findings from the systematic reviews together with additional information from randomized clinical trials.

Grading process

Table 2 : GRADE quality assessment criteria

| Quality of evidence | Study design | Lower if * | Higher if * |
|---------------------|---------------------|---|--|
| High | Randomized trial | Study quality: -1 Serious limitations -2 Very serious limitations | Strong association: +1 Strong, no plausible confounders, consistent and direct evidence** |
| Moderate | | | |
| Low | Observational study | -1 Important inconsistency Directness: -1 Some uncertainty -2 Major uncertainty -1 Sparse data -1 High probability of Reporting bias | +2 Very strong, no major threats to validity and direct evidence*** +1 Evidence of a Dose response gradient +1 All plausible confounders would have reduced the effect |
| Very low | Any other evidence | | |

* 1 = move up or down one grade (for example from high to intermediate)

2 = move up or down two grades (for example from high to low)

** A statistically significant relative risk of >2 (< 0.5), based on consistent evidence from two or more observational studies, with no plausible confounders.

*** A statistically significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity.

Table 3 : Deciding on strength of a recommendation

| Issue | Recommended process |
|---|---|
| Quality of evidence | |
| 1. Quality of evidence | Strong recommendations usually require higher quality evidence for all the critical outcomes. The lower the quality of evidence the less likely is a strong recommendation. |
| Balance of benefits and downsides | |
| 2. Relative importance of the outcomes a. benefits of therapy b. harm of treatment c. burdens of therapy | Seek evidence about the relative values that patients place on outcomes and the actual value they place on them (critical; important but not critical; not important). Seek evidence about variability in preferences and values in patients and other stakeholders. It should be upfront that the relative importance of the outcomes should be included in the considerations before you make recommendations. If values and preferences vary widely a strong recommendation becomes less likely. |
| 3. Baseline risks of outcomes a. benefits of therapy b. harm of treatments c. burdens of therapy | Consider the baseline risk for an outcome. Is the baseline risk going to make a difference? If yes, then consider making separate recommendations for different populations. The higher the baseline risk, the higher the magnitude of benefit and the more likely the recommendation is strong. |
| 4. Magnitude of relative risk a. benefits (reduction in RR) b. harms (increase in RR) c. burden | Consider the relative magnitude of the net effect. Large relative effects will lead to a higher likelihood of a strong recommendation if the balance of benefit, harms and burden go in the same direction. If they go in opposite directions and the relative magnitude of effects is large (large benefits coming with large risk of adverse effects), the recommendation is more likely to be weak. |
| 5. Absolute magnitude of the effect a. benefits b. harms c. burden | Large absolute effects are more likely to lead to strong recommendation. |
| 6. Precision of the estimates of the effects a. benefits of therapy b. harms of treatments c. burdens of therapy | The greater the precision the more likely the recommendation is strong. |
| 7. Factors that modify effects in specific settings/Local factors that may affect translating of the evidence into practice | The more similar the setting and patients for which one is making a recommendation to the setting and patients generating the evidence, the more likely the recommendation is strong. |
| 8. Costs | Consider that important benefits should come at a reasonable cost. The higher the incremental cost, all else being equal, the less likely that the recommendation in favour of an intervention is strong. |

Table 4 : Checklist for developing and grading recommendations

- Define the population, intervention and alternative, and the relevant outcomes.
- Summarize the relevant evidence (relying on systematic reviews).
- If randomized trials available, start by assuming high quality; if well-done observational studies are available assume low quality, but then check for:
 - > serious methodological limitations (lack of blinding, concealment, high loss to follow-up, stopped early);
 - > indirectness in population, intervention, or outcome (use of surrogates);
 - > inconsistency in results;
 - > imprecision in estimates.
- Grade RCTs down from high to moderate, low or very low depending on limitations or observational studies to very low.
- If no randomized trials are available but well-done observational studies are available (including indirectly relevant trials and well-done observational studies), start by assuming low quality, but then check for:
 - > large or very large treatment effect;
 - > all plausible confounders would diminish effect of intervention;
 - > dose-response gradient.
- Grade up to moderate or even high depending on special strengths or weaknesses.
- Studies starting at very low will not be upgraded. Observational studies with limitations will not be upgraded. Only observational studies with no threats to validity can be upgraded.
- Decide on best estimates of benefits, harms, burden and costs for relevant population.
- Decide on whether the benefits are, overall, worth the harms, burden and costs for relevant population and decide how clear and precise this balance is.

Strength of recommendations

The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Desirable effects can include beneficial health outcomes, less burden and savings. Undesirable effects can include harms, more burden and extra costs. Burdens are the demands of adhering to a recommendation that patients or caregivers (e.g. family) may dislike, such as having to undergo more frequent tests or opting for a treatment that may require a longer time for recovery.

Although the degree of confidence is a continuum, two categories are used: strong and weak.

A **strong recommendation** is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

A **weak recommendation** is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. Reasons for not being confident can include:

- absence of high quality evidence;
- presence of imprecise estimates of benefits or harms;
- uncertainty or variation in how different individuals value the outcomes;
- small benefits;
- the benefits may not be worth the costs (including the costs of implementing the recommendation).

Despite the lack of a precise threshold for going from a strong to a weak recommendation, the presence of important concerns about one or more of the above factors make a weak recommendation more likely. Panels should consider all of these factors and make the reasons for their judgements explicit.

Recommendations should specify the perspective that is taken (e.g. individual patient, health-care system or society) and which outcomes were considered (including, if any, costs).

Examples of implications of a strong recommendation are:

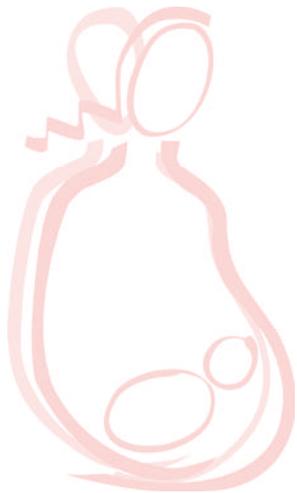
- **For patients:** Most people in your situation would want the recommended course of action and only a small proportion would not.
- **For clinicians:** Most patients should receive the recommended course of action. Adherence to this recommendation is a reasonable measure of good quality care.
- **For policy-makers:** The recommendation can be adapted as a policy in most situations. Quality initiatives could use this recommendation to measure variations in quality.

Examples of implications of a weak recommendation are:

- **For patients:** The majority of people in your situation would want the recommended course of action, but many would not.
- **For clinicians:** Be prepared to help patients to make a decision that is consistent with their own values.
- **For policy-makers:** There is a need for substantial debate and involvement of stakeholders.

Annex 4.
Evidence Profiles

Available on accompanying compact disk



Annex 5. List of participants

WHO Technical Consultation on Prevention of Postpartum Haemorrhage

Château de Penthes, Geneva, Switzerland
18–20 October 2006

External Technical Advisers

Prof. HANY ABDEL-ALEEM

Department of Obstetrics & Gynaecology
Assiut University Hospital
Assiut
Egypt
Tel: +20-88 2333355
Fax: +20-88 2333327
E-mail: aleemh@yahoo.com

Ms DEBORAH ARMBRUSTER

PATH
1800 K St. NW, Suite 800
Washington, DC 20006
United States of America
Tel: +1-202 8220033
Fax: +1-202 4571466
E-mail: darmbruster@path.org

Prof. S. ARULKUMARAN

Head
Division of Obstetrics & Gynaecology
St George's University of London
Cranmer Terrace
London SW17 0RE
United Kingdom
Tel: +44-20 8725 5956
Fax: +44-20 7928 7099
E-mail: sarulkum@sgul.ac.uk

Dr VITTORIO BASEVI

Centre for the Evaluation of Effectiveness
of Health Care (CeVEAS)
Azienda USL di Modena
Viale L.A. Muratori, 201
41100 Modena
Italy
Tel: +39-059 435200
Fax: +39-059 435222
E-mail: v.basevi@ausl.mo.it

Dr M. BOULVAIN*

Maternité
Hôpitaux Universitaires de Genève (HUG)
Case postale
1211 Geneva 14
Switzerland
Tel: +41-22 3724317
Fax: +41-22 382 4424
E-mail: Michel.Boulvain@hcuge.ch

Dr GUILLERMO CARROLI

Centro Rosarino de Estudios Perinatales (CREP)
Pueyrredon 985
Rosario (2000), Santa Fe
Argentina
Tel: +54-341 4472625
Fax: +54-341 4483887 (phonefax)
E-mail: gcarroli@crep.com.ar

Prof. BLAMI DAO

Institut supérieur des Sciences de la Santé
Université polytechnique de Bobo-Dioulasso
CHU Souro Sanou
01BP676 Bobo-Dioulasso
Burkina Faso
Tel: +226-78802444
Fax: +226-20972693
E-mail: bdao@fasonet.bf

Prof. RICHARD J. DERMAN

University of Missouri-Kansas City
School of Medicine
M5-105 Medical School
2411 Holmes Street
Kansas City, MO 64108-2792
United States of America
Tel: +1-816 2351628
Fax: +1-816 2356576
E-mail: dermanr@umkc.edu

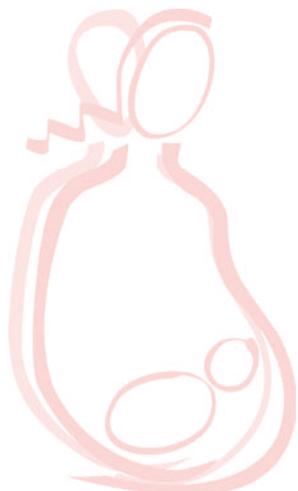
Ms ATF GHERISSI

Teacher, Midwife and Researcher-Consultant
9, rue Isfahane
Notre Dame, Tunis 1082
Tunisia
Tel: +216-97 997 224
Fax: +216-71 844 291 (home)
E-mail: atfgherissi@yahoo.fr

KATHY HERSCHDERFER

International Confederation of Midwives
Eisenhowerlaan 138
2517 KN The Hague
Netherlands
Tel: +31-70 3060520
Fax: +31-70 3555651
E-mail: K.Herschderfer@internationalmidwives.org

* unable to attend



Prof. JACKIE HO
University of Kuala Lumpur
Royal College of Medicine Perak
Greentown 30450
Ipoh
Malaysia
Tel: +60-5 2432635
Fax: +60-5 2432636
E-mail: jho@pc.jaring.my and
jackie@perakmed.edu.my

Prof. JUSTUS HOFMEYR
East London Hospital Complex
Frere Maternity Hospital
Private Bag X9047
East London 5200
South Africa
Tel: +27-43 7082134
Fax: +27-86 6929822
E-mail: gjh@global.co.za

Prof. TINA LAVENDER
Department of Midwifery Studies
University of Central Lancashire
Preston PR1 2HE
United Kingdom
Tel: +44-151 7024107
07764762129 (mobile)
Fax: +44-151 7024076
E-mail: tinalav@yahoo.co.uk

Ms LAURENSIA LAWINTONO
STIK St. Carolus
Jl. Salemba Raya No. 41
Jakarta Pusat 10440
Indonesia
Tel: +62-21 3162193 - office
+62-21 6400879 - home
Fax: +62-21 3162193 - office
+62-21 6409502 - home
E-mail: lawintonol@yahoo.com

Dr JUDITH S. MERCER
Clinical Professor
University of Rhode Island
College of Nursing
76 Woodbury Road
Cranston, RI 02905
United States of America
Tel: +1-401 7806750
Fax: +1-401 8742870

Prof. JAMES NEILSON
Head of School of Reproductive &
Developmental Medicine
University of Liverpool
Liverpool Women's Hospital
Crown Street
Liverpool L8 7SS
United Kingdom
Tel: +44-151 7024100
E-mail: jneilson@liverpool.ac.uk

Dr PIUS CHANCHU NGASSA
Consultant Obstetrician and Gynaecologist
University Teaching Hospital
Centre hospitalier universitaire (CHU)
Yaoundé
Cameroon
Tel: +237 (752) 05 15 (mobile)
Phone/fax: +237 (221) 77 20 (home)
E-mail: ngassap@iccnnet.cm or
piusngassa2004@yahoo.co.uk

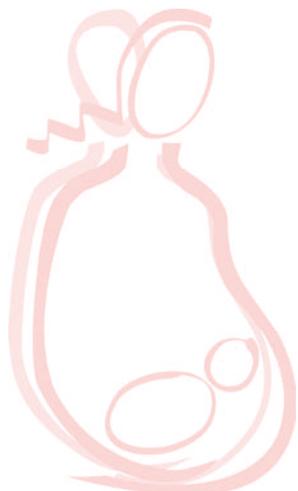
Dr NGUYEN DUC HINH
Director adjoint of NHO
National Hospital for Obstetrics
and Gynecology (NHOG)
43 Trang Thi Street
Hanoi
Viet Nam
Tel: +84-4 9346745
+84-90 3415496 (mobile)
Fax: +84-4 8254638
E-mail: duc_hinh@yahoo.com

Dr SILVIA PREGNO
University of Bologna Department of Public Health
CeVEAS
Centre for the Evaluation of Effectiveness
of Health Care
Azienda USL di Modena
Viale L.A. Muratori, 201
41100 Modena
Italy
Tel: +39-059 435271
Fax: +39-059 435222
E-mail: s.pregno@ausl.mo.it

ZAHIDA QURESHI
Senior Lecturer
Department of Obstetrics & Gynaecology
University of Nairobi
Kenyatta National Hospital
P.O. Box 19676-00202
Nairobi
Kenya
Tel: +254-20 2726360
+254-733 605140 (mobile)
Fax: +254-20 2717706
E-mail: zqureshi@nbnet.co.ke

Dr HARSHAD SANGHVI
1615 Thames Street, Suite 200
Baltimore, MD 21231-3492
United States of America
Tel: +1-410 5371103/5371919
+1-410 3409417 (mobile)
Fax: +1-410 5371479
E-mail: hsanghvi@jhpiego.net

Prof. LAKSHMI SESHADRI
Department of Obstetrics & Gynaecology
Christian Medical College
Vellore 632004
India
Tel: +91-416 2283397/98
Fax: +91-416 2232035/2222103
E-mail: seshadri.lakshmi@gmail.com



Observers

Prof. JIM DORNAN

Senior Vice President & International Officer
Royal College of Obstetricians and Gynaecologists
27 Sussex Place, Regent's Park
London NW1 4RG
United Kingdom
Tel: +44-20 7772 6223
Fax: +44-20 7772 6359
E-mail: jdorman@rcog.org.uk

Ms MARY ELLEN STANTON

Senior Reproductive Health Adviser
U.S. Agency for International Development
GH/HIDN/MCH RRB 3.07-052
1300 Pennsylvania Avenue, NW
Washington, DC 20523
United States of America
Tel: +1-202 712 4208
Fax: +1-202 216 3016
E-mail: MStanton@usaid.gov

Ms LINDA WRIGHT *

National Institute of Child Health and
Human Development (NICHD)
Center for Research for Mothers and Children (CRMC)
6100 Executive Blvd
Room 4B05J, MSC 7510
Bethesda, MD 20892-7510
United States of America
For FedEx use: Rockville, MD 20852
Tel: +1-301 4020830
Fax: +1-301 4807773
E-mail: WrightL@mail.nih.gov

Dr DOYIN OLUWOLE *

Director, Africa Health 2010
Academy for Educational Development
1875 Connecticut Avenue, NW
Washington, DC 2009
United States of America
Tel: +1-202-884-8035
Fax: +1-202-884-8701/8447
E-mail: doluwole@smtp.aed.org

Mr KUL CHANDRA GAUTAM *

Deputy Executive Director
United Nations Children's Fund (UNICEF)
UNICEF House
3 United Nations Plaza
New York, NY 10017
United States of America
Tel: +1-212 326 7006
Fax: +1-212 326 7758
E-mail: kgautam@unicef.org

Mr KUNIO WAKI *

Deputy Executive Director
United Nations Population Fund (UNFPA)
220 East 42nd St.
New York, NY 10017
United States of America
Tel: +1-212 297 5114
Fax: +1-212 370 0201
E-mail: waki@unfpa.org

Dr JACQUES BAUDOY *

Director, HNP
The World Bank
1818 H Street, NW
Washington, DC 20433 USA
United States of America
Tel: +1-202 473 2535
Fax: +1-202 522 3234
E-mail: jbaudouy@worldbank.org

Dr VINCENT FAUVEAU

Senior Advisor, Maternal Health
UNFPA
Geneva Executive Centre
Chemin des Anémones 11
1219 Châtelaine
Switzerland
Tel: +41-22 917 8574
Fax: +41-22 917 8016
E-mail: fauveau@unfpa.org

WHO/HQ (Secretariat)

Making Pregnancy Safer (MPS)

Monir Islam, Director

Tel: +41-22 7915509
E-mail: islamm@who.int

Matthews Mathai

Tel: +41-22 7913210
E-mail: mathaim@who.int

Margareta Larsson

Tel: +41-22 7914528
E-mail: larssonm@who.int

Jelka Zupan

Tel: +41-22 7914221
E-mail: zupanj@who.int

Department of Reproductive Health and Research (RHR)

Metin Gulmezoglu

Tel: +41-22 7913417
E-mail: gulmezoglu@who.int

Medicines Policy and Standards (PSM)

Suzanne Hill

Tel: +41-22 7913522
Email: hills@who.int

Other members of the international panel included:

HS Ba'aqeel, S Bergstrom, E Buchmann, G Cecatti, N Chandiok, KJ Coyaji, C Crowther, L DeBernis, K Kapesa, P Lumbiganon, S McDonald, S Mittal, NTN Ngoc, P Okong, VP Paily, RC Pattinson, N Prata, M Purwar, E Quaye-Kumah, G Rana, U Rehnstrom, K Rogo, D Sherratt, J Smith, TS Thach, C Turan and B Winikoff.

* unable to attend



**World Health
Organization**

Department of Making Pregnancy Safer • Family and Community Health • World Health Organization
Avenue Appia, 20 • Geneva 27, Switzerland
Tel: +41 22 791 4136 / 3346 • Fax: +41 22 791 5853
E-mail: MPSinfo@who.int • www.who.int/making_pregnancy_safer/en/

Annexe 4

GRADE Evidence Profile 1

QUESTION: Should active management of the third stage of labour be used by skilled providers for all women to prevent postpartum hemorrhage (PPH)?

Patient or population: Women expected to deliver vaginally

Settings: Studies undertaken in the UK, Ireland, United Arab Emirates, South Africa, Nigeria, New Zealand, the USA, Nicaragua. Hospital settings.

Systematic reviews:

- a. (PW 00) Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. Cochrane Database of Systematic Reviews 2000, Issue 3. Art. No.: CD000007. DOI: 10.1002/14651858.CD000007. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|-----------------------------|------------|---|--|
| Abu Dhabi 1997 (Ad 97) | 1648 | Active management of the third stage of labour. 10 IU oxytocin intramuscularly was the routine oxytocic for active management. | No oxytocin before delivery of placenta (but 10 IU oxytocin in 500ml saline given IV after delivery of placenta); cord clamped and cut immediately after delivery of baby; no controlled cord traction after signs of separation and then every 2-3 minutes if unsuccessful. |
| Brighton 1993 (Br 93) | 193 | Active management of the third stage of labour (further information not provided). | Physiological management of the third stage of labour |
| Bristol 1988 (Br 88) | 1695 | Active management of the third stage of labour. Syntometrine was the oxytocic of choice. | Physiological management of the third stage of labour |
| Dublin 1990 (Du 90) | 1429 | Active management of the third stage of labour. IV ergometrine was the oxytocic of choice. | Physiological management of the third stage of labour |
| Hinchingbrooke 1998 (Hi 98) | 1512 | Active management of the third stage of labour. IM Syntometrine was the oxytocic of choice. | Physiological management of the third stage of labour |

RCTs:

- b. A systematic search was performed for RCTs published after the last update of the SR; no RCT was retrieved.

QUESTION: Should active management of the third stage of labour be used for all women to prevent PPH when there is no skilled provider?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the footnotes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|--|----------------------------|--|----------------------|---------------------|---------------------|--|-----------------------|---|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Active management | Standard procedures | Baseline Risk (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 8.5 |
| Admission to intensive care unit | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.4 |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 4 PW 00 ¹ Ad 97 Br 88 Du 90 Hi 98 | RCT | serious limitation ^{2,3,17} -1 | no important inconsistency | some uncertainty about directness ^{4,5} -1 | none | 3126 | 3158 | min 8.3% (6.3, 10.3) max 17.9% (15.3, 20.5) | 0.38 (0.32, 0.46) | min 8 (6.7, 11.2) max 16 (11.7, 24.7) | low quality ++oo | 6.3 |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 4 PW 00 ¹ Ad 97 Br 88 Du 90 Hi 98 | RCT | serious limitation ^{2,3,17} -1 | no important inconsistency | some uncertainty about directness ^{4,5} -1 | none | 3126 | 3158 | min 1.5% (0.6-2.4) max 3.2% (2.0-4.4) | 0.33 (0.21, 0.51) | min 41 (26.5, 90.1) max 73 (43.3, 225.5) | low quality ++oo | 7.7 |
| Need for blood transfusion | | | | | | | | | | | | |
| 5 PW 00 ¹ Ad 97 Br 93 Br 88 Du 90 Hi 98 | RCT | minor limitation ^{3,8} | no important inconsistency | some uncertainty about directness ⁷ -1 | none | 3229 | 3248 | 5.7% (4.1-7.2) ¹⁶ | 0.34 (0.22, 0.53) | 28 (18.7, 59,1) ¹⁶ | moderate quality +++o | 7.8 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|--|----------------------------|--|----------------------|---------------------|---------------------|--|--------------------------------------|--|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Active management | Standard procedures | Baseline Risk (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Additional (therapeutic) uterotonics | | | | | | | | | | | | |
| 5 PW 001 Ad 97 Br 93 Br 88 Du 90 Hi 98 | RCT | serious limitation ^{2,3,17} -2 | no important inconsistency | some uncertainty about directness ^{11,12} -1 | none | 3229 | 3248 | min 5.1% (3.6, 6.6) max 29.7% (26.6, 32.8%) | 0.20 (0.17, 0.25) | min 4 (3.7, 5.0) max 35.5 (21.6, 100.3) | very low quality +ooo | 5.9 |
| Decreased mean blood loss (measured in ml) | | | | | | | | | | | | |
| 2 PW 001 Du 90 Hi 98 | RCT | minor limitation ³ | no important inconsistency | some uncertainty about directness ^{13,14} -1 | - | 1453 | 1488 | - | WMD (fixed) - 79.33 (-94.29, -64.37) | - | moderate quality +++o | 5.6 |
| Postpartum anaemia (Maternal Hb <9 g/dl 24 - 48 hours post partum) | | | | | | | | | | | | |
| 4 PW 001 Br 93 Br 88 Du 90 Hi 98 | RCT | minor limitation ^{3,8} | no important inconsistency | some uncertainty about directness ^{4,5} -1 | none | 2108 | 2147 | min 1.2% (0.4, 2.1) max 9.5% (7.3, 11.0) | 0.40 (0.29, 0.55) | min NS max 16 (11.3, 26.1) | moderate quality +++o | 6.1 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|----------------------------|--|----------------------------|--|----------------------|---------------------|---------------------|--|-----------------------|-------------|--|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Active management | Standard procedures | Baseline Risk (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Establishment of breastfeeding (BF) | | | | | | | | | | | | |
| 2 PW 001 Br 88 Hi 98 | RCT not BF at discharge | serious limitation ^{3,17} -2 | no important inconsistency | some uncertainty about directness ^{4,5} -1 | none | 1562 | 1580 | min 25.6% (22.6, 28.5) max 25.8% (22.7, 29.0) | 0.92 (0.82, 1.04) | NS | very low quality +ooo moderate quality++ +o | 5.1 |
| 1 PW 001 Hi 98 | RCT not BF at 6 weeks | minor limitation ³ | one trial only | some uncertainty about directness ¹⁵ -1 | none | 716 | 731 | 46.4% (42.2, 49.9) | 0.93 (0.83, 1.04) | NS | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.8 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|---|--|---|---|---------------------------------|---------------------|---------------------|---|-----------------------|---|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Active management | Standard procedures | Baseline Risk (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms | | | | | | | | | | | | |
| Side effect requiring treatment | | | | | | | | | | | | |
| 1 PW 00 ¹ Hi 98 | RCT iron tablets during the puerperium | minor limitation ³ | one trial only | some uncertainty about directness ¹⁵ -1 | none | 716 | 731 | 28% (24.8, 31.3) | 0.60 (0.49, 0.74) | -9 (-14.5, -6.5) | moderate quality +++o | 6.2 |
| Manual removal of placenta | | | | | | | | | | | | |
| 5 PW 00 ¹ Ad 97 Br 93 Br 88 Du 90 Hi 98 | RCT | serious limitation ^{3,17} -2 | major inconsistency ¹⁸ -1 | some uncertainty about directness ^{4,5} -1 | imprecise and sparse data -1 | 3229 | 3248 | min 0.14% (-0.13, 0.41) max 2.59% (1.53, 3.66) | 1.21 (0.82, 1.78) | min NS max 39 (26.4, 75.2) | very low quality oooo | 6.2 |
| Nausea | | | | | | | | | | | | |
| 3 PW 00 ¹ Br 88 Du 90 Hi 98 | RCT | serious limitation ^{3,17} -2 | no important inconsistency | some uncertainty about directness ^{9,10} -1 | none | 1680 | 1727 | min 8.77% (3.56, 13.99) max 11.50% (9.21, 13.78) | 1.83 (1.51, 2.23) | min 7 (4.0, 24.4) max 18 (11.8, 36.0) | very low quality +ooo | 4.0 |
| Vomiting | | | | | | | | | | | | |
| 3 PW 00 ¹ Br 88 Du 90 Hi 98 | RCT | serious limitation ^{3,17} -2 | no important inconsistency | some uncertainty about directness ^{9,10} -1 | none | 1680 | 1727 | min 1.75 (-0.67, 4.18) max 6.48 (4.82, 8.13) | 2.19 (1.68, 2.86) | min 10 (5.8, 37.9) max 18 (12.0, 35.4) | very low quality +ooo | 4.7 |
| Diarrhoea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.6 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|---------------------|---------------------|-----------------------|-----------------------|-------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Active management | Standard procedures | Baseline Risk (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms | | | | | | | | | | | | |
| Temp >40 °C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.8 |
| Maternal death | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.7 |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.6 |

Notes:

- The trials in this review were not designed to evaluate the relative benefits of the individual components of active or expectant management. Abu Dhabi 1997 cord clamped and cut immediately in both groups.
- Clinical estimation of blood loss in all studies: the lack of objective indices of blood loss is (potential) bias in unblinded trials.
- Hinchingbrooke 1998 did not use allocation concealment.
- The oxytocic in active management was ergometrine given intravenously in one trial; oxytocin given intramuscularly in one trial; a mixture of oxytocin and ergometrine given intramuscularly in the other two trials.
- Abu Dhabi 1997 (1648 women) and Bristol 1988 (1695 women), all women (3343 women); Dublin 1990 (1429 women) and Hinchingbrooke 1998 (1512 women) only low- risk women (2941 women). Low-risk women amount to 39.6%.
- Unclear whether this is actually a randomized controlled trial. Indirect outcome: "a variation of >3% in the reference haematocrit, which would represent a blood loss of >500 cc during labour".
- Ergometrine 0.2 IM + oxytocin 20 mU/ min IV.
- Brighton 2003 no prior power calculation performed; post randomization withdrawals; unclear allocation concealment.
- Bristol 1988 (1695 women) all women; Dublin 1990 (1429 women) and Hinchingbrooke 1998 (1512 women) only low risk women (2941 women). Low risk women amount to 63,4%
- The oxytocic in active management was ergometrine given intravenously in one trial; a mixture of oxytocin and ergometrine was given intramuscularly in the other two trials
- The oxytocic in active management was ergometrine given intravenously in one trial; oxytocin given intramuscularly in one trial; a mixture of oxytocin and ergometrine given intramuscularly in the other three trials
- Abu Dhabi 1997 (1648 women) and Bristol 1988 (1695 women) all women (3343 women); Brighton 1993 (193 women); Dublin 1990 (1429 women) and Hinchingbrooke 1998 (1512 women) only low-risk women (3134 women). Low-risk women amount to 48,3%.
- The oxytocic in active management was ergometrine given intravenously in one trial; a mixture of oxytocin and ergometrine was given intramuscularly in the other trial.
- Dublin 1990 (1429 women) and Hinchingbrooke 1998 (1512 women) only low-risk women (2941 women).
- Not used allocation concealment; only low-risk women.
- Baseline risk and NNT calculated for the study with larger sample size (Bristol 1988, 63.7% of total weight within the SR).
- In this outcome, the lack of information about blinding of outcome's measures is (potential) bias.
- The inconsistency can be explained by heterogeneity of study's population. A significant statistically modification of the direction of the effect is detected in the low-risk subgroup [relative risk: 2.05 (1.20, 3.51)].

Summary of findings¹

Scenario: Should active management of the third stage of labour be used for all women to prevent PPH?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|---|-------------|--|-------------------------|---|--------------------------|--------------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 4 Ad 97 Br 88 Du 90 Hi 98 | 6284 | min 1.5% (0.6-2.4) max 3.2% (2.0-4.4) | 0.33 (0.21, 0.51) | min 41 (26.5, 90.1) max 73 (43.3, 225.5) | low quality ++oo | 1,2,3,4,5,17 | - |
| | Need for blood transfusion | 5 Ad 97 Br 93 Br 88 Du 90 Hi 98 | 6477 | 5.7% (4.1-7.2) | 0.34 (0.22, 0.53) | 28 (18.7, 59.1) | moderate quality +++o | 1,3,7,8,16 | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

1. The trials in this review were not designed to evaluate the relative benefits of the individual components of active or expectant management. Abu Dhabi 1997 cord clamped and cut immediately in both groups.
2. Clinical estimation of blood loss in all studies: the lack of objective indices of blood loss is (potential) bias in unblinded trials.
3. Hinchingsbrooke 1998 did not use allocation concealment.
4. The oxytocic in active management was ergometrine given intravenously in one trial; oxytocin given intramuscularly in one trial; a mixture of oxytocin and ergometrine given intramuscularly in the other two trials.
5. Abu Dhabi 1997 (1648 women) and Bristol 1988 (1695 women) all women (3343 women); Dublin 1990 (1429 women) and Hinchingsbrooke 1998 (1512 women) only low- risk women (2941 women). Low-risk women amount 39,6%.
7. Ergometrine 0.2 IM + oxytocin 20 mU/ min EV.
8. Brighton 2003 no prior power calculation performed; post randomation withdrawals; unclear allocation concealment.
16. Baseline risk and NNT were calculated for the study with larger sample size (Bristol 1988, 63.7% of total weight within the SR).
17. In this outcome, the lack of information about blinding of outcome's measures is (potential) bias.

GRADE Evidence Profile 2

QUESTION: Should oxytocin (10 IU IM) be used for all women by skilled providers to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?

Patient or population: Women expected to deliver vaginally

Settings: Studies undertaken in the Netherlands, USA, Sweden. Hospital setting

Systematic reviews:

- c. (CA 01) Cotter A, Ness A, Tolosa J. Prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2001;(4):CD001808. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|-----------------------|------------|--|--|
| De Groot 1996 (De 96) | 224 | IM 5 IU oxytocin given immediately after birth of baby. Other third stage management expectant (although no information given about timing of cord clamping/ cutting). | Oral 0.4 mg ergometrine given immediately after birth of baby |
| Fugo 1958 (Fu 58) | 473 | IV 2 IU pitocin (natural oxytocin) or IV 2 IU syntocinon (synthetic oxytocin) with anterior shoulder. No other information about management of third stage. | IV 4 mg ergonovine 149 with anterior shoulder. |
| Howard 1964 (Ho 64) | 963 | IV 3.0 IU oxytocin following placental delivery. No information about other aspects of third stage management. | IV 0.2 mg methylergonovine maleate following placental delivery |
| Sorbe 1978 (So 78) | 1049 | IV 10 IU oxytocin after delivery of anterior shoulder. Not clear whether rest of third stage managed actively or expectantly. | IV 0.2 mg ergometrine after delivery of anterior shoulder. |
| Mc Ginty 1956 (Mc 56) | 150 | IV and IM pitocin 5 IU given at birth of anterior shoulder. No information about other aspects of third stage management. | IV 0.2 mg methergine intravenously or 0.2 mg ergonovine given at birth of anterior shoulder. |

RCTs:

- d. A systematic search was performed for RCTs published after the last update of SR; no RCT was retrieved.

QUESTION: Should oxytocin (10 IU IM) be used for all women by non-skilled providers to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the footnotes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|---|--|---|--|-----------------------|--|--|-----------------------|----------------------|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Oxytocin ¹ | Ergometrine/ Methyl-ergometrine ² | Baseline risk Ergometrine/ Methyl-ergometrine ² (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 8.5 |
| Admission to intensive care unit | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.4 |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 3 (CA 01) De 96 Fu 58 Ho 64 | RCT | Serious limitation ^{3,4} -1 | No important inconsistency | Major uncertainty ^{5,6,7} -2 | Imprecise or sparse data ⁸ -1 | 872 | 788 | Min 1.8% (0.6, 3.0); Max 37.0% (29.1, 44.8) | 1.03 (0.73, 1.47) | Min NS Max NS | very low quality oooo | 6.3 |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 2 (CA 01) De 96 Fu 58 | RCT | Serious limitation ^{3,4} -1 | Only one trial ⁹ | Major uncertainty ^{10,11,12} -2 | Imprecise or sparse data ¹³ -1 | 402 | 295 | 8.2% (3.7, 12.7) | 1,09 (0.45, 2.66) | NS ¹⁴ | very low quality oooo | 7.7 |
| Need for blood transfusion | | | | | | | | | | | | |
| 1 (CA 01) De 96 | RCT | Minor limitation ⁴ | Only one trial | Some uncertainty ¹⁵ -1 | Imprecise data ¹⁶ -1 | 78 | 146 | 0.7% (-0.7, 2.0) | 3.74 (0.34, 40.46) | NS | low quality ++oo | 7.8 |
| Need for additional uterotonics | | | | | | | | | | | | |
| 2 (CA 01) De 96 Ho 64 | RCT | Serious limitation ^{3,4} -2 | Important inconsistency ⁶ -1 | Major uncertainty ^{17,18,19} -2 | Imprecise data ²⁰ -1 | 557 | 651 | Min 5.0% (3.1, 6.8) Max 14.4% (8.7, 20.1) | 1.02 (0.67, 1.55) | Min NS Max NS | very low quality oooo | 5.9 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|-------------------------------|----------------|--------------------------------------|----------------------|-----------------------|---|---|--------------------------------------|-------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Oxytocin ¹ | Ergometrine/Methyl-ergometrine ² | Baseline risk Ergometrine/Methyl-ergometrine ² (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Mean blood loss (measured in ml) | | | | | | | | | | | | |
| 1 (CA 01) De 96 | RCT | Minor limitation ⁴ | Only one trial | Some uncertainty ¹⁵ -1 | None | 78 | 146 | | WMD -23.00 (-91.86, 137.86) | - | moderate quality +++o | 5.6 |
| Postpartum anaemia | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.1 |
| Early breastfeeding | | | | | | | | | | | | |
| 0 | - | - | - | - | | | | | | | | 5.1 |
| Less anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | | | | | | | | 4.8 |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|-----------------------|--|----------------------------|--|----------------------|-----------------------|---|---|-----------------------|--|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Oxytocin ¹ | Ergometrine/Methyl-ergometrine ² | Baseline risk Ergometrine/Methyl-ergometrine ² (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect requiring treatment (manual removal of placenta) | | | | | | | | | | | | |
| 2 (CA 01) De 96 Fu 58 | RCT | Minor limitations ⁴ | No important inconsistency | Major Uncertainty ^{10,11,12,21} -2 | None | 402 | 295 | Min 1.4% (-0.52, 3.26) Max 24.2% (17.3, 31%) | 0.71 (0.49, 1.02) | Min NS Max NS | low quality ++oo | 6.2 |
| 3 (CA 01) De 96 Fu 58 So 78 | 2 RCT and 1 quasi-RCT | Very serious limitations ^{4,24} -2 | No important inconsistency | Major uncertainty ^{10,23,24} -2 | None | 908 | 838 | Max 5.9% (3.9, 7.9) Min 24.2% (17.3, 31.0) | 0.57 (0.41, 0.79) | Min NS Max -26 (-62.8, -16.0) | very low quality oooo | 6.2 |
| Nausea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.0 |
| Vomiting | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.7 |
| Diarrhoea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.6 |
| Headache | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.8 |
| Abdominal pain | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.8 |
| High blood pressure (diastolic blood pressure > 100 mm Hg between delivery of the baby and discharge from the labour ward) | | | | | | | | | | | | |
| 1 (CA 01) Mc 56 | Quasi -RCT | Very serious limitations ²⁵ -2 | Only one trial | Major uncertainty ^{26,27,28} -2 | Imprecise data -1 | 50 | 100 | 15% ^{8,22} | 0.53 (0.19, 1.52) | NS | very low quality oooo | 6.5 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|-----------------------|--|--|-----------------------|-------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Oxytocin ¹ | Ergometrine/ Methyl-ergometrine ² | Baseline risk Ergometrine/ Methyl-ergometrine ² (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Shivering | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | 4.7 |
| Temp >40° C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | 6.8 |
| Maternal death | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | 6.7 |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | 4.6 |

Notes:

1. In considered trials: oxytocin, syntocinon, pitocin.
2. In considered trials: ergometrine, methylegometrine, methergine, ergonovine.
3. PPH > or= 500 ml and PPH >or = 1000 ml: clinically estimated blood loss in all trials.
4. De Groot 1996: double-blind for oral ergometrine versus placebo and unblinded for ergometrine and/or placebo versus oxytocin.
5. No details of inclusion/exclusion criteria of study participants (Fugo 1958; Howard 1964;).
6. No trials compared oxytocin 10 IU IM with the ergometrine or with the methylegometrine 0.2 mg IM. In all trials different preparations, doses and routes of administration; DeGroot 1996: oxytocin 5IU IM versus oral ergometrine 0.4 mg; Fugo 1958: oxytocin 2 IU IV or syntocinon 2IU IV versus ergonovine 4 mg IV; Howard 1964: oxytocin 3 IU IV versus methylegometrine 0.2 mg IV.
7. No information about other aspects of third stage of management (Fugo 1958; Howard 1964). De Groot 1996 had expectant management for the third stage of labour.
8. The CIs reported were wide and all across 1 (De Groot 1996; Fugo 1958; Howard 1964); in one trial (Fugo 1958) no events in both arms.
9. In one of the two trials (Fugo 1958) the relative risk cannot be estimable.
10. No details of inclusion/exclusion criteria of study participants (Fugo 1958).
11. No trials compared oxytocin 10 IU IM with the ergometrine or with the methylegometrine 0.2 mg IM. In all trials different preparations, doses and routes of administration: DeGroot 1996: oxytocin 5 IU IM versus oral ergometrine 0.4 mg; Fugo 1958: oxytocin 2 IU IV or syntocinon 2IU IV versus ergonovine 4 mg IV.
12. No information about other aspects of third-stage management (Fugo 1958). De Groot 1996 had expectant management for the third stage of labour.
13. The reported CI is wide and across 1 in De Groot 1996 and cannot be estimable in Fugo 1958. In one trial (Fugo 1958) no events in both arms.
14. Calculated from the data in the De Groot 1996 trial.
15. The only considered trial (DeGroot 1996) compared oxytocin 5IU IM versus oral ergometrine 0.4 mg.

16. The two included trials had results in opposite directions, but the CIs of both trials are wide and overlapping; due to the very small number of trials included it is very difficult to comment on the consistency of results.
17. No details of inclusion/exclusion criteria of study participants (Howard 1964).
18. No trials compared oxytocin 10 IU IM with the ergometrine or with the methylergomethrine 0.2 mg IM. In all trials different preparations, doses and routes of administration: DeGroot 1996: oxytocin 5IU IM versus oral ergometrine 0.4 mg; Howard 1964: oxytocin 3 IU IV versus methylergonovine 0.2 mg IV.
19. No information about other aspects of third-stage management (Howard 1964); De Groot 1996 had expectant management for the third stage of labour.
20. The reported CI is wide and across 1 (De Groot 1996).
21. Fugo 1958 weight in SR 97.3%.
22. Sorbe 1978 trial: quasi-randomized; allocation concealment unclear; not blinded.
23. No trials compared oxytocin 10 IU IM with the ergometrine or with the methylergomethrine 0.2 mg IM. In all trials different preparations, doses and routes of administration: DeGroot 1996: oxytocin 5IU IM versus oral ergometrine 0.4 mg; Fugo 1958: oxytocin 2 IU IV or syntocinon 2IU IV versus ergonovine 4 mg IV; Sorbe 1978 (quasi-RCT): oxytocin 10 IU IV versus 0.2 mg ergometrine IV.
24. No information about other aspects of third-stage management (Fugo 1958; Sorbe 1978); De Groot 1996 had expectant management for the third stage of labour.
25. McGinty 1956 trial: quasi-randomized; allocation concealment unclear; not blinded.
26. Women delivering vaginally under pudendal block and demerol/scopolamine. No more details on participants.
27. Pitocin 5 IU both IV and IM versus methergine 0.2 mg IV or ergonovine 0.2 mg IV.
28. No information about other aspects of third-stage management (McGinty 1956).

Summary of findings 2

Scenario: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|---------------------|-------------|---|-------------------------|-----|--------------------------|----------------------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Footnotes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss \geq 1000 ml | 2 De 96 Fu 58 | 697 | 8.2% (3.7, 12.7) | 1.09 (0.45, 2.66) | NS | very low quality oooo | 3,4,9,10,11,12,13,14 | - |
| | Need for blood transfusion | 1 De 96 | 224 | 0.7% (-0.7, 2.0) | 0.34 (0.22, 0.53) | NS | low quality ++oo | 4,15,16 | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

3. PPH $>$ or = 500ml and PPH $>$ or = 1000 ml: clinically estimated blood loss in all trials.
4. De Groot 1996: double-blind for oral ergometrine versus placebo and unblinded for ergometrine and/or placebo versus oxytocin.
9. In one of the two trials (Fugo 1958) the relative risk cannot be estimated.
10. No details of inclusion/exclusion criteria of study participants (Fugo 1958).
11. No trials compared oxytocin 10 IU IM with the ergometrine or with the methylergometrine 0.2 mg IM. In all trials different preparations, doses and routes of administration: DeGroot 1996: oxytocin 5 IU IM versus oral ergometrine 0.4 mg; Fugo 1958: oxytocin 2 IU IV or syntocinon 2IU IV versus ergonovine 4 mg IV.
12. No information about other aspects of third-stage management (Fugo 1958). De Groot 1996 had expectant management for the third stage of labour.
13. The reported CI is wide and across 1 in De Groot 1996 and cannot be estimated in Fugo 1958. In one trial (Fugo 1958) no events were reported in both arms.
14. Calculated from the data in the De Groot 1996 trial.
15. The only considered trial (DeGroot 1996) compared oxytocin 5IU IM versus oral ergometrine 0.4 mg.
16. The two included trials had results in opposite directions, but the CIs of both trials are wide and overlapping; due to the very small number of trials included it is very difficult to comment on the consistency of results.

GRADE Evidence Profile 2

QUESTION: Should ergometrine/methylergometrine (0.2 mg IM) be used for all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)? [1]

Patients or population: women who expected to deliver vaginally

Settings: studies undertaken in Hong Kong, United Arab Emirates, Australia. Hospital setting.

Systematic reviews and RCTs:

- e. (MS 04) McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine – oxytocin versus oxytocin for the third stage of labour. Cochrane database Syst Rev. 2004; (1) CD000201. See the table below for RCTs included from this SR.

| Name, Year (initials) | Population | Intervention | Control |
|-----------------------|------------|--|---|
| Choy 2002 (Ch 02) | 991 | IM 1 ml of ergometrine-oxytocin (5 units of oxytocin and 0.5 mg ergometrine) | IV 1 ml of oxytocin (10 units of oxytocin) |
| Khan 1995 (Kh 95) | 2028 | IM ergometrine-oxytocin 1 ml with the birth of the anterior shoulder of the baby. | IM oxytocin 10 IU at time of birth of the anterior shoulder of the baby. |
| McDonald 1993 (Mc 93) | 3483 | IM ergometrine-oxytocin 1 ml at time of birth of the anterior shoulder of the baby. | IM oxytocin 10 IU at time of birth of the anterior shoulder of the baby. |
| Yuen 1995 (Yu 95) | 991 | IM ergometrine-oxytocin 1 ml at time of birth of the anterior shoulder of the baby. | IM oxytocin 10 IU at time of birth of the anterior shoulder of the baby. |

RCTs:

- f. A systematic search was performed for RCTs published after the last update of SR: no RCT was retrieved.

QUESTION: Should ergometrine/methylergometrine (0.2 mg IM) be used for all women by non-skilled providers to prevent PPH instead of oxytocin (10 IU IM)? [1]

No evidence available.

NOTE: These GRADE Evidence Profiles have been compiled from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|-------------------------------------|--|---|-----------------------------------|---------------------------------|----------|---|-----------------------|---|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Ergometrine/ Methyl-ergometrine | Oxytocin | Baseline risk (95%CI) (oxytocin) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 8.5 |
| Admission to intensive care unit | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.4 |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 4 (MS 04) Ch 02 Kh 95 Mc 93 Yu 95 | RCT | Minor limitation ³ | No important inconsistency | Major uncertainty ^{4,5} -2 | Imprecise ⁶ -1 | 3742 | 3751 | Min 3.0% (1.9, 4.0); Max 18.0% (16.0, 20.1) | 0.87 (0.76, 0.99) | Min NS Max 20.6 (11.7, 84.2) | very low quality +ooo | 6.3 |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 4 (MS 04) Ch 02 Kh 95 Mc 93 Yu 95 | RCT | Minor limitation ³ | Not important inconsistency | Major uncertainty ^{4,5} -2 | Imprecise data ⁷ -1 | 3742 | 3751 | Min 0.8% (0.0, 1.6) Max 4.7% (3.7, 5.7) | 0.79 (0.60, 1.04) | Min NS Max NS | very low quality +ooo | 7.7 |
| Need for blood transfusion | | | | | | | | | | | | |
| No additional information compared with Cotter 2001 | | | | | | | | | | | | 7.8 |
| Need for additional uterotonic | | | | | | | | | | | | |
| 3 (MS 04) Ch 02 Mc 93 Yu 95 | RCT | Major limitation ³ -1 | Important inconsistency ⁸ -1 | Major uncertainty ^{9,10} -2 | None | 2726 | 2739 | Min 7.3% (5.0, 9.6) Max 20.5% (18.6, 22.4) | 0.86 (0.76, 0.97) | Min 19 (10.8, 76.6) Max 31 (17.4, 186.9) | very low quality oooo | 5.9 |
| Mean blood loss | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | 5.6 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|---------------|----------------|---------------------------------------|----------------------|---------------------------------|----------|----------------------------------|-----------------------|-------------|---------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Ergometrine/ Methyl-ergometrine | Oxytocin | Baseline risk (95%CI) (oxytocin) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Postpartum anaemia | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | 6.1 |
| Early breast feeding (not breastfed at discharge) | | | | | | | | | | | | |
| 1 (MS 04) Mc 93 | RCT | No limitation | Only one trial | Major uncertainty ¹¹ -2 | None | 1713 | 1727 | 13.6% (12.0, 16.2) | 1.98 (0.92, 1.27) | NS | low quality ++oo | 5.1 |
| Less anaemia in infancy | | | | | | | | | | | | |
| 0 | | | | - | | | | | | | | 4.8 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|-------------------------------|-----------------------------|--|----------------------|----------------------|----------|--|-----------------------|--|---------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Ergometrine-Oxytocin | Oxytocin | Baseline risk (oxytocin) (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect requiring treatment (manual removal of placenta) | | | | | | | | | | | | |
| No additional information compared with Cotter 2001 | | | | | | | | | | | | 6.2 |
| Nausea | | | | | | | | | | | | |
| 3 (MS 04) Ch 02 Mc 93 Yu 95 | RCT | Some limitation ¹² | Not important inconsistency | Major uncertainty ^{13,14} -2 | None ¹⁶ | 2721 | 2737 | Min 1.0% (0.3, 2.2) Max 6.7% (5.5, 7.9) | 3.85 (3.2, 4.63) | 5 (4.4, 5.6) ¹⁵ | low quality ++oo | 4.0 |
| Vomiting | | | | | | | | | | | | |
| 3 (MS 04) Ch 02 Mc 93 Yu 95 | RCT | Some limitation ¹² | Not important inconsistency | Major uncertainty ^{13,14} -2 | None ¹⁶ | 2721 | 2737 | Min 0.4% (0.2, 1.0) Max 3.4% (2.5, 4.2) | 5.72 (4.44, 7.38) | 6 (5.2, 6.6) | low quality ++oo | 4.7 |
| Diarrhoea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.6 |
| Headache | | | | | | | | | | | | |
| 0- | - | - | - | - | - | - | - | - | - | - | - | 4.8 |
| Abdominal pain | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.8 |
| High blood pressure (elevation of diastolic blood pressure) | | | | | | | | | | | | |
| 4 (MS 04) Ch 02 Kh 95 Mc 93 Yu 95 | RCT | No limitation | Not important inconsistency | Major uncertainty ^{4,5} -2 | None ¹⁷ | 3737 | 3749 | Min 0.2% (-0.02, 0.4) Max 3.2% (1.7, 4.9) | 2.47 (1.58, 3.86) | Min 51 (25.8, 1449.3) Max 144 (85.2, 458.8) | low quality ++oo | 6.5 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|----------------------|----------|----------------------------------|-----------------------|-------------|---------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Ergometrine-Oxytocin | Oxytocin | Baseline risk (oxytocin) (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Shivering | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.7 |
| Temp >40° C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.8 |
| Maternal death | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 6.7 |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | 4.6 |

Notes:

1. The results reported here are for the outcomes not analysed in Cotter's review, or that could give additional information for the outcomes already analysed in previously mentioned review.
2. Results are presented as Relative Risk for dichotomous data, using a fixed model. These results are obtained transforming Peto Odd Ratio in McDonald's Systematic Review by Statistical Analysis Method available in Cochrane Database Systematic Review.
3. PPH > or = 500 ml and > = clinically estimated blood loss. This kind of assessment is subject to significant subjective error and methods for correction of this are not reported. Because of this, each of the included studies also reported additional indices of blood loss; for example, the need of blood transfusion, haemoglobin, need for therapeutic uterotonics, length of third stage and need for manual removal of the placenta.
4. In all considered trials (Choy 2002; Khan 1995; McDonald 1993; Yuen 1995) the comparisons were not between ergometrine and oxytocin, but between ergometrine–oxytocin and oxytocin. In all considered trials the doses were: ergometrine 0.5 mg +oxytocin 5 IU versus oxytocin 10 IU; all trials had the same route of administration – intramuscularly – both in intervention and in the control group, except in Choy 2002, in which oxytocin in the control group was given IV.
5. Women at low risk in Khan 1995 (exclusion criteria: operative delivery (forceps, ventouse, Caesarean section), antenatal BP 160/100 mmHg, need for antihypertensive drugs in pregnancy, GA, epidural or diazepam during labour, multiple pregnancy, antenatal anaemia 9 g/dl or less and cardiac disease) and in McDonald 1993 (exclusions criteria: planned Caesarean section, general anaesthetic given for operative delivery other than Caesarean section, antepartum hypertension; maternal refusal; maternal distress; advanced stage in labour; language barrier; fetal abnormality or death in utero; and medical disease). In Khan's trial the participants had only spontaneous delivery.
6. The CIs reported were wide and across 1 in three trials. The last consideration refers specifically to McDonald 1993 (weight in Systematic Review: 72.5%).
7. The CIs reported were wide and across 1 in all trials. The last consideration refers specifically to McDonald 1993 (weight in Systematic Review: 76.5%).
8. There is reasonable heterogeneity between the study populations. Some of the trials (Khan 1995 and McDonald 1993) include women at lower risk of need for additional uterotonics (see exclusion criteria cited above).

9. In all considered trials (Choy 2002; McDonald 1993; Yuen 1995) the comparisons were not between ergometrine and oxytocin, but between ergometrine – oxytocin and oxytocin. In all considered trials the doses were: ergometrine 1.5 mg +oxytocin 5 IU versus oxytocin 10 IU; in all trials the same route of administration – intramuscularly – both in intervention and in the control group, except in Choy 2002, in which oxytocin in the control group was given IV.
10. Women at low risk in McDonald 1993 (exclusions criteria: planned Caesarean section, general anaesthetic given for operative delivery other than Caesarean section, antepartum hypertension; maternal refusal; maternal distress; advanced stage in labour; language barrier; fetal abnormality or death in utero; and medical disease).
11. In McDonald's trial the comparison is between ergometrine 1.5 mg +oxytocin 5 IU IM versus oxytocin 10 IU IM, and women are at low risk for PPH.
12. This type of trials is quite difficult to blind completely as the different short-term side effects can be dramatically different (e.g. vomiting).
13. In all considered trials (Choy 2002; McDonald 1993; Yuen 1995) the comparison and the doses were: ergometrine 1.5 mg + oxytocin 5 IU versus oxytocin 10 IU; in all trials the same route of administration – intramuscularly – both in intervention and in the control group, except in Choy 2002, in which oxytocin in the control group was given IV.
14. Women at low risk in McDonald 1993 (exclusions criteria: planned Caesarean section, general anaesthetic given for operative delivery other than Caesarean section, antepartum hypertension; maternal refusal; maternal distress; advanced stage in labour; language barrier; fetal abnormality or death in utero; and medical disease).
15. Calculated from data in McDonald's trial.
16. The reported CIs are wide and across 1 in Choy 2002 and Yuen 1995; few events both in intervention and in control group in Choy's trial (8/500 versus 2/491) and in Yuen 1995 (7/491 versus 5/493), but McDonald 1993 weight for 94.4%.
17. No events in control group in Khan's trial (0/1012) and few in control group in McDonald's trial. Yuen 1995 (3/1753). The reported CI in Yuen 1995 (weight in Systematic Review: 40.1%) is wide and across 1.

Summary of findings 2

SCENARIO: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of ergometrine/methylergometrine (0.2 mg IM)?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------|--|-------------|--|-------------------------|------------------|--------------------------|---------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 4 Ch 02 Kh 95 Mc 93 Yu 95 | 7493 | min 0.8% (0.0-1.6) max 4.7% (3.7-5.7) | 0.79 (0.60, 1.04) | min NS max NS | very low quality +000 | 3,4,5,7 | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

3. PPH > or = 500 ml and > = clinically estimated blood loss. This kind of assessment is subject to significant subjective error and methods for correction of this are not reported. Because of this, each of the included studies also reported additional indices of blood loss; for example, the need of blood transfusion, haemoglobin, need for therapeutic uterotonics, length of third stage and need for manual removal of the placenta.

4. In all considered trials (Choy 2002; Khan 1995; McDonald 1993; Yuen 1995) the comparisons were not between ergometrine and oxytocin, but between ergometrine – oxytocin and oxytocin. In all considered trials the doses were: ergometrine 1.5 mg + oxytocin 5 IU versus oxytocin 10 IU; all trials had the same route of administration – intramuscularly – both in intervention and in the control group, except in Choy 2002, in which oxytocin in the control group was given IV.

5. Women at low risk in Khan 1995 (exclusions criteria: operative delivery (forceps, ventouse, Caesarean section), antenatal BP 160/100 mmHg, need for antihypertensive drugs in pregnancy, GA, epidural or diazepam during labour, multiple pregnancy, antenatal anaemia 9 g/dl or less and cardiac disease) and in McDonald 1993 (exclusions criteria: planned Caesarean section, general anaesthetic given for operative delivery other than Caesarean section, antepartum hypertension; maternal refusal; maternal distress; advanced stage in labour; language barrier; fetal abnormality or death in utero; and medical disease).

In Khan’s trial the participants had only spontaneous delivery.

7. The CIs reported were wide and across 1 in all trials. The last consideration refers specially to McDonald 1993 (weight in Systematic Review: 76.5%).

GRADE Evidence Profile 3

QUESTION: Should oral misoprostol (600 mcg) be used for all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

Patient or population: all women in third stage of labour (vaginal delivery)

Settings: hospital, either in developed or developing countries

Systematic reviews:

- g. (GA 06) Gulmezoglu AM et al. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev. updated 21.07.06. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|------------------------|------------|--|---|
| Belgium 1999 (Be 99) | 213 | Misoprostol 600 mcg orally | IV methylergometrine 200 mcg |
| WHO 1999 (WH 99) | 597 | Misoprostol 600 mcg orally | IV oxytocin 10 IU |
| France 2001 (Fr 01) | 602 | Misoprostol 600 mcg oral after cord clamp | IV oxytocin 2.5 IU given after cord clamp |
| Hong Kong 2001 (Ho 01) | 2058 | Misoprostol 600 mcg oral after delivery of the baby | IM oxytocin 5 IU + ergometrine 0.5 mg at delivery of anterior shoulder |
| WHO 2001 (WH 01) | 18530 | Misoprostol 600 mcg orally | IV/IM oxytocin 10 IU |
| Zimbabwe 2001 (Zi 01) | 500 | Misoprostol 400 mcg orally | IM oxytocin 10 IU |
| Nigeria 2003 (Ni 03) | 496 | Misoprostol 600 mcg oral at delivery of anterior shoulder | IM oxytocin 10 IU at delivery of anterior shoulder |
| Turkey 2003 (Tu 03) | 1800 | IV oxytocin 10 IU plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol or misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol. | IV oxytocin 10 IU or IV oxytocin 10 IU plus IM methylergometrine 1 ml |
| India 2005 (In 05) | 200 | Misoprostol 600 mcg orally immediately after delivery | IV methylergometrine 0.2 mg at delivery of anterior shoulder |

RCTs:

- h. A systematic search was performed for RCTs published after the last update of SR: no RCT was retrieved.

QUESTION: Should oral misoprostol (600 mcg) be used for all women by non-skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|---------------------------------------|---|--|----------------------|---------------------|----------|--|---------------------------------|-------------------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 1 (GA 06) WH 01 | RCT | Minor limitation ¹ | One trial only | Some uncertainty about directness ² -1 | None | 9264 | 9266 | 0% (0, 0.1) | 1 (0.14, 7.10) | NS | moderate quality +++o | |
| Admission to intensive care unit | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 8 (GA 06) | RCT | Minor limitation ^{1,3,4,5,6} | No important inconsistency ⁷ | Some uncertainty about directness ^{8,9} -1 | None | | | | | | | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9659 | 9676 | 13.5% (12.8, 14.2) ²⁹ | 1.42 (1.34, 1.51) overall | -17 (-20.5, -14.3) ²⁹ | moderate quality +++o | |
| Be 99 Fr 01 Ho 01 Tu 03 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1796 | 1805 | Min 4.3% (3.0, 5.5) Max 14.8% (9.8, 19.8) | | Min NS Max -8 (-20, -4.7) | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|-----------------------------------|--------|------------------------------------|---|--|--|---------------------|----------|--|---------------------------------|--------------------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 7 (GA 06) | RCT | Minor limitation ^{1,5,11} | No important inconsistency ⁷ | Some uncertainty about directness ^{8,12} -1 | None | | | | | | | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9677 | 9660 | 2.9% (2.5, 3.2) ³⁰ | 1.34 (1.16, 1.55) overall | -89 (-167.1, -60.8) ³⁰ | moderate quality +++o | |
| Be 99 Fr 01 Ho 01 Tu 03 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1712 | 1700 | Min 0.4% (0, 0.8) Max 6.1% (2.8, 9.5) | | Min NS Max NS | | |
| Need for blood transfusion | | | | | | | | | | | | |
| 6 (GA 06) | RCT | Minor limitation ^{1,4,5} | No important inconsistency ⁷ | Some uncertainty about directness ^{8,14} -1 | Imprecise or sparse data ³⁵ -1 | | | | | | | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9667 | 9675 | 1.1% (0.8, 1.3) ³¹ | 0.80 (0.62, 1.04) overall | NS ³¹ | low quality ++oo | |
| Be 99 Ho 01 Tu 03 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1514 | 1516 | Min 1.6% (0.8, 2.3) Max 3.4% (1.6, 5.2) | | Min NS Max NS | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|-------------------------------------|---|--|----------------------|---------------------|----------|---|---------------------------------|---|-----------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Additional uterotonics | | | | | | | | | | | | |
| 6 (GA 06) | RCT | Minor Limitation ^{1,3,5,6} | No important inconsistency ⁷ | Some uncertainty about directness ^{8,15} -1 | None | | | | | | | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9671 | 9677 | 10.9% ²⁵ (10.2, 11.5) | 1.41 (1.31, 1.50) overall | -23.3 (-5.3, -3.3) ²⁵ | moderate quality +++o | |
| Be 99 Ho 01 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1220 | 1223 | min 4.4% (0.2, 8.6) max 14.0% (11.8, 16.1) | | min -11.9 (-267.3, -6.1) max -11.5 (-18.7, -8.3) | | |
| Mean blood loss (measured in mL) | | | | | | | | | | | | |
| 5 (GA 06) | RCT | Minor limitation ^{1,4,5} | No important inconsistency ⁷ | Some uncertainty about directness ^{8,16} -1 | Imprecise data -1 | | | | | | | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9659 | 9676 | | WMD 10.17 (7.19, 13.15) overall | | low quality ++oo | |
| Ho 01 Tu 03 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1414 | 1416 | | | | | |
| Postpartum anaemia | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|---|---|---|----------------------|---------------------|----------|--|----------------------------------|---------------------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect | | | | | | | | | | | | |
| 1 (GA 06) Zi 01 | RCT | Minor limitation ¹⁷ | One trial only | Major uncertainty about directness ^{18,19} -2 | None | 243 | 256 | 34.8% (28.9, 40.6) | 1.43 (1.16, 1.77) | 7 (4.2, 15.5) | low quality ++oo | |
| Side effect requiring treatment | | | | | | | | | | | | |
| 6 (GA 06) ²² | RCT | Serious Limitation ^{1,3,5,6} -1 | No important inconsistency ⁷ | Some uncertainty about directness ^{8,15} -1 | None | | | | | | low quality ++oo | |
| WH 99 WH 01 Ni 03 | | | | | | 9671 | 9677 | 2.3% ²⁷ (2.0, 2.6) | 0.97 (0.81, 1.16) overall | NS ²⁷ | | |
| Be 99 Ho 01 In 05 | | | | | | 1226 | 1232 | min 1.36% (0.65, 2.06) max 3.0% (-0.36, 6.36) | | min -103 (-609.3, -56.5) max NS | | |
| 3 (GA 06) ²³ | RCT | Minor Limitation ¹ | No important inconsistency ⁷ | Some uncertainty about directness ^{8,24} -1 | None | | | | | | moderate quality +++o | |
| WH 99 WH 01 | | | | | | 9426 | 9432 | 0.15% ²⁸ (0.07, 0.23) | 7.28 (4.71, 11.24) overall | 87 ²⁸ (71.8, 110.6) | | |
| Be 99 | | | | | | 86 | 94 | 8.51% (2.84, 14.18) | | 3 (2.2, 4.7) | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|---|---|--|------------------------------------|---------------------|----------|---|-------------------------------------|---------------------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Nausea | | | | | | | | | | | | |
| 6 (GA 06) | RCT | Serious Limitation ^{1,3,5,6} -1 | Important inconsistency ³⁷ -1 | Major uncertainty about directness ^{8,15} -2 | Imprecise data ³⁸ -1 | | | | 1.12 (0.90, 1.41) overall | | very low quality oooo | |
| WH 99 WH 01 Ni 03 | | | | | | 9673 | 9681 | 0.4% ³² (0.2, 0.5) | | 214 ³² (145.1, 411.1) | | |
| Be 99 Ho 01 In 05 | | | | | | 1213 | 1226 | min 2.6% (1.6, 3.6) max 31.9% (22.4, 41.4) | | min NS max NS | | |
| Vomiting | | | | | | | | | | | | |
| 8 (GA 06) | RCT | Serious limitation ^{1,3,5,6} -1 | Important inconsistency -1 | Major uncertainty about directness ^{8,9} -2 | Imprecise data -1 | | | | 1.24 (0.98, 1.58) overall | | very low quality oooo | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9663 | 9681 | 0.3% ³³ (0.2, 0.4) | | 225 ³³ (154.7-412.4) | | |
| Be 99 Fr 01 Ho 01 Tu 03 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1797 | 1806 | Min 0.5% (-0.5, 1.5) Max 30% (21, 39) | | min 31 (16.2, 299.2) max NS | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|-----------------------------|--------|---|----------------------------|--|----------------------|---------------------|----------|----------------------------------|---------------------------------|-----------------------------------|---------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Diarrhoea | | | | | | | | | | | | |
| 5 (GA 06) | RCT | Serious limitation ^{1,3,6} -1 | No important inconsistency | Major uncertainty about directness ^{8,20} -2 | Imprecise data -1 | | | | 2.52 (1.60, 3.98) overall | | very low quality oooo | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9673 | 9681 | 0.1% ³⁴ (0.0, 0.1) | | 342 ³⁴ (231.6, 651) | | |
| Tu 03 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 488 | 484 | 3.1% (1.4, 4.9) | | NS | | |
| Headache | | | | | | | | | | | | |
| 2 (GA 06) Be 99 Ho 01 | RCT | Minor limitation ⁵ | No important inconsistency | Some uncertainty about directness ^{8,21} -1 | None | 1113 | 1126 | 8-12.8% | 0.97 (0.74, 1.28) | NS | moderate quality ++++o | |
| Abdominal pain | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| High blood pressure | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|---|---|--|----------------------|---------------------|----------|---|---------------------------------|---|---------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any shivering | | | | | | | | | | | | |
| 8 (GA 06) | RCT | Serious limitation ^{1,3,5,6} -1 | No important inconsistency ⁷ | Some uncertainty about directness ^{8,9} -1 | None | | | | 3.29 (3.03, 3.56) overall | | low quality ++oo | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9673 | 9681 | 5% (4.6,5.5) | | NNH 8 (7.5, 8.6) | | |
| Be 99 Fr 01 Ho 01 Tu 03 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1786 | 1806 | Min 4.9% (2.8, 7.1) Max 40.4% (30.5, 50.4) | | NNH min 16 (9.8, 39.1) NNH max 3 (2, 4.4) | | |
| Temp >38 °C | | | | | | | | | | | | |
| 8 (GA 06) | RCT | Serious limitation ^{1,3,5,6} -1 | No important inconsistency ⁷ | Some uncertainty about directness ^{8,9} -1 | None | | | | 6.62 (5.45, 8.05) overall | | low quality ++oo | |
| WH 99 WH 01 Ni 03 | | | | Misoprostol vs. Oxytocin 10IU im | | 9644 | 9653 | 0.8% (0.7, 1.0) | | NNH 19 (17.4, 21.2) | | |
| Be 99 Fr 01 Ho 01 Tu 03 In 05 | | | | Misoprostol vs. uterotonics other than oxytocin 10 IU im | | 1800 | 1812 | Min 1.3% (0.6, 1.9) Max 7% (2, 12) | | NNH min 14 (11, 18.6) NNH max 4 (3.1, 8.5) | | |
| Temp >40 °C | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|---------------------|----------|--------------------------|-----------------------|-------------|---------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Misoprostol | Oxytocin | Baseline risk (oxytocin) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Maternal death | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |
| Anaemia in infancy | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |

Notes:

1. WHO 01 post randomization withdrawal in 50/9264 women in misoprostol group and in 38/9226 women in oxytocin group.
2. WHO 01 includes only low-risk women (exclusion criteria: pyrexia > 38° C on admission to labour ward, severe asthma, bleeding disorders, elective Caesarean section).
3. India 05 allocation concealment not clear, random allocation with no further details.
4. Blood loss estimated and not measured in Belgium 99, Hong Kong 01, Nigeria 03, Turkey 03; in India 05 measurement method not specified.
5. Hong Kong 01 outcome assessments were not blinded.
6. India 05 no mention of missing data or loss to follow-up.
7. Significant results coming from a single large study (WHO 01).
8. All studies include only low-risk women (excluding women with pre-existing diseases and/or women at risk for hemorrhage).
9. Five out of eight studies use drugs or doses other than that considered in the question:
 - a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. France 01 compares misoprostol 600 mcg orally versus oxytocin 2.5 IU intravenously given after cord clamp, versus no uterotonic;
 - c. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - d. India 05 compares misoprostol 600 mcg orally immediately after delivery versus 0.2 mg methylergometrine IV at delivery of anterior shoulder;
 - e. Turkey 03 compares 4 groups; all received corresponding placebos:
 - Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol.
 - Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol.
 - Group 3: oxytocin 10 IU IV.
 - Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
10. Baseline risk and NNT calculated for the study with larger sample size (88.43% of total weight within the SR).
11. Blood loss estimated and not measured in Belgium 99, Hong Kong 01, Nigeria 03, Turkey 03.
12. Four out of seven studies use drugs or doses other than the one considered in the question:
 - a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. France 01 compares misoprostol 600 mcg orally versus oxytocin 2.5 IU intravenously given after cord clamp, versus no uterotonic;

- c. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - d. Turkey 03 compares 4 groups, all received corresponding placebos:
 Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol;
 Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol;
 Group 3: oxytocin 10 IU IV;
 Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
13. Studies included in this sub-group have small sample size.
14. Three out of six studies use drugs or doses other than the one considered in the question:
- a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - c. Turkey 03 compares 4 groups, all received corresponding placebos:
 Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol;
 Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol;
 Group 3: oxytocin 10 IU IV;
 Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
15. Three out of six studies use drugs or doses other than the one considered in the question:
- a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - c. India 05 compares misoprostol 600 mcg orally immediately after delivery versus 0.2 mg methylergometrine IV at delivery of anterior shoulder.
16. Two out of five studies use drugs or doses other than the one considered in the question:
- a. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - b. Turkey 03 compares 4 groups, all received corresponding placebos:
 Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol;
 Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol;
 Group 3: oxytocin 10 IU IV;
 Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
17. Zimbabwe 01 not mentioned whether outcome assessments were blinded or not; placebo used not identical to treatment.
18. Zimbabwe 01 included only low-risk women (excluded women with a history of PPH, disseminated intravascular coagulation, antepartum haemorrhage, coagulation disorders, operative delivery, multiple pregnancy, history of asthma and known allergies to misoprostol or oxytocin).
19. Zimbabwe 01 used misoprostol 400 mcg orally + 1 ml saline (placebo) versus Oxytocin 10 IU IM + 2 placebo tablets.
20. Two out of five studies use drugs or doses other than the one considered in the question:
- a. India 05 compares misoprostol 600 mcg orally immediately after delivery versus 0.2 mg methylergometrine IV at delivery of anterior shoulder.

- b. Turkey 03 compares 4 groups, all received corresponding placebos:
 - Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol.
 - Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol.
 - Group 3: oxytocin 10 IU IV.
 - Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
- 21. The studies use drugs or doses other than the one considered in the question:
 - a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder.
- 22. Manual removal of placenta.
- 23. Severe shivering.
- 24. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV.
- 25. Baseline risk and NNT calculated for the study with larger sample size (82.71% of total weight within the SR).
- 26. Baseline risk and NNT calculated for the study with larger sample size (88.87% of total weight within the SR).
- 27. Baseline risk and NNT calculated for the study with larger sample size (88.87% of total weight within the SR).
- 28. Baseline risk and NNT calculated for the study with larger sample size (63.22% of total weight within the SR).
- 29. Baseline risk and NNT calculated for the study with larger sample size (88.43% of total weight within the SR).
- 30. Baseline risk and NNT calculated for the study with larger sample size (85.60% of total weight within the SR).
- 31. Baseline risk and NNT calculated for the study with larger sample size (76.36% of total weight within the SR).
- 32. Baseline risk and NNT calculated for the study with larger sample size (26.00% of total weight within the SR).
- 33. Baseline risk and NNT calculated for the study with larger sample size (22.79% of total weight within the SR).
- 34. Baseline risk and NNT calculated for the study with larger sample size (31.30% of total weight within the SR).
- 35. The reported CIs are wide and include 1 in Belgium 99, Hong Kong 01, Turkey 03 and WHO 01; no events both in intervention and control group in WHO 99 and Nigeria 03.
- 36. The reported CIs are wide in all studies and include 1 in WHO 99, WHO 01 and Turkey 03.
- 37. The results in four of the six considered trials have different directions in comparison with the WHO 01; the only one with significant results.
- 38. The CIs in four of the six considered trials are wide and include 1.

Summary of findings

SCENARIO: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of oral misoprostol (600 mcg)?

| | By skilled providers | | | | | | | | By no skilled providers |
|-------------------------|----------------------------|----------------------------------|--|--|-------------------------|------------------------|--------------------------|--------------------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 7 | 22749 | | 1.34 (1.16, 1.55) | -89 (-60.8, -167.1) | moderate quality +++o | 1,5,7,8,11,12,30 | - |
| | | WH 99 WH 01 Ni 03 | 19337 | 2.9% (2.5, 3.2) | | | | | |
| | | Be 99 Fr 01 Ho 01 Tu 03 | 3412 | min 0.4% (0.0, 0.8) max 6.1% (2.8, 9.5) | | | | | |
| | Need for blood transfusion | 6 | 22372 | | 0.80 (0.62, 1.04) | NS | low quality ++oo | 1,4,5,7,8,14,31,35 | - |
| | | WH 99 WH 01 Ni 03 | 19342 | 1.1% (0.8-1.3) | | | | | |
| Be 99 Ho 01 Tu 03 | | 3030 | min 1.6% (0.8, 2.3) max 3.4% (1.6, 5.2) | | | | | | |
| Harms | None judged critical | | | | | | | | - |

Notes:

1. WHO 01 post randomization withdrawal in 50/9264 women in misoprostol group and in 38/9226 women in oxytocin group.
4. Blood loss estimated and not measured in Belgium 99, Hong Kong 01, Nigeria 03, Turkey 03, in India 05 measurement method not specified.
5. Hong Kong 01 outcome assessments were not blinded.
7. Significant results coming from a single large study (WHO 01).
8. All studies include only low-risk women (excluding women with pre-existing diseases and or women at risk for haemorrhage).
11. Blood loss estimated and not measured in Belgium 99, Hong Kong 01, Nigeria 03, Turkey 03.
12. Four out of seven studies use drugs or doses other than the one considered in the question:
 - a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. France 01 compares misoprostol 600 mcg orally versus oxytocin 2.5 IU intravenously given after cord clamp, versus no uterotonic;
 - c. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - d. Turkey 03 compares 4 groups, all received corresponding placebos:
Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol;
Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol;
Group 3: oxytocin 10 IU IV;
Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
14. Three out of six studies use drugs or doses other than the one considered in the question:
 - a. Belgium 99 compares misoprostol 600 mcg orally versus methylergometrine 200 mcg IV;
 - b. Hong Kong 01 compares misoprostol 600 mcg oral after delivery of the baby, versus oxytocin 5 IU + ergometrine 0.5 mg IM at delivery of anterior shoulder;
 - c. Turkey 03 compares 4 groups, all received corresponding placebos:
Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg orally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol;
Group 2: misoprostol 400 mcg orally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol;
Group 3: oxytocin 10 IU IV;
Group 4: oxytocin 10 IU IV plus 1 ml methylergometrine IM.
30. Baseline risk and NNT calculated for the study with larger sample size (85.60% of total weight within the SR).
31. Baseline risk and NNT calculated for the study with larger sample size (76.36% of total weight within the SR).
35. The reported CIs are wide and include 1 in Belgium 99, Hong Kong 01, Turkey 03 and WHO 01; no events both in intervention and control group in WHO 99 and Nigeria 03.

GRADE Evidence Profile 4

QUESTION: Should sublingual misoprostol (600 mcg) be used for all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

Patient or population: low-risk women delivering vaginally or by Caesarean section

Settings: Hospital setting in Hong Kong, China, India and Colombia

Systematic reviews:

- i. (GA 04) Gulmezoglu AM et al. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev last updated 21.07.2006. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|-----------------------|------------|--|--|
| Colombia 2002 (Co 02) | 75 | Misoprostol 50 mcg sublingually after cord clamp | IV oxytocin 16 mIU per minute after cord clamp or methylergometrine 0.2 mg after placenta delivery |
| China 2004 a (Ch 04) | 60 | Misoprostol 600 mcg sublingually | IV syntometrine |
| India 2006 a (In 06) | 100 | Misoprostol 400 mcg sublingually | IV oxytocin 20 IU in 1 litre lactated Ringer's solution at 125 ml/h |

RCTs:

- j. A systematic search was performed for RCTs published after the last update of SR; no RCT was retrieved.

QUESTION: Should sublingual misoprostol (600 mcg) be used for all women by non-skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|---------|--|----------------|--------------------------------------|---------------------------------|------------------------|----------|------------------------|-----------------------|-------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Sublingual Misoprostol | Oxytocin | Baseline risk Oxytocin | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Admission to intensive care unit | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 3 (GA 04) | RCT | | | | | | | | | | | |
| | (Ch 04) | minor limitation ¹ | one trial only | major uncertainty ² -2 | imprecise and sparse data -1 | 30 | 30 | 13.3% (1.0, 25.7) | 2.00 (0.36, 12.76) | NS | very low quality +ooo | |
| | (In 06) | very serious limitation ³ -2 | one trial only | major uncertainty ⁴ -2 | none | 50 | 50 | 92% (84.4, 98.0) | 1.02 (0.92, 1.14) | NS | very low quality oooo | |
| | (Co 02) | very serious limitation ⁵ -2 | one trial only | major uncertainty ⁶ -2 | imprecise data -1 | 25 | 25 | 32.0% (13.3, 50.6) | 0.88 (0.37, 2.05) | NS | very low quality oooo | |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 2 (GA 04) | RCT | | | | | | | | | | | |
| | (In 06) | very serious limitation ³ -2 | one trial only | major uncertainty ⁴ -2 | none | 50 | 50 | 20% (8.8, 31.2) | 0.60 (0.24, 1.53) | NS | very low quality oooo | |
| | (Co 02) | very serious limitation ⁵ -2 | one trial only | major uncertainty ⁶ -2 | imprecise and sparse data -1 | 25 | 25 | 12% (-1.0, 25.0) | 0.33 (0.04, 2.99) | NS | very low quality oooo | |
| Need for blood transfusion | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|------------|--|----------------|--------------------------------------|---------------------------------|------------------------|----------|------------------------|---------------------------------|-------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Sublingual Misoprostol | Oxytocin | Baseline risk Oxytocin | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Additional uterotonics | | | | | | | | | | | | |
| 2 (GA 04) | RCT | | | | | | | | | | | |
| | (Ch 04) | minor limitation ¹ | one trial only | major uncertainty ² -2 | imprecise and sparse data -1 | 30 | 30 | 0% | not estimable | NS | very low quality +ooo | |
| | (In 06) | very serious limitation ³ -2 | one trial only | major uncertainty ⁴ -2 | none | 50 | 50 | 36.0% (22.5, 49.4) | 0.89 (0.51, 1.54) | NS | very low quality oooo | |
| Blood loss (MD, measured in mL) | | | | | | | | | | | | |
| 2 (GA 04) | RCT | | | | | | | | | | | |
| | (In 06) | very serious limitation ³ -2 | one trial only | major uncertainty ⁴ -2 | none | 50 | 50 | - | MD -155.0 (-257.5, -52.4) | - | very low quality oooo | |
| | (Co 02) | very serious limitation ⁵ -2 | one trial only | major uncertainty ⁶ -2 | imprecise data -1 | 25 | 25 | - | MD -77.6 (-275.8, 120.6) | - | very low quality oooo | |
| Postpartum anaemia | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | |
| Establishment of breastfeeding | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|------------|--|----------------|--------------------------------------|----------------------|------------------------|----------|------------------------|-----------------------|---------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Sublingual Misoprostol | Oxytocin | Baseline risk Oxytocin | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Side effect requiring treatment | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Nausea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Vomiting | | | | | | | | | | | | |
| 2 (GM 04) | RCT | | | | | | | | | | | |
| | (In 06) | no serious limitation ³ | one trial only | Major uncertainty ⁴ -2 | imprecise data -1 | 50 | 50 | 12.0% (2.9, 21.1) | 1.33 (0.50, 3.56) | NS | very low quality +ooo | |
| | (Co 02) | very serious limitation ⁵ -2 | one trial only | Major uncertainty ⁶ -2 | imprecise data -1 | 25 | 25 | 4.0% (-3.8, 11.8) | not estimable | not estimable | very low quality oooo | |
| Diarrhoea | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | |
| Headache | | | | | | | | | | | | |
| 1 (GA 04) | RCT | | | | | | | | | | | |
| | (In 06) | no serious limitation ³ | one trial only | Major uncertainty ⁴ -2 | imprecise data -1 | 50 | 50 | 16.0% (5.7, 26.2) | 0.75 (0.28, 2.00) | NS | very low quality +ooo | |
| Abdominal pain | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | |
| High blood pressure | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|------------|--|----------------|--------------------------------------|---------------------------------|------------------------|----------|------------------------|-----------------------|---------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Sublingual Misoprostol | Oxytocin | Baseline risk Oxytocin | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Shivering | | | | | | | | | | | | |
| 2 (GA 04) | RCT | | | | | | | | | | | |
| | (In 06) | no serious limitation ³ | one trial only | major uncertainty ⁴ -2 | imprecise data -1 | 50 | 50 | 4% (-1.5, 9.5) | 6.50 (1.55, 27.33) | 5 (2.8, 11.7) | very low quality +ooo | |
| | (Co 02) | Very serious limitation ⁵ -2 | one trial only | major uncertainty ⁶ -2 | imprecise and sparse data -1 | 25 | 25 | 0% | not estimable | not estimable | very low quality oooo | |
| Temp >38° C | | | | | | | | | | | | |
| 1 (GA 04) | RCT | | | | | | | | | | | |
| | (In 06) | no serious limitation ³ | one trial only | major uncertainty ⁴ -2 | imprecise data -2 | 50 | 50 | 4.0% (-1.5, 9.5) | 4.00 (0.89, 17.91) | NS | very low quality oooo | |
| Temp >40° C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Maternal death | | | | | | | | | | | | |
| 0 | | | | | | | | | | | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

Notes:

1. Open, randomized trial. Randomization generated by a random number table. Blood loss was both estimated visually and measured using alkaline hematin technique.
2. Misoprostol 600 mcg sublingually versus syntometrine IV. 60 low-risk women delivering vaginally.
3. Randomization by computer-generated random number list, allocation concealment by opening sealed opaque envelopes. Blood loss measurement: volume of blood in the suction bottle during Caesarean section + weighing of blood-soaked linen.

4. Misoprostol 400 mcg sublingually versus 20 IU oxytocin in 1 litre lactated Ringer's solution at 125 ml/h. 100 women undergoing Caesarean section and with spinal anaesthesia. Surgical management of the third stage.
5. Method of random allocation not stated. No placebo use or blinding of outcome assessments. Method of collection or estimation of blood loss not stated. No reported post randomization exclusions or loss to follow up.
6. Misoprostol 50 mcg sublingually after cord clamp versus oxytocin 16 mIU per minute intravenously after cord clamp versus methylergometrine 0.2 mg after placenta delivery. Exclusion criteria: asthma, coagulopathy, twins, stillbirth, lacerations and "amniotic fluid in the blood collection". No information about management of third stage.

Summary of findings 4

SCENARIO: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of sublingual misoprostol (600 mcg)?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|---------------------|-------------|---|--|----------|-----------------------------|---------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 2 Co 02 In 06 | 150 | min 12% (-1, 25) max 20% (8.8, 31.2) | 0.33 (0.04, 2.99) 0.60 (0.24, 1.53) | NS NS | very low quality oooo | 3,4,5,6 | - |
| | Need for blood transfusion | No data available | - | - | - | - | - | - | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

- Randomization by computer-generated random number list, allocation concealment by opening sealed opaque envelopes. Blood loss measurement: volume of blood in the suction bottle during Caesarean section + weighing of blood-soaked linen.
- Misoprostol 400 mcg sublingually versus 20 IU oxytocin in 1 litre lactated Ringer's solution at 125 ml/h. 100 women undergoing Caesarean section and with spinal anaesthesia. Surgical management of the third stage.
- Method of random allocation not stated. No placebo use or blinding of outcome assessments. Method of collection or estimation of blood loss not stated. No reported post randomization exclusions or loss to follow up.
- Misoprostol 50 mcg sublingually after cord clamp versus oxytocin 16 mIU per minute intravenously after cord clamp versus methylergometrine 0.2 mg after placenta delivery. Exclusion criteria: asthma, coagulopathy, twins, stillbirth, lacerations and "amniotic fluid in the blood collection". No information about management of third stage.

GRADE Evidence Profile 5

QUESTION: Should rectal misoprostol (600 mcg) be used for all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

Patient or population: women expected to deliver vaginally.

Settings: Hospital setting in Canada, Mozambique, South Africa, Turkey, USA.

Systematic reviews and RCTs:

- k. (GA 04) Gulmezoglu AM et al. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev. updated 21.07.2006. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|---------------------------|------------|---|---|
| South Africa 1998 (So 98) | 491 | Misoprostol 400 mcg rectally | IM ergometrine-oxytocin 1 ampoule |
| Mozambique 2001 (Mo 01) | 663 | Misoprostol 400 mcg dissolved in 5 ml saline and administered rectally as a micro-enema | IM oxytocin 10 IU |
| USA 2001 (US 01) | 400 | Misoprostol 400 mcg rectally | IV oxytocin 20 IU |
| Canada 2002 (Ca 02) | 223 | Misoprostol 400 mcg rectally after delivery | IV or IM oxytocin 5 IU , or IM oxytocin 10 IU given after delivery (sometimes given after placenta delivered) |
| Turkey 2002 (Tu 02) | 1633 | Group 1: oxytocin 10 IU IV plus misoprostol 400 mcg rectally after cord clamp, followed by 2 doses 4 and 8 hours after delivery of 100 mcg misoprostol . Group 2: misoprostol 400 mcg rectally after cord clamp followed by 2 doses 4 hours apart of 100 mcg misoprostol . | IV oxytocin 10 IU or IV oxytocin 10 IU IM plus methylergometrine 1 ml . |

RCTs:

- I. A systematic search was performed for RCTs published after the last update of SR; no RCT was retrieved.

QUESTION: Should rectal misoprostol (600 mcg) be used for all women by non- skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------------------|--------|-------------------------------|----------------------------|-----------------------------|--------------------------------|---------------------|----------|--|-----------------------|------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | Imprecise or sparse data -1 | 396 | 407 | Not estimable | Not estimable | Not estimable | low quality ++oo | |
| Admission to ICU | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Blood loss ≥ 500 ml | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 8,1% (5.4, 10.8) | 1.21 (0.78, 1.89) | NS | moderate quality +++o | |
| 3 GA 04 So 98 Mo 01 US 01 | RCT | Serious limitations [2] -1 | No important inconsistency | Major uncertainty [3] -2 | | 708 | 733 | Min 0.4% (-0.4, 1.3) Max 37.9% (37.6, 45.4) | 1.11 (0.87, 1.43) | Min NS Max NS | very low quality +ooo | |
| Blood loss ≥ 1000 ml | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 3.4% (1.7, 5.2) | 1.25 (0.62-2.50) | NS | moderate quality +++o | |
| 2 GA 04 Mo 01 US 01 | RCT | Serious limitations [4] -1 | [5] | Major uncertainty [6] -2 | | 477 | 500 | Min 0.3% (-0.3, 0.9) Max 8.7% (4.3, 13.0) | 1.05 (0.53, 2.05) | Min NS Max NS | very low quality +ooo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|--------------------------------|----------------------------|------------------------------|----------------------|---------------------|----------|---|-----------------------|------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Need for blood transfusion | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 3.2% (1.5, 4.9) | 0.95 (0.44, 2.05) | NS | moderate quality +++o | |
| 3 GA 04 Mo 01 US 01 Ca 02 | RCT | Serious limitations [7] -1 | No important inconsistency | Major uncertainty [8] -2 | | 592 | 618 | Min 0.3% (-0.3, 0.9) Max 1.20% (0.46, 2.87) | 1.40 (0.31, 6.19) | Min NS Max NS | very low quality +ooo | |
| Additional uterotonics | | | | | | | | | | | | |
| 3 GA 04 Ca 02 Mo 01 US 01 | RCT | Serious limitations [7] -1 | No important inconsistency | Major uncertainty [8] -2 | | 592 | 618 | 10.8% (6.1, 15.6) [9] | 1.64 (1.16-2.31) | -8 (-27, -5) [9] | very low quality +ooo | |
| Mean blood loss (measured in WMD, ml) | | | | | | | | | | | | |
| 2 GA 04 So 98 Mo 01 | RCT | Minor limitations [10] | [5] | Major uncertainty [11] -2 | | 554 | 572 | - | 1.77 (-10.07, 13.60) | - | low quality ++oo | |
| Postpartum anaemia | | | | | | | | | | | | |
| 1 GA04 US 01 | RCT | Serious limitations [12] -1 | One trial only | Major uncertainty [13] -2 | | 151 | 160 | 49.4% (41.6, 57.1) | 1.18 (0.46, 1.45) | NS | very low quality +ooo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------------------|--------|-------------|-------------|------------|----------------------|---------------------|----------|---|-----------------------|-------------|---------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Establishment of breastfeeding | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|------------------------|----------------|------------------------------|-------------------------------------|---------------------|----------|---|-----------------------|------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Side effect requiring treatment: manual removal of placenta | | | | | | | | | | | | |
| 1 GA 04 Ca 02 | RCT | Minor limitations [14] | One trial only | Major uncertainty [15] -2 | | 110 | 113 | 5.3% (1.2, 9.5) | 0.17 (0.02, 1.40) | NS | low quality ++oo | |
| Nausea | | | | | | | | | | | | |
| 1 GA 04 Ca 02 | RCT | Minor limitations [14] | One trial only | Major uncertainty [15] -2 | | 105 | 110 | 4.5% (0.6, 8.5) | 1.68 (0.57, 4.96) | NS | low quality ++oo | |
| Vomiting | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | Imprecise or sparse data [16] -1 | 396 | 407 | 0.5% (0.2, 1.2) | 1.03 (0.15, 7.26) | NS | low quality ++oo | |
| 2 GA 04 Ca 02 Mo 01 | RCT | Minor limitations [17] | [5] | Major uncertainty [18] -2 | Imprecise or sparse data [16] -1 | 428 | 447 | Min 0.3% (-0.3, 0.9) Max 3.6% (0.1, 7.1) | 1.67 (0.56, 5.02) | Min NS Max NS | very low quality +ooo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------------------|--------|------------------------|----------------------------|-----------------------------|-------------------------------------|---------------------|----------|---|-----------------------|------------------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Diarrhoea | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 2.2% (0.8, 3.6) | 1.26 (0.53, 3.00) | NS | moderate quality +++o | |
| 1 GA 04 Mo 01 | RCT | Minor limitations [19] | One trial only | Major uncertainty [20] -2 | Imprecise or sparse data [16] -1 | 323 | 338 | 0.6% (-0.2, 1.4%) | 0.21 (0.01, 4.34) | NS | very low quality +ooo | |
| Headache | | | | | | | | | | | | |
| 1 GA 04 Ca 02 | RCT | Minor limitations [14] | One trial only | Major uncertainty [15] -2 | | 105 | 110 | 3.6% (0.1, 7.1) | 2.36 (0.75, 7.42) | NS | low quality ++oo | |
| Abdominal pain | | | | | | | | | | | | |
| 1 GA 04 Ca 02 | RCT | Minor limitations [14] | One trial only | Major uncertainty [15] -2 | | 105 | 110 | 11.8% (5.8, 17.8) | 0.97 (0.46-2.02) | NS | low quality ++oo | |
| High blood pressure | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Shivering | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 3.9% (2.0, 5.8) | 3.02 (1.74, 5.23) | 13 (9, 24) | moderate quality +++o | |
| 3 GA 04 Ca 02 Mo 01 US 01 | RCT | Minor limitations [21] | No important inconsistency | Major uncertainty [8] -2 | | 587 | 613 | Min 4.2% (1.1, 7.3) Max 15.1% (11.3, 19.0) | 2.23 (1.74, 2.86) | Min NS Max 4 (3, 6) | low quality ++oo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|----------|------------------------|----------------|----------------------------|-------------------------------------|---------------------|----------|---|-----------------------|--------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Rectal Misoprostol | Oxytocin | Baseline risk in oxytocin group (95%CI) | Relative risk (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Temp >38° C | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT | No limitations | One trial only | Some uncertainty [1] -1 | | 396 | 407 | 1.5% (0.3, 3.6) | 2.74 (1.08, 6.93) | 39 (21, 336) | moderate quality +++o | |
| 1 GA 04 Ca 02 | RCT | Minor limitations [14] | One trial only | Major uncertainty [15] -2 | | 107 | 112 | 10.7% (5.0, 16.5) | 1.74 (0.90-3.39) | NS | low quality ++oo | |
| Temp >40° C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Maternal death | | | | | | | | | | | | |
| 1 GA 04 Tu 02 | RCT [22] | No limitations | One trial only | Some uncertainty [1] -1 | Imprecise or sparse data [16] -1 | 396 | 407 | - | - | - | low quality ++oo | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

Notes:

[1] The study (Turkey 2002) includes only women of low socioeconomic status.

[2] The study with major weight on effect estimation (USA 2001) has 18.75% exclusions after randomization and blind outcome assessments not mentioned. In one trial (Mozambique 2001) generation of allocation sequence is unclear. In one trial (South Africa 1998a) outcome assessments were not blinded.

[3] All studies used a treatment dose of 400mcg of misoprostol versus oxytocin combined with ergometrine IM (South Africa 1998a), oxytocin 20 IU i.v. (USA 2001) or oxytocin 10 IU IM (Mozambique 2001). Two trials (South Africa 1998a and USA 2001) include only low-risk women. In two trials (USA 2001 and Mozambique 2001) there is no mention of III stage management.

[4] The study with major weight on effect estimation (USA 2001) has 18.75% exclusions after randomization and blind outcome assessments not mentioned. In one trial (Mozambique 2001) generation of allocation sequence is unclear.

[5] It was difficult to comment on consistency of results due to the small number of trials.

[6] The studies used a treatment dose of 400mcg of misoprostol. One study (USA 2001) used 20 IU i.v of oxytocin and includes only low-risk women. In both trials there is no mention of III stage management.

- [7] The study with major weight on effect estimation or a crucial role on statistical significance of results (USA 2001) has 18.75% exclusions after randomization and blind outcome assessments not mentioned. In one trial (Mozambique 2001) generation of allocation sequence is unclear. In one trial (Canada 2002) treatment and outcome assessments were not blinded.
- [8] All studies used a treatment dose of 400mcg of misoprostol versus 5 IU i.v. or 10 IU IM (Canada 2002), 20 IU i.v. (USA 2001) or 10 IU (Mozambique 2001) of oxytocin. Two trials (Canada 2002 and USA 2001) include only low-risk women. All trials have no description of III stage management.
- [9] In this case NNT is calculated from the trial with an intermediate baseline risk (10.8%) that carries to a significant result, and weights 40% on metanalysis.
- [10] One study (Mozambique 2001) has generation of allocation sequence unclear. In one trial (South Africa 1998a) outcome assessments were not blinded.
- [11] The studies used a treatment dose of 400mcg of misoprostol. One trial (South Africa 1998a) used oxytocin combined with ergometrine IM and included only low-risk women. One trial (Mozambique 2001) has no mention of III stage management.
- [12] The study (USA 2001) has 18.75% exclusions after randomization and blind outcome assessments not mentioned.
- [13] The study (USA 2001) used a treatment dose of 400mcg of misoprostol versus 20 IU i.v. of oxytocin. Parameter considered is the number of patients with a drop of haemoglobin values of 10% from admission to postpartum day 1. The trial includes only low-risk women and has no mention of III stage management.
- [14] Treatment and outcome assessments were not blinded.
- [15] The study used a treatment dose of 400mcg of misoprostol versus 5 IU i.v. or 10 IU IM; includes only low-risk women and has no mention of III stage management.
- [16] The numbers involved in this study are too small. The CI is wide and crossed 1.
- [17] In one study (Canada 2002) treatment and outcome assessments were not blinded. One study (Mozambique 2001) has generation of allocation sequence unclear.
- [18] The studies used a treatment dose of 400mcg of misoprostol versus 5 IU i.v. or 10 IU IM (Canada 2002) or 10 IU (Mozambique 2001) of oxytocin. One trial (Canada 2002) includes only low-risk women. All trials have no mention of III stage management.
- [19] Generation of allocation sequence is unclear.
- [20] The study used a treatment dose of 400mcg of misoprostol and has no mention of III stage management.
- [21] One study (USA 2001) has 18.75% exclusions after randomization and blind outcome assessments not mentioned but has low weight on effect estimation. In one trial (Mozambique 2001) generation of allocation sequence is unclear. In one trial (Canada 2002) treatment and outcome assessments were not blinded.
- [22] The study is the same trial considered in beneficial outcomes.

Summary of findings 5

SCENARIO: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of rectal misoprostol (600 mcg)?

Patient or population:

Information sources:

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|------------|-------------|---|-------------------------|---------------|--------------------------|-------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | 1 Tu 02 | 803 | Not estimable | Not estimable | Not estimable | low quality ++oo | - | - |
| | Blood loss ≥1000 ml | 1 Tu 02 | 803 | 3.4% (1.7, 5.2) | 1.25 (0.62, 2.50) | NS | moderate quality +++o | 1 | - |
| | Need for blood transfusion | 1 Tu 02 | 803 | 3.2% (1.5, 4.9) | 0.95 (0.44, 2.05) | NS | moderate quality +++o | 1 | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

1. The study (Turkey 2002) includes only women of low socioeconomic status.

GRADE Evidence Profile 6

QUESTION: Should carboprost 0.25 mg IM/sulprostone 0.5 mg IM be used for all women by skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

Patient or population: all women in third stage of labour

Settings: hospital setting in developed and developing countries

Systematic reviews and RCTs:

m. (GA 06) Gulmezoglu AM et al. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev updated 21.07.2006. See the table below for RCTs included in this SR used for producing the evidence profile.

| Name, Year (initials) | Population | Intervention | Control |
|------------------------|------------|--|---|
| India 1988 c (In 88) | 300 | PGF2alpha 0.125 mg IM | Methylergometrine 0.2 mg IV. |
| Holland 1991 (Ho 91) | 74 | Sulprostone 0.5 mg IM | Oxytocin 5 IU IM |
| Egypt 1993 (Eg 93) | 150 | Carboprost trometamol 0.250 mg IM | Methylergometrine maleate 0.2 mg IV. |
| UK 1994 (UK 94) | 60 | 15-methyl prostaglandin F2alpha, 125 mcg intramyometrial started after delivery of the baby but before delivery of the placenta | 5 IU oxytocin IV bolus injection followed by 15 IU in 500 ml of Ringer's Lactate solution started after delivery of the baby but before delivery of the placenta |
| Holland 1995 (Ho 95) | 69 | Sulprostone 0.5 mg IM at delivery of anterior shoulder | Oxytocin 5 IU IM at delivery of anterior shoulder + methylergometrine 0.2 mg intramuscularly after delivery of placenta |
| Singapore 1995 (Si 95) | 115 | Carboprost trometamol 125 mcg IM | Ergometrine-oxytocin 0.5 mg IM |
| Egypt 1997 (Eg 97) | 132 | Carboprost trometamol 250 mcg IM | Methylergonovine maleate 0.4 mg IV, or oxytocin 10 IU IV. |
| India 2001 (In 01) | 120 | Carboprost 0.250 mg IM | Methylergometrine 0.2 mg IV or Oxytocin 10 IU in 10 ml saline into the umbilical cord; |

RCTs:

n. A systematic search was performed for RCTs published after the last update of SR; no RCT was retrieved.

QUESTION: Should carboprost 0.25 mg IM/sulprostone 0.5 mg IM be used for all women by non-skilled providers to prevent PPH instead of oxytocin (10 IU IM)?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one SR. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------------|------------------------|------------------------------------|-------------------------------|-------------------------------------|-------------------------------|-------------------|---|-----------------------|------------------|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Admission to intensive care unit | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Blood loss ≥ 500 ml (Low risk women) | | | | | | | | | | | | |
| 1 GM 06 Ho 91 | RCT [1] | minor limitation [2] | one trial only | some uncertainty [3] -1 | imprecise or sparse data [28] -1 | 22 | 28 | 25% (8.7, 41.3) | 1.10 (0.40, 3.00) | NS | low quality ++oo | |
| Blood loss ≥ 500 ml (High risk women) | | | | | | | | | | | | |
| 2 GM 06 Ho 95 In 01 | RCT [4,5] | minor limitation [6,7] | important inconsistency [27] -1 | major uncertainty [8,9] -2 | imprecise or sparse data -1 | 73 | 76 | min 7.5% (-0.8, 15.8) max 44.4% (28.0, 60.9) | 1.02 (0.62, 1.68) | min NS max NS | very low quality oooo | |
| Blood loss ≥ 1000 ml (Low risk women) | | | | | | | | | | | | |
| 1 GM 06 Ho 91 | RCT [1] | minor limitation [2] | one trial only | some uncertainty [3] -1 | imprecise or sparse data [29] -1 | 22 | 28 | 7.1% (-2.6, 16.9) | 0.64 (0.06, 6.57) | NS | low quality ++oo | |
| Blood loss ≥ 1000 ml (High risk women) | | | | | | | | | | | | |
| 1 GM 06 Ho 95 | RCT [4] | minor limitation [6] | one trial only | major uncertainty [8] -2 | imprecise or sparse data [29] -1 | 33 | 36 | 25% (10.7, 39.3) | 0.36 (0.11, 1.23) | NS | very low quality +ooo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|-------------------------------|--|----------------------------|---|--------------------------------|-------------------------------|-------------------|-----------------------------------|-----------------------------|---------------------------------|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Need for blood transfusion (Low risk women) | | | | | | | | | | | | |
| 1 GM 06 UK 94 | RCT [10] | no limitation | one trial only | major uncertainty [11] -2 | imprecise or sparse data -1 | 30 | 30 | 6.7% (-2.4, 15.7) | 2.0 (0.40, 10.11) | NS | very low quality +ooo | |
| Need for blood transfusion (High risk women) | | | | | | | | | | | | |
| 1 GM 06 Ho 95 | RCT [4] | minor limitation [6] | one trial only | major uncertainty [8] -2 | imprecise or sparse data -1 | 33 | 36 | 13.9% (2.4%-25.3%) | 0.65 (0.17-2.53) | NS | very low quality +ooo | |
| Additional uterotonics (low risk women only) | | | | | | | | | | | | |
| 3 GM 06 Ho 91 UK 94 Si 95 | RCT [1,10,12] | minor limitation [2,13] | no important inconsistency | major uncertainty [3,11,14] -2 | imprecise or sparse data -1 | 106 | 116 | min 0 max 3.33% (-3.20, 9.87) | 2.5 (0.39, 10.92) | min not estimable max NS | very low quality +ooo | |
| Mean blood loss (measured in WMD, mL) | | | | | | | | | | | | |
| 6 GM 06 Ho 91 Ho 95 UK 94 Eg 93 In 88 Eg 97 | RCT [1, 4, 10, 15, 18, 19] | serious limitation [2, 6, 16, 20, 21] -1 | no important inconsistency | major uncertainty [3,8,11,17,22, 23] -2 | | 353 | 364 | | WMD -70.49 (-73.20, -67.77) | | very low quality +ooo | |
| Postpartum anaemia | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Establishment of breastfeeding | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|-------------------------------|-------------------|-----------------------------------|-----------------------|-------------|---------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|----------------|-------------------------|----------------------------|---------------------------------|--------------------------------|-------------------------------|-------------------|-----------------------------------|-----------------------|-----------------------------|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Side effect requiring treatment: manual removal of placenta (Low risk women) | | | | | | | | | | | | |
| 2 GM06 Ho 91 Si 95 | RCT [1,12] | minor limitation [13] | only one trial with events | some uncertainty [3,14] -1 | imprecise or sparse data -1 | 76 | 86 | Not estimable | 3.22 (0.13, 77.34) | NS | low quality +oo | |
| Side effect requiring treatment: manual removal of placenta (High risk women) | | | | | | | | | | | | |
| 1 GM 06 Ho 95 | RCT [4] | minor limitation [6] | one trial only | major uncertainty [8] -2 | imprecise or sparse data -1 | 33 | 36 | 11,1% (0.7, 21,5) | 0.82 (0.20, 3.39) | NS | very low quality +ooo | |
| Nausea (Low risk women) | | | | | | | | | | | | |
| 2 GM 06 Ho 91 Eg 93 | RCT [1,15] | minor limitation [2,16] | not inconsistency | major uncertainty [3,17] -2 | imprecise or sparse data -1 | 95 | 105 | min 0 max 1.30% (-1.25, 3.84) | 1.05 (0.07, 16,55) | NS | very low quality +ooo | |
| Nausea (High risk women) | | | | | | | | | | | | |
| 1 GM 06 In 01 | RCT [5] | minor limitation [7] | one trial only | major uncertainty [9] -2 | imprecise or sparse data -1 | 40 | 40 | 0 | 5 (0.25, 100.97) | NS | very low quality +ooo | |
| Vomiting (Only low risk women) | | | | | | | | | | | | |
| 2 GM 06 UK 94 Eg 93 | RCT [10,15] | minor limitation [16] | not inconsistency | major uncertainty [11,17] -2 | imprecise data -1 | 103 | 107 | min 0 max 1.30% (-1.25, 3.84) | 10.74 (2.06, 53.02) | min NS max 7 (4.2, 16.1) | very low quality +ooo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|----------------------------------|-------------------|-----------------------------|-----------------------------|---------------------------------------|-------------------------------------|-------------------|-----------------------------------|----------------------------------|--------------------|--------------------------------------|--------------------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Diarrhoea (Low risk women) | | | | | | | | | | | | |
| 3 | GM 06 UK 94 Eg 93 Si 95 | RCT [10,12,15] | minor limitation [13,16] | not inconsistency | major uncertainty [11,14,17] -2 | imprecise or sparse data [24] -1 | 157 | 165 | min 0 max 3.33% (-3.20, 9.87) | 6.65 (2.03, 21.85) | min 12 (6.9, 53.3) max NS [25] | very low quality +ooo |
| Diarrhoea (High risk women) | | | | | | | | | | | | |
| 1 | GM 06 In 01 | RCT [5] | minor limitation [7] | one trial only | major uncertainty [9] -2 | imprecise or sparse data -1 | 40 | 40 | 0 | 15 (0.89, 254.13) | 6 (3.4, 17.9) | very low quality +ooo |
| Headache (Only high risk women) | | | | | | | | | | | | |
| 1 | GM 06 In 01 | RCT [5] | minor limitation [7] | one trial only | major uncertainty [9] -2 | imprecise or sparse data -1 | 40 | 40 | 5% (-1.84, 11.84) | 2 (0.39, 10.31) | NS | very low quality +ooo |
| Abdominal pain (low risk women) | | | | | | | | | | | | |
| 2 | GM 06 Si 95 Eg 93 | RCT [12,15] | minor limitation [13,16] | not important inconsistency | major uncertainty [14,17] -2 | imprecise and sparse data -1 | 127 | 135 | min 0 max 3.45 (-1.29, 8.19) | 5.33 (1.40, 20.30) | min 12 (6.9, 53.3) max NS | very low quality +ooo |
| Abdominal pain (high risk women) | | | | | | | | | | | | |
| 1 | GM 06 Ho 95 | RCT [4] | minor limitation [6] | one trial only | major uncertainty [8] -2 | imprecise or sparse data -1 | 33 | 36 | 0 | 3.26 (0.14, 77.46) | NS | very low quality +ooo |
| High blood pressure | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Shivering | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|-------------|-----------------------|----------------|------------------------------|----------------------|-------------------------------|-------------------|-----------------------------------|-----------------------|--------------------|---------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Carboprost IM/ sulprostone IM | Other uterotonics | Baseline risk (other uterotonics) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Temp >38 °C | | | | | | | | | | | | |
| 1 GM 06 Si 95 | RCT [12] | minor limitation [13] | one trial only | major uncertainty [14] -2 | | 54 | 58 | 0 | not estimable [26] | not estimable [26] | low quality ++oo | |
| Temp >40 °C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Maternal death | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |

Notes:

- Holland 91: 74 low-risk women with spontaneous labour and vaginal delivery.
- Holland 91: Method of generation of numbers was not stated. Outcome assessments were not blinded. More multiparous women with fewer episiotomies in the sulprostone group despite randomization.
- Holland 91: Sulprostone 0.5 mg IM vs oxytocin 5 IU IM.
- Holland 95: 69 women with a history of previous postpartum blood loss of more than 1000 ml.
- India 01: 120 women with at least one risk factor for atonic haemorrhage.
- Holland 95: 12/81 (15%) excluded after randomization and before the intervention. No further exclusions after participation in the trial.
- India 01: No details on randomization method. Blood loss measurement not mentioned.
- Holland 95: Sulprostone 0.5 mg IM at delivery of anterior shoulder + placebo after delivery of placenta versus oxytocin 5 IU IM at delivery of anterior shoulder + methylergometrine 0.2 mg intramuscularly after delivery of placenta.
- India 01: Group A: Methylergometrine 0.2 mg IV; Group B: Oxytocin 10 IU in 10 ml saline into the umbilical cord; Group C: Carboprost 0.250 mg IM.
- UK 94: 60 low-risk women undergoing elective Caesarean section in an academic hospital. Exclusion criteria: hypertensive disease, asthma, heart disease.
- UK 94: women undergoing elective Caesarean section in an academic hospital. Prostaglandin group: 15-methyl prostaglandin F2alpha, 125 mcg intramyometrial + placebo. Oxytocin group: 5 IU oxytocin IV bolus injection followed by 15 IU in 500 ml of Ringer's Lactate solution + placebo. Both interventions were started after delivery of the baby but before delivery of the placenta.
- Singapore 95: 115 women with spontaneous labour and delivery in Singapore. Exclusion criteria: multiple pregnancy, any antenatal complications.
- Singapore 95: 3/115 (2.6%) women were excluded after randomization.
- Singapore 95: carboprost trometamol 125 mcg IM versus ergometrine-oxytocin 0.5 mg IM.
- Egypt 93: 150 low-risk women after vaginal delivery. Excluded: labour <2 hours; prolonged labour (>24 hours); magnesium sulphate therapy during labour; history of postpartum haemorrhage, chorioamnionitis, multiple pregnancy, antepartum haemorrhage and episiotomy.

16. Egypt 93: no mention of blinding or placebo use.
17. Egypt 93: carboprost trometamol 0.250 mg IM versus methylergometrine maleate 0.2 mg IV.
18. India 88c: 300 women in three centres in India. No mention of risk status. No note of exclusion criteria. This trial weight 90.98% in SR.
19. Egypt 97: 132 high-risk women after vaginal delivery. "High risk" risk factors included: previous history of postpartum haemorrhage, high parity, uterine overdistention due to multiple pregnancy, polyhydramnios or fetal macrosomia, prolonged labour, placental abnormalities or chorioamnionitis. Exclusion criteria: organic heart disease, bronchial asthma, epilepsy, renal disease, Caesarean section, episiotomy.
20. India 88c: no placebo use or blinding of outcome assessments; no mention of third stage management technique.
21. Egypt 97: no mention of blinding or placebo use.
22. India 88c: PGF2alpha 0.125 mg IM versus methylergometrine 0.2 mg IV.
23. Egypt 97: Carboprost trometamol* 250 mcg IM versus methylergonovine maleate 0.4 mg IV, versus oxytocin 10 IU IV.
24. In two trials there were no events in the control or in-treatment groups.
25. Singapore 1995: weight in SR 27.94%. RR 17.19 (2.36, 125.22). Baseline risk 1.79% (-1.71, 5.29). NNH 4 (2.5, 6.6).
26. No events both in treatment and in control group.
27. Inconsistent result from differences in baseline risks.
28. The numbers involved in this study are small. The CI is wide and crossed 1.
29. The difference detected between low- and high-risk groups is in the extent, not in the direction of effect.

Summary of findings 6

SCENARIO: Should oxytocin (10 IU IM) be used for all women to prevent PPH instead of carboprost 0.25 mg IM/sulprostone 0.5 mg IM?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|----------------------|-------------|---|-------------------------|-----|-------------------------------|----------------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 2 Low risk Ho 91 | 50 | 7.1 % (-2.6, 16.9) | 0.64 (0.06, 6.57) | NS | very low quality +ooo | 1,2,3,4,6,8,29 | - |
| | | | 69 | 25% (10.7, 39.3) | 0.36 (0.11, 1.23) | NS | very very low quality oooo | | |
| | Need for blood transfusion | 2 Low risk UK 94 | 60 | 6.7% (-2.4, 15.7) | 2.0 (0.40, 10.11) | NS | very low quality +ooo | 4,6,8,10,11 | - |
| | | | 69 | 13.9% (2.4, 25.3) | 0.65 (0.17, 2.53) | NS | very low quality +ooo | | |
| | Harms | None judged critical | | | | | | | |

Notes:

- Holland 91: 74 low-risk women with spontaneous labour and vaginal delivery.
- Holland 91: Method of generation of numbers was not stated. Outcome assessments were not blinded. More multiparous women with fewer episiotomies in the sulprostone group despite randomization.
- Holland 91: Sulprostone 0.5 mg IM vs oxytocin 5 IU IM.
- Holland 91: 69 women with a history of previous postpartum blood loss of more than 1000 ml.
- Holland 95: 12/81 (15%) excluded after randomization and before the intervention. No further exclusions after participation in the trial.

8. Holland 95: Sulprostone 0.5 mg IM at delivery of anterior shoulder + placebo after delivery of placenta versus oxytocin 5 IU IM at delivery of anterior shoulder + methylergometrine 0.2 mg intramuscularly after delivery of placenta.
10. UK 94: 60 low-risk women undergoing elective Caesarean section in an academic hospital. Exclusion criteria: hypertensive disease, asthma, heart disease.
11. UK 94: women undergoing elective Caesarean section in an academic hospital. Prostaglandin group: 15-methyl prostaglandin F2alpha, 125 mcg intramyometrial + placebo. Oxytocin group: 5 IU oxytocin IV bolus injection followed by 15 IU in 500 ml of Ringer's Lactate solution + placebo. Both interventions were started after delivery of the baby but before delivery of the placenta.
29. The difference detected between low- and high-risk groups is in the extent, not in the direction of effect.

GRADE Evidence Profile 7

QUESTION: In the absence of active management, should uterotonics be used alone for prevention of PPH by skilled providers?

Patient or population: Women who expected to deliver vaginally

Settings: Two university hospitals, a midwifery school and independent midwives in the Netherlands; hospital in Sweden; community setting (four primary health-centre areas) in rural India, with drugs administered by auxiliary nurses-midwives opportunely trained

Systematic reviews: Cotter A, Ness A, Tolosa J. Prophylactic oxytocin for the third stage of labour. Cochrane Database of Systematic Reviews 2001, Issue 4 (CA 01).

| Name, Year (initials) | Population | Intervention | Control |
|--|------------|--|----------------------------|
| DeGroot 96 (DG 96) Nordstrom 1997 (NL 97) | 1221 | DG 96: IM 5 IU oxytocin NL 97: IV 10 IU oxytocin immediately after birth of baby | Placebo + expectant |

RCTs:

- o. Derman RJ et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. Lancet. 2006;368:1248-53

| Name, Year (initials) | Population | Intervention | Control |
|-----------------------|------------|--------------------------------------|----------------|
| India 2006 (In 06) | 1620 | Misoprostol 600 mcg orally | Placebo |

QUESTION: In the absence of active management, should uterotonics be used alone for prevention of PPH by non-skilled providers?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from one RCT. The source of the information is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included study. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|--------|----------------------------|----------------------------|-------------------------------------|----------------------|---------------------|---------|--|-----------------------|----------------------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Utero-tonics | Placebo | Baseline risk (placebo) (95% CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Maternal deaths | | | | | | | | | | | | |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | Sparse data -1 | 812 | 808 | 0.1% (-0.1, 0.4) | 0.33 (0.01, 8.13) | NS | ⊕⊕⊕0 | 8.5 |
| Admission to intensive care unit | | | | | | | | | | | | |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | Sparse data -1 | 812 | 808 | 0.2% (-0.1, 0.6) | 1 (0.14, 7.05) | NS | ⊕⊕⊕0 | 6.4 |
| Blood loss ≥500 ml | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | None | 591 | 630 | min 35.93% (31.67, 40.20) max 38.46% (30.46, 46.46) | 0.61 (0.51, 0.73) | min NS max 6 (4.7, 9.8) | ⊕⊕⊕0 | 6.3 |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | None | 812 | 808 | 12% (9.8, 14.2) | 0.53 (0.39, 0.74) | 18 (11.9, 35.8) | ⊕⊕⊕⊕ | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|-------------------------------|----------------------------|-------------------------------------|----------------------|---------------------|---------|--|-----------------------|-------------------------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Uterotonics | Placebo | Baseline risk (placebo) (95% CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Blood loss ≥1000 ml | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | None | 591 | 630 | min 8.83% (6.31, 11.35) max 11.19% (6.0, 16.37) | 0.73 (0.49, 1.07) | NS | ⊕⊕⊕0 | 7.7 |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | Sparse data -1 | 812 | 808 | 1.2% (0.5, 2.0) | 0.20 (0.04, 0.91) | 101 (54.7, 642.2) | ⊕⊕⊕0 | |
| Need for blood transfusion | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | imprecise data -1 | 591 | 630 | | 1.30 (0.50, 3.39) | NS | ⊕⊕00 | 7.8 |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | Sparse data -1 | 812 | 808 | 0.9% (0.2, 1.5) | 0.14 (0.02, 0.85) | 135 (70.1, 1674) | ⊕⊕⊕0 | |
| Need for additional uterotonics | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | None | 591 | 630 | min 13.76% (10.70, 16.82) max 18.18% (11.84, 24.53) | 0.66 (0.48, 0.90) | min NS max 17 (10.2, 47.2) | ⊕⊕⊕0 | 5.9 |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | Sparse data -1 | 812 | 808 | 0.7% (0.2, 1.3) | 0.50 (0.12, 1.98) | NS | ⊕⊕⊕0 | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--------------------------------|--------|-------------------------------|----------------------------|-------------------------------------|----------------------|---------------------|---------|----------------------------------|---------------------------------|-------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Utero-tonics | Placebo | Baseline risk (placebo) (95% CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Mean blood loss | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | None | 591 | 630 | | WMD -83.58 (-118.01, -49.14) | | ⊕⊕⊕0 | 5.6 |
| In 06 | RCT | No limitation | One trial only | no uncertainty about directness | None | 812 | 808 | 262±203 ml | -48 ml (-65, -30) | - | ⊕⊕⊕⊕ | |
| Postpartum anaemia | | | | | | | | | | | | |
| 2 CA 01 NL 97 [3] | RCT | Serious limitations [1] -1 | one trial only | no uncertainty about directness | None | 485 | 458 | | 0.63 (0.36, 1.09) | | ⊕⊕⊕0 | |
| Early breast feeding | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | |
| Less anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|-------------------------------|----------------------------|-------------------------------------|---------------------------------|---------------------|---------|----------------------------------|-----------------------|---------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Utero-tonics | Placebo | Baseline risk (placebo) (95% CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect requiring treatment (manual removal of placenta) | | | | | | | | | | | | |
| 2 CA 01 DG 96 NL 97 | RCT | Serious limitations [1] -1 | no important inconsistency | no uncertainty about directness [2] | imprecise and sparse data -1 | 591 | 630 | | 1.67 (0.82, 3.41) | | ⊕ ⊕ ○ ○ | 6.2 |
| Nausea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Vomiting | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Diarrhoea | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Headache | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Abdominal pain | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| High blood pressure | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |
| Shivering | | | | | | | | | | | | |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | None | 812 | 808 | 17.3% (14.7, 19.9) | 3.01 (2.56, 3.55) | 3 (2.6, 3.3) | ⊕ ⊕ ⊕ ⊕ | 4.7 |
| Temp >38°C | | | | | | | | | | | | |
| In 06 | RCT | No limitation | One trial only | No uncertainty about directness | None | 812 | 808 | 1.1% (0.4, 1.8) | 3.76 (1.81, 7.79) | 32 (21.6, 66) | ⊕ ⊕ ⊕ ⊕ | 5.4 |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---------------------------|--------|-------------|-------------|------------|----------------------|---------------------|---------|----------------------------------|-----------------------|-------------|---------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Utero-tonics | Placebo | Baseline risk (placebo) (95% CI) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Temp >40° C | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Maternal death | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| Anaemia in infancy | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

Notes:

1. PPH > or =500ml and PPH > or =1000 ml: clinically estimated blood loss in both trials. De Groot 1996: unblinded for placebo versus oxytocin.
2. De Groot 1996: expectant management for the third stage of labour, but no information given about timing of cord clamping/cutting.
3. Maternal haemoglobin concentration (Hb) <9 gm/decilitre 24 to 48 hours postpartum.
4. De Groot 1996: only one event in intervention group and no event in control group.

GRADE Evidence Profile 8

QUESTION a: Should the cord be clamped early (within 1 minute) or later (after cessation of pulsations) for all babies during active management of the third stage of labour by skilled providers?

Patient or population: at-term babies

Settings: hospital setting, Mexico, Argentina, India, Guatemala, Libya, Germany and Canada; not specified setting in urban area South Africa

Systematic reviews: van Rheenen P, Brabin BJ. Late umbilical cord-clamping as an intervention for reducing iron deficiency anaemia in term infants in developing and industrialised countries: a systematic review. *Ann Trop Paediatr* 2004;24:3-16 (vRP 04).

| Developing countries | | | |
|-----------------------------|------------|---|---|
| Name, Year (initials) | Population | Control: Early clamping | Intervention: Delayed clamping |
| Lanzkowsky P 1960 (LP 60) | 133 | immediately after the baby is delivered | after signs of placental separation and after cord stripping 4-5 times from vulva to infant's umbilicus |
| Geethanath RM 1997 (GRM 97) | 107 | | after placental descent in to vagina |
| Grajeda R 1997 (GR 97) | 88 | | when cord stopped pulsating |
| Gupta R 2002 (GR 02) | 102 | | after placental descent in to vagina |

Note: The studies conducted in developed countries and comprised in the vRP 04 were excluded from this analysis because they were not RCT.

| Developed countries | | | |
|-------------------------------|------------|---|--------------------------------|
| Name, Year (initials) | Population | Control: Early clamping | Intervention: Delayed clamping |
| Saigal S 1972 (SS 72) | 45 | immediately after the baby is delivered | 1 and 5 minutes after delivery |
| Nelle M 1993 (NM 93) | 30 | | 3 minutes after delivery |
| Nelle M 1995 and 1996 (NM 96) | 30 | | 3 minutes after delivery |
| Linderkamp 1996 (LO 96) | 30 | | 3 minutes after delivery |

RCTs:

- p. (EM 04) Emhamed MO, van Rheenen P, Brabin BJ. The early effect of delayed cord clamping in term infants born to Libyan mothers. *Tropical Doctor*. 2004;34:218-22.
- q. (CC 06) Chaparro CM et al, Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. *Lancet* 2006;367:1997-2004.
- r. (CCJ 06) Ceriani Cernadas JM et al. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. *Pediatrics* 2006;117:779-86.

| Name, Year (initials) | Population | Early clamping | Delayed clamping |
|-----------------------------------|------------|--|--|
| Emhamed M 2004 (EM 04) | 102 | within 10 seconds after birth | after the cord stopped pulsating |
| Chaparro CM 2006 (CC 06) | 265 | withing 10 seconds after birth | 2 minutes after delivery of the shoulder |
| Ceriani Cernadas JM 2006 (CCJ 06) | 179 | within the first 15 seconds or at 1 minute | at 3 minutes |

QUESTION b: Should the cord clamped early (within 1 minute) or later (after cessation of pulsations) for all babies during active management of the third stage of labour by non-skilled providers?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--------------------------------|-------------------|---|----------------|--------------------------------------|----------------------|---------------------|----------------|--|--|-----------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Delayed clamping | Early clamping | Infant mean Hb or ferritin (SD) or Baseline risk (95% IC) (in early) | Infant mean Hb (SD) or ferritin (in delayed) or Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Less anaemia in infancy | | | | | | | | | | | 4.8 | |
| 4 ¹⁶ (vRP 04) | RCT ²⁰ | | | | | | | | | | | |
| | (LP 60) | minor limitations ¹⁹ | one trial only | some uncertainty ²¹ -1 | none | 70 | 63 | Early 11.1 ± 1.0 g/dl Hb | Delayed 11.1 ± 0.9 g/dl Hb | | moderate quality +++o | |
| | (GRM 97) | no limitations | one trial only | some uncertainty ²² -1 | none | 59 | 48 | Early 8.9 ± 1.6 g/dl Hb | Delayed 8.3 ± 2.1 g/dl Hb | | moderate quality +++o | |
| | (GR 97) | serious limitations ¹⁷ -1 | one trial only | some uncertainty ²³ -1 | none | 59 | 29 | 88.24% ²⁵ (72.45, 100) | 0.54 (0.38, 0.77) | 2 (1.6, 5.3) | low quality ++oo | |
| | (GR 02) | serious limitations ¹⁸ -1 | one trial only | some uncertainty ²⁴ -1 | none | 49 | 53 | 86.21% ²⁶ (73.43, 98.98) | 0.52 (0.38, 0.80) | 2 (1.6, 5.3) | low quality ++oo | |
| | (GRM 97) | no limitations | one trial only | some uncertainty ²² -1 | none | 59 | 48 | Early 55.7 ± 3.7 mcg/L ferritin ²⁷ | Delayed 73.6 ± 3.1 mcg/L ferritin | | moderate quality +++o | |
| | (GR 97) | serious limitations ¹⁷ -1 | one trial only | some uncertainty ²³ -1 | none | 59 | 29 | Early 119.3 ± 91.6 mcg/L ferritin ²⁷ | Delayed 131.2 ± 55.4 130.8 ± 69.8 mcg/L ferritin ²⁸ | | low quality ++oo | |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|-------------------------------|-----------------------|---|----------------|--------------------------------------|----------------------|---------------------|----------------|--|---|------------------|--------------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Delayed clamping | Early clamping | Infant mean Hb or ferritin (SD) or Baseline risk (95% IC) (in early) | Infant mean Hb (SD) or ferritin (in delayed) or Relative risk (95%CI) | NNT (95%CI) | | |
| | (GR 02) | serious limitations ¹⁸ -1 | one trial only | some uncertainty ²⁴ -1 | none | 49 | 53 | Early 73.0 (range 15-180) mcg/L ferritin ²⁹ | Delayed 118.4 (range 30-500) mcg/L ferritin ²⁹ | | low quality ++oo | |
| 1 (CC 06) ⁶ | RCT | no limitation | one trial only | some uncertainty ⁷ -1 | none | 133 | 132 | 12.9% (7.1, 18.6) | 1 (0.5, 2.0) | NS | moderate quality +++o | |
| 1 (CCJ 06) ⁹ | RCT [¹³] | no limitation | one trial only | some uncertainty ¹⁰ -1 | none | 90 ¹² | 89 | 5.6% (1.52, 16.86) | 0.20 (0.06, 0.6) | 7 (4.5, 20.6) | moderate quality +++o | |
| 1 (EM 04) ¹ | RCT ¹⁵ | serious limitation ^{2,4} -1 | one trial only | some uncertainty ³ -1 | sparse data -1 | 57 | 45 | Early 17.1 ± 1.9 g/dl Hb | Delayed 18.5 ± 2.1 g/dl Hb | | very low quality +ooo | |
| Additional uterotonics | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|-----------------------------------|-----------------------------|---------------------------------------|----------------|--------------------------------------|----------------------|---------------------|----------------|--------------------------|--|-------------|--------------------------|------------|
| | | | | | | No of patients | | Effect | | | Quality | Importance |
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | Delayed clamping | Early clamping | Baseline Risk (in early) | Relative (95%CI) | NNH (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect | | | | | | | | | | | | |
| 1 (EM 04) ⁵ | RCT Increased bilirubina | major limitation ^{2,4} -1 | one trial only | some uncertainty ³ -1 | sparse data -1 | 57 | 45 | 4.4% (-1.6; 10.5) | not calculated (cell containing zero value) | NS | very low quality +ooo | |
| 1 (CC 06) ⁸ | RCT Clinical jaundice | no limitation | one trial only | some uncertainty ⁷ -1 | None | 172 | 160 | 13.8% (8.4- 19.1) | 1.26 (0.76, 2.10) | NS | moderate quality +++o | |
| 1 (CCJ 06) ¹¹ | RCT Htc >65% | no limitation | one trial only | some uncertainty ¹⁰ -1 | None | 90 | 89 | 2.3 (- 0.85, 5.34) | 3.46 (0.74, 16.21) | NS | moderate quality +++o | |
| Manual removal of placenta | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |

Notes:

1. Emhamed 04, Libya. Early clamping within 10 seconds after birth, delayed clamping after the cord stopped pulsating. Hb assessed 16-24 hours after birth. Infants put on mother abdomen.
2. Post randomization withdrawal (5 out of 62 in delayed cord clamping and 5 out of 50 in early cord clamping). Not clear if analysis is based on intention to treat.
3. Only low-risk women (excluded twin pregnancy, low birth weight, preterm delivery, maternal gestational diabetes, pre-eclampsia, haemorrhage during pregnancy or delivery, medical history of PPH).
4. More women in late clamping group had anaemia on admission (29% versus 9% in early clamping group). This is a plausible confounder and it would have reduced the effect.
5. Increased bilirubina requiring phototherapy (>15 mg/dl on day 1).
6. Chaparro 06, Mexico. Early clamping withing 10 seconds after birth, delayed clamping 2 minutes after delivery of the shoulder. Hb assessed at 6 months of age. Infants maintained at the level of mother's uterus.
7. Women excluded if: planned delivery by Caesarean section, pregnancy of 36 weeks or less, or 42 weeks or more, as established by the date of last menstrual period or estimated delivery date; pre-eclampsia or eclampsia (also in any previous pregnancies), haemorrhage needing clinic or hospital admission, placental abnormalities, anomalies or Down's syndrome of the fetus, or had a diagnosis at any time of diabetes (all types), hypertension, heart disease or chronic renal disease, not planning to breastfeed for at least 6 months, smoked at all during pregnancy, unwillingness to return for follow-up visits at the same hospital, or were participating in another research study at the hospital.
8. Clinical jaundice.
9. Ceriani 06, Argentina. Cord clamping within the first 15 seconds (group 1), at 1 minute (group 2), or at 3 minutes (group 3) after birth. Infants held in mother's arms. Hematocrit value measured 6 hours after birth.
10. Women excluded in case of: non-cephalic delivery, multiple pregnancy; diabetes, preeclampsia, hypertension, preterm delivery, infants with evidence of congenital malformations or intrauterine growth restriction (estimated fetal weight <10th percentile).
11. Htc >65%.
12. Cord clamping at three minutes.
13. Anaemia measured as haematocrit level of <45% at 24 to 48 hours.
14. Polycythemia measured as haematocrit level of >45% at 24 to 48 hours.
15. Hb level after 24h higher in delayed clamp group (18.5 g/dL, SD 2.1g/dL vs 17.1g/dL, SD 1.9g/dL; $p=0.0005$).
16. Four studies conducted in developing countries: Lanzkowsky P 1960 South Africa; Geethanath RM 1997 India; Grajeda R 1997, hospital Guatemala; Gupta R 2002 hospital, India.
17. Lost at follow-up 19/88 (21.59%). There were significantly more low-birthweight in drop-outs.
18. Lost at follow-up 44/102 (43.13%). There were significantly more mothers with lower mean ferritin in the lost to follow-up.
19. Lost at follow-up 21/133 (15.78%). Lost to follow-up did no differ between groups.
20. Adequately randomized; because of the type of intervention, blinding was not possible; no information about intention-to-treat analysis.
21. Not maternal anaemia; not antenatal iron supplementation; no data on oxytocics prior to cord clamping; baby between mothers legs; no data about IUGR; infant use of iron supplement was an exclusion factor; no malaria endemicity.
22. Maternal anaemia was an exclusion factor, no data on oxytocics prior to cord clamping; baby within 10 cm below introitus; no data about IUGR; no infant use of iron supplement; very low malaria endemicity.
23. Not maternal anaemia; no data on oxytocics prior to cord clamping; baby at level of placenta in one sub-group and below level of placenta in other sub-group; no data about IUGR; no infant use of iron supplement; no malaria endemicity.

24. Maternal anaemia was an inclusion factor; no data on oxytocics prior to cord clamping; baby within 10 cm below introitus; no data about IUGR; no infant use of iron supplement; very low malaria endemicity.
25. Proportion of infants at 2 months in early clamped cord group with anaemia defined as Ht<33%.
26. Proportion of infants at 3 months in early clamped cord group with anaemia defined as Hb<10 g/dl.
27. Infant ferritin evaluated at 3 months.
28. Infant ferritin evaluated at 2 months, in the subgroup with baby at placenta level and in the subgroup with baby below placenta.
29. Infant ferritin evaluated at 3 months.

QUESTION c: Should the cord be clamped early (within 1 minute) or later (after cessation of pulsations) for preterm babies during active management of the third stage of labour?

Patient or population: preterm babies

Settings: hospital setting

Systematic reviews:

- a. (RH 04) Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003248. DOI: 10.1002/14651858.CD003248.pub2.
See the table below for RCTs included in this SR used for producing the evidence profile.

RCTs:

A systematic search was performed for RCTs published after the last update of SR:

- b. (MJ 06) Mercer JS et al. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular haemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics 2006;117;1235-42.

| Name, Year (initials) | Population | Early | Delayed |
|------------------------|------------|--|--|
| Hofmeyr 1988 (Ho 88) | 38 | cord clamping immediately after birth | 60 seconds after birth ±ergometrine |
| Hofmeyr 1993 (Ho 93) | 86 | cord clamping immediately after birth | 60-120 seconds after birth infant held at level of uterus |
| Kinmond 1993 (Ki 93) | 36 | management at the attendant's discretion | 30 seconds after birth , infants held 20 cm below introitus |
| McDonnell 1997 (Mc 97) | 46 | cord clamping immediately after birth | 30 seconds after birth , infants held between legs of the mother, syntocinon at birth |
| Nelle 1998 (Ne 98) | 19 | cord clamping immediately after birth | 30 seconds after birth , infants held 30 cm below placenta |
| Oh 2002 (Oh 02) | 33 | immediate cord clamping < 5 s | 30-45 seconds after birth |
| Rabe 2000 (Ra 00) | 40 | cord clamping at 20 s | 45 seconds after birth , below the level of placenta, if possible oxytocin given after birth |
| Mercer JS 2006 (MJ 06) | 72 | Cord clamping <10 sec after birth. Infant held approximately 10 to 15 inches below the mother's introitus at vaginal delivery or below the level of the incision at cesarean section | Cord clamping 30-45 sec after birth . Infant held approximately 10 to 15 inches below the mother's introitus at vaginal delivery or below the level of the incision at cesarean section |

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

| Quality assessment | | | | | | Summary of findings | | | | | | |
|---|-------------------------------------|-------------------------------|----------------------------|--|----------------------|---------------------|----------------|---|--------------------------|-----------------------------------|---------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Delayed clamping | Early clamping | Baseline risk (early) | Relative risk (95%CI) | NNT (95%CI) | | |
| Benefits: | | | | | | | | | | | | |
| Infant anaemia | | | | | | | | | | | | |
| 3 (RH 04) ¹ Ki 93 Mc 97 Ra 00 | RCT Transfused for anaemia | minor limitation ² | no important inconsistency | some uncertainty about directness ^{3,4} -1 | sparse data -1 | 55 | 56 | min 26.1% (7.7-44.4) max 80% (62-96) | 0.49 (0.30, 0.81) | min NS max 3 (1.6-29.6) | low quality ++oo | |
| 4 (RH 04) ⁵ Ki 93 Mc 97 Ne 98 Oh 02 | RCT Mean Htc 4 hours after birth | minor limitation ² | no important inconsistency | some uncertainty ^{3,6} -1 | sparse data -1 | 67 | 67 | Htc 47.35% | WMD 5.4% (3.52, 7.28) | | low quality ++oo | |
| 1 (MJ 06) ⁷ | RCT Infant transfused | no limitations | one trial only | some uncertainty ⁸ -1 | sparse data -1 | 36 | 36 | 61.1% (45-77.3) | 0.82 (0.54, 1.25) | NS | low quality ++oo | |
| Additional uterotonics | | | | | | | | | | | | |
| 0 | - | - | - | - | - | - | - | - | - | - | - | - |

| Quality assessment | | | | | | Summary of findings | | | | | | |
|--|--------|-------------------------------|----------------------------|--|----------------------|---------------------|----------------|--|-----------------------|-----------------------------------|---------------------|------------|
| No of studies (Ref) | Design | Limitations | Consistency | Directness | Other considerations | No of patients | | Effect | | | Quality | Importance |
| | | | | | | Delayed clamping | Early clamping | Baseline risk (early) | Relative risk (95%CI) | NNT (95%CI) | | |
| Harms: | | | | | | | | | | | | |
| Any side effect (intraventricular haemorrhage) | | | | | | | | | | | | |
| 5 (RH 04) ⁹ Ho 88 Ho 93 Mc 97 Oh 02 Ra 00 | RCT | minor limitation ² | no important inconsistency | some uncertainty ^{3,10} -1 | sparse data -1 | 113 | 112 | min 6.3% (-6, 18.5) max 76.9% (53.1, 100.8) | 0.59 (0.35, 0.92) | min NS max -2 (-1.4, -9.8) | low quality ++oo | |
| 1 (MJ 06) ¹¹ | RCT | no limitations | one trial only | some uncertainty ⁸ -1 | sparse data -1 | 36 | 36 | 36.1% (20.2, 52) | 0.28 (0.09, 0.9) | -4 (-2.4, -38.3) | low quality ++oo | |
| 1 (MJ 06) ¹² Late onset sepsis | RCT | no limitations | one trial only | some uncertainty ⁸ -1 | sparse data -1 | 36 | 36 | 22.2% (8.4, 36) | 0.12 (0.03, 0.95) | -5 (-2.9, -21.6) | low quality ++oo | |
| Manual removal of placenta | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - | - |

Notes

1. Rabe 04. Anaemia defined as “transfused for anaemia”. Preterm infants: from 24 to 35 weeks gestational age or infants weighing less than 2000 g.
2. No information available on blinded of outcome assessors.
3. Rabe 04. Excluded multiple pregnancies, Rhesus incompatibility, fetal hydrops, congenital malformation, IUGR, fetal distress, haemolytic disease.
4. Rabe 04 intervention varies in different studies
 - a. Kinmond 93: 30 seconds after birth, infants held 20 cm below introitus
 - b. McDonnell 97: 30 seconds after birth, infants held between legs of the mother, syntocinon at birth
 - c. Rabe 00: 45 seconds after birth, below the level of placenta, if possible oxytocin given after birth.
5. Rabe 04. Anaemia defined as “mean Haematocrit at 4 hours after birth”
6. Rabe 04 intervention varies in different studies
 - a. Kinmond 93: 30 seconds after birth, infants held 20 cm below introitus
 - b. McDonnell 97: 30 seconds after birth, infants held between legs of the mother, syntocinon at birth
 - c. Nelle 98: 30 seconds after birth, infants held 30 cm below placenta
 - d. Oh 02: 30–45 seconds after birth.

- 7 . Mercer 06. Anaemia defined as “infants transfused”. Preterm infants: from 24 to 31.6 weeks gestational age. Early cord clamping <10 seconds after birth, delayed cord clamping 30–45 seconds after birth. Infant held approximately 10 to 15 inches below the mother’s introitus at vaginal delivery or below the level of the incision at Caesarean section.
- 8 . Mercer 06. Exclusion criteria included: major congenital anomalies or multiple gestations, intent to withhold care, severe maternal illnesses or placenta abruption or previa.
- 9 . Rabe 04. Intra ventricular hemorrhage.
- 10 . Rabe 04 intervention varies in different studies
 - a. Hofmeyr 88: 60 seconds after birth ±ergometrine
 - b. Hofmeyr 93: 60–120 seconds after birth infant held at level of uterus
 - c. McDonnel 97: 30 seconds after birth, infants held between legs of the mother, syntocinon at birth
 - d. Oh 02: 30–45 seconds after birth
 - e. Rabe 00: 45 seconds after birth, below the level of placenta, if possible oxytocin given after birth.
- 11 . Mercer 06. Intraventricular hemorrhage.
- 12 . Mercer 06. Late-onset sepsis.

Summary of findings 8

SCENARIO: Should the cord be clamped early (within 1 minute) or later (after cessation of pulsations) during active management of the third stage of labour?

| | | By skilled providers | | | | | | | By no skilled providers |
|-----------------------|-------------------------------|----------------------|-------------|--|-------------------------------|--------------------------------------|--------------------------|----------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | - |
| At term babies | | | | | | | | | |
| Benefits | Infant anaemia | 1 | 265 | 12.9% (7.1, 18.6) | 1 (0.5, 2.0) | NS | moderate quality +++o | | - |
| | | 1 | 179 | 5.6% (1.52, 16.86) | 0.20 (0.06, 0.6) | 7 (4.5, 20.6) | moderate quality +++o | | - |
| | | 1 | 102 | Early 17.1 ± 1.9 g/dl Hb | Delayed 18.5 ± 2.1 g/dl Hb | | very low quality +ooo | | - |
| Harms | None judged critical | - | - | - | - | - | - | - | - |
| Preterm babies | | | | | | | | | |
| Benefits | Infant transfused for anaemia | 3 | 111 | min 26.1% (7.7, 44.4) max 80% (62, 96) | 0.49 (0.30, 0.81) | min NS max 3 (1.6-29.6) | low quality ++oo | 1,2,3,4 | |
| | | 1 | 72 | 61.1% (45, 77.3) | 0.82 (0.54, 1.25) | NS | low quality ++oo | 7,8 | |
| Harms | Intraventricular haemorrhage | 5 | 225 | min 6.3% (-6, 18.5) max 76.9% (53.1, 100.8) | 0.59 (0.35, 0.92) | min NS max -2 (-1.4, -9.8) | low quality ++oo | 2,3,9,10 | |
| | | 1 | 72 | 36.1% (20.2, 52) | 0.28 (0.09, 0.9) | -4 (-2.4, -38.3) | low quality ++oo | 8,11 | |

Notes:

1. Rabe 04. Anaemia defined as "transfused for anaemia". Preterm infants: from 24 to 35 weeks gestational age or infants weighing less than 2000 g.
2. No information available on blinded of outcome assessors.
3. Rabe 04. Excluded multiple pregnancies, Rhesus incompatibility, fetal hydrops, congenital malformation, IUGR, fetal distress, haemolytic disease.
4. Rabe 04 intervention varies in different studies

- a. Kinmond 93: 30 seconds after birth, infants held 20 cm below introitus
 - b. McDonnell 97: 30 seconds after birth, infants held between legs of the mother, syntocinon at birth
 - c. Rabe 00: 45 seconds after birth, below the level of placenta; if possible oxytocin given after birth.
7. Mercer 06. Anaemia defined as “infants transfused”. Preterm infants: from 24 to 31.6 weeks gestational age. Early cord clamping <10 seconds after birth, delayed cord clamping 30–45 seconds after birth. Infant held approximately 10 to 15 inches below the mother’s introitus at vaginal delivery or below the level of the incision at Caesarean section.
 8. Mercer 06. Exclusion criteria included: major congenital anomalies or multiple gestations, intent to withhold care, severe maternal illnesses, or placenta abruption or previa.
 9. Rabe 04. Intraventricular hemorrhage.
 10. Rabe 04 intervention varies in different studies
 - a. Hofmeyr 88: 60 seconds after birth ±ergometrine
 - b. Hofmeyr 93: 60–120 seconds after birth infant held at level of uterus
 - c. McDonnell 97: 30 seconds after birth, infants held between legs of the mother, syntocinon at birth
 - d. Oh 02: 30–45 seconds after birth
 - e. Rabe 00: 45 seconds after birth, below the level of placenta, if possible oxytocin given after birth.
 11. Mercer 06. Intraventricular hemorrhage.

GRADE Evidence Profile 9

QUESTION: Should the placenta be delivered in all women by skilled providers through controlled cord traction with or without other components of active management?

Patient or population: Women delivered vaginally during third phase of labour

Settings: Hospital setting, United Arab Emirates

Systematic reviews:

None available

RCTs:

Khan, GQ et al. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: A randomized controlled trial. *Am J Obstet Gynecol* 177, 4. 770-774.

We identified no studies with comparison of controlled cord traction with or without other components of active management. We have excluded the studies in which the controlled cord traction was associated to placental cord drainage [Sharma, JB et al. Evaluation of placental drainage as a method of placental delivery in vaginal deliveries. *Arch Gynecol Obstet* (2005) 271:343–5. Giacalone, PL et al. A randomised evaluation of two techniques of management of the third stage of labour in women at low risk of postpartum haemorrhage. *British Journal of Obstetrics and Gynaecology* (2000) 107:396-400].

We have found only one indirect evidence for the question. This trial compared controlled cord traction plus oxytocin during delivery plus immediate cord clamping versus immediate cord clamping plus oxytocin after delivery of the placenta and no cord traction.

We have reported the results of this trial in PPH GRADE evidence profile no. 7.

| Name, Year (initials) | Population | Intervention | Control |
|------------------------------|------------|--|---|
| Quadir Khan 1997 (QKG 97) | 1648 | Oxytocin 10 IU IM before delivery of placenta + other components: cord traction and cord clamping immediately after delivery of baby | Oxytocin 10 IU IV after delivery of placenta without cord traction + cord clamping immediately after delivery of baby |

QUESTION: Should the placenta be delivered in all women by non-skilled providers through controlled cord traction with or without other components of active management?

No evidence available.

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of studies listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgements that were made are provided in the notes.

Summary of findings 9

SCENARIO: Should the placenta be delivered in all women through controlled cord traction with or without other components of active management?

| | By skilled providers | | | | | | | | By no skilled providers |
|-----------------|----------------------------|-------------------|-------------|---|-------------------------|--------------------|---------------------|-------|-------------------------|
| | Critical outcomes | Studies n. | Patients n. | Baseline Risk without treatment (95%CI) | Relative effect (95%CI) | NNT | Quality | Notes | |
| Benefits | Maternal deaths | No data available | - | - | - | - | - | - | - |
| | Blood loss ≥1000 ml | 1 | 1648 | 3.2% (2.0, 4.4) | 0.23 (0.09, 0.55) | 41 (26.5, 90.1) | low quality ++oo | 3,4 | - |
| | Need for blood transfusion | 1 | 1648 | 0.5% (0.01, 0.1) | 0.25 (0.03, 2.22) | NS | low quality ++oo | 3,4 | - |
| Harms | None judged critical | | | | | | | | - |

Notes:

3. Interventions not blinded. Blood loss was measured by the attendant midwife or obstetrician by collecting blood and clots in a graduated jug and weighing swabs and linen. The amount of blood loss was confirmed by a second midwife who was not aware of the group allocation and not involved in the delivery.

4. Different timing in oxytocin administration (before versus after delivery of placenta); different routes of oxytocin administration (10 IU IM vs 10 IU IV); in both groups, oxytocin given associated with clumping of umbilical cord immediately after delivery of the baby.