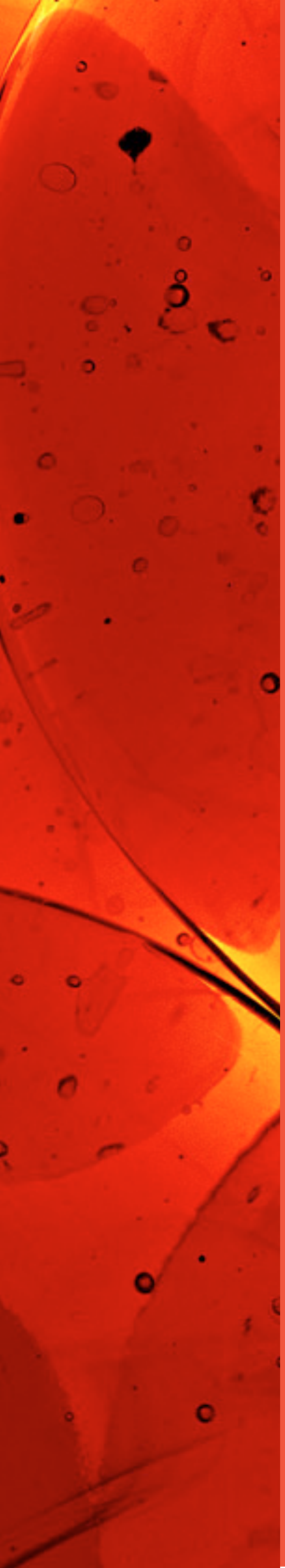

WHO guidelines for the management of postpartum haemorrhage and retained placenta

World Health Organization

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Contents

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WHO Secretariat will review the questions below in the update of this guideline planned for 2010–2011.

Declarations of interest

Six temporary advisors (Hany Abdel-Aleem, Jennifer Blum, Richard Derman, Justus Hofmeyr, Pisake Lumbiganon and Tran Son Thach) and one observer (Beverly Winikoff) declared that they had received grants for conducting research and made presentations on the research they conducted regarding the use of misoprostol and other aspects of PPH prevention and management which were reviewed during the meeting. None of these grants was from commercial entities. One observer, Ms Mary Ellen Stanton, declared that she may present an organization's position (USAID) if required in this field.

The interests declared reflect the academic interest and opinions of the experts and the Secretariat does not believe that there are any undeclared commercial or financial interests among the guideline review group.

The two observers did not participate in the voting processes and were not asked to approve or provide comments to the document.

Background

One of the Millennium Development Goals set by the United Nations in 2000 is to reduce maternal mortality by three-quarters by 2015. If this is to be achieved, maternal deaths related to postpartum haemorrhage (PPH) must be significantly reduced. In support of this, health workers in developing countries need to have access to appropriate medications and to be trained in relevant procedures. But beyond this, countries need evidence-based guidelines on the safety, quality, and usefulness of the various interventions. These will provide the foundation for the strategic policy and programme development needed to ensure realistic and sustainable implementation of appropriate interventions.

PPH is generally defined as blood loss greater than or equal to 500 ml within 24 hours after birth, while severe PPH is blood loss greater than or equal to 1000 ml within 24 hours. PPH is the most common cause of maternal death worldwide. Most cases of morbidity and mortality due to PPH occur in the first 24 hours following delivery and these are regarded as primary PPH whereas any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally is regarded as secondary PPH.

PPH may result from failure of the uterus to contract adequately (atony), genital tract trauma (i.e. vaginal or cervical lacerations), uterine rupture, retained placental tissue, or maternal bleeding disorders. Uterine atony is the most common cause and consequently the leading cause of maternal mortality worldwide.

In practice, blood loss after delivery is seldom measured and it is not clear whether measuring blood loss improves the care and outcome for the women. In addition, some women may require interventions to manage PPH with less blood loss than others if they are anaemic.

Risk factors for PPH include grand multiparity and multiple gestation. However, PPH may occur in women without identifiable clinical or historical risk factors. It is therefore recommended that active management of the third stage of labour be offered to all women during childbirth, whenever a skilled provider is assisting with the delivery (1). Active management should include: (i) administration of a uterotonic soon after the birth of the baby; (ii) clamping of the cord following the observation of uterine contraction (at around 3 minutes); and (iii) delivery of the placenta by controlled cord traction, followed by uterine massage.

Even with these efforts to prevent PPH, some women will still require treatment for excessive bleeding. Multiple interventions (medical, mechanical, invasive non-surgical and surgical procedures), requiring different levels of skill and technical expertise, may be attempted to control bleeding. For the purposes of these guidelines, it is assumed that the patient with PPH is being treated by a health-care worker in a medical facility. Efforts in the community to prevent and treat PPH are not covered here.

Effective treatment of PPH often requires simultaneous multidisciplinary interventions. The health care provider needs to begin resuscitative efforts quickly,

establish the cause of the haemorrhage, and possibly obtain the assistance of other care providers, such as an obstetrician, anaesthetist or radiologist. Avoiding delays in diagnosis and treatment will have a significant impact on sequelae and chance of survival. These guidelines therefore include "care pathways" (or algorithms) for management of PPH, as a practical guide for clinicians. (A loose-leaf insert of these care pathways has been included for use as a wall chart.)

This document is not intended to be a comprehensive guide on management of PPH and retained placenta. Rather, it reflects the questions that were regarded as high priority by a multidisciplinary panel of international health workers and consumers.

Methods

Staff from the WHO Departments of Reproductive Health and Research, Making Pregnancy Safer, and Essential Medicines and Pharmaceutical Policies drafted questions on interventions and a list of possible outcomes in the treatment of atonic postpartum haemorrhage and retained placenta (Annex 1).

These questions and outcomes were sent by email to an international panel of experts (midwives, obstetricians, neonatologists, researchers, methodologists, consumers and programme experts). Members of the panel were invited to comment on the relevance of the questions and outcomes, and were asked to rate each of them on a scale of 1 to 9. A critical outcome was defined as an outcome with an average score between 7 and 9. Questions and outcomes that scored between 4 and 6 were considered important but not critical, while those that scored less than 4 were considered not important (2). Panel members were also encouraged to revise the questions or suggest new questions and outcomes.

Two reminders were sent to the members of the panel. The results of the scoping exercise were sent to all respondents for review. All of the responses were reviewed by WHO staff. The responses and scores are presented in Annex 1. In the preparation of the care pathways for management of PPH and retained placenta, questions that scored lower than critical points in the scoping exercise were included in the search for evidence and appraisal process.

Centro Rosarino de Estudios Perinatales (CREP), a WHO Collaborating Centre in Maternal and Perinatal Health, was commissioned to search, review and grade the evidence to answer the questions, using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (Annex 3). The initial search for evidence was conducted in November 2007. Records were searched in the Cochrane library, Pubmed, Embase, and Lilacs. The search terms used are given in Annex 2. Ad hoc searches in Pubmed were also conducted before the Technical Consultation to make sure that relevant studies were not missed and that studies identified by experts in the field were included.

GRADE tables were prepared for the highest level of evidence available; systematic reviews and randomized controlled trials (RCTs) or, in their absence, observational studies were used. When RCTs were available, observational study data were not

summarized in the GRADE tables. However, they were mentioned in the evidence summary and taken into account in the recommendation. GRADE tables were not prepared for case series or reports.

The draft GRADE tables were reviewed by the WHO Secretariat together with CREP staff. Recommendations relating to the questions and outcomes proposed were then drafted ahead of the Technical Consultation. A draft of the methodology, results, and recommendations was sent for review to a subgroup of the experts participating in the Technical Consultation before the meeting.

Decision-making during the technical consultation

For each question, the participants in the Technical Consultation discussed the draft text prepared by the Secretariat, with the aim of reaching a consensus. Consensus was defined as agreement by the majority of participants, provided that those who disagreed did not feel strongly about their position. Any strong disagreements were recorded as such.

During the meeting, in addition to the documentation prepared by the Secretariat, preliminary results from four unpublished trials were made available. While the presentation of the most recent data from large trials was welcomed and used to inform the recommendations, some participants expressed a need for more time to review these results before making recommendations. The GRADE tables in this document include evidence from the search as well as the data presented and discussed during the Technical Consultation.

The system used to establish the strength and ranking of the recommendations involved assessing each intervention on the basis of: (i) desirable and undesirable effects; (ii) quality of available evidence; (iii) values and preferences related to interventions in different settings; and (iv) cost of options available to health care workers in different settings.

Scope of the guidelines

The draft questions and list of outcomes related to the treatment of PPH and management of retained placenta were sent to 144 experts from all parts of the world. Responses were received from 60 of these experts: 46 physicians, 7 midwives, and 7 non-clinicians (policy-makers, researchers and consumers), representing all 6 WHO regions.

There were 39 questions in 6 domains:

- assessment of blood loss (1 question);
- drugs for atonic PPH (13 questions);
- non-drug interventions for atonic PPH:
  - mechanical (6 questions);
  - radiological (1 question);
  - surgical (8 questions);

- retained placenta (4 questions);
- organizational and educational interventions (5 questions);
- crystalloid versus colloid fluids for resuscitation (1 question). This question was included following a suggestion from the respondents during the survey.

The average scores for questions and outcomes are shown in Annex 1.

It should be noted that not all outcomes are applicable to all questions. As mentioned above, questions that scored less than 7 are also included in the guidelines.

Evidence and recommendations

A. Diagnosis of PPH

1. Should blood loss be routinely quantified during management of the third stage of labour for the purpose of diagnosing PPH?

Several related studies that looked at measurement of blood loss following childbirth, with the objective of ensuring timely diagnosis of PPH and improving health outcomes, were assessed. No study was found that directly addressed the question.

Summary of evidence

Visual versus quantitative methods for estimating blood loss after vaginal delivery

One RCT (3) compared visual estimation of blood loss with measurement of blood collected in a plastic drape. Six observational studies (4–9), with a total of 594 participants, compared visual estimation with known values in the delivery room or in simulated scenarios. Three studies (10–12) compared visual or quantified estimations with laboratory measurement in 331 vaginal deliveries.

In the RCT (3), visual estimation underestimated blood loss when compared with drape measurement (mean difference 99.71 ml) (page 27, GRADE Table A1). Visual methods underestimated blood loss when compared with known simulated volumes.

Training courses on estimating blood loss after vaginal delivery

One RCT (13) compared the accuracy of estimation of blood loss by 45 nurses attending a course on blood loss estimation and 45 nurses not attending the course. In this small RCT (13), with seven simulated scenarios, blood loss was accurately estimated by 75.55% of the nurses attending a training course compared with 24.44% without training (relative risk (RR) 3.09; 95% confidence interval (CI) 1.80–5.30) (page 27, GRADE Table A2).

In three studies (14–16), a total of 486 staff members of maternity services visually estimated blood loss in simulated scenarios before and after training courses. The three uncontrolled studies (14–16) show results in the same direction as the RCT.

Recommendation

After childbirth, blood loss and other clinical parameters should be closely monitored. At present, there is insufficient evidence to recommend quantification of blood loss over clinical estimation. **(Quality of evidence: low. Strength of recommendation: strong)**

Remarks

The participants identified several priority research topics related to the definition and diagnosis of PPH.

- What quantity of blood loss should be the marker for diagnosis of PPH?
- Does the act of quantifying blood loss alter (or lead to improved) clinical outcomes for the mother and her baby?
- Which clinical consequences of blood loss are of greatest value for the diagnosis and treatment of PPH?

B. Management of atonic PPH

As a general preventive approach, the use of oxytocin for active management of the third stage of labour is strongly recommended, because it reduces PPH by more than 60% (17).

1. Medical interventions for management of PPH

The Consultation was asked to assess the value of injectable uterotonics (oxytocin, ergometrine, fixed dose combination of oxytocin and ergometrine, carbetocin and injectable prostaglandin), misoprostol (tablet form used via oral, sublingual and rectal routes), injectable tranexamic acid and injectable recombinant factor VIIa in the management of PPH thought to be due to uterine atony.

For oxytocin, ergometrine and prostaglandin F2α, the Consultation agreed with the doses recommended in the WHO guide, *Managing complications in pregnancy and childbirth* (18), as given in Table 1 (overleaf).

The recommendations below may also be used in cases of PPH due to uterine atony following caesarean section. The Consultation acknowledged that these recommendations were based primarily on data following vaginal birth, and that specific data on PPH due to uterine atony following caesarean section were scarce and not evaluated separately from data on vaginal births.

(a) Which uterotonics should be offered in the management of PPH due to uterine atony?

Summary of evidence

Except for the specific misoprostol trials evaluated in section (b), the evidence has been extrapolated from research on prevention of PPH. Systematic reviews comparing the effects of oxytocin with ergometrine (19), a fixed-dose combination

of oxytocin and ergometrine (20), carbetocin (21) and prostaglandins (22) in the prevention of PPH were reviewed. The guidelines on prevention of postpartum haemorrhage published by WHO synthesized and graded the evidence and made recommendations (1). That publication includes the relevant GRADE tables.

Separate GRADE tables were not prepared for this question and the evidence is summarized below narratively. One RCT comparing oxytocin to ergometrine in 600 women (23) was published subsequent to the systematic review and publication of the WHO guidelines.

Table 1. Drug doses for management of PPH

	Oxytocin	Ergometrine/ Methyl-ergometrine	15-Methyl prostaglandin F2a
Dose and route	IV: Infuse 20 units in 1 l IV fluids at 60 drops per minute	IM or IV (slowly): 0.2 mg	IM: 0.25 mg
Continuing dose	IV: Infuse 20 units in 1 l IV fluids at 40 drops per minute	Repeat 0.2 mg IM after 15 minutes If required, give 0.2 mg IM or IV (slowly every 4 hours	0.25 mg every 15 minutes
Maximum dose	Not more than 3 l of IV fluids containing oxytocin	5 doses (Total 1.0 mg)	8 doses (Total 2 mg)
Precautions/ contraindications	Do not give as an IV bolus	Pre-eclampsia, hypertension, heart disease	Asthma

Prostaglandin F2a should not be given intravenously. It may be fatal. *Managing complications in pregnancy and childbirth.* Geneva, World Health Organization, 2000, page S-28, table S-8.

IV intravenous
IM intramuscular

Oxytocin vs ergometrine

One trial (24) included in the systematic review reported on the critical outcomes of blood loss of ≥1000 ml and need for blood transfusion. There was no difference in incidence of blood loss ≥1000 ml (RR 1.09, 95%CI 0.45–2.66). Blood transfusion was given to 2 of 78 women receiving oxytocin compared with 1 of 146 women receiving ergometrine (RR 3.74, 95%CI 0.34–40.64). No significant difference was observed in the use of additional uterotonics in two trials in the systematic review (24, 25): in 35 of 557 women given oxytocin and 46 of 651 women given ergometrine (RR 1.02, 95% CI 0.67–1.55).

In the later Nigerian trial (23), the use of additional uterotonics was reported in 18 of 297 patients receiving oxytocin in the third stage of labour compared with 30 of 303 receiving ergometrine (RR 0.61, 95%CI 0.35–1.07). The incidence of adverse side-effects was significantly lower in women receiving oxytocin than in those given ergometrine; for vomiting, the RR was 0.09 and the 95% CI 0.05–0.16); for elevated blood pressure, RR was 0.01 and 95% CI 0.00–0.15).

Oxytocin-ergometrine fixed dose combination vs oxytocin

With regard to blood loss ≥1000 ml, decreased blood loss was observed in the group given the fixed-dose combination of oxytocin (5 IU) and ergometrine (0.5 mg) although the difference was not statistically significant (Peto odds ratio (OR) 0.78, 95%CI 0.58–1.03). In four studies that reported on the use of blood transfusion, there was no significant difference and wide confidence interval compatible with either direction of effect (Peto OR 1.37, 95%CI 0.89–2.10). Three studies reported a slight, but statistically significant, lower use of additional uterotonics in the group receiving fixed dose oxytocin-ergometrine combination (RR 0.83, 95%CI 0.72–0.96). Four studies reported on the incidence of side-effects, notably a higher incidence of elevated diastolic blood pressure in the group given the oxytocin-ergometrine fixed dose combination (RR 2.40, 95%CI 1.58–3.64).

Oxytocin-ergometrine fixed dose combination vs ergometrine

None of the critical outcomes was addressed in the studies.

Carbetocin vs oxytocin

No data on blood loss ≥1000 ml, blood transfusion or surgical treatments were available. For the other priority outcomes, the use of additional uterotonics was similar in the two groups (RR 0.93, 95%CI 0.44–1.94), but there was less use of uterine massage in the carbetocin group (RR 0.70, 95% CI 0.51–0.94). Data on side-effects were too limited to allow any judgements to be made (nausea: RR 0.66, 95%CI 0.22–2.00; vomiting: RR 0.07, 95%CI 0.00–1.25; headache: RR 0.51, 95%CI 0.20–1.30).

Carbetocin vs Oxytocin-ergometrine fixed dose combination

Of 150 women given carbetocin and 150 given oxytocin-ergometrine fixed dose combination, only one woman given the combination experienced blood loss ≥1000 ml (26). Use of additional uterotonics was similar, with wide confidence intervals (RR 1.3, 95%CI 0.56–3.13), but the occurrence of side-effects was lower in the carbetocin group (nausea: RR 0.18, 95%CI 0.04–0.78; hypertension up to 60 minutes postpartum: RR 0.11, 95%CI 0.03–0.47). In a smaller observational study (27), fewer women in the carbetocin group had a blood loss of >1000 ml (1 of 55 given carbetocin and 9 of 62 given the combination (RR 0.12, 95%CI 0.15–0.94)).

Intramuscular prostaglandins vs injectable uterotonics)

No difference was observed in the risk of blood transfusion between these two treatments (RR 1.05, 95%CI 0.39–2.86). Use of additional uterotonics was not significantly different between the prostaglandin group (4 of 106) and the injectable uterotonic group (2 of 116) (RR 2.05, 95%CI 0.39–10.92). Vomiting was observed in 15 of 103 patients receiving prostaglandin and 1 of 107 patients receiving injectable uterotonics (RR 10.74, 95%CI 2.06–56.02).

Sulprostone vs injectable uterotonics

Two RCTs conducted in the Netherlands (28, 29) reported on estimated blood loss of ≥1000 ml. There was a nonsignificant reduction in the risk of severe PPH in both

low-risk (28) and high-risk women (29) (RR 0.41, 95%CI 0.14–1.20) in women receiving sulprostone. The Van Selm study (29) was terminated early because of concerns regarding myocardial infarctions in women treated with sulprostone and mifepristone.

Carboprost vs misoprostol

No evidence was found relating to the priority outcomes regarding blood loss. Of 60 patients in the carboprost group, none received a blood transfusion compared with 1 of 60 in the misoprostol group (RR 0.33, 95%CI 0.01–8.02) (30). No patients in the carboprost group reported shivering, compared with 5 in the misoprostol group (RR 0.09, 95%CI 0.01–1.61).

Misoprostol vs injectable uterotonics

When compared with injectable uterotonics there was an increase in the risk of blood loss of ≥1000 ml in women receiving oral misoprostol (400–800 µg) (RR 1.32, 95%CI 1.16–1.51), but no statistically significant difference in the incidence of severe morbidity, including maternal death (RR 1.00, 95%CI 0.14–7.10). These trials did not report the outcome of invasive or surgical treatments.

Recommendations

- For management of PPH, oxytocin should be preferred over ergometrine alone, a fixed-dose combination of ergometrine and oxytocin, carbetocin, and prostaglandins. **(Quality of evidence: very low to low. Strength of recommendation: strong.)**
- If oxytocin is not available, or if the bleeding does not respond to oxytocin, ergometrine or oxytocin-ergometrine fixed-dose combination should be offered as second-line treatment. **(Quality of evidence: very low to low. Strength of recommendation: strong.)**
- If the above second-line treatments are not available, or if the bleeding does not respond to the second-line treatment, a prostaglandin should be offered as the third line of treatment. **(Quality of evidence: very low to low. Strength of recommendation: strong.)**

Remarks

- The above recommendations are based largely on data from prevention trials or case series. However, data from treatment RCTs were available for misoprostol versus oxytocin.
- The pharmacokinetics, bioavailability and mode of action of oxytocin and ergometrine and the uterotonic effects of misoprostol in other obstetric and gynaecological uses were considered by the participants in the Consultation in making the recommendations.
- Misoprostol may be considered as a third line of treatment for the management of PPH, because of its ease of administration and low cost compared with injectable prostaglandins (see also section (b)).

- The Consultation noted that the cost of carbetocin was high compared with the other options. Moreover, it found no evidence that carbetocin has a significant advantage over oxytocin.

(b) Should misoprostol be offered in the management of PPH due to uterine atony?

The Consultation made recommendations relating to two separate scenarios: women who received prophylactic oxytocin during the third stage of labour and those who did not.

(i) Should misoprostol be offered for the management of PPH in women who have received prophylactic oxytocin during the third stage of labour?

Summary of evidence

Four trials assessed the use of misoprostol as an adjunct following active management of the third stage of labour with oxytocin (31–34). The three published trials (31–33) were relatively small, with a total of 465 women participating. The unpublished WHO-Gynuity trial (34) included 1400 women in Argentina, Egypt, South Africa, Thailand and Viet Nam. In three trials (31, 33, 34), 600 µg of misoprostol was administered orally or sublingually, while in the fourth trial (32) 1000 µg was administered orally, sublingually or rectally. The results of the WHO-Gynuity trial (34) were presented to the Consultation and are included in the GRADE table (page 28, GRADE Table B1).

Taken altogether, when misoprostol as an adjunct was compared with placebo in women receiving other standard treatments, there were no statistical differences in the critical outcomes of additional blood loss ≥500 ml (RR 0.83, 95%CI 0.64–1.07), additional blood loss ≥1000 ml (RR 0.76, 95%CI 0.43–1.34) and blood transfusion (RR 0.96, 95%CI 0.77–1.19). Similarly, in the large WHO-Gynuity trial (34), the critical outcomes of additional blood loss ≥500 ml (RR 1.01, 95%CI 0.78–1.30), additional blood loss ≥1000 ml (RR 0.76, 95%CI 0.43–1.34) and blood transfusion (RR 0.89, 95%CI 0.69–1.13) were not clinically or statistically significantly different in the two groups.

Recommendation

There is no added benefit of offering misoprostol as adjunct treatment for PPH in women who have received oxytocin during the third stage of labour. Where oxytocin is available, and is used in the management of the third stage of labour, oxytocin alone should be used in preference to adjunct misoprostol for the management of PPH. **(Quality of evidence: moderate to high. Strength of recommendation: strong.)**

Remark

The recommendation is based mainly on data from one large unpublished randomized controlled trial (34).

(ii) Should misoprostol be offered as a treatment for PPH in women who did not receive prophylactic oxytocin during the third stage of labour?

Summary of evidence

The evidence relating to this question came from one large RCT conducted in Ecuador, Egypt and Viet Nam (35), which compared 800 µg of misoprostol given sublingually with 40 IU of oxytocin given intravenously. Unpublished trial results were presented to the Consultation (page 29, GRADE Table B2). Women who received misoprostol had a significantly increased risk of additional blood loss ≥500 ml (RR 2.66, 95%CI 1.62–4.38) and of needing additional therapeutic uterotonics (RR 1.79, 95%CI 1.19–2.69). There were few cases of additional blood loss ≥1000 ml (5 of 488 in the group given misoprostol and 3 of 489 given oxytocin). There was an increased risk of blood transfusion in the misoprostol group, of borderline statistical significance (RR 1.54, 95%CI 0.97–2.44).

Regarding side-effects, 66 of 488 women receiving misoprostol had a body temperature above 40 °C, compared with none of 490 given oxytocin. Most of the cases of high temperature occurred in Ecuador, where 36% of the women given misoprostol had a temperature above 40 °C. There were no cases in Egypt. Seven of the women with high temperature had delirium.[1]

Recommendation

In women who have not received oxytocin as a prophylactic during the third stage of labour, oxytocin alone should be offered as the drug of choice for the treatment of PPH. **(Quality of evidence: moderate to high. Strength of recommendation: strong.)**

Remarks

- Evidence of the superiority of oxytocin over misoprostol for the treatment of PPH came from one large trial, which showed oxytocin to have higher effectiveness and fewer side-effects.
- The Consultation recognized that oxytocin may not be available in all settings. It encouraged health care decision-makers in these settings to strive to make oxytocin and other injectable uterotonics available. However, because the use of a uterotonic is essential for the treatment of PPH due to atony, it considered that misoprostol may be used until oxytocin can be made available.
- The Consultation noted that the doses of misoprostol used in the trials on prevention of PPH ranged from 200 µg to 800 µg, administered orally, sublingually or rectally. In the PPH treatment trials, doses from 600 µg to 1000 µg were administered orally, sublingually or rectally. Side-effects, primarily high fever and shivering, were associated with higher doses; few life-threatening events have been reported. Hence, doses of 1000–1200 µg are not recommended. The Consultation noted that the largest trial of misoprostol for treatment of PPH (35) reported use of a dose of 800 µg, given sublingually. The majority of the participants felt that, in the treatment of PPH, where the first- and second-line uterotonics are not available or have failed, as a last resort 800 µg can be used. However, three members strongly disagreed with this conclusion because

[1] Final numbers were confirmed after the meeting by Gynuity.

of concerns about safety. Because of the disagreement the discussion of dose is included here, rather than as a recommendation.

- In view of the uncertainty and disagreement among the participants regarding the safe dose of misoprostol, WHO will commission a further review of misoprostol doses and routes of administration.

(c) Should tranexamic acid be offered in the treatment of PPH due to uterine atony?

Tranexamic acid is an antifibrinolytic agent that has been on the market for several decades. Antifibrinolytic agents are widely used in surgery to reduce blood loss. A systematic review of randomized controlled trials of antifibrinolytic agents in elective surgery showed that tranexamic acid reduced the risk of blood transfusion by 39% (36). Another Cochrane review showed that tranexamic acid reduced heavy menstrual bleeding without side-effects (37).

Summary of evidence

There have been no RCTs on the use of tranexamic acid for the treatment of PPH following vaginal delivery that address the priority outcomes. Tranexamic acid has been evaluated as prophylaxis following caesarean section in one RCT (38). The average blood loss in the two hours after the caesarean section was 42.75±40.45 ml in the study group and 73.98±77.09 ml in the control group.

One case report was found of a woman given tranexamic acid for treatment of massive postpartum haemorrhage after caesarean section (39).

Recommendation

Tranexamic acid may be offered as a treatment for PPH if: (i) administration of oxytocin, followed by second-line treatment options and prostaglandins, has failed to stop the bleeding; or (ii) it is thought that the bleeding may be partly due to trauma. **(Quality of evidence: very low. Strength of recommendation: weak.)**

Remarks

Evidence for this recommendation was extrapolated from the literature on surgery and trauma, which shows tranexamic acid to be a safe option in trauma-related bleeding.

The benefits of use of tranexamic acid in PPH treatment should be investigated in research studies.

(d) Should recombinant factor VIIa be offered in the treatment of PPH due to uterine atony?

Recently, recombinant factor VIIa (rFVIIa) has generated interest as an option for treatment of PPH, mainly in industrialized countries. The evidence regarding its use in the treatment of PPH is limited to reviews of case reports and case series (40, 41) and two observational studies (42,43) (page 30, GRADE Table B3).

Hossain (43) described a retrospective cohort study of 34 patients with more than 1500 ml blood loss in which 18 were treated with rFVIIa. Ahonen (42) compared the outcomes of 26 women who received rFVIIa to those of 22 women treated in the same time period for PPH without rFVIIa.

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

The risk of maternal death appeared to be lower in women treated with rFVIIa (OR 0.38, 95%CI 0.09–1.60), and remained lower following adjustment for baseline haemoglobin and activated partial thromboplastin time (aPTT) (OR 0.04, 95%CI 0.002–0.83) (43). The risk of subsequent need for hysterectomy is difficult to ascertain, as the drug was administered as a 'last resort' treatment. The authors note that as confidence in its use increased, rFVIIa began to be offered prior to hysterectomy. In Ahonen's report (42), 8 women received rFVIIa following hysterectomy, but none of the remaining 18 women treated with rFVIIa subsequently underwent hysterectomy.

A high rate of thrombotic events (185 events in 165 treated patients) has been reported in patients receiving rFVIIa for off-label use (44). Ahonen (42) described one report of a pulmonary embolus; the woman was subsequently diagnosed with antithrombin deficiency.

The Consultation discussed the evidence from observational studies and heard about ongoing research on rFVIIa.

Recommendation

The Consultation agreed that there was not enough evidence to make any recommendation regarding the use of recombinant factor VIIa for the treatment of PPH. Recombinant factor VIIa for the treatment of PPH should be limited to women with specific haematological indications.

Remark

Use of rFVIIa could be life-saving, but it is also associated with life-threatening side-effects. Moreover, recombinant factor VIIa is expensive to buy and may be difficult to administer.

2. Non-medical interventions for management of PPH

A range of mechanical interventions to compress or stretch the uterus have been proposed, either as temporizing measures or as definitive treatment. These interventions are summarized below.

(a) Should uterine massage be offered in the treatment of PPH?

Uterine massage as a therapeutic measure is defined as rubbing of the uterus manually over the abdomen sustained until bleeding stops or the uterus contracts.

Initial rubbing of the uterus and expression of blood clots is not regarded as therapeutic uterine massage.

Summary of evidence

There have been no RCTs on the use of uterine massage in the treatment of PPH. A case report series (45) and indirect evidence from one systematic review (46) on the use of uterine massage in PPH prevention were found.

In one RCT of the prophylactic use of uterine massage involving 200 women, massage was associated with a nonsignificant decrease in incidence of blood loss ≥500 ml (RR 0.52, 95%CI 0.16–1.67) and a significant reduction in the use of additional uterotonics (RR 0.20, 95%CI 0.08–0.50) (page 31, GRADE Table B4).

Recommendation

Uterine massage should be started once PPH has been diagnosed. **(Quality of evidence: very low. Strength of recommendation: strong.)**

Remarks

- Uterine massage to ensure the uterus is contracted and there is no bleeding is a component of active management of the third stage of labour for the prevention of PPH.
- The low cost and safety of uterine massage were taken into account in making this recommendation strong.

(b) Should bimanual uterine compression be offered in the treatment of PPH?

Summary of evidence

No RCTs on the use of bimanual uterine compression in the treatment of PPH were identified. One case report (47) was found.

Recommendation

Bimanual uterine compression may be offered as a temporizing measure in the treatment of PPH due to uterine atony after vaginal delivery. **(Quality of evidence: very low. Strength of recommendation: weak.)**

Remark

The Consultation noted that health care workers would need to be appropriately trained in the application of bimanual uterine compression and that the procedure may be painful.

(c) Should uterine packing be offered in the treatment of PPH?

Summary of evidence

No RCTs on the use of uterine packing in the treatment of PPH were found. Seven case series and one case report (48–55), with a total of 89 women (the largest involved 33 women), and four overviews were identified. Success rates (i.e. no need for hysterectomy or other invasive procedure) ranging from 75% to 100% are reported in these studies.

Recommendation

Uterine packing is not recommended for the treatment of PPH due to uterine atony after vaginal delivery. **(Quality of evidence: very low. Strength of recommendation: weak.)**

Remark

The Consultation noted that there was no evidence of benefit of uterine packing and placed a high value on concerns regarding its potential harm.

(d) Should intrauterine balloon or condom tamponade be offered in the treatment of PPH?

Summary of evidence

There have been no RCTs on the use of uterine tamponade in the treatment of PPH. Nine case series and twelve case reports, evaluating 97 women (56–76), and two reviews were identified (77, 78). The instruments used included Sengstaken-Blakemore and Foley catheters, Bakri and Rusch balloons, and condoms.

Case series have reported success rates (i.e. no need for hysterectomy or other invasive procedure) ranging from 71% to 100%.

Recommendation

In women who have not responded to treatment with uterotonics, or if uterotonics are not available, intrauterine balloon or condom tamponade may be offered in the treatment of PPH due to uterine atony. **(Quality of evidence: low. Strength of recommendation: weak.)**

Remark

The Consultation noted that the application of this intervention requires training and that there are risks associated with the procedure, such as infection. The use of uterine balloon or condom tamponade in the treatment of PPH was considered a research priority.

(e) Should external aortic compression be offered in the treatment of PPH?

Summary of evidence

No trials were found describing the use of external aortic compression in the treatment of PPH. A prospective study was performed in Australia to determine the haemodynamic effects of external aortic compression in nonbleeding postpartum women (79). Successful aortic compression, as documented by absent femoral pulse and unrecordable blood pressure in a lower limb, was achieved in 11 of 20 subjects. The authors concluded that the procedure is safe in healthy subjects and may be of benefit as a temporizing measure in treatment of PPH while resuscitation and management plans are made. Subsequently, one case report from Australia described the use of internal aortic compression as a temporizing measure to control severe PPH due to placenta percreta at the time of caesarean section (80).

Recommendation

External aortic compression for the treatment of PPH due to uterine atony after vaginal delivery may be offered as a temporizing measure until appropriate care is available. **(Quality of evidence: very low. Strength of recommendation: weak.)**

Remarks

- External aortic compression has long been recommended as a potential life-saving technique, and mechanical compression of the aorta, if successful, slows down blood loss.
- The Consultation placed a high value on the procedure as a temporizing measure in treatment of PPH.

(f) Should nonpneumatic antishock garments be offered in the treatment of PPH?

Summary of evidence

There have been no RCTs on the use of pneumatic or nonpneumatic antishock garments in the treatment of PPH. Case studies and case series have, however, been published and summarized (81–87). The use of nonpneumatic antishock garments (NASGs) has been reported in a before-and-after study of 634 women with obstetric haemorrhage (43% with uterine atony) in Egypt (88).

Women treated with an NASG had a median blood loss 200 ml lower (range 300–100 ml lower) than women who received standard treatment (hydration with intravenous fluids, transfusion, uterotonics, vaginal or abdominal surgery, as needed) in the "before" period (i.e. before the introduction of NASG). The risk of blood transfusion was higher in those treated with NASG (RR 1.23, 95%CI 1.06–1.43); the risk of surgical procedures was not statistically significantly different (RR 1.35, 95%CI 0.90–2.02) (page 31, GRADE Table B5).

A cluster RCT (Miller S, personal communication) is under way in Zambia and Zimbabwe to examine whether early application of an NASG by midwives prior to transfer to a referral hospital can decrease morbidity and mortality. No data were available for review.

Recommendation

The Consultation decided not to make a recommendation on this question.

Remark

The Consultation noted that research was ongoing to evaluate the potential benefits and harms of this intervention, and decided not to make a recommendation until these research results become available.

(g) Should uterine artery embolization be offered in the treatment of PPH?

Percutaneous transcatheter arterial embolization of the uterine artery has been reported from institutions that have adequate radiological facilities for this intervention.

Summary of evidence

There have been no RCTs on the use of arterial embolization in the treatment of PPH. One retrospective cohort study (89) compared 15 women treated with embolization with 14 women receiving other treatments for PPH. The majority of these patients had been transferred from local hospitals. Ten of 13 women were successfully treated for PPH with arterial embolization. Of 11 women originally treated with conservative surgical methods, two subsequently underwent arterial embolization; one of these was successful while the second patient eventually required hysterectomy. Eighteen case series and 15 case reports (90–122) have been published, describing the intervention in 340 women. Studies report success rates (i.e. no need for hysterectomy or other invasive procedures) ranging from 82% to 100% (page 32, GRADE Table B6).

Recommendation

If other measures have failed and resources are available, uterine artery embolization may be offered as a treatment for PPH due to uterine atony. **(Quality of evidence: very low. Strength of recommendation: weak.)**

Remark

Uterine artery embolization requires significant resources, in terms of cost of treatment, facilities and training of health care workers.

3. Surgical interventions in the treatment of PPH

A wide range of surgical interventions have been reported to control postpartum haemorrhage that is unresponsive to medical or mechanical interventions. They include various forms of compression sutures, ligation of the uterine, ovarian or internal iliac artery, and subtotal or total hysterectomy.

Summary of evidence

There have been no RCTs on the use of uterine compressive sutures in the treatment of PPH. Thirteen case series and twelve case reports describing a total of 113 women were identified (123–147). Eight overviews on compression sutures have also been published (77, 78, 148–153). The B-Lynch technique seems to be the most commonly reported procedure. Success rates (i.e. no need for hysterectomy or other invasive procedure) range from 89% to 100%.

Similarly, no RCTs on the use of selective artery ligation in treatment of PPH were identified. Twenty-one case series and 13 case reports have been published, describing the intervention in 532 women (123, 154–186). Studies report success rates (i.e. no need for hysterectomy or other invasive procedure) ranging from 62% to 100%.

Recommendation

If bleeding does not stop in spite of treatment with uterotonics, other conservative interventions (e.g. uterine massage), and external or internal pressure on the uterus, surgical interventions should be initiated. Conservative approaches should be tried first, followed – if these do not work – by more invasive procedures. For example,

compression sutures may be attempted first and, if that intervention fails, uterine, utero-ovarian and hypogastric vessel ligation may be tried. If life-threatening bleeding continues even after ligation, subtotal (also called supracervical or total hysterectomy) should be performed. **(Quality of evidence: no formal scientific evidence of benefit or harm. Strength of recommendation: strong.)**

Remark

The Consultation acknowledged that the level of skill of the health care providers will play a role in the selection and sequence of the surgical interventions.

C. Management of retained placenta

1. Should uterotonics be offered as treatment for retained placenta?

Summary of evidence

One double-blind RCT was found that compared sulprostone with placebo in 50 women with retained placenta (187). Originally designed to recruit over 100 patients, the trial was stopped prematurely and sulprostone was given to all remaining cases.

The authors reported a lower risk of manual removal of the placenta (RR 0.51, 95%CI 0.34–0.86) and an increased risk of blood transfusion in the sulprostone group (RR 2.26, 95%CI 1.14–4.12) (page 33, GRADE Table C1). There is no empirical evidence for or against the use of other uterotonics for treatment of retained placenta.

Recommendations

- If the placenta is not expelled spontaneously, clinicians may offer 10 IU of oxytocin in combination with controlled cord traction. **(No formal scientific evidence of benefit or harm. Strength of recommendation: weak.)**
- Ergometrine is not recommended, as it may cause tetanic uterine contractions, which may delay expulsion of the placenta. **(Quality of evidence: very low. Strength of recommendation: weak.)**
- The use of prostaglandin E2 (dinoprostone or sulprostone) is not recommended. **(Quality of evidence: very low. Strength of recommendation: strong.)**

Remarks

- The Consultation found no empirical evidence to support recommendation of uterotonics for the management of retained placenta in the absence of haemorrhage. The above recommendation was reached by consensus.
- The WHO guide, *Managing complications in pregnancy and childbirth* (18), states that if the placenta is not expelled within 30 minutes after delivery of the baby, the woman should be diagnosed as having retained placenta. Since there is no evidence for or against this definition, the delay used to diagnose this condition is left to the judgement of the clinician.

- The same guide also recommends that, in the absence of haemorrhage, the woman should be observed for a further 30 minutes following the initial 30 minutes, before manual removal of the placenta is attempted. The Consultation noted that, in the absence of bleeding, spontaneous expulsion of the placenta can still occur; thus, a conservative approach is advised and the timing of manual removal as the definitive treatment is left to the judgement of the clinician.
- The recommendation about prostaglandin E2 is based on the lack of evidence, as well as concerns regarding adverse events, notably cardiac events.

2. Should intra-umbilical vein injection of oxytocin with or without saline be offered as treatment for retained placenta?

Summary of evidence

One systematic review on umbilical vein injection for the management of retained placenta has been published (188). RCTs comparing the use of intraumbilical vein injection of saline with expectant management (four studies, 413 women), intraumbilical vein injection of saline+oxytocin with expectant management (five studies, 454 women), and intraumbilical vein injection of saline+oxytocin with saline (ten studies, 649 women) were identified.

The results of one unpublished study (189) were made available to the Consultation by the investigators. In this multicentre trial, 577 women in Pakistan, Uganda and the United Kingdom were randomized to receive either intraumbilical vein injection of 50 IU of oxytocin in 30 ml of saline (*n*=292) or matching placebo (*n*=285).

Intraumbilical vein injection of saline versus expectant management

There were no significant differences in rates of manual removal of the placenta (RR 0.97, 95%CI 0.83–1.19), blood loss ≥500 ml (RR 1.04, 95%CI 0.55–1.96), blood loss ≥1000 ml (RR 0.73, 95%CI 0.17–3.11), or blood transfusion (RR 0.76, 95%CI 0.41–1.39) (page 34, GRADE Table C2).

Intraumbilical vein injection of saline+oxytocin versus expectant management

There was a slightly lower rate of manual removal of the placenta in the group given saline+oxytocin, although the difference was not statistically significant (RR 0.86, 95%CI 0.72–1.01). Rates of blood loss ≥500 ml (RR 1.53, 95%CI 0.78–2.67), blood loss ≥1000 ml (RR 1.29, 95%CI 0.38–4.34), and blood transfusion (RR 0.89, 95%CI 0.5–1.58) were similar with wide confidence intervals (page 35, GRADE Table C3).

Intraumbilical vein injection of saline+oxytocin versus saline

There was a lower risk of manual removal of the placenta in the group given saline+oxytocin (RR 0.79, 95%CI 0.69–0.91). No differences were found in rates of blood loss ≥500 ml (RR 1.43, 95%CI 0.83–2.45), blood loss ≥1000 ml (RR 1.71, 95%CI 0.45–6.56) or blood transfusion (RR 1.17, 95%CI 0.63–2.19) and the confidence intervals were wide because there were few events (page 36, GRADE Table C4).

The unpublished RELEASE trial (189) data showed no benefit of intraumbilical vein injection of saline with oxytocin over placebo in terms of manual removal of the placenta (RR 0.98, 95%CI 0.87–1.12), blood loss ≥500 ml (RR 0.98, 95%CI 0.78–1.23), blood loss ≥1000 ml (RR 1.09, 95%CI 0.67–1.76) and blood transfusion (RR 0.77, 95%CI 0.46–1.26) (page 37, GRADE Table C5).

Recommendations

- Intraumbilical vein injection of oxytocin with saline may be offered for the management of retained placenta. **(Quality of evidence: moderate. Strength of recommendation: weak.)**
- If, in spite of controlled cord traction, administration of uterotonics and intraumbilical vein injection of oxytocin+saline, the placenta is not delivered, manual extraction of the placenta should be offered as the definitive treatment. **(No formal assessment of quality of evidence. Strength of recommendation: strong.)**

Remarks

- During the discussion on this topic, a new meta-analysis of the available data was performed, by including data from the recent large unpublished study with the existing published meta-analysis. Sensitivity analyses by quality of data and a fixed-versus-random-effects analysis were also conducted. In all these secondary analyses, the summary estimate reflected a modest effect, with the relative risk of manual removal being 0.89 (95%CI 0.81–0.98) with a fixed-effect model and 0.82 (95%CI 0.68–0.98) with a random-effect model. The Consultation was concerned about the possibility of publication bias in the meta-analysis, and was split between making a weak recommendation and not recommending intra-umbilical vein injection of oxytocin+saline.
- The Consultation recommended by a majority the use of umbilical vein injection of oxytocin+saline for retained placenta. In making the recommendation, the Consultation considered the advantages of avoiding an invasive intervention, such as manual removal of the placenta, and the low cost and absence of any side-effects with umbilical vein injection. It was noted that a potential disadvantage was that this intervention may delay the administration of other effective interventions. These considerations should be taken into account in the local adaptation of these guidelines.

3. Should antibiotics be offered after manual extraction of the placenta as part of the treatment of retained placenta?

Summary of evidence

A systematic review of antibiotic prophylaxis after manual removal of the placenta, published in 2006, found no RCTs (190).

One retrospective study (191) of 550 patients evaluated prophylactic antibiotic therapy in intrauterine manipulations (such as forceps delivery, manual removal of the placenta and exploration of the cavity of the uterus) during vaginal delivery.

Recommendation

A single dose of antibiotics (ampicillin or first-generation cephalosporin) should be offered after manual removal of the placenta. **(Quality of evidence: very low. Strength of recommendation: strong.)**

Remarks

- Direct evidence of the value of antibiotic prophylaxis after manual removal of the placenta was not available. The Consultation considered indirect evidence of the benefit of prophylactic antibiotics from studies of caesarean section (192) and abortion, and observational studies of other intrauterine manipulations.
- Current practice suggests that ampicillin or first-generation cephalosporin may be administered when manual removal of the placenta is performed.
- This question was identified as a research priority for settings in which prophylactic antibiotics are not routinely administered and those with low infectious morbidity.

D. Choice of fluid for replacement or resuscitation

1. Should crystalloids be offered for fluid replacement in women with PPH?

Fluid replacement is an important component of resuscitation for women with PPH, but the choice of fluid is controversial. Although outside the initial scope of these guidelines, this question was put to the Consultation in view of its importance.

Summary of evidence

There have been no RCTs comparing the use of colloids with other replacement fluids for resuscitation of women with PPH. There is indirect evidence from a Cochrane review that evaluated 63 trials on the use of colloids in the resuscitation of critically ill patients who required volume replacement secondary to trauma, burns, surgery, sepsis and other critical conditions (193). A total of 55 trials reported data on mortality for the following comparisons.

Colloids versus crystalloids

No statistical difference in the incidence of mortality was found when albumin or plasma protein fraction (23 trials, 7754 patients, RR 1.01, 95%CI 0.92–1.10), hydroxyethyl starch (16 trials, 637 patients, RR 1.05, 95%CI 0.63–1.75), modified gelatin (11 trials, 506 patients, RR 0.91, 95%CI 0.49–1.72), or dextran (nine trials, 834 patients, RR 1.24, 95%CI 0.94–1.65) were compared with crystalloids (page 38, GRADE Table D1).

Colloid versus hypertonic crystalloid

One trial, which compared albumin or plasma protein fraction with hypertonic crystalloid, reported one death in the colloid group (RR 7.00, 95%CI 0.39–126.92). Two trials that compared hydroxyethyl starch and modified gelatin with crystalloids

observed no deaths among the 16 and 20 participants, respectively (page 39, GRADE Table D2).

Colloids in hypertonic crystalloid versus isotonic crystalloid

The outcome of death was reported in eight trials, including 1283 patients, which compared dextran in hypertonic crystalloid with isotonic crystalloid (RR 0.88, 95%CI 0.74–1.05) and in one trial with 14 patients (page 39, GRADE Table D3).

Recommendation

Intravenous fluid replacement with isotonic crystalloids should be used in preference to colloids for resuscitation of women with PPH. **(Quality of evidence: low. Strength of recommendation: strong.)**

Remark

Available evidence suggests that high doses of colloids, which are more expensive than isotonic crystalloids, may cause adverse effects.

E. Health systems and organizational interventions

1. Should health care facilities have a protocol for management of PPH?

Summary of evidence

The literature search did not reveal any research evidence for or against the use of PPH management protocols. Although no systematic review was carried out, the Consultation considered that management protocols are generally useful and unlikely to be harmful.

Recommendation

Health care facilities should adopt a formal protocol for the management of PPH. **(Quality of evidence: no formal evidence reviewed; consensus. Strength: strong.)**

Remark

The Consultation acknowledged that the implementation of formal protocols is a complex process, which will require local adaptation of general guidelines.

2. Should health care facilities have a formal protocol for referral of women diagnosed as having PPH?

Summary of evidence

The literature search did not reveal any research evidence for or against the use of PPH referral protocols. Although no systematic review was carried out, the Consultation considered that referral protocols are generally useful and unlikely to be harmful.

Recommendation

Health care facilities should adopt a formal protocol for patient referral to a higher level of care. **(Quality of evidence: no formal evidence reviewed; consensus. Strength of recommendation: strong.)**

3. Should simulation of PPH treatment be part of training programmes for health care providers?

Summary of evidence

The literature search did not reveal any research evidence for or against the use of PPH simulation programmes. Although no systematic review was carried out, the Consultation considered that PPH simulation programmes are generally useful and unlikely to be harmful.

Recommendation

Simulations of PPH treatment may be included in pre-service and in-service training programmes. **(Quality of evidence: no formal evidence reviewed; consensus. Strength of recommendation: weak.)**

Remarks

This recommendation is extrapolated from non-obstetric literature.

The Consultation placed a high value on the costs of simulation programmes acknowledging that there are different types of simulation programmes. Some of those programmes are hi-tech, computerized and costly while others are less expensive and more likely to be affordable in low and middle income countries.

The Consultation identified improvement in communication between health care providers and patients and their family members as an important priority in training of health care providers in PPH management.

The Consultation identified this area as a research priority.

PPH care pathways

Postpartum haemorrhage can present in different clinical scenarios. Bleeding may be immediate and in large amounts, it may be slow and unresponsive to treatments, or it may be associated with systemic problems, such as clotting disorders. The recommendations related to PPH prevention, namely, active management of the third stage of labour, should be routinely applied (1).

It is critical that health workers remain vigilant during the minutes and hours following birth, in order to identify problems quickly. The care pathways presented (see insert) assume the presence of a skilled caregiver and a facility with basic surgical capacity. A stepwise approach is recommended. The initial step is to assess the woman and take immediate nonspecific life-saving measures, such as resuscitation, calling for help and monitoring vital signs. The second step is to give directive therapy following the diagnosis of PPH. In a given clinical situation, not all diagnostic assessments can be done simultaneously. The caregiver should assess the situation according to the circumstances surrounding the birth and immediate subsequent events.

The causes of PPH can be broadly classified into problems with uterine tone (atony), retained placenta, trauma (of the lower genital tract and uterus), and coagulation problems, which may be pre-existing or acquired as a result of other pathology (such as disseminated intravascular coagulation). If the birth was assisted with forceps or vacuum extraction, the likelihood of trauma will be higher. Alternatively, if labour was prolonged, uterine atony may be more likely. The care pathways suggest starting with the more effective, less invasive and less costly measures and, if those fail to stop the bleeding, moving towards invasive and more costly methods that require expertise and specific facilities.

It is acknowledged that some facilities will not have the expertise and equipment to undertake all the steps on the care pathways. The recommendations represent essential steps that should be undertaken at facility level. In facilities with more limited capacity, transfer of women with haemorrhage to a higher care facility should be organized without delay.

Methodology

The following algorithms were reviewed:

- Managing complications in pregnancy and childbirth (18).
- Algorithm presented as an attachment to the *Textbook of postpartum hemorrhage* (194).
- Algorithm of the Society of Obstetricians and Gynaecologists, Canada (195).
- French PPH management guideline (196).
- Argentinian PPH management algorithm (197).
- Guideline for the management of post-partum haemorrhage in the community (version 2.1.1) of Good Hope Hospital (198).
- Essential O&G Guidelines for district hospitals, South Africa (199).
- Guidelines for obstetric care at Coronation, Johannesburg and Natalspruit Hospitals, South Africa (200).

Draft care pathways were produced by the Secretariat and adjusted according to the recommendations made by the Consultation on uterotonics, mechanical measures to compress or stretch the uterine musculature, other pharmaceutical approaches, such as tranexamic acid, and surgery.

The Consultation agreed to follow the stepwise approach adopted in the Canadian guidelines. This approach identifies the initial measures, and moves to more invasive, costly and risky interventions only if the directed therapy for the diagnosed pathology fails. The approach taken by the Consultation assumes that more than one pathology may exist in one patient, and that the care provider should be vigilant in looking for other pathologies. The potential existence of additional pathologies will be more relevant if the initial therapeutic approaches fail, as the possibility

of both an existing (undiagnosed) pathology and the development of a new one (e.g. coagulopathy) increase as time passes.

Therapeutic approaches related to partially retained placenta, traumatic haemorrhage and coagulopathies are included in the care pathways but not in the recommendations. For these, there was no formal search for evidence, appraisal and review, and the recommendations in the care pathways reflect the consensus of the Consultation.

The Consultation considered it important to highlight the emergency resuscitation measures in the care pathways. While not all PPH cases are associated with massive blood loss and shock, the health care worker should be aware that large blood losses can occur within a short period and that vigilance is needed at all times.

Some interventions are recommended as temporizing measures, especially during transfer of the patient to a higher level of care; occasionally, bleeding may stop with some of these measures.

It should be noted that for some categories, such as uterine atony, there is a hierarchy within the interventions listed in each group of directive therapy (uterotonics, mechanicals, surgery, etc.), starting with the more effective, less expensive methods with a larger safety margin.

Research implications

The Consultation noted the questions for which the quality of evidence was low or very low. In general, the fact that recommended practices are based on evidence of low or very low quality would suggest that further research is needed. However, those areas may not be of high priority, for various reasons. The Consultation agreed that the following questions should be considered as high priority for research in the international community. (The list below is in order of discussion, not level of priority.)

1. Accuracy of blood loss assessment

The Consultation agreed that quantification of blood loss is important, and that it may be useful to study the level of blood loss that is considered as requiring active management of PPH (i.e. when should treatment be started?). The large data set compiled by Gynuity from their various studies could be scrutinized for this purpose before any primary research is undertaken.

2. Interventions

(a) Medications

The dosage of misoprostol generated a lot of discussion and disagreement, because of concerns over safety. Investigation of the effects of lower doses of misoprostol was suggested. However, given that oxytocin is clearly superior, such studies could only be conducted in places that have no access to oxytocin.

Clarification of the role of tranexamic acid in PPH and obstetric haemorrhage was identified as a priority. Some clinicians in the Consultation mentioned that they already use tranexamic acid, while others did not. There seems to be uncertainty among clinicians and an absence of evidence. The Consultation was informed that a large multicentre trial is planned.

(b) Procedures

Uterine massage is recommended for routine care of women in the immediate postnatal period up to two hours. However, it has not been evaluated as a therapeutic option in a clearly defined way. Since this is a simple intervention that can even be self-administered, the Consultation considered that evaluating strategies to train health workers and mothers in the use of uterine massage would be worth while.

Balloon or condom tamponade for the treatment of PPH is highly valued by some practitioners, but not used at all by others. The Consultation considered that this intervention can be highly effective, but may also have potential complications; it should be rigorously evaluated as a priority.

The Consultation noted the lack of evidence regarding the role of antibiotics following manual extraction of a retained placenta. In settings where antibiotics are not currently routinely administered, it may be worth while to evaluate the benefits and harms.

(c) Training programmes

The Consultation noted that there was no primary evidence on the effectiveness of training programmes in obstetric haemorrhage and agreed that evaluations of such programmes should be a priority, since they require financial and human resources.

(d) Implementation research

The Consultation noted that some strategies for implementation of guidelines have been shown to be effective. However, there may be a need for new primary research projects in different contexts to study the implementation of these particular recommendations.

Plans for local adaptation of the recommendations

The WHO Department of Reproductive Health and Research works with international partners, including its collaborating centres and WHO country and regional offices, to promote the dissemination and adaptation of its recommendations. Specifically, the Department has been collaborating with the United Nations Population Fund (UNFPA) since 2004 in a Strategic Partnership Programme to support country-level adaptation and implementation of sexual and reproductive health guidelines. The Department

has also published a document, outlining the principles and processes of guideline adaptation and implementation (201).

The text of the recommendations and remarks points out where local adaptation might be considered.

Plans for supporting implementation of these recommendations

These recommendations have been developed in collaboration with external partners and the International Federation of Obstetricians and Gynaecologists (FIGO). The current document will be distributed to all WHO regional and country offices. During 2009–2010, the recommendations will be presented in scientific meetings and a short summary will be published in a peer-reviewed journal. They will also be included on the Department's Website and in *The WHO Reproductive Health Library,* online and on CD-ROM, which reaches around 50 000 health workers. The care pathways for the management of PPH and retained placenta have been produced on a wallchart included in this publication and will be sent to all WHO country and regional offices and international partners.

The WHO Secretariat will collect comments on the quality, user-friendliness and implementation of these recommendations by seeking feedback from its collaborating institutions and WHO country and regional offices. An update of the recommendations is planned for 2010–2011.

GRADE tables

A. Diagnosis of PPH (Tables A1 and A2)
B. Management of atonic PPH (Tables B1–B6)
C. Management of retained placenta (Tables C1–C5)
D. Choice of fluid for replacement or resuscitation (Tables D1–D3)

A. Diagnosis of PPH

Table A1. Visual versus quantitative methods for estimating blood loss after vaginal delivery (3)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Visual estimation	Measured estimation	Relative (95% CI)	Absolute		
Mean blood loss												
1	Randomized trial	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	Reporting bias[4]	61	62	–	Mean difference − 99.71 (−157.19 to −42.23)	⊕◯◯◯ Very low	Important

[1] Method of allocation concealment not described.
[2] Related to settings where it is feasible to use the drape method.
[3] Wide range.
[4] Intervention not blinded.

Table A2. Training courses on estimating blood loss after vaginal delivery (13)

Quality assessment							Summary of findings					Importance
							No. of subjects making accurate estimation		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Attending training course on blood loss estimation	Controls	Relative (95% CI)	Absolute		
Blood loss estimated accurately												
1	Randomized trial	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	34/45 (75.6%)	11/45 (24%)	RR 3.09 (1.80−5.30)	522 more per 1000[4]	⊕◯◯◯ Very low	Not important

[1] Methods of randomization and allocation concealment not described.
[2] Limited to setting; may be difficult to generalize.
[3] Wide confidence intervals.
[4] 522 more cases per 1000 accurately estimated.

B. Management of atonic PPH

Table B1. Adjunct use of misoprostol in women who received prophylactic oxytocin in the third stage of labour (34)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Primary outcomes	Controls	Relative (95% CI)	Absolute		
Additional blood loss ≥500 ml												
4	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	170/929 (18.3%)	200/950 (21.1%)	RR 0.83 (0.64–1.07)	29 fewer per 1000	⊕⊕⊕⊕ High	Critical
Additional blood loss ≥1000 ml												
3	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	20/899 (2.2%)	27/915 (3.1%)	RR 0.76 (0.43–1.34)	7 fewer per 1000	⊕⊕⊕◯ Moderate	Critical
Blood transfusion												
4	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	138/927 (14.9%)	147/949 (14.5%)	RR 0.96 (0.77–1.19)	6 fewer per 1000	⊕⊕⊕⊕ High	Critical
Hysterectomy												
3	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/900 (0.6%)	5/919 (0.4%)	RR 0.93 (0.16–5.41)	0 fewer per 1000	⊕⊕◯◯ Low	Critical
Additional uterotonics												
3	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	253/894 (28.3%)	271/910 (28.3%)	RR 0.96 (0.84–1.1)	11 fewer per 1000	⊕⊕⊕⊕ High	Critical
Shivering												
4	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	556/928 (59.9%)	270/948 (17.7%)	RR 2.24 (1.72–2.91)	219 more per 1000	⊕⊕⊕◯ Moderate	Important

[1] Wide confidence interval.

Table B2. Misoprostol vs oxytocin for treatment of postpartum haemorrhage in women who did not receive prophylactic oxytocin in the third stage of labour (35)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin	Relative (95% CI)	Absolute		
Additional blood loss ≥500 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	52/488 (10.7%)	19/489 (4%)	RR 2.74 (1.64-4.56)	69 more per 1000	⊕⊕⊕⊕ High	Critical
Additional blood loss ≥1000 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1]	None	5/488 (1%)	3/489 (0.6%)	RR 1.67 (0.4-6.95)	4 more per 1000	⊕⊕◯◯ Low	Critical
Blood transfusion												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	43/488 (8.8%)	28/489 (6%)	RR 1.54 (0.97-2.44)	32 more per 1000	⊕⊕⊕◯ Moderate	Critical
Additional uterotonics												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	59/489 (12.1%)	33/488 (7%)	RR 1.79 (1.19-2.69)	55 more per 1000	⊕⊕⊕⊕ High	Critical
Temperature > 40 °C												
1	Randomized trial	No serious limitations	No serious inconsistency	Serious[3]	Serious[4]	Strong association[5]	64/488 (13.1%)	0/489 (0%)	RR 129.27 (8.01-2883.1)	0 more per 1000	⊕⊕⊕◯ Moderate	Critical

[1] From a 40% reduction to a sevenfold increase.
[2] From a 3% reduction to a 2.5-fold increase.
[3] Results concentrated in one setting.
[4] Although significant, confidence intervals are wide.
[5] Large effect in the intervention group.

Table B3. Recombinant factor VIIa for treatment of postpartum haemorrhage (42, 43)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rFVIIa	Controls	Relative (95% CI)	Absolute		
Need for surgical treatment												
2	Observational study	No serious limitations	No serious inconsistency	Serious[1, 2]	Serious[3]	None	8/36[4] (22.2%)	13/38 (34.2%)	OR 0.59 (0.19–1.77)	122 fewer per 1000 (from 264 fewer to 181 more)	⊕○○○ Very low	Critical
Hysterectomy												
2	Observational study	No serious limitations	No serious inconsistency	Serious[1, 2]	Serious[3]	None	13/36[5] (36.1%)	13/32 (40.6%)	OR 0.98 (0.34–2.57)	22 fewer per 1000 (from 244 fewer to 366 more)	⊕○○○ Very low	Critical
Death												
1	Observational study	No serious limitations	No serious inconsistency	Serious[1, 2]	Serious[3]	None	5/50 (10%)	8/44 (18.2%)	OR 0.38 (0.09–1.6)[6]	107 fewer per 1000 (from 163 fewer to 88 more)	⊕○○○ Very low	Critical
Procedure-related complications												
1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	1/26[7] (6.3%)	0/22 (0%)	OR 2.65 (0.10–68.30)	0 per 1000 (from 0 fewer to 0 more)	⊕⊕○○ Low	Critical

[1] Study included PPH following vaginal delivery and caesarean section.
[2] Study included PPH due to uterine atony, cervical tears, lacerations, abnormal placentation, and medical or pregnancy-related disorders.
[3] Wide confidence interval.
[4] Hossain study (43) did not indicate timing of rFVIIa administration in relation to need for procedure.
[5] Ahonen study (42) included 8 women who received rFVIIa after hysterectomy; they are not included here. No women required hysterectomy following rFVIIa administration.
[6] Authors also reported OR of maternal mortality adjusted for baseline haemoglobin and aPTT (OR=0.04, 95%CI: 0.002–0.83).
[7] One reported case of pulmonary embolism in patient subsequently diagnosed with antithrombin deficiency.

Table B4. Uterine massage for treatment of postpartum haemorrhage (46)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine massage	Controls	Relative (95% CI)	Absolute		
Blood loss ≥500 ml (follow-up 1 hour; blood collected in plastic drapes)												
1	Randomized trial	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	4/98 (4.1%)	8/102 (8%)	RR 0.52 (0.16–1.67)	38 fewer per 1000	⊕○○○ Very low	critical
Additional uterotonics												
1	Randomized trial	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	5/98 (5.1%)	26/102 (25%)	RR 0.20 (0.08–0.50)	200 fewer per 1000	⊕○○○ Very low	

[1] Possibility of assessment bias. Small sample size.
[2] Intervention is for PPH prevention, not treatment.
[3] Wide confidence interval.

Table B5. Nonpneumatic antishock garment for treatment of postpartum haemorrhage (88)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	NASG	Controls (before)	Relative (95% CI)	Absolute		
Median blood loss (range of scores – better indicated by less)												
1	Before and after study	Serious[1]	No serious inconsistency	Serious	No serious imprecision	None	180	149	-	Median difference −200 ml (−300 to −100 ml)	⊕○○○ Very low	Important
Blood transfusion												
1	Before and after study	Serious[1]	No serious inconsistency	Serious	No serious imprecision	None	155/206 (75.2%)	96/158 (60.8%)	RR 1.23 (1.06–1.43)	140 more per 1000 (from 36 more to 261 more)	⊕○○○ Very low	Critical
Surgical procedures												
1	Before and after study	Serious[1]	No serious inconsistency	Serious	Serious[2]	None	51/206 (24.8%)	29/158 (18.4%)	RR 1.35 (0.90–2.02)	64 more per 1000 (from 18 fewer to 188 more)	⊕○○○ Very low	Critical

[1] "Before and after" design.
[2] From a 10% reduction to a twofold increase.

Table B6. Uterine artery embolization for treatment of postpartum haemorrhage (89)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Uterine artery embolization	Control	Relative (95% CI)	Absolute		
Hysterectomy												
1	Observational study	No serious limitations	No serious inconsistency	Serious[1]	Serious[2]	None	4/15[3] (26.7%)	2/9 (22.2%)	OR 1.27 (0.18–8.89)	48 more per 1000	⊕○○○ Very low	Critical
Procedure-related complication												
1	Observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	1/15[4] (6.7%)	0/14 (0%)	OR 1.97 (0.007–54.84)	0 per 1000	⊕⊕○○ Low	Critical

[1] Study included women who gave birth by caesarean section as well as women who had vaginal delivery.
[2] Wide confidence interval.
[3] Includes women treated with embolization after conservative surgical methods.
[4] Adverse event was rash caused by contrast material.

C. Management of retained placenta

Table C1. Uterotonics for management of retained placenta (187)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Uterotonics	Controls	Relative (95% CI)	Absolute		
Manual removal of the placenta												
1	Randomized trial	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	11/24 (45.8%)	22/26 (84.6%)	RR 0.54 (0.34–0.86)	34 fewer per 1000 (from 195 fewer to 161 more)	⊕⊕○○ Low	Critical
Blood transfusion												
1	Randomized trial	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/24 (66.7%)	8/26 (30%)	RR 2.26 (1.14–4.12)	378 more per 1000	⊕⊕○○ Low	Critical

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

Table C2. Intraumbilical vein injection of saline solution vs expectant management for retained placenta (188)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical vein injection of saline solution	Expectant management	Relative (95% CI)	Absolute		
Manual removal of the placenta												
4	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	114/206 (55.3%)	119/207 (58%)	RR 0.97 (0.83–1.19)	17 fewer per 1000	⊕⊕⊕⊕ High	Critical
Blood loss ≥500 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	15/62 (24.2%)	14/60 (23.3%)	RR 1.04 (0.55–1.96)	9 more per 1000	⊕⊕⊕○ Moderate	Critical
Blood loss ≥1000 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	3/62 (4.8%)	4/60 (7%)	RR 0.73 (0.17–3.11)	18 fewer per 1000	⊕⊕⊕○ Moderate	Critical
Blood transfusion												
2	Randomized trial	No serious limitations	Serious[3]	No serious indirectness	Serious[4]	None	15/118 (12.7%)	19/110 (17%)	RR 0.76 (0.41–1.39)	40 fewer per 1000	⊕⊕○○ Low	Critical

[1] Anything from a 45% reduction to a twofold increase.
[2] Anything from an 83% reduction to a threefold increase.
[3] No events in one trial.
[4] Anything from a 59% reduction to a 39% increase.

Table C3. Intraumbilical vein injection of saline + oxytocin vs expectant management for retained placenta (188)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical vein injection with saline + oxytocin	Expectant management	Relative (95% CI)	Absolute		
Manual removal of the placenta												
5	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	117/234 (50%)	129/220 (59%)	RR 0.86 (0.72–1.01)	82 fewer per 1000	⊕⊕⊕⊕ High	Critical
Blood loss ≥500 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	25/70 (35.7%)	14/60 (23%)	RR 1.53 (0.78–2.67)	121 more per 1000	⊕⊕⊕◯ Moderate	Critical
Blood loss ≥1000 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	6/70 (8.6%)	4/60 (6.7%)	RR 1.29 (0.38–4.34)	19 more per 1000	⊕⊕⊕◯ Moderate	Critical
Blood transfusion												
2	Randomized trial	No serious limitations	Serious[3]	No serious indirectness	Serious[4]	None	18/120 (15%)	19/117 (16%)	RR 0.89 (0.5–1.58)	17 fewer per 1000	⊕⊕◯◯ Low	Critical

[1] Anything from a 22% reduction to a threefold increase.
[2] Anything from a 62% reduction to a more than fourfold increase.
[3] No events in one trial.
[4] Anything from a 50% reduction to a 58% increase.

Table C4. Intraumbilical vein injection of saline + oxytocin vs saline for retained placenta (188)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical vein injection of saline + oxytocin	Intraumbilical vein injection of saline	Relative (95% CI)	Absolute		
Manual removal of the placenta												
10	Randomized trial	No serious limitations	Serious[1]	No serious indirectness	No serious imprecision	None	158/335 (47.2%)	184/314 (59%)	RR 0.79 (0.69-0.91)	123 fewer per 1000	⊕⊕⊕◯ Moderate	Critical
Blood loss ≥500 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	25/70 (35.7%)	15/60 (25%)	RR 1.43 (0.83-2.45)	107 more per 1000	⊕⊕⊕◯ Moderate	Critical
Blood loss ≥1000 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	6/70 (8.6%)	3/60 (5%)	RR 1.71 (0.45-6.56)	35 more per 1000	⊕⊕⊕◯ Moderate	Critical
Blood transfusion												
2	Randomized trial	No serious limitations	Serious[4]	No serious indirectness	Serious[5]	None	18/120 (15%)	15/118 (13%)	RR 1.17 (0.63-2.19)	22 more per 1000	⊕⊕◯◯ Low	Critical

[1] Heterogeneity: I2 = 45.5%.
[2] Anything from a 27% reduction to a 2.5-fold increase.
[3] Anything from a 55% reduction to a more than sixfold increase.
[4] No events in one trial.
[5] Anything from a 37% reduction to a twofold increase.

Table C5. Intraumbilical vein injection of 50 IU oxytocin+30 ml saline vs placebo for retained placenta (189)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intraumbilical vein injection of 50 IU oxytocin in saline	Placebo	Relative (95% CI)	Absolute		
Manual removal of the placenta												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	179/292 (61.3%)	177/285 (62.1%)	RR 0.98 (0.87-1.12)	12 fewer per 1000 (from 81 fewer to 75 more)	⊕⊕⊕⊕ High	Critical
Blood loss ≥500 ml												
1	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	99/292 (33.9%)	99/285 (34.7%)	RR 0.98 (0.78-1.23)	7 fewer per 1000 (from 76 fewer to 80 more)	⊕⊕⊕◯ Moderate	Critical
Blood loss ≥1000 ml												
1	randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	31/292 (10.6%)	28/285 (9.8%)	RR 1.09 (0.67-1.76)	9 more per 1000 (from 32 fewer to 74 more)	⊕⊕⊕◯ Moderate	Critical
Blood transfusion												
1	randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[3]	None	43/292 (14.7%)	36/285 (12.6%)	RR 0.77 (0.46-1.26)	29 fewer per 1000 (from 68 fewer to 33 more)	⊕⊕⊕◯ Moderate	Critical

[1] Anything from a 22% reduction to a 23% increase.
[2] Anything from a 33% reduction to a 76% increase.
[3] Anything from a 54% reduction to a 26% increase.

D. Choice of fluid for replacement or resuscitation

Table D1. Colloids vs crystalloids for fluid replacement in critically ill patients (193)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Colloids	Crystalloids	Relative (95% CI)	Absolute		
Death (albumin or plasma protein fraction vs crystalloids)												
23	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	782/3870 (20.2%)	778/3884 (20%)	RR 1.01 (0.92-1.1)	2 more per 1000 (from 16 fewer to 20 more)	⊕⊕⊕⊕ High	Critical
Death (hydroxyethyl starch vs crystalloids)												
16	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/375 (6.4%)	18/262 (6.9%)	RR 1.05 (0.63-1.75)	3 more per 1000	⊕⊕⊕⊕ High	Critical
Death (modified gelatin vs crystalloids)												
11	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/224 (5.8%)	15/282 (5.3%)	RR 0.91 (0.49-1.72)	4 fewer per 1000	⊕⊕⊕⊕ High	Critical
Death (dextran vs crystalloids)												
9	Randomized trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	96/412 (23.3%)	57/422 (13.5%)	RR 1.24 (0.94-1.65)	32 more per 1000	⊕⊕⊕⊕ High	Critical

Table D2. Colloids vs hypertonic crystalloids for fluid replacement in critically ill patients (193)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Colloid	Hypertonic crystalloid	Relative (95% CI)	Absolute		
Deaths (albumin or plasma protein fraction vs hypertonic crystalloids)												
1	Randomized trial	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious	None	3/19 (15.8%)	0/19 (0%)	RR 7.00 (0.39-126.92)	0 per 1000	⊕○○○ Very low	Critical
Deaths (hydroxyethyl starch vs crystalloids)												
1	Randomized trial	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[1]	None	0/8 (0%)	0/8 (0%)	RR 0 (0-0)	0 per 1000	⊕○○○ Very low	Critical
Deaths (modified gelatin vs hypertonic crystalloids)												
1	Randomized trial	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[1]	None	0/10 (0%)	0/10 (0%)	RR 0 (0-0)	0 per 1000	⊕○○○ Very low	Critical

[1] Underpowered study.

Table D3. Colloid in hypertonic crystalloid vs isotonic crystalloid for fluid replacement in critically ill patients (193)

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Colloid in hypertonic crystalloid	Isotonic crystalloid	Relative (95% CI)	Absolute		
Deaths (albumin or plasma protein fraction vs crystalloids)												
1	randomized trial	very serious[1]	no serious inconsistency	no serious indirectness	serious	none	1/7 (14.3%)	2/7 (28.6%)	RR 0.50 (0.06-4.33)	143 fewer per 1000	⊕○○○ Very low	critical
Deaths (dextran vs isotonic crystalloids)												
8	randomized trial	no serious limitations[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/667 (27.3%)	179/616 (29.1%)	RR 0.88 (0.74-1.05)	34 fewer per 1000	⊕⊕⊕⊕ High	critical

[1] Underpowered trial.
[2] As evaluated by the Cochrane reviewer.

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Annex 1. Scoping document with average scores

Scoping results: Management of PPH due to uterine atony and retained placenta

Dear colleagues,

Please find for your review, the overall (averaged) responses to our questions and outcomes related to the management of:

(1) postpartum haemorrhage due to uterine atony;

(2) retained placenta following an uncomplicated delivery.

In separate analysis, items shaded were scored >7 by at least one category of respondents (nurse midwives, physicians, or non-clinicians).

Proposed questions		
A. Blood loss estimation for the management of PPH		
Score the importance of the question in the management of PPH on a scale from 1 to 9, where 1 = not important, 9 = critical	Should blood loss be routinely quantified during delivery for the appropriate management of PPH due to uterine atony, instead of visual estimation of blood loss?	6.06
B. Medical interventions for the management of PPH		
Assumptions • Clinicians may perform several interventions simultaneously (i.e. uterine massage while medications are administered). • Clinicians are aware of standard contraindications of medications (although this will be reiterated in the final guideline and any derivative products).		
For each drug listed score the importance of determining its efficacy as a uterotonic (with or without postpartum haemorrhage) on a scale from 1 to 9, where 1=not important, 9=critical	**Drug (in clinically accepted doses and routes of administration)**	**Need to determine efficacy**
	Carbetocin	5.98
	Carboprost (PGF_{2a})	4.85
	Ergometrine	5.43
	Misoprostol	6.92
	Oxytocin	5.30
	rFactor VIIa	5.95
	Syntometrine (fixed dose combination 5IU oxytocin + 0.5 mg ergometrine maleate)	5.20
	Sulprostone (PGE_2)	5.20
	Tranexamic acid	5.72
For each question, please rate its importance in the management of PPH on a scale from 1 to 9, where 1=not important, 9=critical	Should certain combinations of medications be administered in the treatment of PPH?	6.92
	Should medications be administered in a sequential manner?	7.41
	Should use of one type of prostaglandin preclude use of other prostaglandins?	5.84
	Should the route of misoprostol administration vary if used as a first line (stand alone) treatment versus a second line treatment (in addition to, or sequentially with other medications)?	5.72

C. Interventions for the management of PPH

	Intervention	Procedure	Need to determine efficacy
For each procedure listed please score the relative importance of determining its efficacy in the management of PPH on a scale from 1 to 9, where 1=not important, 9=critical	Non surgical	Uterine fundal massage	7.02
		Bimanual uterine massage	6.75
		Uterine packing	6.47
		Uterine tamponade	6.90
		External aortic compression	6.40
		Anti-shock garments	6.78
	Radiologic	Uterine artery embolization	6.44
	Conservative surgical interventions	Compressive uterine sutures	6.90
		Uterine artery ligation	6.24
		Hypogastric (internal iliac) artery ligation	5.92
	Definitive	Subtotal hysterectomy	5.39
		Total hysterectomy	5.53

For each question please score its importance in the management of PPH on a scale from 1 to 9, where 1=not important 9=critical	Should non surgical interventions be attempted as a temporizing measure?	7.73
	Should invasive interventions be attempted sequentially?	7.60
	Should one surgical intervention be considered over others?	6.76

D. Interventions for the management of retained placenta

For each question, please score it's relative importance in the management of retained placenta on a scale from 1 to 9, where 1=not important 9=critical	Should uterotonics be administered if retained placenta has been diagnosed (usually after 30 minutes)?	7.58
	Should intraumbilical vein injection of oxytocin/saline be administered after clinical diagnosis of retained placenta?	6.76
	Should a retained placenta be manually extracted after 30 minutes?	6.92
	Should antibiotics be routinely administered following manual extraction of a retained placenta?	7.33

E. The role of health systems and institutions in the management of PPH due to uterine atony

For each question please score it's relative importance in the management of PPH on a scale from 1 to 9, where 1=not important 9=critical	Should each health system/institution have a formal protocol for the management of PPH?	8.51
	Should only physicians prescribe/administer uterotonics?	4.17
	Should only physicians perform interventions (non-surgical and surgical)?	5.49
	Should each facility have a formal protocol for the referral of patients?	8.27
	Should specific training courses with simulation of the management of PPH be offered to staff attending deliveries for the appropriate management of PPH, instead of routine curricula training?	7.93

Proposed outcomes

			Importance
Please score the importance of each individual outcome in the management of PPH, on a scale from 1 to 9, where 1=not important 9=critical	Measurement and magnitude of blood loss	Accuracy in blood loss assessment	6.68
		Mean blood loss	5.70
		An additional blood loss ≥500 ml (following initial PPH diagnosis)	7.17
		An additional blood loss ≥1000 ml (following initial PPH diagnosis)	7.76
Please do not attempt to rank the outcomes		Postpartum anaemia (HgB <11.0 g/dl)	6.49
		Blood transfusion	7.25
	Need for continued treatment	Additional uterotonics	7.44
	PPH management often involves a step-wise progression, so that need for one procedure may be seen as an outcome of another	Invasive nonsurgical treatment (uterine packing, bimanual uterine massage, tamponade)	7.21
		Surgical treatment (arterial ligation, compressive uterine sutures)	7.57
		Additional nonsurgical interventions (external aortic compression and compression garments)	6.82
		Arterial embolization	6.61
		Hysterectomy for PPH	7.69
	Adverse outcomes	Nausea, vomiting or shivering	5.48
		Maternal temperature greater than 38°C	5.92
		Maternal temperature greater than 40°C	7.54
		Delayed initiation of breastfeeding	5.68
		Prolonged hospitalization	6.70
		Procedure related complications	7.26
		Infection	7.48
		Severe morbidity (including coagulopathy, organ failure and ICU admission)	8.60
		Maternal transfer	7.33
	Systems	Reduction of time from decision making to implementation	8.20
		Availability of drugs and treatment	8.57

Annex 2. Search strategy

The search strategy aimed to identify references dealing with the treatment of PPH. No limits were placed on the search regarding type of study, language or time frame.

In November 2007, the Cochrane library, Pubmed, Embase, and Lilacs were searched using the following terms:

- oxytocin
- ergometrine
- syntometrine
- misoprostol
- carboprost
- sulprostone
- factor VIIa
- tranexamic acid
- carbetocin
- bimanual or manual
- massage
- packing
- tamponade
- balloon
- catheter
- Bakri or Blakemore or Foley or condom
- compressive or compression or B-Lynch
- (arterial or vessel or vascular or artery or arteries) and ligation
- anti shock garments
- postpartum or post partum
- hemorrhage or haemorrhage or bleeding.

Annex 3. GRADE methodology

The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Critical elements of using the GRADE system is described below. More information on GRADE methodology is presented at the web site http://www.gradeworkinggroup.org/index.htm.

Table 1. GRADE quality assessment criteria

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

* Move up or down the indicated number of grades.

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

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

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 reports of randomized trials are available, start by assuming high quality. If reports of well-done observational studies are available, assume low quality. 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.
- If there are limitations, downgrade RCTs from high to moderate, low or very low and 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. Then check:
  - for large or very large treatment effect;
  - whether all plausible confounders would diminish effect of intervention;
  - for dose-response gradient.

- Grade up to moderate or even high, depending on special strengths.
- Studies starting at very low are not upgraded. Observational studies with limitations are not upgraded. Only observational studies with no threats to validity can be upgraded.
- Decide on best estimates of benefits, harms, burden and costs for relevant populations.
- Decide on whether the overall benefits are worth the potential harms, burden and costs for the 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 outweigh the undesirable effects. Desirable effects can include beneficial health outcomes, lower burden and cost savings. Undesirable effects can include harms, higher burden and extra costs. Burdens are the demands of adhering to a recommendation that patients or caregivers (e.g. family) may find onerous, such as having to undergo more frequent tests or requiring a longer time to recover.

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

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

A **weak recommendation** is one for which the group concludes that the desirable effects of adherence probably outweigh the undesirable effects, but is not confident about these trade-offs. Reasons for not being confident may 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. Groups 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 costs).

Examples of implications of a strong recommendation are:

- **For patients**: Most patients 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 patients 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.

Table 2. 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 harm	
2. Relative importance of the outcomes a. benefits of therapy b. harm of treatment c. burdens of therapy	Seek evidence about the relative and actual values that patients place on outcomes (critical; important but not critical; not important). Seek evidence about variability in preferences and values among patients and other stakeholders. The relative importance of the outcomes should be included in the considerations before recommendations are made. 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 potential benefit and the higher the likelihood of a strong recommendation.
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 translation 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.

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