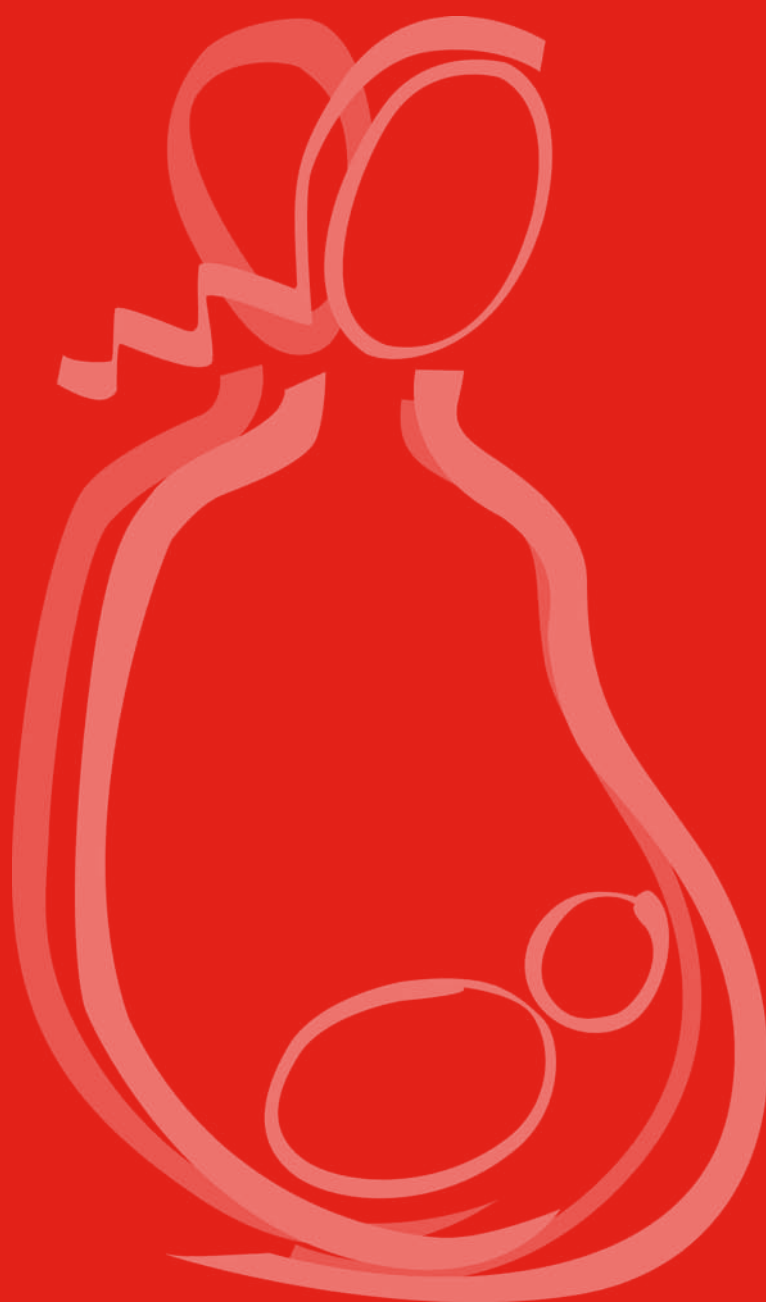


WHO Recommendations for the Prevention of Postpartum Haemorrhage



**World Health
Organization**

Department of Making Pregnancy Safer

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TABLE OF CONTENTS

1. BACKGROUND	4
2. METHODS	6
3. RESULTS	7
4. EVIDENCE AND RECOMMENDATIONS	9
5. KEY DISCUSSION POINTS	17
6. REFERENCES	20
7. ANNEXES	22
1. Questions for Panel	22
2. List of Outcomes	24
3. Methods used for developing guidelines	25
4. GRADE Evidence Profiles	32
5. List of Participants	34



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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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
- methylegometrine
- 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
- methylegometrine
- 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
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