No. 235 October 2009 (Replaces No. 88, April 2000)

Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage

This Clinical Practice Guideline has been prepared by the Clinical Practice Obstetrics Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR

Dean Leduc, MD, Ottawa ON

Vyta Senikas, MD, Ottawa ON

André B. Lalonde, MD, Ottawa ON

CLINICAL PRACTICE OBSTETRICS COMMITTEE

Dean Leduc (Chair), MD, Ottawa ON

Charlotte Ballerman, MD, Edmonton AB

Anne Biringer, MD, Toronto ON

Martina Delaney, MD, St. John's NL

Louise Duperron, MD, Montreal QC

Isabelle Girard, MD, Montreal QC

Donna Jones, MD, Calgary AB

Lily Shek-Yun Lee, MD, Vancouver BC

Debra Shepherd, MD, Regina SK

Kathleen Wilson, RM, Ilderton ON

Disclosure statements have been received from all members of the committee.

Abstract

Objective: To review the clinical aspects of postpartum hemorrhage (PPH) and provide guidelines to assist clinicians in the prevention and management of PPH. These guidelines are an update from the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline on PPH, published in April 2000.

Evidence: Medline, PubMed, the Cochrane Database of Systematic Reviews, ACP Journal Club, and BMJ Clinical Evidence were searched for relevant articles, with concentration on randomized controlled trials (RCTs), systematic reviews, and clinical practice guidelines published between 1995 and 2007. Each article was screened for relevance and the full text acquired if determined to be relevant. Each full-text article was critically appraised with use of the Jadad Scale and the levels of evidence definitions of the Canadian Task Force on Preventive Health Care.

Values: The quality of evidence was rated with use of the criteria described by the Canadian Task Force on Preventive Health Care.

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Key Words: Prevention, hemorrhage, obstetrics, obstetric hemorrhage

Recommendations

Prevention of Postpartum Hemorrhage

1. Active management of the third stage of labour (AMTSL) reduces the risk of PPH and should be offered and recommended to all women. (I-A)
2. Oxytocin (10 IU), administered intramuscularly, is the preferred medication and route for the prevention of PPH in low-risk vaginal deliveries. Care providers should administer this medication after delivery of the anterior shoulder. (I-A)
3. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL per hour) is an acceptable alternative for AMTSL. (I-B)
4. An IV bolus of oxytocin, 5 to 10 IU (given over 1 to 2 minutes), can be used for PPH prevention after vaginal birth but is not recommended at this time with elective Caesarean section. (II-B)
5. Ergonovine can be used for prevention of PPH but may be considered second choice to oxytocin owing to the greater risk of maternal adverse effects and of the need for manual removal of a retained placenta. Ergonovine is contraindicated in patients with hypertension. (I-A)
6. Carbetocin, 100 μg given as an IV bolus over 1 minute, should be used instead of continuous oxytocin infusion in elective Caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics. (I-B)
7. For women delivering vaginally with 1 risk factor for PPH, carbetocin 100 μg IM decreases the need for uterine massage to prevent PPH when compared with continuous infusion of oxytocin. (I-B)
8. Ergonovine, 0.2 mg IM, and misoprostol, 600 to 800 μg given by the oral, sublingual, or rectal route, may be offered as alternatives in vaginal deliveries when oxytocin is not available. (II-1B)
9. Whenever possible, delaying cord clamping by at least 60 seconds is preferred to clamping earlier in premature newborns (< 37 weeks' gestation) since there is less intraventricular hemorrhage and less need for transfusion in those with late clamping. (I-A)
10. For term newborns, the possible increased risk of neonatal jaundice requiring phototherapy must be weighed against the

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[54]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[54]

physiological benefit of greater hemoglobin and iron levels up to 6 months of age conferred by delayed cord clamping. (I-C)

11. There is no evidence that, in an uncomplicated delivery without bleeding, interventions to accelerate delivery of the placenta before the traditional 30 to 45 minutes will reduce the risk of PPH. (II-2C)
12. Placental cord drainage cannot be recommended as a routine practice since the evidence for a reduction in the duration of the third stage of labour is limited to women who did not receive oxytocin as part of the management of the third stage. There is no evidence that this intervention prevents PPH. (II-1C)
13. Intraumbilical cord injection of misoprostol (800 μg) or oxytocin (10 to 30 IU) can be considered as an alternative intervention before manual removal of the placenta. (II-2C)

Treatment of PPH

14. For blood loss estimation, clinicians should use clinical markers (signs and symptoms) rather than a visual estimation. (III-B)
15. Management of ongoing PPH requires a multidisciplinary approach that involves maintaining hemodynamic stability while simultaneously identifying and treating the cause of blood loss. (III-C)
16. All obstetric units should have a regularly checked PPH emergency equipment tray containing appropriate equipment. (II-2B)
17. Evidence for the benefit of recombinant activated factor VII has been gathered from very few cases of massive PPH. Therefore this agent cannot be recommended as part of routine practice. (II-3L)
18. Uterine tamponade can be an efficient and effective intervention to temporarily control active PPH due to uterine atony that has not responded to medical therapy. (III-L)
19. Surgical techniques such as ligation of the internal iliac artery, compression sutures, and hysterectomy should be used for the management of intractable PPH unresponsive to medical therapy. (III-B)

Recommendations were quantified using the evaluation of evidence guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1).

J Obstet Gynaecol Can 2009;31(10):980–993

ABBREVIATIONS

AMTSL active management of the third stage of labour
PPH postpartum hemorrhage
RCT randomized controlled trial

INTRODUCTION

Postpartum hemorrhage is the leading cause of maternal death worldwide, with an estimated mortality rate of 140 000 per year, or 1 maternal death every 4 minutes.[1] PPH occurs in 5% of all deliveries and is responsible for a major part of maternal mortality.[2,3] The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour.[4,5] Nonfatal PPH results in further interventions, iron deficiency anemia, pituitary infarction (Sheehan's syndrome) with associated poor lactation, exposure to blood products, coagulopathy, and organ damage with associated hypotension and shock.

Since all parturient women are at risk for PPH, care providers need to possess the knowledge and skills to practise active management of the third stage of labour to prevent PPH and to recognize, assess, and treat excessive blood loss.

DEFINITION OF PPH

Primary PPH is defined as excessive bleeding that occurs in the first 24 hours after delivery.

Table 2. Signs and symptoms of shock resulting from blood loss

Degree of shock	Blood loss	Signs and symptoms
Mild	< 20%	Diaphoresis Increased capillary refilling Cool extremities Anxiety
Moderate	20% to 40%	Above plus Tachycardia Tachypnea Postural hypotension Oliguria
Severe	> 40%	Above plus Hypotension Agitation/confusion Hemodynamic instability

Traditionally the definition of PPH has been blood loss in excess of 500 mL after vaginal delivery and in excess of 1000 mL after abdominal delivery. For clinical purposes, any blood loss that has the potential to produce hemodynamic instability should be considered PPH. The amount of blood loss required to cause hemodynamic instability will depend on the pre-existing condition of the woman. Hemodynamic compromise is more likely to occur in conditions such as anemia (e.g., iron deficiency, thalassemia) or volume-contracted states (e.g., dehydration, gestational hypertension with proteinuria).

Hypovolemic Shock[6]

Excessive bleeding, or hemorrhage, results in net loss of intravascular volume and decreased oxygen delivery to tissues and organs. Physiological compensatory mechanisms such as reflex tachycardia, peripheral vasoconstriction, and increased myocardial contractility help to maintain tissue perfusion. Increasing blood loss results in circulatory collapse, end-organ damage, and eventual death.

Ideally, care providers should be able to assess the amount of blood loss in order to estimate the volume of fluid that needs to be replaced. However, research has shown that clinicians often underestimate the actual loss.[7] The signs and symptoms listed in Table 2 should be used at the bedside to evaluate the amount of blood loss since, in general, the degree of shock parallels the amount of blood loss that results in these clinical markers.[6]

Etiology of PPH

In regard to the underlying causes of PPH, it may be helpful to think in terms of the 4 Ts:

- Tone: uterine atony, distended bladder
- Tissue: retained placenta and clots
- Trauma: vaginal, cervical, or uterine injury
- Thrombin: coagulopathy (pre-existing or acquired)

The most common and important cause of PPH is uterine atony. The primary protective mechanism for immediate hemostasis after delivery is myometrial contraction causing occlusion of uterine blood vessels, the so-called living ligatures of the uterus. Thus blood flow from the vascular space to the uterine cavity via the myometrium is impeded.

Maternity care providers should recognize the risk factors for PPH due to the 4 Ts, as listed in Table 3, and take appropriate action.

PREVENTION OF PPH

AMTSL involves interventions to assist in expulsion of the placenta with the intention to prevent or decrease blood loss. Interventions include use of uterotonics, clamping of the umbilical cord, and controlled traction of the cord. In contrast, with expectant, or physiological, management, spontaneous delivery of the placenta is allowed, with subsequent intervention, if necessary, that involves uterine massage and use of uterotonics.

Prendiville and colleagues' meta-analysis[8] demonstrated the benefits of AMTSL to prevent and reduce PPH after vaginal delivery for women at low risk of PPH. Studies included in the meta-analysis had design methods that involved routine use of uterotonics after delivery of the newborn and before delivery of the placenta, early cord clamping, and controlled cord traction. The primary goal of these interventions was to assist placental delivery, thereby allowing the uterus to contract and reduce blood flow across the myometrium.

The meta-analysis concluded that active compared with expectant management significantly reduced the risk in all areas, including mild PPH (estimated blood loss > 500 mL; OR 0.38; 95% CI 0.32 to 0.46), severe PPH (estimated blood loss > 1000 mL; OR 0.32; 95% CI 0.21 to 0.50), low postpartum hemoglobin level (< 9 g/dL; OR 0.38; 95% CI 0.27 to 0.53), need for transfusion (OR 0.33; 95% CI 0.21 to 0.52), and need for additional uterotonic medication (OR 0.17; 95% CI 0.14 to 0.21). There was no difference in the incidence of retained placenta or management of this complication by manual or surgical removal. There was significantly more nausea and hypertension in the actively managed group given ergonovine (OR 1.83; 95% CI 1.51 to 2.23).

A review of the data resulted in a joint statement in 2004 by the International Confederation of Midwives and International Federation of Gynaecologists and Obstetricians endorsing the need for all deliveries to be attended by a caregiver trained in AMTSL, which should include routine use of uterotonics, controlled cord traction, and uterine massage.[9] Delaying cord clamping by 1 to 3 minutes was

Table 3. Risk factors for postpartum hemorrhage (PPH)

Etiologic category and process	Clinical risk factors
Tone: abnormalities of uterine contraction	
Overdistension of uterus	Polyhydramnios Multiple gestation Macrosomia
Uterine muscle exhaustion	Rapid labour Prolonged labour High parity Oxytocin use
Intra-amniotic infection	Fever Prolonged rupture of membranes
Functional/anatomic distortion of uterus	Fibroids Placenta previa Uterine anomalies
Uterine-relaxing medications	Halogenated anesthetics Nitroglycerin
Bladder distension, which may prevent uterine contraction [4]	
Tissue: retained	
Retained products of conception	Incomplete placenta at delivery Previous uterine surgery High parity
Abnormal placentation	Abnormal placenta seen on ultrasonography
Retained cotyledon or succenturiate lobe	Atonic uterus
Retained blood clots	
Trauma: of the genital tract	
Lacerations of the cervix, vagina, or perineum	Precipitous delivery Operative delivery
Extensions, lacerations at cesarean section	Malposition Deep engagement
Uterine rupture	Previous uterine surgery
Uterine inversion	High parity Fundal placenta Excessive cord traction
Thrombin: abnormalities of coagulation	
Pre-existing states	History of hereditary coagulopathies or liver disease
Hemophilia A	
Von Willebrand's disease	
History of previous PPH	
Acquired in pregnancy	
Idiopathic thrombocytopenic purpura	Bruising, elevated blood pressure
Thrombocytopenia with preeclampsia	
Disseminated intravascular coagulation	
Gestational hypertensive disorder of pregnancy with adverse conditions	Elevated blood pressure
a) Dead fetus in utero	Fetal demise
b) Severe infection	Fever, neutrophilia/neutropenia
c) Abruption	Antepartum hemorrhage
d) Amniotic fluid embolus	Sudden collapse
Therapeutic anticoagulation	History of thrombotic disease

favoured over early cord clamping to reduce anemia in the newborn.

A similar review of the literature in 2006 by the World Health Organization[10] highlighted the most common cause of PPH as uterine atony and the fact that most women with PPH have no identifiable risk factors. The review resulted in several recommendations to minimize maternal morbidity and mortality rates.

1. Active management should be offered to all women by skilled care providers.
2. Skilled attendants should offer uterotonics (oxytocin preferred over ergonovine, misoprostol, and carboprost) to prevent PPH.
3. Early cord clamping is recommended only when the newborn needs to be resuscitated.

4. Despite the lack of evidence to support cord traction, this practice should be continued as part of active management.

Uterotonics

During the third stage of labour the muscles of the uterus contract downward, causing constriction of the blood vessels that pass through the uterine wall to the placental surface and stopping the flow of blood. This action also causes the placenta to separate from the uterine wall. The absence of uterine contractions, clinically defined as atony, may result in excessive blood loss. Uterotonics promote uterine contractions to prevent atony and speed delivery of the placenta.

The uterotonic agents include oxytocin, ergonovine, carbetocin, misoprostol, and Syntometrine (a combination of ergonovine and oxytocin, unavailable in Canada).

Oxytocin and ergonovine

The 1997 Abu Dhabi study[11] included in Prendiville and colleagues'meta-analysis[8] randomly allocated low-risk women who delivered vaginally to receive either 10 IU of oxytocin IM with delivery of the anterior shoulder followed by controlled cord traction upon signs of placental separation or minimal intervention. The results revealed a benefit for the oxytocin group: a lower incidence of blood loss > 500 mL (OR 0.50; CI 0.34 to 0.73) and > 1000 mL (OR 0.22; CI 0.08 to 0.57), fewer retained placentas (OR 0.31; CI 0.15 to 0.63), and less need for additional uterotonics (OR 0.44; CI 0.24 to 0.78).

A 2004 Cochrane Review[12] compared the efficacy of Syntometrine and oxytocin alone, both administered IM, in AMTSL. The results showed a small benefit for Syntometrine in preventing blood loss > 500 mL (OR 0.82; 95% CI 0.71 to 0.95) but no difference in preventing losses > 1000 mL. The group receiving Syntometrine were more likely to have elevated diastolic blood pressure (OR 2.40; 95% CI 1.58 to 3.64), nausea (OR 4.07; 95% CI 3.43 to 4.84), and vomiting (OR 4.92; 95% CI 4.03 to 6.00). The authors favoured oxytocin alone on the basis of the lower incidence of maternal side effects.

A 2008 meta-analysis[13] included 14 studies assessing the benefits of oxytocin in AMTSL for vaginal deliveries. Seven trials comparing oxytocin and no uterotonics found a lower incidence of blood loss > 500 mL (RR 0.50; 95% CI 0.43 to 0.59) and less need for therapeutic oxytocin (RR 0.5; 95% CI 0.39 to 0.64) in the groups receiving oxytocin. Six trials found no difference between the results with oxytocin and ergonovine except that the groups receiving oxytocin had fewer manual removals of the placenta (RR 0.57; 95% CI 0.41 to 0.79) and a tendency to a lower incidence of raised blood pressure (RR 0.53; 95% CI 0.19 to 1.52) than the groups receiving ergonovine. Five trials showed little evidence of a synergistic effect of adding oxytocin to ergonovine versus ergonovine alone.

One double-blind randomized controlled trial[14] compared the efficacy of 10 IU of oxytocin in saline solution with saline solution alone in cephalic vaginal deliveries in low-risk women. The oxytocin group had a lower mean blood loss (407 vs. 527 mL), a lower incidence of blood loss > 800 mL (8.8% vs. 5.2%), and a lower rate of use of additional ergonovine (3.5% vs. 2.3%). Another double-blind RCT[15] found no difference in the incidence of PPH among women with low-risk vaginal deliveries given an IV bolus of oxytocin (20 IU in 500 mL of crystalloid) before or after delivery of the placenta.

The use of a slow IV bolus in management of the third stage of labour has been adopted as standard practice although there is little supporting evidence in the literature. The Dublin trial[16] was the only study in Prendiville and colleagues'meta-analysis[8] in which a uterotonic (Syntometrine) was administered IV; the result was a lower incidence of PPH but more retained placentas.

There has been concern about the safety of such rapid administration of oxytocin in the third stage, although 99 women given 10 IU in an IV push after vaginal delivery did not have significant hemodynamic effects. The study, however, was underpowered to demonstrate a reduction in the incidence of PPH.[17]

For women undergoing elective Caesarean section, recent studies have demonstrated adverse maternal effects of an oxytocin IV bolus. One double-blind RCT found hemodynamic changes in 30 patients given 5 IU IV over 30 seconds compared with women who received the same dose over 5 minutes.[18] In another double-blind RCT, 40 patients given 10 IU of oxytocin as an IV bolus manifested electrocardiographic changes consistent with myocardial ischemia when compared with pregnant women who received 0.2 mg of ergonovine and nonpregnant women; the effect was transient, with onset at 1 minute and resolution by 5 minutes after exposure to oxytocin.[19] These studies suggest a potential maternal effect of the rapid administration (within 30 seconds) of oxytocin, and it may be dose-related.

Oxytocin given as part of AMTSL has been shown to reduce the need for manual removal of a retained placenta compared with expectant management.[8,13] The greater need for manual removal noted in the Dublin trial[16] was attributed to the use of Syntometrine as an IV bolus. A 2001 Cochrane review[13] of prophylactic IM oxytocin use during the third stage of labour demonstrated a significantly reduced need for manual removal of the placenta compared with ergometrine use (RR 0.57; 95% CI 0.41 to 0.79).

Recommendations

Recommendations were quantified using the evaluation of evidence guidelines developed by the Canadian Task Force on Preventive Health Care (Table 1).

1. AMTSL reduces the risk of PPH and should be offered and recommended to all women. (I-A)
2. Oxytocin (10 IU), administered intramuscularly, is the preferred medication and route for the prevention of PPH in low-risk vaginal deliveries. Care providers should administer this medication after delivery of the anterior shoulder. (I-A)
3. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL per hour) is an acceptable alternative for AMTSL. (I-B)
4. An IV bolus of oxytocin, 5 to 10 IU (given over 1 to 2 minutes), can be used for PPH prevention after vaginal birth but is not recommended at this time with elective Caesarean section. (II-B)
5. Ergonovine can be used for prevention of PPH but may be considered second choice to oxytocin owing to the greater risk of maternal adverse effects and of the need for manual removal of a retained placenta. Ergonovine is contraindicated in patients with hypertension. (I-A)

Carbetocin

Carbetocin is a long-acting oxytocin studied by Dansereau et al.,[20] who performed an RCT comparing the incidence of PPH in women undergoing elective Caesarean section who received either carbetocin as a 100-μg IV bolus or oxytocin as a continuous infusion for 8 hours (25 IU of oxytocin in 1000 mL of Ringer's lactate, 125 mL per hour). The carbetocin group had a decreased incidence of PPH and of the need for therapeutic oxytocics (4.7% vs. 10.1%; $P < 0.05$). The recommended dose of carbetocin is 100 μg given either IM or slowly (over 1 minute), the pharmacokinetics of the 2 administration routes being almost the same.[21]

Boucher and colleagues' double-blind 2003 RCT[22] demonstrated that women with at least 1 risk factor for PPH who were given carbetocin (100 μg IM) immediately after placental delivery were less likely to required uterine massage as a uterotonic intervention than those given a continuous infusion of oxytocin over 2 hours: 43.4% of women in the carbocetin group (36/83 [43.4%]; 95%CI, 32.7% to 54% vs. 48/77 [62.3%] of women in the oxytocin group; 95% CI, 51.5% to 73.2%) required the massage ($P = 0.02$). There was no difference in the requirement for additional uterotonic medication (i.e., oxytocin, ergonovine), estimated blood loss, or difference in hemoglobin level before and after vaginal delivery. There was no significant benefit of carbetocin over oxytocin in the prevention of PPH. The authors commented on the advantage of IM intervention in a setting where IV treatment is unavailable.

A 2007 Cochrane Review[23] included 4 RCTs that compared carbetocin with oxytocin for prevention of PPH. The results were consistent with the results of the trials conducted by Dansereau and Boucher and their colleagues.[20,22] Since none of the trials included low-risk women, there was insufficient evidence that 100 μg of carbetocin given IV is as effective as oxytocin in the prevention of PPH in low-risk vaginal deliveries.

An RCT by Leung et al.[24] compared IM administration of carbetocin and Syntometrine in AMTSL for singleton vaginal deliveries after 34 weeks. The results showed no difference in the incidence of a low hemoglobin level, blood loss > 500 mL, retained placenta, or use of additional uterotonic agents. Carbetocin recipients had less nausea (RR 0.18; 95%CI 0.04 to 0.78), vomiting (RR 0.1; 95% CI 0.01 to 0.74), and hypertension 30 minutes (0 vs. 8 cases, $P < 0.01$) and 60 minutes (0 vs. 6 cases, $P < 0.05$) after delivery. There was a higher incidence of maternal tachycardia (RR 1.68; 95% CI 1.03 to 3.57) in the carbetocin group.

We did not identify any published reports of trials comparing oxytocin and carbetocin, each administered IM for AMTSL, in low-risk term vaginal deliveries.

Recommendations

6. Carbetocin, 100 μg given as an IV bolus over 1 minute, should be used instead of continuous oxytocin infusion in elective Caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics. (I-B)
7. For women delivering vaginally with 1 risk factor for PPH, carbetocin 100 μg IM decreases the need for uterine massage to prevent PPH when compared with continuous infusion of oxytocin. (I-B)

Misoprostol

Misoprostol is a prostaglandin that has generated considerable interest as an effective uterotonic agent owing to its ease of administration, safety profile, cost, and ease of storage. The first study of misoprostol as a uterotonic agent was an uncontrolled prospective study for prevention of PPH.[25]

A systematic review[26] that analyzed the pharmacokinetics of misoprostol concluded the following:

- There is a shorter time to peak concentration with oral and sublingual administration than with vaginal or rectal administration.
- Sublingual administration results in the most rapid onset of effects and the highest peak concentration.
- The initial increase in tonus is more pronounced after oral than after vaginal administration.

- The effects have a slower onset but longer duration with rectal and vaginal routes than with oral and sublingual routes.
- Pyrexia is more common when the dose exceeds 600 μg.

There have been 3 systematic reviews of the use of misoprostol for the prevention of PPH.[27–29] The WHO multicentre trial[30] and the Cochrane review[27] suggested that the observed lesser efficacy of misoprostol compared with injectable uterotonics may be due to the later achievement of peak plasma levels with oral and sublingual administration of misoprostol: 30 minutes versus 1 to 2 minutes for IM or IV administration of oxytocin. All of the reviews concluded that misoprostol was not as effective as oxytocin for the prevention of PPH and that maternal pyrexia was a significant adverse effect.

A 2007 study comparing 800 μg of misoprostol administered rectally with 10 IU of oxytocin administered IM in a developing country found these 2 agents to be equally effective in minimizing blood loss during the third stage of labour.[31] There was more pyrexia in the misoprostol group, however.

The systematic review by Joy and colleagues[29] compared the efficacy of misoprostol with that of oxytocin, other uterotonic agents, and placebo in preventing PPH in the third stage of labour. Compared with placebo, misoprostol was associated with a decreased need for additional uterotonics (OR 0.64; 95% CI 0.46 to 0.90) and an increased risk of shivering and pyrexia. Oxytocin was superior to misoprostol in preventing blood loss and the need for additional agents, and the patients had less shivering and pyrexia. The authors proposed that misoprostol is a reasonable agent for management of the third stage of labour when other agents are not available for reasons of cost, storage, or difficulty of administration.

There have been no studies to determine the benefit of a combination of oxytocin and misoprostol compared with either agent alone.

Recommendation

8. Ergonovine, 0.2 mg IM, and misoprostol, 600 to 800 μg given by the oral, sublingual, or rectal route, may be offered as alternatives in vaginal deliveries when oxytocin is not available. (II-1B)

Management of the Placenta

Timing of cord clamping

Clamping of the umbilical cord is a necessary part of the third stage of labour. Its timing varies widely throughout the world, early clamping being the predominant practice in Western countries.[32] Physiological studies have shown that 25% to 60% of the fetal–placental circulation is found in the placental circulation.[33,34] Early cord clamping in term newborns results in a decrease of 20 to 40 mL/kg of blood, which is equivalent to 30 to 35 mg of iron. A delay in clamping, causing increased neonatal blood volume, may lead to complications such as respiratory distress, neonatal jaundice, and polycythemia.

Prendiville and colleagues' meta-analysis espousing the benefit of AMTSL[8] included studies that applied early cord clamping, controlled traction, and uterotonics before delivery of the placenta. In these studies, early cord clamping was included as part of controlled traction and was not independently studied to demonstrate a benefit.

A 2004 Cochrane Review by Rabe et al.[35] and a prospective study by Ibrahim et al.[36] demonstrated that delaying cord clamping by 30 to 120 seconds resulted in less need for transfusion because of anemia (RR 2.01; 95% CI 1.24 to 3.27) and less intraventricular hemorrhage (RR 1.74; 95% CI 1.08 to 2.81) in nonresuscitated premature infants (< 37 weeks' gestation).

A systematic review and meta-analysis comparing cord clamping done early (less than 1 minute after delivery of the infant) and late (at least 2 minutes after delivery) showed that late clamping conferred physiological benefit to the newborn that extended up to 6 months into infancy.[37] Advantages included prevention of anemia over the first 3 months of life and enhanced iron stores (weighted mean difference 19.90; 95% CI 7.67 to 32.13) and ferritin concentration (weighted mean difference 17.89; 95% CI 16.58 to 19.21) for up to 6 months. There was no increase in respiratory distress, defined as tachypnea or grunting. Neonates were at increased risk of asymptomatic polycythemia (RR 3.82; 95% CI 1.11 to 13.21). There was no significant difference between the early and late groups in bilirubin levels and proportions of infants receiving phototherapy.

A 2008 Cochrane review included 11 RCTs that compared the effect on maternal and neonatal outcomes of cord clamping done early (up to 60 seconds after delivery) and late (beyond 60 seconds after delivery).[38] The results showed no difference in the incidence of PPH but an increased incidence of neonatal jaundice requiring phototherapy, higher newborn hemoglobin levels up to 6 months of age, and higher ferritin levels at 6 months of age after late clamping.

Recommendations

9. Whenever possible, delaying cord clamping by at least 60 seconds is preferred to clamping earlier in premature newborns (< 37 weeks' gestation) since there is less intraventricular hemorrhage and less need for transfusion in those with late clamping. (I-A)

10. For term newborns, the possible increased risk of neonatal jaundice requiring phototherapy must be weighed against the physiological benefit of greater hemoglobin and iron levels up to 6 months of age conferred by delayed cord clamping. (I-C)

Timing of placental delivery

Placental delivery is essential to allow the uterus to contract and thus reduce blood loss in the third stage of labour. This process is completed within 5 minutes in 50% of deliveries and by 15 minutes in 90%. Failure of the placenta to be delivered in such a timely manner is a well-known risk factor of PPH.[39,40]

The traditional definition of retained placenta includes failure of placental delivery within 30 to 45 minutes and a requirement of intervention to assist with delivery. One study published in 2006 concluded that the risk of PPH increases if the placenta has not been delivered by 10 minutes, although research is needed to determine if the risk of PPH can be reduced by intervening at this stage.[41]

Recommendation

11. There is no evidence that, in an uncomplicated delivery without bleeding, interventions to accelerate delivery of the placenta before the traditional 30 to 45 minutes will reduce the risk of PPH. (II-2C)

Placental cord drainage

Drainage of cord blood has been proposed to assist with delivery of the placenta.

A 2005 Cochrane review[42] included only 2 studies addressing this intervention, which makes it difficult to draw conclusions. The selection criteria for the review were low-risk vaginal deliveries in which a cord clamped within 30 seconds of delivery and separated was unclamped, which allowed the blood from the placenta to drain freely. The measured outcomes included incidence of retained placenta (at 30 to 45 minutes), manual removal of the placenta, PPH, length of the third stage of labour, need for blood transfusion, decrease in maternal hemoglobin level, and maternal pain. The outcomes reported were a decreased incidence of retained placenta at 30 minutes (RR 0.28; 95% CI 0.10 to 0.73) and a shorter third stage (weighted mean difference –5.46; 95% CI –8.02 to –2.90) after cord drainage. A major confounding factor was the lack of use of uterotonics and the varied definition of a prolonged third stage: from 30 to 45 minutes.

Sharma et al.[43] randomly assigned 958 women to either placental cord drainage or controlled traction after administration of 0.2 mg of ergonovine with delivery of the anterior shoulder and immediate cord clamping. Measured outcomes were PPH and length of the third stage. The third stage had a mean duration of 3.24 and 3.20 minutes in the drainage group versus 8.57 and 6.20 minutes in the traction group in primigravid ($P < 0.05$) and multigravid ($P < 0.05$) women, respectively. There was no significant difference between the groups in the incidence of blood loss > 500 mL and the need for transfusion ($P > 0.05$), and none of the women had a retained placenta.

The limited number of studies makes it difficult to recommend a change in practice to support routine cord drainage, but this intervention does appear to reduce the length of the third stage of labour and the risk of a retained placenta. More research is required to determine if the length of the third stage is reduced with routine drainage after the use of uterotonics and if this intervention reduces the risk of PPH.

Recommendation

12. Placental cord drainage cannot be recommended as a routine practice since the evidence for a reduction in the duration of the third stage of labour is limited to women who did not receive oxytocin as part of the management of the third stage. There is no evidence that this intervention prevents PPH. (II-1C)

Injection of the umbilical vein

Injection of the umbilical vein has been proposed to assist in uterine contractions and dehiscence of the placenta from the uterine wall to effect delivery. If successful, this intervention would avoid manual removal of the placenta, an invasive procedure with potential complications, including hemorrhage, infection, and trauma. A 2001 Cochrane Review[44] assessed if injection of various agents would reduce the need for manual removal of a retained placenta. The authors derived the following conclusions.

- Saline versus expectant management: no difference (RR 0.97; 95% CI 0.83 to 1.14).
- Saline plus oxytocin versus expectant management: nonsignificant reduction in the incidence of manual removal (RR 0.86; 95% CI 0.72 to 1.01) with the use of saline plus oxytocin.
- Saline plus oxytocin versus saline: significantly lower incidence of manual removal of the placenta (RR 0.79; 95% CI 0.69 to 0.91) (number needed to treat: 8; 95% CI 5 to 20) with the use of saline plus oxytocin.
- Saline plus oxytocin versus plasma expander: nonsignificantly greater incidence of manual removal of the placenta (RR 1.34; 95% CI 0.97 to 1.85) with the use of saline plus oxytocin.
- Saline plus prostaglandin versus saline: significantly lower incidence of manual removal of the placenta (RR 0.05; 95% CI 0.00 to 0.73) with the use of saline plus prostaglandin but no difference in the incidence of blood loss, fever, pain, and oxytocin augmentation.

Figure 1. Pipingas technique for injection of the intraumbilical vein if the placenta has not separated or delivered within 45 minutes after delivery of the baby

- Prepare a syringe of misoprostol (800 μg) or oxytocin (50 IU) dissolved in 30 mL of normal saline.
- Insert a size 10 nasogastric suction catheter along the umbilical vein. If resistance is felt, retract the catheter 1 to 2 cm and advance it further, if possible. If the catheter cannot be advanced further without force, inject the solution in this position.
- If most of the catheter has been inserted when resistance is felt, indicating that it has reached the placenta, retract it 3 to 4 cm to ensure that the tip is in the umbilical vein and not in a placental branch.
- Connect the syringe to the catheter and inject the solution. Clamp the catheter in situ and record the time of the injection.
- Allow 30 minutes for the placenta to deliver before undertaking further intervention.

- Saline plus prostaglandin versus saline plus oxytocin: no difference (RR 0.10; 95% CI 0.01 to 1.59).

This review suggests that umbilical vein injection of uterotonics assists with the third stage of labour but provides no convincing evidence of the benefit; the last 3 conclusions were based on the results of a single small trial. The authors conclude that umbilical vein injection of oxytocin may reduce the need for manual removal of a retained placenta, but further investigation is required. There is an ongoing systematic review to determine if routine injection of the umbilical vein with a uterotonic within 15 minutes of birth will affect perinatal and maternal outcomes.[45]

An RCT compared the effect of intraumbilical vein injection of Syntocinon (synthetic oxytocin; 50 IU in 30 mL of normal saline), misoprostol (800 μg in 30 mL of normal saline), or normal saline (30 mL) on the need for manual removal of the placenta in a prolonged third stage of labour in 87 low-risk women at term.[46] The Pipingas technique (Figure 1) was used for injection. All the women had AMTSL with either oxytocin or Syntometrine with delivery of the anterior shoulder, early cord clamping, and cord traction when signs of placental separation were observed. The women whose third stage exceeded 30 minutes were randomly assigned to intervention at 45 minutes with 1 of the 3 injections. The trial was stopped when the misoprostol group had many fewer instances of manual removal of the placenta (9 of 21 women) compared with the Syntocinon group (16 of 20 women) and the saline group (7 of 13 women).

Recommendation

13. Intraumbilical cord injection of misoprostol (800 μg) or oxytocin (10 to 30 IU) can be considered as an alternative intervention before manual removal of the placenta. (II-2C)

TREATMENT OF ESTABLISHED PPH

Research has shown that care providers poorly estimate blood loss[7] and consistently underestimate the loss of a large volume of blood.[43] Clinical signs and symptoms (Table 2) are useful bedside indicators of ongoing blood loss and will assist clinicians in management. A previously established plan of action is of great value when preventive measures have failed. This plan should include aggressive fluid resuscitation, control of bleeding to minimize loss, and access to a surgical room and support personnel (Table 4).

The initial goal of management is to determine the cause of blood loss while instituting resuscitative measures. Evaluation of uterine tone and a complete inspection of the lower genital tract are required. The goal of resuscitative measures is to maintain hemodynamic stability and oxygen perfusion of the tissues. An IV infusion of crystalloid solution should be instituted, using large-bore tubing, along with oxygen supplementation. The "ABCs" should be observed and vital signs, oxygen saturation, and urinary output monitored. A visual assessment of clotting can be done at the bedside while blood is sent for analysis and matching for transfusion.

PPH emergencies often occur unexpectedly and, depending on the volume of deliveries in each institution, may be infrequent. When a situation does not resolve with the usual interventions, there is a need for more equipment that may not be readily available when needed. For these reasons, every obstetric unit should have a readily available tray with all of the necessary equipment. Since clinicians may rarely apply these interventions, this equipment should be accompanied by appropriate diagrams illustrating the relevant anatomy and technique. A previously prepared PPH tray in a large Canadian birthing centre was used in 1 in 250 Caesarean sections and 1 in 1000 vaginal deliveries.[47]

Recommendations

14. For blood loss estimation, clinicians should use clinical markers (signs and symptoms) rather than a visual estimation. (III-B)

15. Management of ongoing PPH requires a multidisciplinary approach that involves maintaining hemodynamic stability while simultaneously identifying and treating the cause of blood loss. (III-C)

Table 4. Treatment of PPH

Initial assessment and treatment for primary PPH		Assess etiology	Directed therapy	If bleeding continues	If bleeding continues	If bleeding continues
Call for help Resuscitation • Assess the "ABC" • Oxygen by mask • IV line • Crystalloid, isotonic fluid replacement • Monitor BP, P, R • Empty bladder, monitor urine output Laboratory tests • Complete blood count • Coagulation screen • Blood grouping and cross	Uterus soft and relaxed	Uterine atony	Uterine massage Uterotonic drugs	Nonsurgical uterine compression • Bimanual uterine compression • External aortic compression • Uterine packing • Balloon (condom) tamponade	Compression sutures • B-Lynch • Vertical compression • Cho square Uterine artery embolization	Artery ligation (uterine, hypogastric) Hysterectomy (subtotal or total)
	Placenta not separated or partially separated (with or without hemorrhage)	Retained placenta	Whole placenta in uterus • Uterotonics • Controlled cord traction • Intraumbilical vein injection	Placenta still retained Manual removal	Placenta still retained (placenta accreta) Partial or complete removal of placenta through laparotomy Hysterectomy	
			Incomplete separation • Manual vacuum aspiration • Manual exploration • Gentle curettage		Hysterectomy	
	Excess bleeding or shock shortly after birth, uterus contracted	Low genital tract trauma	→ Repair tears in perineum, vagina and cervix			
		Uterine rupture	→ Laparotomy: • Primary repair • Hysterectomy			
	Uterine fundus not felt abdominally OR visible vaginally	Uterine inversion	→ Correct inversion in theatre under general anaesthesia	If nonsurgical correction fails, ensure that uterus remains contracted by continued oxytocin infusion	Surgery Correction via laparotomy Hysterectomy	
		Clotting	Clotting disorder • Treat accordingly with blood products			

Adapted with permission of the World Health Organization from Postpartum Hemorrhage Technical Consultation Meeting Document[55]

16. All obstetric units should have a regularly checked PPH emergency equipment tray containing appropriate equipment. (II-2B)

Uterine Massage and Additional Uterotonic Administration

Since the most common cause of PPH is uterine atony, the clinician's initial efforts should be directed at preventing ongoing blood loss by performing the initial basic maneuvres of uterine massage and administering additional uterotonics, which include the following.

1. Oxytocin
   - 10 IU IM. Consider ability of the medication to reach a uterus with poor tissue perfusion.
   - 5 IU IV push
   - 20 to 40 IU in 250 mL of normal saline, infused IV at an hourly rate of 500 to 1000 mL.
2. 15-methyl prostaglandin (carboprost tromethamine [Hemabate])
   - 250 μg IM or intramyometrially
   - Can be repeated every 15 minutes to a maximum of 2 mg (8 doses).
   - Asthma is a relative contraindication.
3. Carbetocin
   - 100 μg IM or IV over 1 minute
   - Shown to reduce bleeding due to uterine atony in Caesarean sections but not low-risk vaginal deliveries.
4. Misoprostol (off-label use not approved for PPH by Health Canada)
   - 400 to 800 μg. Onset of effects is faster with oral or sublingual than with rectal administration.
   - 800 to 1000 μg. Effects are longer lasting with rectal than with oral administration.
   - Higher incidence of pyrexia with oral than with rectal administration.
5. Ergonovine
   - 0.25 mg IM or IV, can be repeated every 2 hours
   - Contraindicated in women with hypertension and those taking certain drugs (e.g., proteases for HIV infection).
6. Recombinant activated factor VII
   - Has been used in women with massive PPH but in a limited number of studies, all without randomization.
   - A review by Franchini et al.[48] suggests a potential role, although further research is required to determine this agent's role and benefit.

Recommendation

17. Evidence for the benefit of recombinant activated factor VII has been gathered from very few cases of massive PPH. Therefore this agent cannot be recommended as part of routine practice. (II-3L)

Tamponade

The quickest method of tamponade is with bimanual compression of the uterus. One hand is placed over the uterus externally; the other is placed in the vagina to apply pressure on the lower segment. Consistent compression with the 2 hands results in external compression of the uterus to reduce blood flow. This can be continued until further measures are taken or assistance arrives.

In the case of uterine atony, the following can be placed inside the uterus to provide direct compression of the uterine wall and thus decrease blood loss.

- Bakri SOS tamponade balloon catheter
- Sengstaken Blakemore esophageal catheter
- Foley catheter filled with 60 to 80 mL of sterile solution
- Rusch hydrostatic urologic balloon
- Hydrostatic condom catheter
- Uterine packing

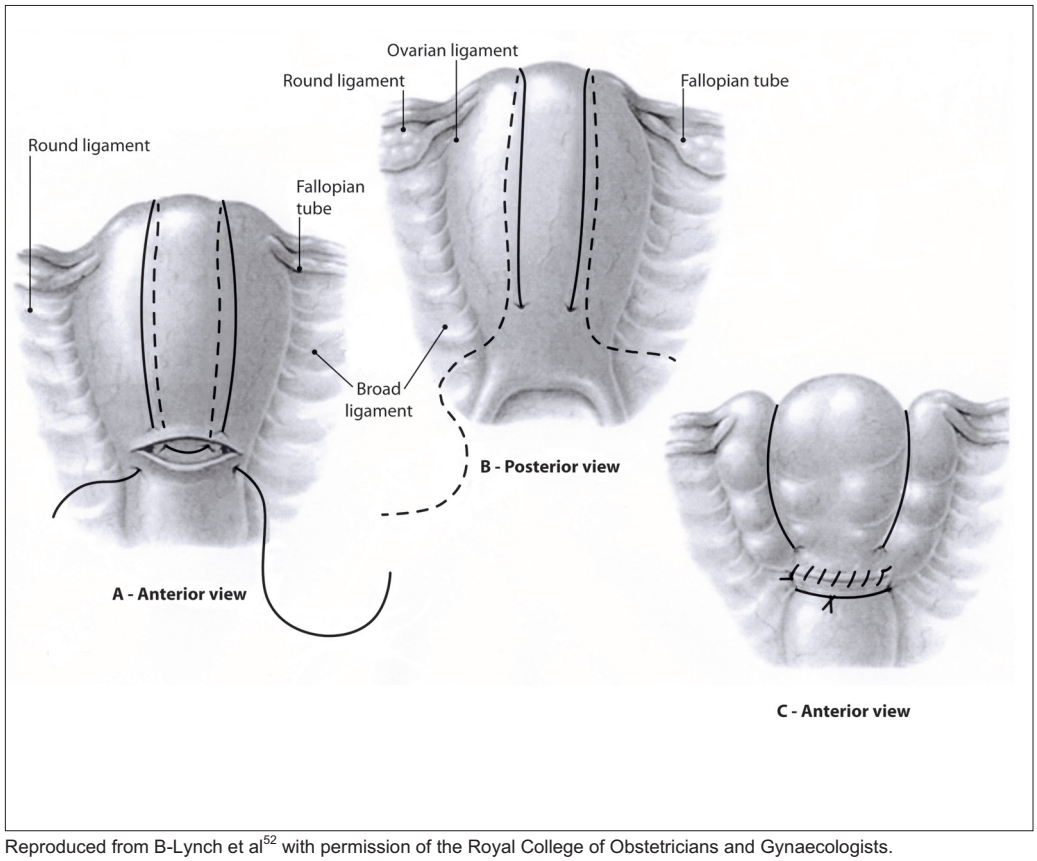
All the above have been reported to be successful for the temporary control of active bleeding. The insertion technique for a balloon device is relatively simple and requires the operator to ensure that the entire balloon is positioned past the cervical canal. Once inserted, the balloon is filled with sterile solution until there is no further bleeding. After successful tamponade, continued oxytocin infusion may be required to maintain uterine tone. Prophylactic antibiotic therapy should be considered. The balloon can be left in place for 8 to 48 hours and then gradually deflated and removed.

Uterine packing requires greater skill and experience to properly pack the uterus with enough gauze to control bleeding while avoiding trauma to the uterine wall. Other disadvantages include risk of infection, unrecognized bleeding with blood soaking the packing material, and the possible need for another surgical procedure to remove the material.

Recommendation

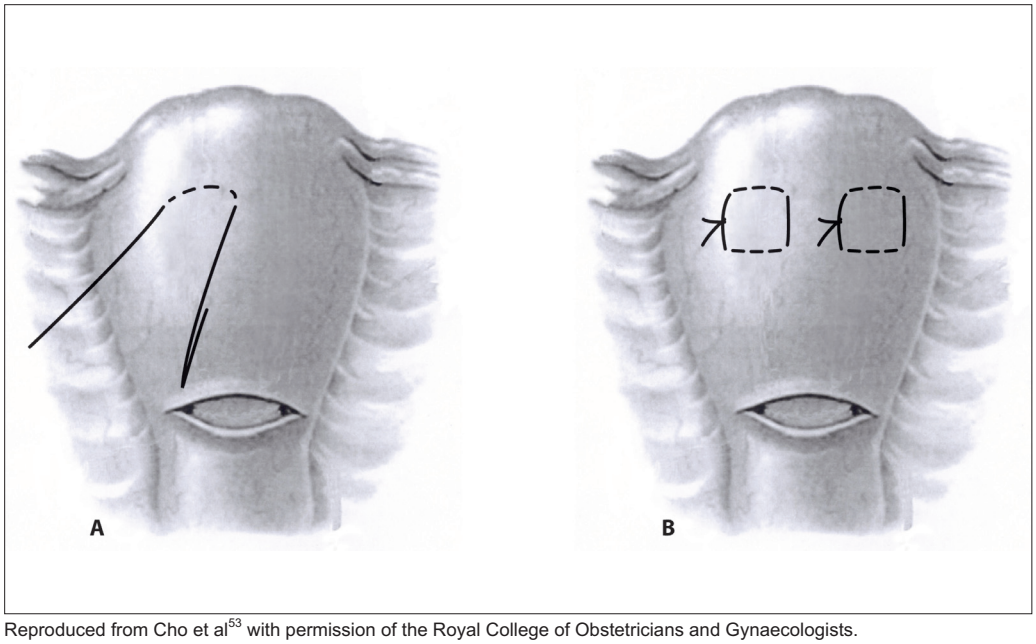
18. Uterine tamponade can be an efficient and effective intervention to temporarily control active PPH due to uterine atony that has not responded to medical therapy. (III-L)

Figure 2. B-Lynch technique for uterine compression sutures



Reproduced from B-Lynch et al[52] with permission of the Royal College of Obstetricians and Gynaecologists.

Figure 3. Cho technique for uterine compression sutures



Reproduced from Cho et al[53] with permission of the Royal College of Obstetricians and Gynaecologists.

Radiologic Methods

Percutaneous transcatheter arterial embolization is an option when there is active bleeding in a hemodynamically stable woman and before surgical intervention.[49] A review of the literature found success rates of 100% after 49 vaginal deliveries and 89% after 18 Caesarean sections. This technique preserves the uterus and adnexa and thus fertility. The procedure requires rapid access to imaging technology and interventional radiologists, which is not available to all centres.

Surgical Methods

Ligation of the internal iliac artery was used to control intraoperative bleeding from cervical cancer before being applied to obstetric cases.[50] A retrospective study found this technique to be useful for preventing PPH in women at high risk of hemorrhage and for treating PPH due to uterine atony or genital tract injury.[51] The timing of this intervention is important: it must be done without delay, before excessive blood loss has occurred. Surgical skill is required to avoid failure and complications such as damage to other vascular structures and the ureters.

Uterine compression sutures, described by B-Lynch[52] (Figure 2) and Cho[53] (Figure 3), have the benefit of preserving the uterus. Both techniques involve external compression of the uterus to control bleeding, followed by application of sutures into and over the uterus. The sutures are tied down to maintain uterine compression and control further bleeding. A hysterotomy at the lower segment is required to ensure that there are no retained products that would prevent compression of the uterus and subsequent failure of pregnancy.

Peripartum hysterectomy is indicated when massive hemorrhage has not responded to previous interventions and requires a surgical intervention familiar to surgeons. Indications include abnormal placentation (previa, accreta), atony, trauma, rupture, and sepsis. The disadvantage of peripartum hysterectomy is the loss of fertility in women who wish to continue childbearing.

Recommendation

19. Surgical techniques such as ligation of the internal iliac artery, compression sutures, and hysterectomy should be used for the management of intractable PPH unresponsive to medical therapy. (III-B)

REFERENCES

1. AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003;67:1–11.
2. Reynders FC, Senten L, Tjalma W, Jacquemyn Y. Postpartum hemorrhage: practical approach to a life-threatening complication. Clin Exp Obstet Gynecol 2006;33:81–4.
3. Subtil D, Sommé A, Ardiet E, Depret-Mosser S. [Postpartum hemorrhage: frequency, consequences in terms of health status, and risk factors before delivery]. J Gynecol Obstet Biol Reprod (Paris) 2004;33(8 Suppl):4S9–4S16.
4. Ramanathan G, Arulkumaran S. Postpartum haemorrhage. Curr Obstet Gynaecol 2006;16(1):6–13.
5. Kane TT, el-Kady AA, Saleh S, Hage M, Stanback J, Potter L. Maternal mortality in Giza, Egypt: magnitude, causes, and prevention. Stud Fam Plann 1992;23:45–57.
6. Maier RV. Approach to the patient with shock. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2004:1600–6.
7. Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. BJOG 2006;113:919–24.
8. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. Cochrane Database Syst Rev 2000;(3):CD000007.
9. International Confederation of Midwives, International Federation of Gynaecologists and Obstetricians. Joint statement: management of the third stage of labour to prevent post-partum haemorrhage. J Midwifery Womens Health 2004;49:76–77.
10. World Health Organization. Recommendations for the Prevention of Postpartum Haemorrhage. Geneva: WHO; 2007.
11. Khan GQ, John IS, Wani S, Doherty T, Sibai BM. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. Am J Obstet Gynecol 1997;177(4):770–4.
12. McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine–oxytocin versus oxytocin for the third stage of labour. Cochrane Database Syst Rev 2004;(1):CD000201.
13. Cotter A, Ness A, Tolosa J. Prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev 2001;(4):CD001808.
14. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. Br J Obstet Gynaecol 1997;104:781–6.
15. Jackson KW Jr, Allbert JR, Schemmer GK, Elliot M, Humphrey A, Taylor J. A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. Am J Obstet Gynecol. 2001 Oct;185(4):873–7.
16. Begley C. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990;6:3–17.
17. Davies GA, Tessier JL, Woodman MC, Lipson A, Hahn PM. Maternal hemodynamics after oxytocin bolus compared with infusion in the third stage of labor: a randomized controlled trial. Obstet Gynecol 2005;105:294–9.
18. Thomas JS, Koh SH, Cooper GM. Hemodynamic effects of oxytocin given as IV bolus or infusion on women undergoing caesarean section. Br J Anaesth 2007;98;116–9.
19. Svanström MC, Biber B, Hanes M, Johansson G, Näslund U, Balfors EM. Signs of myocardial ischemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during caesarean section. Br J Anaesth 2008;100:683–9.
20. Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol 1999;180(3 Pt 1):670–6.
21. Sweeney G, Holbrook AM, Levine M, Yip M, Alfredsson K, Cappi S, et al. Pharmacokinetics of a long-acting oxytocin analogue, in non-pregnant women. Curr Ther Res 1990;47:528–40.
22. Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE, Varin J. Comparison of carbetocin and oxytocin for the prevention of

postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. J Obstet Gynaecol Can 2004;26:481–8.

23. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum hemorrhage. Cochrane Database Syst Rev 2007;(3):CD005457.
24. Leung SW, Ng PS, Wong WY, Cheung TH. A randomized trial of carbetocin versus Syntometrine in the management of the third stage of labour. BJOG 2006;113:1459–64.
25. El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Misoprostol for third stage of labour [letter]. Lancet 1996;347:1257.
26. Hofmeyr GJ, Walraven G, Gülmezoglu AM, Maholwana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum haemorrhage: a systematic review. BJOG 2005;112:547–53.
27. Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage. Cochrane Database Syst Rev 2004;(1):CD000494.
28. Villar J, Gülmezoglu AM, Hofmeyr GJ, Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol 2002;100:1301–12.
29. Joy SD, Sanchez-Ramos L, Kaunitz AM. Misoprostol use during the third stage of labor. Int J Gynaecol Obstet 2003;82:143–52.
30. Gülmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689–95.
31. Parsons SM, Walley RL, Crane JMG, Matthews K, Hutchens D. Rectal misoprostol versus oxytocin in the management of the third stage of labour. J Obstet Gynaecol Can 2007;29:711–8.
32. Morley G. Cord closure: Can hasty clamping injure the newborn? OBG Manage 1998;July:29–36.
33. Dixon LR. The complete blood count: physiologic basis and clinical usage. J Perinat Neonatal Nurs 1997;11:1–18.
34. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet 1969;2:871–3.
35. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev 2004;(4):CD003248.
36. Ibrahim HM, Krouskop RW, Lewis DF, Dhanireddy R. Placental transfusion: umbilical cord clamping and preterm infants. J Perinatol 2000;20:351–4.
37. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA 2007;297:1241–52.
38. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2008;(2):CD004074.
39. Dombrowski MP, Bottoms SF, Saleh AA, Hurd WW, Romero R. Third stage of labor: analysis of duration and clinical practice. Am J Obstet Gynecol 1995;172:1279–84.
40. Combs CA, Laros RK. Prolonged third stage of labor; morbidity and risk factors. Obstet Gynecol 1991;77:863–7.
41. Magann EF, Doherty DA, Briery CM, Niederhauser A, Morrison JC. Timing of placental delivery to prevent post-partum haemorrhage: lessons learned from an abandoned randomised clinical trial. Aust N Z J Obstet Gynaecol 2006;46:549–51.
42. Soltani H, Dickinson F, Symonds I. Placental cord drainage after spontaneous vaginal delivery as part of the management of the third stage of labour. Cochrane Database Syst Rev 2005;(4):CD004665.
43. Sharma JB, Pundir P, Malhotra M, Arora R. Evaluation of placental drainage as a method of placental delivery in vaginal deliveries. Arch Gynecol Obstet 2005;271:343–5.
44. Carroli G, Bergel E. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev 2001;(4):CD001337.
45. Nardin JM, Carroli G, Weeks a.d., Mori R. Umbilical vein injection for the routine management of third stage of labour [Protocol]. Cochrane Database Syst Rev 2006;(4):CD006176.
46. Rogers MS, Yuen PM, Wong S. Avoiding manual removal of placenta: evaluation of intra-umbilical injection of uterotonics using the Pipingas technique for management of adherent placenta. Acta Obstet Gynecol 2007;86:48–54.
47. Baskett TF. Surgical management of severe obstetrical hemorrhage: experience with an obstetrical hemorrhage equipment tray. J Obstet Gynaecol Can 2004;26:805–8.
48. Franchini M, Lippi G, Franchi M. The use of recombinant activated factor VII in obstetric and gynaecological haemorrhage. BJOG 2007;114:8–15.
49. Vedantham S, Goodwin SC, McLucas B, Mohr G. Uterine artery embolization: an underused method of controlling pelvic hemorrhage. Am J Obstet Gynecol 1997;176:938–48.
50. Kelly HA. Ligation of both internal iliac arteries for hemorrhage in hysterectomy for carcinoma uteri. Bull Johns Hopkins Hosp 1984;5:53.
51. Joshi V, Otiv SR, Majumder R, Nikam YA, Shrivastava M. Internal iliac artery ligation for arresting postpartum haemorrhage. BJOG 2007;114:356–61.
52. B-Lynch C, Coker A, Lawal AH, Abu J, Cowen MJ. The B-Lynch surgical technique for the control of massive postpartum haemorrhage: An alternative to hysterectomy? Five cases reported. Br J Obstet Gynaecol 1997;104:372–5.
53. Cho JH, Jun HS, Lee CN. Hemostatic suturing technique for uterine bleeding during cesarean delivery. Obstet Gynecol 2000;96(1):129–31.
54. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169(3):207–8.
55. Mathai M, Gulmezoglu AM. Postpartum haemorrhage and retained placenta. WHO guideline. Geneva: World Health Organization;2009.