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The views expressed in this guideline are strictly those of the Association of Ontario Midwives. No official endorsement by the Ministry of Health and Long-Term Care is intended or should be inferred.

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The AOM is committed, through our statement on Gender Inclusivity and Human Rights, to reflect and include trans, genderqueer and intersex communities in all aspects of our work.

In this document, there are references to sources that use gendered language to refer to populations of pregnant and birthing people. In order to accurately represent these sources, we may have maintained gendered language.

We support research and knowledge translation that engages and reflects the entire childbearing population.

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Postpartum Hemorrhage

INTRODUCTION

This document replaces AOM Clinical Practice Guideline No. 9: Prevention and Management of Postpartum Hemorrhage. The original guideline was published in 2006.

Statement of purpose

The goal of this document is to provide an evidence-based clinical practice guideline (CPG) for Ontario midwives and their clients that is consistent with the midwifery philosophy and model of care. Midwives are encouraged to use this CPG as a tool in clinical decision-making. This CPG is independent of and not intended to replace the standards of the College of Midwives of Ontario (CMO).

Objectives

The objective of this CPG is to provide a critical review of the research literature on the prevention and management of postpartum hemorrhage (PPH). Evidence relating to the following will be discussed:

- Definition, incidence and causes
- Risk factors
- Prevention
- Treatment
- Recovery
- Client experiences

Abbreviations

AOM	Association of Ontario Midwives	IV	intravenous
AOR/OR	adjusted odds ratio/odds ratio	NICE	National Institute for Health and Care Excellence
ARR	adjusted risk ratio	NICU	neonatal intensive care unit
BMI	body mass index	PAE	pelvic artery embolization
CI	confidence interval	PO	by mouth
CMO	College of Midwives of Ontario	PPH	postpartum hemorrhage
CPG	clinical practice guidelines	PR	by rectum
CS	caesarean section	PTSD	post-traumatic stress disorder
dBP	diastolic blood pressure	RCOG	Royal College of Obstetricians and Gynaecologists
DIC	disseminated instravascular coagulation		
FIGO	International Federation of Gynecology and Obstetrics	RCT	randomized controlled trial
		RR	risk ratio
GA	gestational age (in weeks)	SL	sublingual
GRADE	Grading of Recommendations Assessment, Development and Evaluation	SOGC	Society of Obstetricians and Gynaecologists of Canada
Hb	hemoglobin	TXA	tranexamic acid
HELLP	hemolysis, elevated liver enzymes, low platelet count	UBT	uterine balloon tamponade
ICM	International Confederation of Midwives	UVI	umbilical vein injection
ICU	intensive care unit	WHO	World Health Organization
IM	intramuscular		

Outcomes of interest

The following outcomes were rated as either 'critical' or 'important' following the GRADE process for each research question addressed in the guideline:

Critical:

- Maternal mortality
- Serious maternal morbidity (admission to ICU, renal or respiratory failure)
- Hysterectomy
- Blood loss > 1000 mL
- Maternal blood transfusion
- Manual removal of the placenta
- Admission/readmission to hospital due to bleeding

Important:

Maternal

- Blood loss > 500 mL
- Hb measurement at 24 to 72 hours post-birth
- Use of additional therapeutic uterotonics
- Maternal dBP > 90 mmHg
- Nausea / vomiting between birth and discharge
- Administration of analgesia between birth and discharge
- Breastfeeding
- Afterpains and/or analgesia secondary to afterpains between birth and 24 hours

Neonatal

- Admission to NICU/special care nursery
- Neonatal jaundice requiring phototherapy or exchange transfusion
- Apgar < 7 at 5 mins

Methods

This CPG uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for guideline development. Recommendations in this CPG are graded as either strong or weak according to the GRADE approach. The strength of recommendation reflects the extent to which the PPH CPG Work Group is confident that the benefits of a recommended intervention outweigh its harms, or vice versa. The strength of recommendation is influenced by the quality of supporting evidence, the balance between desirable and undesirable effects, and the perceived variability or uncertainty in clients' values and preferences with respect to the intervention. Because recommendations take into account this range of considerations, a strong recommendation may be based on low or very low-quality evidence. (1-5)

The work group's judgements about the quality of evidence reflect the work group's confidence that available evidence correctly reflects the true effect of the intervention and is sufficient to support decision-making. Complete GRADE evidence tables used to summarize research and inform the recommendations in this guideline are available on the AOM website. A full description of the AOM's approach to clinical practice guideline development using GRADE is also available on the AOM website.

QUALITY OF EVIDENCE	How certain we ought to be about an estimate of effect or association
High	Further research is very unlikely to change confidence in the estimate of effect. • This evidence provides a very good basis for decision-making.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • This evidence provides a good basis for decision-making.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • This evidence provides some basis for decision-making.
Very low	Any estimate of effect is very uncertain. • This evidence does not provide much of a basis for decision making.

Based on: (3-5)

STRENGTH OF RECOMMENDATION	The extent to which the CPG Work Group is confident that benefits of the recommended intervention outweigh its harms (or vice versa)
Strong	Benefits clearly outweigh risks and burdens (or vice versa). *Can be interpreted as:* • Most clients should be offered the intervention, assuming that they have been informed about and understand its benefits, harms and burdens. • Most clients would want the recommended course of action and only a small proportion would not.
Weak	Benefits, risks and burdens are closely balanced. *Can be interpreted as:* • The majority of clients would want the suggested course of action, but an appreciable proportion would not. • Values and preferences vary widely.

Based on: (1-4)

Literature search

A search of the Medline and CINAHL databases and Cochrane library from 1995-2013 was conducted using a defined search strategy. Additional search terms and hand searching were used to provide more detail on individual topics as they related to postpartum hemorrhage. Older and newer studies were accessed in cases of commonly cited statistics, or significant impact on clinical practice.

Review

This CPG was reviewed using a modified version of the AGREE instrument, the AOM Values-based Approach to CPG Development, as well as consensus of the Postpartum Hemorrhage Work Group; the CPG Committee; the Quality, Insurance and Risk Management Program Steering Committee; the AOM Board of Directors; and member consultation.

BACKGROUND

Definition and assessment of PPH

There is no standard definition of PPH. In Canada, PPH is typically described as bleeding in excess of 500 mL after a vaginal birth and 1000 mL after a caesarean section (CS). (6–8) Severe PPH is defined as bleeding in excess of 1000 mL after a vaginal birth. (6,8) PPH is often further classified as primary (in the first 24 hours postpartum) or secondary (delayed, after 24 hours postpartum). Clinically, any amount of blood loss that results in signs and symptoms of hypovolemic shock or hemodynamic instability should be considered PPH. (9) This amount may be lower than 500 mL in a woman with anemia or volume contraction (due to dehydration or gestational hypertension with proteinuria). (7) PPH is variably defined by guideline developers, see appendix A for a list of recent definitions.

Some guideline developers have suggested using definitions of PPH that combine estimated blood loss and clinical signs of hypovolemic shock. The Royal College of Obstetricians and Gynaecologists (RCOG) takes a "pragmatic approach" to defining PPH, suggesting that intervention be initiated with an estimated blood loss of more than 1000 mL or a smaller loss accompanied by signs of shock. (10) An international expert panel in obstetrics, gynecology, hematology, anesthesia and transfusion suggests defining primary PPH as "active bleeding > 1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage." (11) Such definitions are specifically intended to identify women at high risk of adverse outcomes for whom resuscitative efforts may be considered.

Alternatively, other researchers have suggested defining PPH based on a percentage change in hematocrit or hemoglobin (Hb) levels. Hematocrit or Hb values may not reflect current hematologic status and can also be affected by maternal hydration (especially with intravenous loading for epidural analgesia). Furthermore, hematocrit or Hb concentrations may be difficult to assess in an acute clinical emergency. (6)

The physiological consequences of blood loss vary by individual. The increase in blood volume during pregnancy means that parturients can lose as much as

30% of pre-delivery blood volume without hemodynamic consequences. (12) Studies conducted during the 1960s suggest postpartum blood loss on average is 300 to 550 mL at vaginal birth and 500 to 1000 mL at CS. (13) Postpartum bleeding may occur over several hours, and blood may be diluted by urine and fluid. (6,14)

Research suggests that visual estimates of blood loss at birth are often inaccurate and inconsistent and health-care providers may under- or over-estimate blood loss. (6,14) Research with midwives and other health-care providers show that with larger volumes, blood loss is often under-estimated. (15,16)

Direct quantitative measurement of blood loss by volume (using calibrated drapes or containers) or weight (by weighing swabs, pads and towels) offers a more objective method of assessment. Weighing blood accurately requires prior knowledge of the dry weights of items commonly used to absorb blood, and accurate scales. Weighing must be done in a timely manner to avoid evaporation loss. Weighing used pads and other items that come into contact with blood, then subtracting their dry weight from the total weight once used, may be more accurate than collection of blood into calibrated bags or other containers, but is time and labour-intensive. (14) These methods are often used in research trials evaluating blood loss but may be impractical to use in a clinical or community setting without trained staff and/or equipment dedicated to these tasks. (17)

No research was found comparing outcomes based on differing definitions of PPH. While it is important to estimate and document blood loss, the physiological consequences of blood loss vary by individual and may depend on multiple factors. Midwives' ability to assess the effects of blood loss using an individualized approach to care enables decision-making in an emergency and permits retrospective assessment for purposes of data collection or to inform future decision-making.

SUMMARY STATEMENTS

- PPH is defined variably by guideline developers and obstetrical/midwifery textbooks.
- Research suggests that quantitative measurement of blood loss by volume or weight is more accurate than visual estimation and requires a coordinated effort and dedicated staff time. Routine quantification of blood loss is an emerging area of research and not used widely in Canada at this time.

RECOMMENDATIONS

1. Midwives should consider any significant postpartum loss of blood that causes signs and symptoms of hypovolemic shock or hemodynamic instability to be a postpartum hemorrhage.

   Strong recommendation; no evidence available.

2. Midwives should continue to visually estimate and document postpartum blood loss.

   Weak recommendation; no evidence available.

   These recommendations recognize that effects of blood loss vary by individual and support individualized care. They recognize midwives' ability to assess effects of blood loss and the need for timely decision-making. Documentation of blood loss permits retrospective assessment and informs immediate and ongoing client care. Accurate blood loss estimation contributes to midwifery data collection and research.

Incidence of PPH

Primary PPH is estimated to occur in 2% to 6% of all births worldwide. (18,19) Secondary or delayed PPH is thought to occur in 1% to 3% of all births. (20,21) In Janssen and colleagues' study of outcomes of births attended by midwives in British Columbia between January 2000 and December 2004, PPH (not defined) occurred in 3.8% of planned home births and 6% of planned hospital births. (22) In Hutton and colleagues' study of home births and a matched sample

of hospital births attended by Ontario midwives, PPH was documented in 2.5% of home and 3.0% of hospital births. (23) This is based on database entries where midwives classify PPH "based on estimated blood loss greater than 1000 mL, symptoms or required level of intervention." (23) Other measures of severe PPH such as rates of blood transfusion were not available.

Mehrabadi and colleagues assessed temporal trends in postpartum hemorrhage (defined as blood loss of ≥ 500 mL following vaginal birth or ≥ 1 000 mL following CS) using population-level data from live births that occurred between 2003 and 2010 (n > 2 000 000) in Canadian hospitals (excluding Quebec). Though rates of PPH varied widely across provinces and territories, they observed an overall rate of primary PPH of 6.2% in 2010 (up from 5.1% in 2003). This increase in PPH rates was driven by a rise in incidence of atonic PPH, which increased from 3.9% in 2003 to 5% in 2010; rates of non-atonic PPH or PPH due to retained placenta did not change significantly. Rates of PPH in Ontario ranged from 3.6% to 3.8% during this time period. (24) The trends observed by Mehrabadi and colleagues are consistent with an earlier study based on Canadian hospital births occurring between 1991 and 2004, which observed an increase in rates of PPH from 4.1% in 1991 to 5.1% in 2004; this increase was also attributable to atonic PPH. (25)

Similar increases in rates of PPH attributable to uterine atony have also been observed in Australia, the United States and Sweden. (26–29) Researchers have not been able to identify a clear cause for these recent population-level increases in PPH incidence; controlling for possible maternal and labour-related risk factors (e.g., high body mass index, older maternal age at birth, induction of labour or mode of delivery) does not appear to change temporal trends. (24,26)

Complications of PPH

Between 2003 and 2009, PPH was directly responsible for 20% of maternal deaths worldwide and 8% of maternal deaths in high-income countries. (30) Maternal deaths due to PPH are rare in the Canadian context, occurring at a rate of approximately 30/100 000 cases of PPH diagnosed from 1991-2010. (24,25)

Potential complications of PPH include organ dysfunction, coagulopathy, sepsis and pituitary infarction (Sheehan's syndrome). (7,18,19) Less severe clinical outcomes associated with PPH include iron deficiency anemia, fatigue and delayed lactogenesis, though the incidence of such outcomes is difficult to quantify. (31,32)

American researchers have used administrative data from a representative sample of U.S. hospitals to assess the absolute risks and the odds of complications associated with PPH after receiving blood transfusions following a diagnosis of PPH associated with uterine atony. Their data (summarized in Table 1) suggests that severe adverse outcomes are relatively rare even in cases of PPH serious enough to warrant blood transfusion. (27)

TABLE 1: CLINICAL COMPLICATIONS ASSOCIATED WITH PPH DUE TO UTERINE ATONY AND BLOOD TRANSFUSION

	N (%)	Odds ratio (95% CI)[a]
Length of stay > 7 days	656 (2.6)	2.1 (1.9-2.3)
Hysterectomy	529 (2.1)	89.1 (75.7-104.9)
Coagulopathy	445 (1.8)	4.7 (4.2-5.2)
Acute respiratory failure	105 (0.4)	10.9 (8.7-13.6)
Acute renal failure	82 (0.3)	13.8 (10.6-17.8)
Prolonged mechanical ventilation (≥ 96 hours)	13 (0.1)	6.5 (3.6-11.8)
Sepsis	25 (0.1)	3.7 (2.5-5.6)

[a] Association of PPH with the unadjusted odds of developing these complications in all births from 2004.

Source: (27)

Causes of PPH

A helpful way to conceptualize the pathophysiology of PPH is by considering the 4 Ts: tone, tissue, trauma and thrombin. As the majority of PPH cases are due to uterine atony, this guideline focuses on this cause. However, midwives should consider other possible causes of abnormal bleeding when approaching the management of PPH.

TONE	Accounts for an estimated 70% of cases of PPH
Abnormalities of uterine contraction • Exhaustion of the uterine muscles • Over-distended uterus • Chorioamnionitis • Anatomic distortion of the uterus • Uterine-relaxing agents	
TISSUE	**Accounts for an estimated 10% of cases of PPH**
Retained placental tissue or clots prevent occlusion of uterine blood vessels • Retained placenta, placental fragments, clots, lobe or membranes • Abnormal placentation - placenta accreta/increta/percreta	
TRAUMA	**Accounts for an estimated 20% of cases of PPH**
Blood loss due to genital tract trauma • Lacerations and hematomas of vagina, perineum or cervix • Laceration at CS, extension of incision • Uterine rupture • Uterine inversion	
THROMBIN	**Accounts for an estimated 1% of cases of PPH**
Coagulation abnormalities prevent effective clot formation • Pre-existing coagulation disorders » Von Willebrand's disease » Hemophilia • Coagulation disorders acquired in pregnancy or labour » Disseminated intravascular coagulation (DIC) » Thrombocytopenia » Hemolysis, elevated liver enzymes, low platelet count (HELLP) • Therapeutic anti-coagulant use	

From: (7,33–36)

RISK FACTORS ASSOCIATED WITH PPH

PPH often occurs in the absence of known risk factors. Major identifiable risk factors for PPH were present in only 38% of cases of atonic PPH treated with blood transfusion included in a population-based U.S. study of hospital births between 1995-2004. (27) In a population-based study of births in Norway between 1999 and 2004, risk factors were noted in 70% of cases of severe obstetric hemorrhage (blood loss > 1500 mL or blood loss of any volume treated with blood transfusion). (37)

While numerous studies have assessed risk factors for postpartum hemorrhage, many of these studies are older and/or conducted in low-income settings and may not be generalizable to a modern, high-resourced obstetrical population. Table 2 describes antenatal and intrapartum factors associated with PPH in large, population-level studies based on Canadian, American and Norwegian administrative records. (24,27,37–39) While these studies do not address all potential risk factors for PPH, as they are based on data sources that cannot provide detailed information about maternal characteristics (e.g., BMI) or interventions during labour and birth, their large sizes permit relatively precise estimates of association. It is not clear how the presence of multiple risk factors affect the overall risk of PPH in a given pregnancy.

TABLE 2: SELECTED RISK FACTORS FOR SEVERE POSTPARTUM HEMORRHAGE FROM POPULATION-LEVEL STUDIES

		Range of adjusted ORs	Sources
	Stronger risk factors (OR ≥ 4)		
Known before birth	Placenta previa	6.38-10.9	(24,38,39)
	Uterine fibroids	4.0	(38)
Known after birth	Cervical laceration	24.83-26.70	(24,39)
	High vaginal laceration	5.27-7.72	(24,39)
	Retained placenta	4.10	(27)
	Moderate risk factors (OR 2 to 4)		
Known before birth	Parity ≥ 5 (see discussion below)	2.53	(39)
	Multifetal gestation	2.34-3.77	(24,27,37,39)
	Chorioamnionitis	2.27-2.66	(24,27,39)
	Hypertensive disorders of pregnancy	1.92-2.88	(24,27,39)
	Placental abruption	1.81-3.02	(24,39)
Known after birth	Perineal tear (3°/4°)	2.35-2.75	(24,39)
	Operative delivery (forceps and/or vacuum)	1.98-3.11	(24,39)
	Birthweight ≥ 4500 g	1.78-2.15	(24,37,39)
	Caesarean section (see discussion below)	1.39-4.8	(24,38,39)
	CS with labour	1.3-3.61	(27,37)
	CS without labour	1.7-2.47	(27,37)
	Weaker risk factors (OR < 2)		
Known before birth	Polyhydramnios	1.47-1.90	(24,27)
	Age < 20	1.47-1.80	(24,27,39)
	Previous CS	1.46	(37)
	32-36 weeks GA	1.42	(39)
	Age ≥ 40	1.41-1.70	(27,37)
	Induction of labour	1.22-1.60	(24,37,39)
	Parity = 0	1.10-1.30	(37,39)
Study details:	Al-Zirqi et al., 2008 (37)	Norway 1999-2004 N = 307 415	
	Bateman et al., 2010 (27)	United States 2004 N = 876 641	
	Kramer et al., 2011 (38)	Quebec 1978-2007 N = 103 726	
	Mehrabadi et al., 2013 (39)	British Columbia 2001-2009 N = 372 259	
	Mehrabadi et al., 2014 (24)	Canada 2003-2010 (excluding QC) N = 2 193 425	

Selected and emerging risk factors for PPH

The following descriptions for selected risk factors were identified as having emerging evidence or of being of particular interest to midwifery practice:

Previous CS and future risk of placenta accreta

Previous CS was an independent risk factor for PPH with blood loss > 1500 mL and/or blood transfusion in one of the population-level studies included in Table 2 (AOR 1.46, 95% CI 1.02-2.20) (37); this relationship was non-significant in 3 other studies. (24,38–40) Kramer et al.'s study, based on computerized records from a tertiary care hospital in Montreal, also found an association between previous uterine surgery and PPH > 1500 mL (AOR 4.6, 95% CI 1.2-17.7). (38)

The relationship between previous CS and PPH in a subsequent pregnancy could be partly explained by placenta accreta, because the risk of placenta accreta is highest with a history of prior CS and current placenta previa, and increases with each prior CS. (41,42) In a prospective observational cohort study of more than 30 000 people who had CS without labour, those with placenta previa had a subsequent risk of placenta accreta of 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, fifth, and sixth or more subsequent CS deliveries, respectively. (43)

While risk of placenta accreta is increased by previous CS, most cases occur in those who have not had a previous CS. A cohort study (n = 115 502) in 25 U.S. hospitals from 2008-2011 identified all cases of 'morbidly adherent placenta' (placenta accreta, increta and percreta). 18% of cases identified were nulliparous and 37% had no prior CS. In cases not identified prenatally as having a morbidly adherent placenta, 19% experienced severe PPH, 45% hysterectomy, and 22% intensive care unit admission ($p < .05$ for all). (41)

Parity

While *grand multiparity* (parity ≥ 5) has traditionally been considered a risk factor for PPH, this relationship has not been consistent across studies or populations and is likely confounded. (44) An Australian retrospective cohort study using data from a regional hospital found that grand multiparas were significantly older, more likely to have had previous caesarean sections and less likely to have received prenatal care compared to those of lower parity. (45) Once these characteristics were controlled for, grand multiparas were no more likely to experience postpartum hemorrhage. (45) Parity ≥ 5 was an independent risk factor for PPH with blood loss > 1500 mL and/or blood transfusion in one of the recent population-level studies summarized in Table 2 above (37,39) and non-significant in another study. (37) Three studies did not include information on parity ≥ 5. (24,38–40)

Nulliparity was an independent risk factor for PPH with blood loss > 1500 mL and/or blood transfusion in 2 of the recent population-level studies summarized in Table 2; (37,39) the association was non-significant in one of the studies. (38)

Gestational Diabetes Mellitus

While previous studies have suggested an increased risk of postpartum hemorrhage in the context of diabetes mellitus, (46) no association was found between pre-pregnancy and/or gestational diabetes and PPH with blood loss > 1500 mL and/or blood transfusion in the 3 studies summarized in Table 2 above that included diabetes status. (24,27,38)

Body mass index (BMI)

There is conflicting evidence that a high BMI is a risk factor for postpartum hemorrhage. A retrospective cohort study based on New Zealand hospital data for 11 363 nulliparas found increased rates of PPH ≥ 1000 mL in overweight (BMI 25-29.9 kg/m^2) and obese (BMI ≥ 30 kg/m^2) women (9.7% and 15.6%, respectively, versus 7.2% with BMI 18.5-24.9 kg/m^2). After adjustment for confounders, BMI ≥ 30 kg/m^2 was associated with an adjusted OR of 1.86 (95% CI 1.51-2.28) for PPH ≥ 1000 mL following any delivery, 1.73 (95% CI 1.32-2.28) following CS and 2.11 (95% CI 1.54-2.89) following vaginal delivery. (47)

A population-based study of Swedish births between 1997 and 2008 included 1 114 071 women categorized in 6 BMI classes. (29) This study noted a slight but increasing risk of PPH > 1000 mL with increasing BMI. However, the absolute risk of PPH was relatively similar across BMI classes, ranging from 4.1% (BMI <18.5 kg/m^2) to 4.8% (BMI 35-39.9 kg/m^2). (29)

Previous PPH

An Australian records-based study examined the occurrence and recurrence of PPH in 125 295 women.

Of the 5.8% of women who had a PPH in their first pregnancy, the rate of PPH in a second consecutive pregnancy was 14.8%. For those who experienced PPH in 2 consecutive pregnancies, 21.7% had a recurrence of PPH in their third pregnancy. (48) Similar findings were noted in a study of over 500 000 births in Sweden between 1997 and 2009. A history of previous PPH was associated with a threefold increase in risk of PPH in the second pregnancy, compared to those who did not have a history of PPH (15% vs 5%). In this study, risk of PPH was 26.6% after 2 previous pregnancies with PPH. Adjustment for other risk factors associated with PPH did not significantly change the association between past and recurrent PPH. (49)

Antidepressant use

Several studies have reported inconsistent findings in comparing risk of PPH and antidepressant use, based on the theory that selective serotonin reuptake inhibitor (SSRI) antidepressants can impair platelet function and increase the risk of hemorrhage. (50,51)

A retrospective cohort study of 30 198 participants who gave birth between 2002-2008 compared 3 groups: those with exposure to antidepressants in late pregnancy (n = 558), those with a psychiatric diagnosis but no antidepressant use (n = 1292), and those with neither antidepressant use nor psychiatric illness (n = 28 348). (52) Separating participants with psychiatric illness but no medication use was an attempt to control for underlying illness that might confound the association between antidepressant use and PPH. Relative risks were also adjusted for socio-demographics and other comorbidities. Exposure to antidepressants was associated with an increased risk of PPH ≥ 500 mL for vaginal birth and ≥ 1000 mL for CS (ARR 1.53; 95% CI 1.25–1.86), but no increased risk was seen for those with psychiatric illness but no antidepressant use (ARR 1.04; 95% CI 0.89–1.23). Late gestation antidepressant use was associated with an increased risk of severe PPH (≥ 1000 mL for any mode of birth, ARR 1.84; 95% CI 1.39–2.44), and postpartum iron deficiency anemia (ARR 1.80; 95% CI 1.46–2.22). These differences in risk could not be explained by adjustment for known risk factors for PPH in the group who used antidepressants. (52)

Similarly, another large cohort study based on U.S. Medicaid data from 2000-2007 observed associations between antidepressants prescribed for mood or anxiety disorders and risk of atonic postpartum hemorrhage. (53) Risk of PPH was 2.8% among women without exposure to antidepressants, 4% in users of serotonin reuptake inhibitors, and 3.8% in users of non-serotonin reuptake inhibitors. After adjusting for confounders, current use of serotonin reuptake inhibitors was associated with a relative risk of 1.47 for PPH (95% CI 1.33-1.62) and use of non-serotonin reuptake inhibitors was associated with a relative risk of 1.39 (95% CI 1.07-1.81). (53)

Induction and/or augmentation of labour

Researchers have suggested that increases in the proportion of labours that are induced may explain at least part of the recent increase in rates of PPH noted in Canada, Australia, the U.K. and the U.S. (25,26,28) Three studies included in Table 2 found an association between induction of labour and subsequent atonic PPH > 1500 mL or atonic PPH requiring blood transfusion. As these studies were based on administrative data, researchers were unable to consider method of induction or its indication.

Other studies have examined the relationship in greater depth. A French case-control study involving women without known risk factors for PPH found higher odds of PPH (blood loss ≥ 500 mL) and severe PPH (blood loss ≥ 1000 mL) when labour was induced with intravenous (IV) oxytocin (AORs 1.52, 95% CI 1.19-1.93 and 1.57, 95% CI 1.11-2.20). Cervical ripening with prostaglandins was significantly associated with severe PPH only (AOR 1.42, 95% CI 1.04-1.94). The researchers also noted an association between augmentation of labour with oxytocin and severe PPH (AOR 1.35, 1.07-1.70). (54)

A case-control study conducted by American researchers found that women with atonic PPH requiring blood transfusion were exposed to greater total amounts of oxytocin and for longer periods of time than matched controls. The relationship between amount and duration of oxytocin and risk of severe PPH persisted after controlling for confounding variables. After controlling for race, BMI, admission hematocrit, induction status, magnesium therapy and chorioamnionitis, oxytocin continued to predict severe PPH and an increase in oxytocin exposure during labour resulted in an adjusted OR of 1.58 (95% CI, 1.05-2.57, p = .026) for PPH secondary to uterine atony. (55)

Maternal position during the second stage

Two studies have examined the relationship between maternal position during birth and the third stage of labour. (56,57) In a non-randomized longitudinal study comparing water birth to 6 other non-water birth positions found that birth on a birth stool was associated with a higher incidence of PPH (OR 2.04, 95%CI 1.44-2.90) than water birth. (56) A Cochrane systematic review assessing the effects of different positions during the second stage of labour acknowledges this finding, concluding that there is the "possibility of increased risk of blood loss greater than 500 mL" when women give birth in upright positions (RR 1.65; 95% CI 1.32-2.60). (58) A secondary analysis of data from a trial involving 1646 low-risk women found that among women with perineal trauma, semi-sitting and sitting positions were associated with a greater likelihood of blood loss greater than 500 mL than recumbent positions. This association was not found among women who had intact perineums. The authors theorized that increased edema in upright positions, due to obstructed venous return, may be the cause of increased blood loss when perineal trauma occurs. (57)

Place of birth and risk of PPH

Using data from the Dutch national perinatal databases, de Jonge et al. compared incidence of severe maternal morbidities in low-risk women with singleton, term, cephalic pregnancies. (59) People planning home births were more likely to be of Dutch origin, multiparous, older and more socioeconomically advantaged than those who planned hospital births, and more likely to give birth at a later gestational age. Fewer women who planned home births underwent augmentation of labour or operative delivery. Blood loss > 1000 mL occurred in 2.92% of planned home births, compared to 3.99% of planned hospital births; the difference in rates of PPH was statistically significant only among multiparas (AOR 0.5, 95% CI 0.46-0.55). (59)

An analysis of records from low- and medium-risk hospital and home births from 1988-2000 attended by health-care professionals affiliated with an U.K. regional health authority found a higher incidence of blood loss ≥ 1000 mL among women who planned to give birth in hospital (1.04%) than women who planned home births (0.38%). (60) For women at low- and medium-risk for PPH, the adjusted odds of experiencing a PPH with a planned hospital birth were 2.5 the odds of PPH with a planned home birth (AOR 2.5, 95% CI 1.7-3.8). (60)

Janssen et al. analyzed outcomes of planned home births attended by midwives in British Columbia from 2000-2004. (22) For women with a similar risk profile and attended by the same midwives, risk of PPH (amount of blood loss not defined) was lower for home compared to hospital birth (RR 0.62, 95% CI 0.49-0.77). (22) For midwife-attended low-risk births in Ontario from 2003-2006, risk of blood loss ≥ 1000 mL was lower among women who planned home births (RR 0.68, 95% CI 0.49-0.96). (61) A subsequent study of Ontario midwifery births from 2006-2009 also showed an association between home birth and lower PPH rates (RR 0.82, 95% CI 0.70-0.96). However, PPH was not clearly defined and absolute incidence of PPH was low in both settings, 2.5% at home and 3.0% in hospital. (23) In all three studies midwifery clients who planned home births experienced fewer intrapartum interventions, including induction, augmentation, episiotomy and operative delivery. (22,23,61)

SUMMARY STATEMENTS

- PPH often occurs in the absence of risk factors.
- Researchers have identified numerous antenatal and intrapartum factors associated with increased risk of PPH. Most factors are not strongly predictive of PPH. It is not clear how presence of multiple risk factors affect overall risk of PPH.
- Risk factors most strongly associated with PPH include previous PPH (see postpartum section of CPG), abnormal placentation, multiple pregnancy, and cervical and high vaginal lacerations at delivery.
- Previous CS and placenta previa in the current pregnancy are strong risk factors for placenta accreta and severe PPH. However, a significant minority of cases of abnormal placentation causing severe PPH are not identified prenatally.
- Research suggests that home or out-of-hospital birth is associated with a similar or reduced risk of PPH compared to hospital birth. Medical interventions that are more likely to occur in a hospital setting (induction, augmentation, operative delivery) may explain some of the differences observed between groups.

RECOMMENDATION

3. Identification of risk factors for PPH should occur in an ongoing manner throughout the course of antenatal and intrapartum care. Midwives should consider risk factors in an informed choice discussion about options for management of the third stage of labour and choice of birthplace.

   Strong recommendation; moderate-quality evidence.

   This recommendation recognizes continuity of care and the ability of the midwife to identify emerging risk factors for PPH.

Management of the third stage of labour

Physiologic management

The term "physiologic management" is often used interchangeably with "expectant management" in the context of obstetric research (such as the Cochrane review of active vs. expectant management). (62) Expectant management may describe the absence of active management rather than the coordinated activities employed by the midwife in providing physiological third-stage care to a client who has chosen to forego active management of the third stage of labour. (63) Newer research supports an evolving model of physiologic management based on support for physiologic birth, rather than the absence of the interventions that constitute active management. (64,65)

Traditionally, expectant third-stage management has been characterized as a "hands-off" approach:

- A uterotonic agent is not administered prophylactically.
- Signs of placental separation are awaited.
- The umbilical cord is neither clamped nor cut until cord pulsation has ceased or the placenta has delivered.
- The placenta is born spontaneously with the aid of maternal effort or gravity. (62,63)

Physiologic 'care', as described by midwifery researchers, encompasses additional actions meant to promote the physiologic processes of the third stage during physiologic management. (63,66) While there is no consensus about what constitutes physiologic third-stage care, the following factors are often included in more expansive definitions:

- facilitating a comfortable, warm environment;
- encouraging an upright position to facilitate birth of placenta;
- refraining from fundal massage;
- paying close attention to signs of excessive blood loss;
- being mindful of direct and indirect signs of placental separation, including those observed by the parturient;
- occasionally "lifting" or "easing" the cord to bring out a placenta once separation has occurred; and
- facilitating immediate skin-to-skin contact with newborn and early breastfeeding. (63,66)

Hastie and Fahy's model of "Midwifery Guardianship" proposes additional criteria for "holistic psychophysiological" third-stage care provided in a physical and emotional environment conducive to sensations of calmness, mindfulness, and safety. They theorize that environmental conditions that facilitate feelings of relaxation, skin-to-skin contact and early breastfeeding optimize processes that encourage oxytocin release and uptake and uterine contraction and retraction. (64,65) Hastie and Fahy suggest that when the sympathetic branch of the autonomic nervous system is dominant, epinephrine out-competes with oxytocin for binding sites on the myometrium. This is posited to disrupt the neuroendocrine mechanisms that lead to uterine contraction and retraction during third stage and increase risk of atonic PPH. (65) Psychophysiologic care, on the other hand, is thought to stimulate parasympathetic processes, producing a cascade of hormones (oxytocin, endorphins, prolactin, adrenocorticotrophic hormone and catecholamines) that stimulate the endogenous physiological processes of the third stage of labour. (64)

Active management

In 2003, an international joint policy statement endorsed by the Society of Obstetricians and Gynaecologists of Canada (SOGC) was developed by the International Confederation of Midwives and the International Federation of Gynaecologists and Obstetricians (ICM/FIGO). This statement describes the usual components of active management as:

- administration of uterotonic agents;
- controlled cord traction; and
- uterine massage after delivery of the placenta, as appropriate. (67)

The current WHO guideline for the prevention and treatment of postpartum hemorrhage identifies use of a uterotonic (oxytocin) as the main intervention of active management. (19) There is variation, however, in the implementation of active management.

- Different uterotonics may be used, in different doses and using different routes of administration. (68)
- Uterotonics may be administered at different times – after the delivery of the anterior shoulder, within 60 seconds of birth, or after delivery of the placenta or after clamping of the cord. (68)
- Timing of clamping and cutting of the cord may

differ. In recognition of the growing body of research supporting benefits of delayed cord clamping, a 2006 update to the ICM/FIGO joint statement suggested delaying cord clamping by 1 to 3 minutes to reduce anemia in the newborn. (69) Current WHO guidelines include a similar recommendation. (19)

- Controlled cord traction may be initiated before or after signs of placental separation are apparent. (62)
- Uterine massage for prevention of PPH was initially included as a component of active management in the 2006 ICM/FIGO PPH statement but appears to be used infrequently in practice. (67,68) Evidence does not suggest it is effective. (70) Current WHO guidelines recommend against uterine massage for prevention of PPH in women who have received prophylactic oxytocin. (19)

Variations in how active and physiologic management approaches are defined and implemented, and changes that have occurred over time, present challenges in analyzing research comparing active and physiologic management packages. This includes the evolving definition of physiologic management from the absence of interventions associated with active management, to an approach that includes evidence-based aspects of supporting physiologic birth. Table 3 summarizes approaches to management of the third stage of labour used in research studies.

Health-care providers who do not routinely administer a prophylactic uterotonic, but who do use controlled cord traction (sometimes called the Brandt-Andrews manoeuvre), may consider their management style to be physiologic rather than active. According to the definitions used in relevant clinical trials, this approach falls into neither the physiologic nor the expectant category.

TABLE 3: APPROACHES TO MANAGEMENT OF THE THIRD STAGE OF LABOUR

	Physiologic	Expectant*	Active WHO (2012)	Active ICM/ FIGO (2006)
Prophylactic uterotonic	No	No	Yes, oxytocin recommended	Yes
Cord clamping	After cord pulsation stops or after delivery of placenta	After cord pulsation stops or after delivery of placenta	1-3 mins after birth	After pulsation stops, 1-3 mins
Controlled cord traction	Usually not	No	Yes, if skilled birth attendant available No, if no skilled birth attendant	Yes
Uterine massage	No	No	No	Yes
Other aspects	• Immediate skin-to-skin • Early breastfeeding • Upright position			

*As defined in original trials of active management (71–73)

Sources: (19,63,69,74)

Effects of active management compared to physiologic management

Three randomized controlled trials relevant to Ontario midwifery practice were found that compared active versus physiologic management of the third stage of labour: the Dublin (72), Bristol (71) and Hinchingbrooke (73) trials. These 3 studies were conducted in the 1980s and 1990s in hospital settings in the U.K. and Ireland with third-stage care provided primarily by midwives. (71–73) (GRADE Table 1) While these trials underlie many organizations' recommendations for active management, they do not show that active management reduces blood loss in women at low risk of PPH.

Two of the included studies were limited to participants deemed to be at low risk of PPH (cephalic, singleton pregnancies, no previous history of PPH or antepartum hemorrhage, parity < 5) (GRADE Table 1a). When the analysis was restricted to these 2 low risk of PPH studies, active management was not associated with a statistically significant difference in blood loss > 1000 mL (RR 0.31, 95% CI 0.05-2.17). (72,73) Among participants at low risk of PPH, active management was associated with a single side-effect: increased diastolic blood pressure (> 100 mmHg) between birth and discharge from hospital. (72,73) Since a combination of ergonovine and oxytocin were used in some trials, this may explain side-effects such as vomiting and increased diastolic blood pressure.

When data from trial participants at all level of risk for PPH were pooled, active management (compared to physiologic management) was associated with statistically significant reductions in blood loss > 500 mL (RR 0.34, 95% CI 0.27-0.44), blood loss > 1000 mL (RR 0.34, 95% CI 0.14-0.87), maternal blood transfusion (RR 0.39, 95% CI 0.24-0.66), maternal Hb < 90 to 100g/L at 24 to 48 hours postpartum (RR 0.53, 95% CI 0.44-0.64), and use of therapeutic uterotonic during the third stage or within 24 hours of birth (RR 0.18, 95% CI 0.14-0.23).

Side-effects associated with uterotonic use (either oxytocin or ergonovine/oxytocin) occurred with greater frequency with active management, including vomiting between birth and discharge from hospital (RR 2.47, 95% CI 1.36-4.48) and diastolic blood pressure > 100 mmHg between birth and discharge (RR 4.1, 95% CI 1.63-10.3). Afterbirth pains requiring oral (PO) or intramuscular (IM) analgesia occurred more frequently in the active management group (RRs 2.05, 95% CI 1.04-4.08 and 8.22, 95% CI 1.03-65.52).

There has been considerable criticism of the design, implementation and findings of these 3 trials. While each study's protocol defined how active and physiologic management were meant to be implemented, there was variation in how the approaches were used in a clinical setting. High rates of non-adherence to allocated intervention were noted in the physiologic management arms of 2 of the studies: only 47% of participants allocated to the physiologic management arm of the Bristol trial and 64% of participants allocated to the physiologic management arm of the Hinchingbrooke trial received the full physiologic management package. (71,73) Non-adherence noted in the physiologic management arms may have reflected participating midwives' lack of familiarity with physiologic management approaches. Researchers have questioned whether the midwives participating in this trial were given sufficient training in physiologic management; this lack of comfort may have made midwives reluctant to adhere to the physiologic management protocol or apply it in a piecemeal (and possibly ineffective) way. (62,75) Consequently, the findings of these studies may not necessarily capture the true effects of physiologic management. It is possible that a suboptimal form of physiologic management applied by unconfident practitioners may have increased bleeding in women in the physiologic management arm. (71,73) Finally, as blinding was not possible, the assessment of some outcomes (particularly blood loss) could have been influenced by the provider's knowledge of study allocation. The possibility of bias is highest in the 2 studies in which blood loss was visually estimated. (71,73) Problems with the design and implementation of these studies limit confidence in their findings and it is unclear whether the observed decrease in risk of PPH associated with active management (for all levels of risk) actually represents a true effect.

Third-stage management and place of birth

Observational studies led by midwife researchers from high- and moderate-income countries suggest that home or out-of-hospital birth is associated with a similar or reduced risk of PPH compared to hospital births. Because clients who give birth at home may have different risk profiles than those who give birth in hospital, researchers try to design studies that consider groups with similar characteristics, or adjust their analyses to take known risk factors into account. Selection bias may nevertheless affect the association observed.

Similarly, differences in outcomes in these studies between clients who receive active management and those who receive physiologic management may also be affected by selection bias.

A retrospective study based on the New Zealand College of Midwives research database examined the effects of place of birth and method of third-stage management on blood loss > 1000 mL in 16 210 low-risk women. (76) Incidence of blood loss > 1000 mL was 1.3% overall and did not vary significantly based on place of birth (home, birth centre, secondary or tertiary hospital). Across birth settings, active management was associated with increased risk of blood loss > 1000 mL compared to physiologic management (adjusted RR 2.12, 95% CI 1.39-3.22). (76)

An Australian cohort study comparing outcomes in a maternity unit of a tertiary-level hospital to a nearby freestanding, midwife-led birth unit found a higher incidence of blood loss ≥ 500 mL in the hospital unit (11.2%) compared to the midwife-led unit (2.8%) for women at low-risk of PPH. (77) Women with risk factors for PPH were excluded from the analysis for both settings. The midwife-led birth unit used a continuity of midwifery care model while the hospital was staffed by midwives on shift, with obstetricians on call. The difference may also in part be explained by differences in third-stage management between settings: most women who gave birth in the hospital unit (97%) received active management of the third stage of labour, while most women in the midwife-led unit (86%) received "holistic psychophysiological" care. When rates of PPH were compared among women receiving active management in each setting, and women receiving physiologic care in each setting, no significant differences based on setting were noted. (77)

Active management of the third stage of labour and global health

The 2012 *WHO recommendations for the prevention and treatment of postpartum hemorrhage* notes care providers should "consider…the use of uterotonics as the main intervention within the active management of third stage of labour package." (19) The WHO guidelines recommend offering prophylactic uterotonics to all people giving birth as well as selective application of other traditional components of active management depending on the birth attendant's skill level. The recommendation for universal active management may be more applicable and have greater beneficial impact in low-resource settings where access to care and treatment options are limited and prevalence of iron deficiency anemia is high, or other risk factors are present. (See appendix B for WHO recommendations for the prevention of PPH.)

Which uterotonic agent is most effective to prevent PPH?

A number of RCTs have compared the effects of various uterotonic drugs given as prophylaxis in the third stage of labour.

Oxytocin vs no oxytocin/placebo

Six randomized trials were found, which included more than 4000 participants, comparing the use of prophylactic oxytocin and placebo for identified outcomes of interest. (78–83) (GRADE Table 3) Among all studies, oxytocin use was associated with a lower incidence of blood loss > 1000 mL (RR 0.62, 95% CI 0.44-0.87), blood loss > 500 mL (RR 0.53, 95% CI 0.38-0.74), and reduced need for therapeutic uterotonics (RR 0.56, 95% CI 0.36-0.87) when compared to no oxytocin or placebo.

When analysis was limited to trials comparing oxytocin to no oxytocin which were considered to be at low risk of bias (78–80) (GRADE Table 3a) there were no differences between groups for:

- blood loss > 1000 mL
- maternal Hb < 90g/L at 24 to 48 hours postpartum
- blood transfusion
- manual removal of the placenta

Oxytocin use was significantly associated with a lower incidence of blood loss > 500 mL (RR 0.61, 95% CI 0.48-0.77) and reduced need for therapeutic uterotonics (RR 0.58, 95% CI 0.36-0.92).

Oxytocin vs ergot alkaloids

Five trials that included more than 2000 participants were identified comparing the use of prophylactic oxytocin vs ergometrine for outcomes of interest. (79,84–87) These trials ranged in sample size from 10 to nearly 2000 women and were conducted in a range of settings. All births included in these trials were attended by midwives or physicians in hospitals or birth centres. In the 2 trials considered to be at low risk of bias (79,85), use of oxytocin was not associated with a significant difference in blood

loss-related outcomes when compared to prophylactic use of ergot alkaloids. Table 4 summarizes the results of trials comparing oxytocin to ergot alkaloids for the prevention of PPH, more detailed evidence summaries can be found in GRADE Tables 4 and 5.

Syntometrine vs oxytocin

Six trials of more than 8000 participants compared the use of prophylactic syntometrine vs oxytocin for identified outcomes of interest. (88–93) These trials range in sample size, dose and route of administration and were conducted in a range of settings (Australia, Asia, U.K.). All births included in these trials were attended by midwives or physicians in hospitals or birth centres. Among all studies comparing use of syntometrine vs oxytocin, syntometrine use was associated with a reduced risk of PPH > 500 mL.

TABLE 4: OXYTOCIN VS ERGOT ALKALOIDS FOR THE PREVENTION OF PPH

	Blood loss > 500 mL	Blood loss > 1000 mL	Side-effects	Need for therapeutic uterotonics
	Risk of outcome			
Oxytocin vs ergot alkaloids (5 trials)	Lower with oxytocin RR 0.76 (95% CI 0.61-0.94	No difference	Lower with oxytocin Vomiting RR 0.07 (95% CI 0.02-0.25) Nausea RR 0.18 (95% CI 0.06-0.53)	No difference
Syntometrine (5 IU oxytocin + 0.5 mg ergonovine) vs oxytocin (6 trials)	Lower with syntometrine RR 0.79 (95% CI 0.63-0.98)	No difference	Higher with syntometrine Vomiting RR 3.77 (95% CI 1.69-4.57) Nausea RR 2.18 (95% CI 1.08-4.41)	No difference

For full evidence quality grading see GRADE Tables 4 and 5

Other uterotonic agents

Carbetocin vs syntometrine

Four trials of more than 1000 participants were found comparing the use of prophylactic carbetocin (synthetic oxytocin analogue) and syntometrine. No significant differences in blood loss-related outcomes were noted. Across all trials, carbetocin use was associated with reduced incidence of vomiting, nausea, uterine and/or abdominal pain, and BP at or above 140/90 at both 30 and 60 minutes after delivery. (GRADE Tables 6, 6a)

Carboprost vs ergometrine/syntometrine

Meta-analysis of 3 trials comparing carboprost (hemabate) to ergometrine/syntometrine found no difference in hemorrhage-related outcomes (blood loss > 500 mL, need for additional uterotonics, manual removal of the placenta, mean postpartum Hb). The quality of this evidence is considered low to very low due to serious risk of bias in the included trials and the imprecision of the estimates of effect. (GRADE Table 7)

Should misoprostol be used to prevent PPH?

Misoprostol has been proposed as an alternative strategy for prevention of PPH in settings where oxytocin or other conventional injectable uterotonics are not available. Its advantages over oxytocin include the potential for oral, sublingual or rectal administration (eliminating the need for sterile equipment) and stability at room temperature. Therefore, it has been intensively researched over the last 20 years as an intervention to improve maternal health and reduce maternal mortality in settings where

skilled birth attendants are not present or refrigeration capabilities are restricted (See Table 5 for summary of research related to misoprostol for the prevention of PPH). Oxytocin is associated with less blood loss and fewer side-effects (diarrhea, shivering and fever) than misoprostol. When skilled birth attendants are present and oxytocin is available, it is the uterotonic of choice for prevention of PPH. (19,94)

TABLE 5: MISOPROSTOL VS OXYTOCIN FOR THE PREVENTION OF PPH

	Blood loss > 500 mL	Blood loss > 1000 mL	Side-effects	Need for therapeutic uterotonics
	Risk of outcome			
Oral misoprostol				
Oral misoprostol vs oxytocin (Any dose, 7 trials)	No difference	Lower with Oxytocin 3.8% vs 2.7% RR 1.38 (95% CI 1.18-1.62)	Higher with misoprostol: Shivering 20.3% vs 5.8% RR 3.9, (95% CI 2.34-6.52) **Fever ≥ 38C** **6.1% vs 0.8%** **RR 6.26 (95% CI 2.17-18.07)**	No difference
Subgroup by dose: **800 µg**	No difference	No events	Higher with misoprostol: Shivering RR 22.5 (95% CI 11.36-44.56)	No difference
600 µg	No difference	No difference	Higher with misoprostol: Diarrhea RR 4.37 (95% CI 2.24-8.55) Shivering RR 3.32 (95% CI 2.61-4.24) **Fever RR 4.55 (95% CI 1.96-10.59)**	No difference
400 µg	No difference	No difference	Higher with misoprostol: Shivering RR 2.25 (95% CI 1.18-4.31)	No difference
Rectal misoprostol				
Rectal misoprostol vs oxytocin (4 trials)	No difference	No difference		No difference
Subgroup by dose: **800 µg**	No difference	No difference	Higher with misoprostol: Shivering 27.3% vs 7.4% RR 4.47 (95%CI 1.55-12.93)	No difference
400 µg	No difference	No difference	Higher with misoprostol: Shivering 35% vs 15% RR 2.36 (95% CI 1.82-3.05)	No difference

For full evidence quality grading see GRADE Tables 8 and 9

Misoprostol vs oxytocin

Seven trials comparing oral misoprostol (any dose) and oxytocin during the third stage of labour were identified. (95–101) Over three-quarters of the observations included in the meta-analysis of the 7 trials are from a single, large multi-centre trial. (96)

Meta-analysis of the trials suggests that oral misoprostol is associated with a slightly increased incidence of blood loss > 1000 mL (3.8% for misoprostol vs 2.7% for oxytocin, RR 1.38, 95% CI 1.18-1.62). Use of oral misoprostol vs oxytocin was significantly associated with a higher incidence of diarrhea: 0.5% vs 0.2%, RR 2.86 (95% CI 1.24- 6.62), shivering: 20.3% vs 5.8%, RR 3.9 (95% CI 2.34-6.52), and fever: 6.1% vs 0.8%, RR 6.26 (95% CI 2.17-18.07). Similar findings were noted when different doses of oral misoprostol (800 µg, 600 µg, 400 µg) were considered. Meta-analysis found no difference in hemorrhage-related outcomes (blood loss > 500 mL, need for additional uterotonics, manual removal of the placenta, mean postpartum Hb). (GRADE Tables 8a, 8b, 8c)

Four trials compared use of rectal misoprostol (any dose) and oxytocin during the third stage of labour. (102–105) For different doses of rectal misoprostol (400 µg, 800 µg), meta-analysis revealed no significant differences in hemorrhage-related outcomes (blood loss, need for additional uterotonics, blood transfusion, postpartum Hb). Use of rectal misoprostol (400 µg and 800 µg doses) was significantly associated with a higher incidence of shivering compared to oxytocin: 35% vs 15%, RR 2.36 (95% CI 1.82-3.05) and 27.3% vs 7.4%, RR 4.47 (95% CI 1.55-12.93). (GRADE Tables 9a, 9b)

Misoprostol vs other injectable uterotonics

Five trials compared use of oral misoprostol (any dose) and injectable uterotonics other than oxytocin during the third stage of labour. (106–110) Meta-analysis of the trials revealed no significant differences in hemorrhage-related outcomes (blood loss, need for additional uterotonics, blood transfusion, postpartum Hb). Use of oral misoprostol vs ergometrine or syntometrine was significantly associated with higher incidence of shivering (31.8% vs 10.8%, RR 3.06, 95% CI 1.88-4.99) and fever (11.2% vs 1.6%, RR 6.37, 95% CI 4.16-9.73). Similar findings were noted when different doses of oral misoprostol (600 µg, 400 µg) were considered individually. (GRADE Tables 10a, 10b)

A separate meta-analysis of trials comparing misoprostol to ergot alkaloids (methylergometrine, syntometrine) during the third stage of labour revealed no significant differences in hemorrhage-related outcomes (blood loss, need for additional uterotonics, blood transfusion, postpartum Hb). (111–114) Misoprostol was associated with significantly higher rates of vomiting, shivering and fever. (GRADE Tables 11, 12)

Should tranexamic acid be used to prevent PPH?

Tranexamic acid (TXA) is an anti-fibrinolytic agent used in surgery to prevent the breakdown of clots (fibrinolysis), thereby reducing blood loss. It is inexpensive, stable and can be administered orally or parenterally. TXA works by competitively blocking the enzyme that activates the degradation of fibrinogen and fibrin and is thought to be particularly useful in preventing or treating cases of PPH that are attributable to causes other than uterine atony, such as blood loss associated with placenta previa or genital tract trauma. (115) Methodologically limited and small studies suggest that TXA may decrease blood loss after birth. However, the anti-fibrinolytic effects of TXA may theoretically increase risk of thrombosis, and available trials have been underpowered to assess potential severe side-effects.

Two trials (n = 559) have assessed the efficacy of TXA (in addition to oxytocin) for preventing PPH following vaginal delivery. (116,117) Pooled results from these studies suggest a lower incidence of blood loss > 500 mL (RR 0.43, 95% CI 0.23-0.80) and less frequent use of additional uterotonics with TXA combined with oxytocin vs oxytocin alone (RR 0.35, 95% CI 0.16-0.72). For both studies, rates of blood loss ≥ 1000 mL were lower in women who received TXA plus oxytocin than women who received placebo plus oxytocin, but these differences were not statistically significant. Higher incidence of nausea, vomiting and diarrhea were noted with TXA use. (GRADE Table 17) The small size of these 2 studies limited researchers' abilities to assess risk of thrombosis. A large trial currently underway is anticipated to provide more definitive information about the effectiveness and safety profile of TXA as a prophylactic agent used in the third stage of labour. (118)

COMPONENTS OF THE ACTIVE MANAGEMENT PACKAGE

What is the best time to administer a prophylactic uterotonic?

Few published studies have assessed the ideal timing of administering a prophylactic uterotonic. No studies were found comparing uterotonic administration following delivery of the anterior shoulder versus immediately or soon after birth – common times at which a uterotonic is administered prophylactically in the Canadian setting. The 2 studies included in a Cochrane review compare uterotonic administration before and after expulsion of the placenta. Their findings suggest no difference in any outcomes assessed, including blood loss (mean, > 500 mL or > 1000 mL), blood transfusion, incidence of retained placenta or hypotension. (119)

Administering a uterotonic with the birth of the anterior shoulder (the timing specified in the original trials assessing the effectiveness of active management) could theoretically entrap an undiagnosed twin. Waiting until after birth to administer a prophylactic uterotonic reduces this risk and gives the midwife time to assess and palpate the fundus to exclude the presence of another baby after birth. (120)

What route (IM or IV) is most effective for administration of prophylactic oxytocin?

One trial has been published comparing IM vs IV administration of oxytocin for active management of the third stage. In a prospective RCT from Turkey, 600 participants were randomized to 1 of 4 groups: IV oxytocin after birth, IV oxytocin with anterior shoulder, IM oxytocin after birth, and IM oxytocin with anterior shoulder. Rates of postpartum blood loss, postpartum Hb and hematocrit, and need for additional uterotonics were similar among all groups. (121)

How does timing of cord clamping affect PPH and neonatal outcomes?

A Cochrane review of 15 studies comparing early (within 60 seconds) and delayed cord clamping suggests that timing of cord clamping has no effect on hemorrhage-related outcomes, including: blood loss > 500 mL, > 1000 mL, overall mean blood loss, maternal Hb levels, need for blood transfusion, manual removal of the placenta, or use of therapeutic uterotonics. (122) The 2012 WHO guideline on PPH recommended that cord clamping take place 1 to 3 minutes after birth. This recommendation appears to be based on expert opinion related to neonatal benefits from delaying cord clamping rather than on hemorrhage-related outcomes; no studies have examined the relative efficacy of active management of the third stage using different cord clamping intervals. (19)

Questions remain regarding the effect of prophylactic uterotonics on placental transfusion when cord clamping is delayed. An RCOG scientific impact paper states that administration of prophylactic IM oxytocin is "unlikely to have a major effect on placental transfusion" when cord clamping is delayed. This is because IM oxytocin results in uterine contractions approximately 2.5 minutes after administration, whereas placental transfusion is largely completed by 2 minutes for a term birth. However, there is no research examining potential clinically relevant impacts of neonatal exposure to oxytocin before cord clamping if placental transfusion is not complete. (123)

An increasingly large body of evidence suggests that delayed cord clamping does not affect the risk of PPH. Delayed cord clamping is associated with beneficial impacts on neonatal outcomes including improved long-term iron stores and Hb concentration and a slight increase in risk of jaundice requiring phototherapy. (122) Waiting until after the cord has stopped pulsating prior to clamping the cord allows the neonate to reap the benefits of delayed cord clamping. Recognizing when cord pulsation has ceased is a core midwifery skill.

What is the effect of umbilical cord drainage?

Umbilical cord drainage requires clamping and cutting the umbilical cord, followed by immediate unclamping of the maternal side to allow the blood from the cord to drain into a receptacle. A Cochrane review included 3 studies comparing outcomes with or without cord drainage; it found no clear differences in amount of blood loss or need for manual removal of the placenta. (124)

What are the effects of uterine massage?

Randomized controlled trials have assessed the value of uterine massage as part of the active management package, as recommended by ICM/FIGO. (67) These studies, conducted in Egypt, South Africa and China, suggest that sustained uterine massage (administered either before or after the delivery of the placenta) has no additional benefit over oxytocin alone. The uterine

massage administered in these studies consisted of sustained and firm manual stimulation of the surface of the uterus, administered routinely for prophylactic purposes. Potential side-effects of uterine massage, including pain, were not assessed. (78,125,126) It is important to differentiate the use of uterine massage intended for prevention vs treatment of PPH; for example, uterine massage used to expel clots may be used therapeutically, not as a routine preventative practice.

One randomized controlled trial (n = 1964) in hospital settings in Egypt and South Africa (GRADE Table 2d) randomized participants with low risk of PPH and who were expected to deliver vaginally to receive either active management (10 IU oxytocin, immediate cord clamping and controlled cord traction) or active management plus 30 minutes of firm, steady manual stimulation of the external surface of the uterus. (78) Researchers noted no significant differences between groups in terms of blood loss > 1000 mL or > 500 mL, maternal Hb < 80 g/L at 12 to 24h postpartum, need for blood transfusion, therapeutic uterotonics, or manual removal of the placenta. Similar findings were noted in 2 trials that involved uterine massage after delivery of the placenta (GRADE Table 2e). In one of these studies, uterine massage was administered every 10 minutes for an hour-long period; the other study involved 30 minutes of sustained massage. (125,126)

What are the effects of controlled cord traction?

Active management and controlled cord traction

Three relevant randomized controlled trials have compared active management of the third stage of labour with and without controlled cord traction (GRADE Table 2b). These studies were conducted both in high- and low-resource hospital settings in Uruguay (127), France (128), and in a multicentre study that took place in Argentina, Egypt, Kenya, the Philippines, South Africa, Thailand and Uganda (129). Active management protocols included the administration of 5 to 10 IU prophylactic oxytocin and, in the case of the 2 larger trials (127,129), delayed cord clamping. Participants in each study were randomly assigned to either receive controlled cord traction consistent with ICM/FIGO guidance (67) performed by skilled birth attendants, or to deliver their placenta with maternal effort or using gravity.

In these 3 studies, the addition of controlled cord traction to active management was associated with a very slight reduction in risk of blood loss > 500 mL (RR 0.94, 95% CI 0.88-0.99) and a larger reduction in manual removal of the placenta (RR 0.69, 95% CI 0.57-0.83). No significant differences in blood loss > 1000 mL, blood transfusion, or use of therapeutic uterotonics were noted. Active management with controlled cord traction was associated with a reduction in maternal pain during the third stage of labour (RR 0.78, CI 95% 0.61-0.99). In the one study in which this outcome was assessed, there was an increased risk of cord rupture (RR 44.28, 95% CI 10.92-179.58); however, there was no difference in rates of manual removal of the placenta. (128)

A multicentre observational study conducted at secondary- and tertiary-level hospitals in Egypt, Burkina Faso, Turkey and Vietnam assessed the contributions of different components of the active management package as part of a bigger study of treatment options for PPH (GRADE Table 2f). (130) Participants at study sites where prophylactic oxytocin and controlled cord traction were routinely used experienced lower rates of blood loss ≥ 500 mL and ≥ 700 mL than those cared for at sites where oxytocin alone was administered (3% vs 18% and 1.8% vs 3.2%). (130) Country- and site-level differences in study population and obstetric practice (such as timing of cord clamping and induction or augmentation of labour) may explain some of the differences noted. (130)

Expectant management and controlled cord traction

The multicentre observational study described above also assessed the effects of controlled cord traction in settings were prophylactic uterotonics were not routinely administered during the third stage of labour (GRADE Table 2g). (130) Parturients cared for at study sites where controlled cord traction was routinely used on its own experienced lower rates of estimated blood loss ≥ 500 mL and ≥ 700 mL than those cared for at sites where no components of active management were routinely used (5.1% vs 16.5% and 4.9% vs 8.4%). (130) No complications related to controlled cord traction (such as uterine inversion or cord rupture) were noted in this study. (130)

Use of controlled cord traction in the absence of a uterotonic is similar to the Brandt-Andrews manoeuvre. Because limited research suggests that controlled cord traction by itself may slightly reduce blood loss, both approaches (either physiologic management or Brandt-Andrews) are reasonable variations to offer clients.

SUMMARY STATEMENTS

- Available randomized trials show a significant reduction in the following outcomes with active vs expectant management when applied to ALL participants, regardless of presence or absence of risk factors for PPH:
  - » Blood loss > 1000 mL
  - » Maternal blood transfusion
- Available research does not show that active management of the third stage of labour reduces the likelihood of postpartum bleeding > 1000 mL in women at low risk of PPH.
- Research suggests that oxytocin is the most effective uterotonic overall for prevention of PPH, with the fewest side-effects.
- Syntometrine compared to oxytocin was found to reduce blood loss > 500 mL, but showed no difference for blood loss > 1000 mL and is associated with more side-effects (nausea, vomiting).
- Oxytocin is more effective than misoprostol for reducing blood loss ≥ 500 mL or ≥ 1000 mL and has fewer side-effects (diarrhea, shivering and fever).
- Based on the research exploring the efficacy of different aspects of the active management package, WHO describes the use of a uterotonic as the primary intervention of active management.
- Delayed cord clamping does not affect the risk of PPH, and has beneficial impacts on neonatal outcomes, including improved long-term iron stores and Hb concentration.
- Research has found no difference in amount of blood loss or need for manual removal of the placenta with or without cord drainage.
- Controlled cord traction appears to be slightly beneficial for preventing PPH, both when used as part of an active management and as part of an expectant management approach (Brandt-Andrews manoeuvre).
- Uterine massage does not appear to be an effective component of the active management package for prevention of PPH. It is important to differentiate use of uterine massage as part of a PPH prevention strategy and using uterine massage to expel uterine blood clots as an intervention in the treatment of PPH.
- More research is needed to determine the efficacy of tranexamic acid for the prevention of PPH.
- More midwifery research is needed to identify the effects of physiologic care in the third stage of labour.

RECOMMENDATIONS:

4. The risks and benefits of physiologic management compared with active management should be discussed with all clients as part of an informed choice discussion. This discussion should address:

    - how risk factors, if present, may increase the client's risk of PPH and impact considerations about choice of birthplace; and
    - the client's values and preferences.

    This discussion, including the client's choice, should be appropriately documented in the client's chart.

    Strong recommendation; low-quality evidence.

    This recommendation recognizes the client as the primary decision-maker. This recommendation recognizes that the presence of one or more risk factors is not necessarily predictive of PPH, and that the original trials of active management may be interpreted differently in a low-risk population.

5. When active management is chosen for the prevention of PPH, midwives should:

    - Use oxytocin as the uterotonic.
    - Once pulsation stops, clamp and cut the cord.
    - Use controlled cord traction to deliver the placenta.

    Strong recommendation; moderate-quality evidence.

    This recommendation recognizes a large body of research recognizing the effectiveness of oxytocin at preventing blood loss with minimal side-effects compared to other uterotonics for active management, the neonatal benefits of delayed cord clamping, and the modest clinical benefit of controlled cord traction.

6. When physiologic management is chosen, midwives should:

    - Await signs of placental separation and monitor for excessive blood loss.
    - Refrain from clamping or cutting the umbilical cord until pulsation stops or the placenta has delivered.
    - Allow the placenta to be born spontaneously with maternal effort or gravity.
    - Encourage immediate skin-to-skin contact with infant, early breastfeeding and other measures that may encourage the release and uptake of oxytocin.

    Strong recommendation; low-quality evidence.

    This recommendation recognizes the physiology of normal birth. More research is needed to identify the most effective aspects of physiologic care in the third stage of labour.

7. Midwives may offer controlled cord traction to clients choosing physiologic management.

    Weak recommendation; very low-quality evidence

    This recommendation recognizes observational data that associates a reduction in PPH > 700 mL with the use of controlled cord traction without a prophylactic uterotonic as well as randomized trials that show a slight reduction in blood loss > 500 mL, duration of the third stage, and manual removal of the placenta with use of controlled cord traction during active management of the third stage.

8. Uterine massage is not recommended for the prevention of PPH. Postpartum assessment of fundal tone is recommended.

    Strong recommendation; low-quality evidence.

    This recommendation recognizes the importance of identifying uterine atony. Available research does not support the routine use of uterine massage after prophylactic oxytocin has been administered. There is no evidence available on the use of uterine massage where no prophylactic uterotonic has been administered.

TREATMENT OF PPH

Which uterotonic is most effective for treatment of primary PPH due to uterine atony?

Despite the relatively frequent incidence of PPH, little trial-based evidence exists to identify the most effective pharmacologic agents for treatment. Uterotonic agents vary by mechanism of action, resulting in different effects on the uterus, and the underlying pathophysiology of the PPH may influence a midwife's choice of agent for treatment.

Similar to the case of PPH prevention, much of the research available investigates the efficacy and safety of misoprostol as a treatment for primary PPH based on its potential advantages over traditional injectable uterotonics in low-resource settings where skilled birth attendants and refrigerated storage facilities are not universally available. Despite a long history of use in midwifery care, there is no trial that compares ergometrine vs oxytocin as a first-line treatment for PPH due to uterine atony. There is currently a randomized trial underway in Egypt designed to fill this research gap. (131)

Should oxytocin vs. misoprostol be used as a first-line treatment for PPH?

Two related multicentre trials have compared outcomes of misoprostol vs oxytocin for treatment of PPH. (132,133) One trial involved participants not exposed to oxytocin during the second or third stage of labour (133), and the other trial involved participants who were given oxytocin prophylaxis during the third stage (132). Both trials used similar study protocols and are of high methodological quality. In both cases, participants were recruited to the study after experiencing measured blood loss > 700 mL due to suspected uterine atony following vaginal delivery.

Misoprostol vs oxytocin (no active management)

One of the above-mentioned trials compared a high dose of sublingual (SL) misoprostol (800 µg) vs oxytocin (40 IU in 1000 mL IV solution over 15 minutes) for the treatment of PPH for those who had not previously been exposed to oxytocin. (133) Neither active management nor oxytocin induction and/or augmentation was used routinely at the sites at which the study was conducted (Ecuador, Egypt, Vietnam). (GRADE Table 13)

Among those not previously exposed to oxytocin, treatment of PPH with sublingual misoprostol was associated with a higher incidence of additional blood loss ≥ 300 mL (30.1% vs 16.9%, RR 1.78; 95% CI 1.4-2.26) and ≥ 500 mL (10.9% vs 4.1%, RR 2.66; 95% CI 1.62-4.38). Additionally, there was a greater use of additional uterotonics (12.5% vs 6.3%, RR 1.98; 95% CI 1.31-2.99) and fluids and/or plasma expanders (18.2% vs 9.6%, RR 1.9; 95% CI 1.37-2.65) in the misoprostol group.

Use of misoprostol was also associated with an increased incidence of side-effects, compared to oxytocin, including:

- shivering: 46.9% vs 16.7%, RR 2.8 (95% CI 2.25-3.49)
- shivering described as "intolerable": 11.3% vs 0.2%, RR 55.23 (95% CI 7.67-397.48)
- fever (any): 44.5% vs 5.5%, RR 8.07 (95% CI 5.52-11.8)
- fever ≥ 40°C: 13.5% vs 0%. RR 133.54 (95% CI 8.29-151.28
- fever described as "intolerable": 9.2% vs 0%, RR 91.37 (95% CI 5.64-1479)
- vomiting: 4.9% vs 1.4%, RR 3.44 (95% CI 1.5-7.92)

Misoprostol vs oxytocin (following active management)

The second trial compared misoprostol (800 µg SL) and oxytocin (40 IU in 1000 mL IV solution over 15 minutes) for the treatment of PPH in participants who had previously received oxytocin prophylaxis during the third stage of labour. (132) Approximately 50% of participants in both arms of the study also received oxytocin to augment labour. Other aspects of active management were used variably across sites.

Among those previously exposed to oxytocin, treatment of PPH with sublingual misoprostol vs oxytocin was associated with a higher incidence of:

- additional blood loss ≥ 1000 mL: 2.7% vs 0.7%, RR 3.62 (95% CI 1.02-12.88)
- shivering: 37.3% vs 14.7%, RR 2.54 (95% CI 1.95-3.32)
- fever: 21.6% vs 14.7%, RR 1.47 (95% CI 1.09-1.99)

Misoprostol vs oxytocin and ergometrine

A small double-blind trial conducted in hospitals in South Africa compared rectal (PR) misoprostol (800 µg) to standard local treatment for PPH: syntometrine (5 IU oxytocin plus 500 µg ergometrine) IM and oxytocin 10 IU diluted in 500 mL normal saline. (134) (GRADE Table 15) Study participants had been diagnosed with PPH within 24 hours of vaginal or caesarean delivery (based on estimated blood loss > 500 mL and a poorly-contracted uterus). Active management was used regularly at the hospitals at which the study was conducted. While blood loss was assessed visually, providers were blinded to treatment arm. A higher proportion of caesarean, vacuum and forceps deliveries occurred in the misoprostol arm of the study.

In this small study, misoprostol PR (800 µg) was associated with the following outcomes, compared to syntometrine/oxytocin:

- active bleeding was controlled within 20 minutes in a greater proportion of participants who received misoprostol: 93.8% vs 65.6%, RR 1.43 (95% CI 1.09-1.86); and
- reduced use of additional uterotonic drugs with misoprostol: 6.3% vs 34.4%, RR 0.18 (95% CI 0.04-0.76).

Should adjuncts to oxytocin be used for treatment of PPH?

Misoprostol

Four trials have assessed the effectiveness of misoprostol as an adjunct to standard uterotonics, compared to standard uterotonics alone. (135–139) The dose and route of uterotonic varied by study. (GRADE Table 16) Criteria for trial enrollment varied by study: 2 studies required measured blood loss > 500 mL and 2 studies required a subjectively-determined diagnosis of PPH (e.g., "more than expected bleeding"); all studies were limited to hemorrhage attributable to uterine atony. Active management was standard in all settings.

No significant differences in blood loss-related outcomes were noted in meta-analysis of trials assessing misoprostol as an adjunct to standard uterotonics, compared to standard uterotonics alone. However, adjunct use of misoprostol was associated with an increased incidence of side-effects, compared to standard uterotonics alone:

- shivering (within 1 hour of treatment): 56.9% vs 28.5%, RR 2.24 (95% CI 1.72-2.91)
- severe shivering (within 1 hour of treatment): 10.9% vs 5.1%, RR 11.64 (95% CI 5.41-25.03)
- fever (within 1 hour of treatment): 37.3% vs 12.7%, RR 2.91 (95% CI 2.42-3.5)
- vomiting (within 1 hour of treatment): 5.2% vs 2.3%, RR 2.29 (95% CI 1.3-4.01)

Tranexamic acid

One published RCT has evaluated TXA as an adjunct to standard treatment for PPH (GRADE Table 18). The French EXADELI trial randomized 144 participants to receive either TXA or no additional treatment following blood loss of > 800 mL treated with standard management: bladder catheterization, manual exploration

of the uterus, visual inspection of the genital tract and 30 IU oxytocin; a similar proportion of participants in each group (43% to 48%) also received a prostaglandin. (140)

Participants who received TXA were less likely to experience persistent bleeding 30 minutes after randomization than those in the control group (36% vs 54%) and were less likely to experience a ≥ 40 g/L decline in Hb after delivery. Differences in rates of packed red blood cell transfusion or ICU admission were not significant. Other critical clinical outcomes were not reported. Non-severe side-effects such as nausea/vomiting, visual disturbances or dizziness occurred in 23% of participants who received TXA, compared to 5% in the control group. (140) While a thrombotic event occurred in 2 participants who received TXA and one participant who was in the control group; this study was not adequately powered to address rare adverse events and this difference was not statistically significant.

WHO recommendations call for further research on TXA for treatment of PPH. A large international trial currently underway is anticipated to provide more definitive information about the efficacy of TXA as an adjunct to standard treatment for PPH in situations where the care provider is "substantially uncertain whether or not to use an antifibrinolytic agent." This double-blinded and placebo-controlled RCT has a target enrollment of 15 000 and will have the statistical power to examine rare severe maternal morbidity outcomes such as hysterectomy and thrombotic events. (141)

Which second-line uterotonics should be used for treatment of primary PPH due to uterine atony?

There is no consensus on the most effective second-line uterotonic for the treatment of primary PPH due to uterine atony, when oxytocin has failed to stop bleeding. Trial-based research is generally not feasible due to the emergency nature of PPH, therefore observational data must be used to compare the effectiveness of different uterotonic agents and regimens. Because of this lack of evidence, there is little to guide midwives in balancing the risks and benefits of each uterotonic while also considering the client's specific clinical context. (142)

Three observational studies were found describing and comparing the use of secondary uterotonics for uterine atony that was unresponsive to first-line therapy with oxytocin.

Using data from a large birth registry in the United States, one study included CS or vaginal birth after caesarean and use of either methylergonovine or carboprost for the treatment of refractory uterine atony. (143) Details on active management protocols were not available, but previously published data indicated that oxytocin was routinely used for prophylaxis in this setting. Researchers excluded participants with abnormal placentation, hypertensive disorders of pregnancy or asthma, resulting in a cohort of 1335. Primary outcomes were severe complications of PPH (transfusion, uterine artery ligation or hysterectomy). After adjusting for confounders, the risk of maternal morbidity related to hemorrhage was significantly increased for women who received carboprost vs methylergonovine (RR, 1.7; 95% CI, 1.2-2.6). (143)

Secondly, a retrospective cohort study from the United States used chart review to identify cases at term with diagnosed primary PPH and requiring a second-line uterotonic after oxytocin. Eighteen participants received methylergonovine and 40 received misoprostol. The study did not find any significant difference in demographic factors between the groups. There was also no significant difference in rates of blood transfusion, need for third-line uterotonics, or surgical intervention. These results suggest that misoprostol is comparable to methylergonovine for second-line treatment of PPH, but this evidence is very low quality due to the design and small size of the study. (144)

A third study did not directly compare outcomes based on pharmacologic agents, but described hospital-level patterns of second-line uterotonic use (methylergonovine, carboprost, or misoprostol) in the treatment of uterine atony in a large sample of births from the United States. (142) Adjusting for demographic characteristics, mode of birth, medical and obstetrical conditions, year of delivery, and hospital characteristics did not explain the variation in practice, suggesting that the second-line uterotonic use is largely based on non-medical factors such as physician preference, drug availability, cost, and community standards. (142) These results are in agreement with the WHO recommendation that, because data is lacking, decisions for second-line uterotonic use where oxytocin has failed to stop bleeding "must be guided by the experience of the provider, the availability of the drugs, and by known contraindications." (19)

SUMMARY STATEMENTS

- Research suggests oxytocin is more effective than misoprostol for the treatment of primary PPH due to uterine atony and causes fewer side-effects.
- Uterotonics have different mechanisms of action and the midwife is encouraged to consider this when choosing the appropriate uterotonic(s) for prevention and treatment of PPH. See appendix C for description of uterotonics, dosages and mechanisms of action.
- There appears to be no benefit to using misoprostol as an adjunct to conventional injectable uterotonics as a first-line treatment for PPH.
- More research is needed on efficacy of tranexamic acid for the treatment of PPH, specifically large enough trials to show risk of rare adverse effects.
- There is insufficient evidence to clearly guide midwifery practice in choosing the most effective second- and third-line uterotonics for treatment of PPH due to atony.
    - » One small retrospective observational study suggests methylergonovine is a better second-line uterotonic than carboprost.
    - » One small, low-quality retrospective observational study suggests there are no differences in outcomes when either misoprostol or methylergonovine are used as a second line uterotonic.
    - » In-depth information on uterotonic drugs including storage and stability is included in Appendix C: Drugs in the Midwifery Pharmacopeia for Management of PPH.

RECOMMENDATIONS:

9. Midwives should use oxytocin as the first line uterotonic for the treatment of PPH due to uterine atony.

    Strong recommendation; moderate-quality evidence.

    No high-quality evidence has shown superior efficacy of any uterotonic drug vs oxytocin in settings where it is available. The CMO requires that midwives carry at least 2 uterotonics: oxytocin plus 1 additional drug. The comparative effectiveness of uterotonics for treatment of PPH is identified as a research gap.

10. Available research does not clearly support the use of one particular uterotonic over another for second-line treatment of primary PPH due to uterine atony (ergot alkaloids, prostaglandins and carbetocin). Midwives should choose their second-line uterotonic based on clinical context.

    Strong recommendation; very low-quality evidence.

    Access to each drug may vary by community. In the absence of clear evidence, midwives should use their clinical experience, community standards, and the clinical context of the client and birth to guide second-line uterotonic use.

Non-pharmacologic treatment for PPH

Uterine massage

Although uterine massage is used as an intervention to treat PPH and to expel clots, no research was identified evaluating its use. Available evidence discussed in the prevention section above does not support the routine use of uterine massage for prevention of PPH when oxytocin prophylaxis has been administered. (145)

There is no research available on uterine massage in the absence of oxytocin prophylaxis. However, uterine massage is recommended by the WHO as well as by the AOM PPH CPG Work Group for treatment of PPH based on expert opinion taking into account the safety of uterine massage. Uterine massage is also suggested as a first step in treatment for atonic PPH in the AOM emergency skills workshop manual, as long as the placenta is delivered. (9)

Bimanual compression

There are few published studies addressing the effectiveness of bimanual uterine compression on PPH outcomes. Various guidelines on emergency management of PPH recommend that compression of the uterus be maintained for 5 to 10 minutes and some suggest that 30 to 60 minutes of sustained compression may be necessary to arrest bleeding. (146)

In a study comparing one-provider vs two-provider technique for bimanual compression, obstetricians, nurse-midwives, midwifery students, and unskilled birth attendants performed bimanual uterine compression using a simulator which tracked the degree and duration of uterine compression. (146) Bimanual compression by one provider could not produce adequate compression of the uterus for more than 150 seconds continuously. The researchers suggest that even when bimanual compression is correctly performed by a single provider, it may not be sufficient to compress the uterus for the recommended amount of time. (146)

Uterine balloon tamponade

An emerging body of literature including retrospective and prospective case series suggest uterine balloon tamponade (UBT) is effective in the treatment of atonic PPH unresponsive to uterotonic agents. (147–160) A range of both improvised and purpose-built devices have been tested for use in UBT, such as Bakri balloon, Sengstaken-Blakemore tube, hydrostatic condom catheter, Rusch balloon and Foley catheter. UBT has been studied in a variety of tertiary care, community and low-resource settings around the world.

Use of UBT has been reported to eliminate the need for surgery in 71% to 85% of cases of severe PPH, and allow time for transfer to facilities providing embolization, therefore avoiding surgery. (154,155) In a study using Bakri balloons after UBT was added to a PPH management protocol, those with severe PPH following vaginal birth had reduced odds of arterial embolization (OR 0.26, 95% CI 0.09-0.72) and surgical procedures (OR 0.29, 95% CI 0.07-0.95) compared to a similar group of participants treated for severe PPH during an earlier time period. (161)

Clinician-researchers support the implementation of UBT in remote or low-resource settings (147–150) as well as the integration of UBT into all practice settings, including tertiary care. (152,153,162) The WHO, SOGC and RCOG also recommend the integration of UBT into PPH guidelines and protocols. (7,10,19) One group of researchers propose that any health-care provider trained in cervical examination should be able to implement UBT. (162)

Currently, there are no clinical trials assessing the risks and benefits of UBT use compared to no UBT (or other intervention). The development of higher quality evidence on the comparative risks and benefits of UBT would require prospective trials that involve a comparison group. In the absence of a comparison group, there is no way to be certain whether tamponade definitively affects outcomes. However, due to the rarity of severe PPH and its high chance of morbidity, large trials assessing management options for PPH using comparison groups or randomization are unlikely. Available research has not identified major adverse effects associated with use of UBT, though isolated cases have been complicated by infection or fever. (158,159) Continued internal bleeding is possible with use of UBT, so close inspection of the genital tract as well as close monitoring of vital signs is important even when visible bleeding has stopped. (163)

SUMMARY STATEMENTS

- Uterine massage and bimanual compression are conservative first steps for the management of atonic PPH.
- UBT is an effective, potentially life-saving intervention for severe PPH unresponsive to uterotonics, particularly in cases where prolonged transport times are anticipated.
- A growing body of case-series and observational literature suggests that earlier use of UBT significantly reduces maternal morbidity related to severe PPH in a variety of settings.
- Training in the safe and effective placement and monitoring of UBT devices is suggested for all obstetric care providers, including midwives.

RECOMMENDATION:

11. Midwives should consider the use of uterine balloon tamponade for PPH that is unresponsive to uterotonics, and where transport to hospital is necessary.

Weak recommendation; very low-quality evidence.

This recommendation recognizes the growing body of literature supporting the use of UBT at all care levels and for all obstetric providers. It acknowledges that midwives attend births in the community and that use of UBT for intractable uterine atony is a potentially life-saving measure. It also recognizes the need for midwives to access the training and equipment needed to safely and effectively use UBT devices, when appropriate, for PPH unresponsive to other interventions.

Surgical treatment for PPH

Where severe PPH is unresponsive to pharmacologic therapy, hysterectomy and other surgical interventions may be the last-resort measure to control bleeding and prevent maternal morbidity and mortality. Because of the emergency nature and complexity of these interventions, their use and timing varies widely. (164) There is a small body of evidence suggesting that increasing use of uterine balloon tamponade and other second-line surgical interventions for women with severe PPH is associated with a decreased incidence of hysterectomy as a last resort. (165) The most recent Cochrane review on treatment for primary PPH identifies a research gap on the best approach to treatment of PPH that has failed to respond to uterotonic therapy, (166) and the NICE 2014 guideline on intrapartum care states that "no particular surgical procedure can be recommended over any other for treating postpartum haemorrhage." (167)

SUMMARY STATEMENT

- Future research is needed to identify the most effective approaches to treating clients with severe PPH who fail to respond to uterotonic therapy.

How is blood volume best replaced?

In a review of the evidence on blood volume replacement after severe PPH, midwifery researchers recommend that IV use of crystalloid fluids (either Ringer's lactate solution or normal saline (0.9% NaCl)) should be "limited to the treatment of mild to moderate hemorrhage [undefined], and blood products, including packed RBCs, fresh frozen plasma, and platelets, should be the main volume replacement used during severe PPH". (168) If blood loss continues, large quantities of crystalloid fluids can dilute clotting factors and fibrinogen and impair coagulation, potentially dislodging clots that were preventing further bleeding. (168)

Clients experiencing PPH who decline blood products

Management of PPH for clients who refuse blood and blood products presents a challenge to maternity care providers. The majority of research on this topic involves members of Jehovah's Witnesses, a religious group whose members may refuse blood and blood products. (169,170) Jehovah's Witnesses may accept clotting factors, plasma proteins, and the usage of an epidural blood patch or other bloodless alternatives (which may contain plasma portions and cellular components) at their own discretion and under particular circumstances. (169,171) For Jehovah's Witnesses, blood acceptance decisions are contingent on an individual's conscience and interpretation of certain Biblical passages. (172)

A retrospective study from the U.K. followed 90 Jehovah's Witnesses having a total of 116 births over 14 years. The rate of PPH ≥ 1000 mL was 6% and one maternal death occurred. (173) Participants in this study experienced a risk of death due to PPH 65-times higher than the national population-level rate. (173) A second retrospective cohort study conducted at a New York City hospital found that obstetric hemorrhage > 1000 mL occurred in 6% of participants who were Jehovah's Witnesses, corresponding to a RR of 44 (95% CI 9-211) versus the hospital's general obstetric

population. (174) While these studies suggest that Jehovah's Witnesses are at increased risk of adverse outcomes related to PPH, the small size of these studies limit the precision of these findings.

Options for the management of clients who refuse blood products and transfusion include recombinant factor VIIa (rVIIa), tranexamic acid, desmopressin, aprotonin and epoetin alfa. (175) There is insufficient evidence to support the effectiveness of these treatments.

Because individuals vary in their choices regarding use of blood products and because availability of bloodless alternatives may vary in different communities, a care plan is warranted in the event of severe PPH. The care plan, developed antenatally, will be informed by an exploration of client preferences for treatment in the event of severe PPH. If available in the community, midwives may consider offering clients a prenatal consult with a physician to discuss alternatives to blood products and their hospital protocol for management of severe PPH.

RECOMMENDATION:

12. For clients who refuse blood and blood products, midwives should discuss possible increased risks of morbidity and mortality following severe PPH. Midwives should develop or facilitate a plan of care in the event of severe PPH, where blood or blood products would normally be recommended.

    Strong recommendation; very low-quality evidence.

    This recommendation recognizes the degree of potential risk for clients who refuse blood products. It also values the importance of respectful care and interprofessional collaboration to provide client access to options available in the community.

What is the most effective management for retained placenta?

Suggested timelines for diagnosis of retained placenta vary. The 2014 NICE guideline on intrapartum care recommends diagnosing retained placenta if the placenta remains undelivered 30 minutes post-birth with active management, and 60 minutes with physiologic management. (167) In the context of active management, manual removal of the placenta (under anesthesia) is typically indicated if the placenta has not been expelled within 30 minutes after birth. (42) Retained placenta occurs in 0.5% to 3% of births (176) and can be divided into 3 distinct pathologies: placenta adherens, trapped placenta, and placenta accreta, each with its own clinical signs which may be difficult to recognize. (177)

Should pharmacologic treatment be used for retained placenta?

A systematic review of pharmacologic interventions for the treatment of retained placenta (defined as placenta undelivered after > 30 minutes of active management) found 16 RCTs including 1683 participants. The review found no statistically significant differences in rates of manual removal of the placenta based on whether the participant was treated with placebo or oxytocin, a prostaglandin, nitroglycerin or oxytocin/nitroglycerin. (177)

Umbilical vein injection

A separate Cochrane review comparing umbilical vein injection of saline vs oxytocin, plasma expanders or prostaglandin solutions for treatment of retained placenta does not support the use of umbilical vein injection (UVI) with oxytocin or saline for the treatment of retained placenta. (178) The WHO recognizes that although there is little quality research to guide practice, umbilical vein injection has not been shown to cause harm and research shows a non-significant trend toward a reduced risk of manual removal of placenta with the use of oxytocin or prostaglandins. (19)

Should antibiotics be offered following manual removal of placenta?

A 2014 Cochrane review did not find any randomized trials evaluating the outcomes of prophylactic antibiotics for manual removal of retained placenta. (179) Indirect evidence for the use of antibiotic prophylaxis in other obstetrical interventions is also lacking. A 2014 Cochrane review of antibiotic prophylaxis for operative

vaginal delivery found no significant association between antibiotic use and improved outcomes for endomyometritis or length of hospital stay based on low-quality evidence. (180) WHO recommends offering a single dose of ampicillin or first-generation cephalosporin after manual removal of placenta (weak recommendation, very low-quality evidence), based on very low-quality, indirect evidence from trials of antibiotic prophylaxis after CS, abortion and other observational studies. (19)

SUMMARY STATEMENTS

- Current evidence does not support pharmacologic treatment for retained placenta when bleeding is controlled.
- Evidence does not clearly support the use of umbilical vein injection for the treatment of retained placenta.
- More research is needed to evaluate the effects of antibiotic prophylaxis after manual removal of the placenta.

Herbal agents used for the prevention and treatment of PPH

Grey literature and anecdotal reports suggest that herbal remedies such as blue cohosh, raspberry leaf tea, stinging nettle, Zhi Bayed 11 and Angelica sinensis are potentially effective in PPH prevention. However, their efficacy, benefits and risks have not been assessed using research methodologies.

Commonly used herbal medies to treat PPH include Caulophyllum thalictroides (blue cohosh) and Capsella bursa-pastoris (shepherd's purse). No research was found on the effectiveness of these herbs for the treatment of PPH. There are reports of adverse outcomes associated with blue cohosh in animal studies (181,182) and human case reports related to the use of blue cohosh during pregnancy for induction of labour, not as a treatment for PPH. (182,183)

SUMMARY STATEMENT

- More research is needed to determine the efficacy of herbal agents for the prevention and treatment of PPH.

RECOVERY AND CARE FOLLOWING PPH

Bleeding in the postpartum period

A systematic review of 18 studies looking at lochia patterns among participants who were not diagnosed with primary PPH found an average duration of lochia of 24 to 26 days. However, as bleeding beyond 6 weeks postpartum was also commonly observed, the authors emphasize the lack of a standard definition of clinically acceptable postpartum blood loss. (21) Heavy bleeding was defined as "requiring more than four pads per day for 10 days or more, or a perineal pad saturated every hour". The type or size of pads was not specified. One included study found that those who had long labours and instrumental delivery experienced increased duration and amount of lochia. (184) The review authors also noted considerable variation in defining delayed postpartum hemorrhage. The review did not identify any standardized methods for quantifying delayed PPH. (21)

A cohort study from the Philippines examined postpartum bleeding in 447 breastfeeding women. The women were followed prospectively from delivery and kept a journal. Researchers found that mean duration of lochia was 27 days, and did not vary by age, sex or weight of the baby, nor by breastfeeding frequency or use of formula supplementation. It was common for lochia to stop and start again after a period of time without bleeding. (185) Finally, a case-control study was conducted to determine risk factors for excessive vaginal bleeding and uterine infection from 24 hours to 3 months postpartum. Participants (n = 243) were matched with 2 controls each. Analysis identified 28 possible variables associated with being in or readmitted to hospital with excessive bleeding from 24 hours to 3 months postpartum. After multivariable analysis, 9 factors remained associated with excessive bleeding: history of secondary PPH (OR 6.0, 95% CI 2.1-16.8), vaginal bleeding < 24 weeks' gestation (OR 3.0, 95% CI 1.6-5.9), third trimester hospital admission (OR 2.0 95% CI 1.4-2.8), maternal smoking (OR 2.7 95% CI 1.8-3.9), prolonged (OR 3.1 95% CI 1.2-7.5) or incomplete third stage (OR 2.1 95% CI 1.0-4.4), and primary PPH > 500 mL (OR 4.7, 95% CI 1.9-11.6). No significant association was found for parity or method of delivery. (186)

Overall, there is a paucity of research to determine normal postpartum bleeding vs bleeding patterns indicating medical intervention. Midwives must therefore use their clinical judgment to determine when follow-up care is needed, as well as discuss normal bleeding patterns with their clients as part of postpartum teaching and how to reach the midwife when excessive bleeding is suspected. (21)

SUMMARY STATEMENT

- Research has not adequately described the duration and volume of normal vs abnormal lochia, and what amount of bleeding should be considered delayed PPH. More research is needed on delayed PPH and association with birth interventions or complications. Low-quality research has found a strong association between delayed PPH and history of delayed PPH or primary PPH > 500 mL.

RECOMMENDATION:

13. Midwives should review with all clients:
    - Normal postpartum blood loss in the immediate postpartum period (within the first 24 hours).
    - How to estimate postpartum blood loss and recognize signs and symptoms that may be indicative of shock or hemodynamic instability.
    - How to contact the midwife and access urgent care when necessary.

    Strong recommendation; no evidence available.

    This recommendation is based on expert opinion. It recognizes the skill of midwives in providing health information to clients and normalizes care provided in the community setting.

Breastfeeding following PPH

Severe PPH may be a predictor of breastfeeding difficulties. In one nested multicenter study using qualitative and quantitative survey data from 206 postpartum women who experienced PPH (≥ 1500 mL and/or peripartum Hb ≤ 70g/L), 70% of women with PPH of < 2000 mL who had planned to breastfeed were fully breastfeeding (following the WHO definition) in the first postpartum week, whereas less than 50% of those with blood loss ≥ 3000 mL reported being able to do so. (31) While 63% of women successfully breastfed from birth, 85% reported that they had intended to ($p < .001$). Approximately 50% of participants who intended to breastfeed attempted to latch their baby within 1 hour of birth. PPH > 1500 mL was associated with mother and infant separation within 1 hour of birth, and less than one third of babies were in their mother's arms within 1 hour of birth, which may have had an impact on breastfeeding success. Participants also self-reported delays in milk production after PPH. Overall, despite experiencing PPH, participants desiring to breastfeed achieved a high rate of breastfeeding initiation and duration compared to data on healthy Australian women, and much higher rates than those reported in the U.K. and U.S. However, there was a trend toward later initiation and higher rates of formula supplementation as estimated blood loss increased. (31)

Research on the impact of PPH on milk production is limited. In rare cases, difficulties with breastfeeding can be an initial symptom of absent or deficient prolactin secretion attributable to Sheehan's syndrome, a rare complication of severe PPH. (31) Sheehan's is a necrosis of the pituitary gland and can be caused by hypovolemic shock and/or vascular insult. (31,187) A major sign of Sheehan's syndrome is failure to lactate following a severe obstetric hemorrhage. Other possible postpartum signs and symptoms include amenorrhea, oligomenorrhea, weakness, fatigue, hot flashes, decreased muscle mass, or decreased libido. (31,187)

Management of the third stage of labour and breastfeeding

Some evidence suggests active management of the third stage of labour using prophylactic uterotonics may be associated with lower breastfeeding rates. (188,189) The Cardiff Births Survey assessed the impacts of prophylactic uterotonic drugs commonly given during birth on breastfeeding at 48 hours postpartum. The study found that use of oxytocin, ergometrine or both in active management was significantly associated with reduced rates of breastfeeding at 48 hours. Ergometrine used alone was associated with the greatest reduction in breastfeeding (RR 0.64, 95% CI 0.48-0.85, $p = .002$). (189)

One study of 288 women who had a vaginal birth within 6 months of the study used a self-report questionnaire to examine exposure to injectable uterotonics during the third stage of labour and breastfeeding outcomes. (188) For women who received injected prophylactic uterotonics, no association was found between infant feeding practice at birth (human milk vs formula), but overall breastfeeding rates were significantly less at 2 and 6 weeks postpartum, and study participants were more likely to report pain or difficulty as the reason for stopping breastfeeding. The authors identify a lack of evidence of association between exposure to uterotonics intrapartum and breastfeeding outcomes. (188)

SUMMARY STATEMENTS

- PPH may disrupt the opportunity for immediate skin-to-skin contact and early breastfeeding. PPH may increase the time from birth to breastfeeding initiation.
- Limited and poor-quality research suggests there may be an association between the use of prophylactic uterotonics and lower breastfeeding rates ≥ 48 hours. More research is needed on the effect of intrapartum exposure to uterotonics on breastfeeding success and duration.

Iron deficiency anemia following PPH

For clients who experience PPH, risk of anemia in the postpartum is high. (190) Since anemia can impact quality of life, assessing and treating iron deficiency anemia postpartum is an important concern after PPH. A client's risk of anemia in the postpartum will be dependent on both their prenatal iron status and the extent of blood loss. (12,191) When PPH occurs, monitoring and treating iron deficiency anemia when warranted may impact both lab values and clinically

relevant outcomes such as fatigue and quality of life for the client.

Prevalence of anemia following PPH

In a large retrospective analysis conducted in Germany (n = 40 263), 22% of postpartum women included in the study had Hb < 100 g/L and 3% had Hb values < 80 g/L in the postpartum period, irrespective of peripartum blood loss. (191) The rate of anemia (80 g/L) was 13% among women with a blood loss of 501 to 1000 mL and 43.6% for women with blood loss > 1000 mL. (191) A retrospective, multicentre study in the U.K. observed rates of postpartum anemia (Hb > 100 g/L) of 45%, 65%, and 70% for blood losses of < 500 mL, 500 to 1000 mL, and > 1000 mL, respectively. (190)

Monitoring postpartum iron levels

Clinically significant anemia is usually described as Hb < 100 g/L at 24 to 48 hours postpartum. (192,193) Some researchers suggest that due to hemodynamic change combined with blood loss during the intrapartum period, a period of at least 48 hours should be allowed to pass before assessing Hb levels. (12,192) One study suggests that if Hb is assessed between 24 and 48 hours postpartum, a lower diagnostic cutoff of < 80 g/L may be used. (191) Other authors suggest that assessment of Hb may be most reliable at 1 week postpartum, once the body has returned to pre-pregnant circulating blood volume. (12,192)

Serum ferritin values of < 15 µg/L are often considered to be highly sensitive and specific for the diagnosis of anemia during pregnancy. (190,192) However, because ferritin is an acute-phase reactant that is elevated in the presence of inflammation, and the immediate postpartum period is associated with a systemic inflammatory response, ferritin levels are likely to be artificially elevated for 1 to 6 weeks after delivery and therefore may be unreliable for diagnosing anemia during this period. (12,192,194,195) A summary of suggested criteria for the diagnosis of postpartum iron deficiency anemia is shown in Table 6.

TABLE 6: LAB VALUES FOR THE DIAGNOSIS OF POSTPARTUM IRON DEFICIENCY ANEMIA

Iron deficiency anemia diagnosis in the postpartum		
Lab Test	Value	Description
Hb	< 100 g/L	≥ 48 hours postpartum
	< 80 g/L	< 48 hours postpartum
	Note: Hb concentration should be given an opportunity to stabilize before any postpartum assessment of iron deficiency anemia. Some researchers and guideline developers suggest that at least 48 hours should pass following birth before obtaining a blood sample for Hb assessment. (12,192,196)	
Ferritin	N/A	Ferritin is an unreliable marker for assessing iron in the immediate postpartum.
	Note: Ferritin levels are likely to be artificially elevated for 1 to 6 weeks following birth. (12,192,194)	

Treatment of iron deficiency anemia following PPH

The most common approach to treating postpartum iron deficiency anemia is to recommend oral iron supplements. (197,198) Gastrointestinal side-effects and poor compliance are common barriers to effective use of oral iron for treatment of iron deficiency anemia. (193,194,198) A variety of oral iron supplements are available in Canada currently, including ferrous sulfate, ferrous gluconate, ferrous fumarate and iron-polysaccharide complexes. (193) While no primary research was found regarding an expected therapeutic response to oral iron, expert opinion suggests that an increase in Hb levels of 10 to 30g/L should be observed following 2 weeks of treatment with oral iron, and that follow-up testing of ferritin and Hb should be conducted after 12 weeks of treatment. (192,197)

A 2015 Cochrane review of treatment for postpartum iron deficiency anemia identified 22 low-quality RCTs that included 2858 women. (199) Few of the trials

included reported on the primary or secondary outcomes chosen by the reviewers: maternal mortality, fatigue, constipation and allergic reactions. The review's authors suggest that available evidence does not permit a clear conclusion about the relative efficacy of treatments for postpartum iron deficiency anemia. Also, when oral iron was compared to placebo it remains unknown whether treatment improves anemia symptoms compared to known gastrointestinal harms. Further research is needed to address clinically important outcomes. (199)

Clients in some communities may experience higher rates of nutritional deficiencies and midwives should take this into consideration when recommending or offering treatment for iron deficiency anemia after PPH. Midwives should consider the client in their wider social and cultural context, exploring underlying issues related to food security, cultural factors and nutrition as part of the informed choice discussion on iron deficiency anemia following PPH and treatment options.

Oral iron therapy versus IV iron therapy

Parenteral iron is increasingly presented as a safe and effective alternative treatment to oral iron therapy for significant postpartum anemia. (193–195,198,200) Parenteral preparations currently available in Canada include iron dextran, iron sucrose and sodium ferric gluconate. (193). The Cochrane review noted above included 10 studies (n = 1553) comparing IV and oral iron. (199) While cardiac complications and allergic reactions occurred in the IV iron group, the small number of events limit the confidence of these findings. IV iron was associated with a lower incidence of GI side-effects. (199) One trial included in the Cochrane review noted no significant difference in Hb levels between the oral iron group and the IV iron group at 8 weeks or at 12 weeks postpartum. (198)

Blood transfusion to treat postpartum iron deficiency anemia

Researchers discourage blood transfusion for postpartum women except as a life-saving measure. (193,197,201,202) Risks of blood transfusions include transmission of pathogens, transfusion reactions and allo-immunization. (193,201,202) One review suggests that blood transfusion be restricted to women with severe PPH causing hypovolemic shock, or for cases of profound anemia (Hb < 60 g/L). (197)

Research on transfusion for women with acute anemia (Hb 48-79 g/L 12-24hrs postpartum), without severe anemic symptoms or comorbidities, showed mild improvement in physical fatigue scores per day compared with a non-intervention group. (202) The authors considered the clinical significance of improvements in fatigue scores in the transfusion arm to be "negligible." At 6 weeks postpartum, concentrations of Hb were comparable between the 2 study arms, with the mean value of 121 g/L (113-126) in the transfusion arm and a mean value of 119 g/L (109-126) in the non-intervention arm (n = 261) (p = 0.18). (203)

SUMMARY STATEMENTS

- Hemoglobin values < 100 g/L should be used diagnose postpartum iron deficiency anemia, ideally at ≥ 48 hours postpartum. Serum ferritin levels are not accurate during the postpartum period to assess iron stores.
- There is little evidence on the effects of iron therapy for clinically relevant symptoms of postpartum anemia.
- Further research focused on clinically significant outcomes and adverse effects is required to best evaluate the relative efficacy of different treatment routes and regimens for postpartum iron deficiency anemia.

RECOMMENDATION:

14. Midwives should offer oral iron supplementation to clients with Hb < 100 g/L ideally measured at ≥ 48 hours postpartum, or to clients who have experienced PPH and who have signs and symptoms of iron deficiency anemia.

Weak recommendation; low-quality evidence.

This recommendation recognizes the lack of high-quality evidence on the clinical effectiveness of treating postpartum iron deficiency anemia.

Placental encapsulation for PPH

The practice of placentophagy (consuming the placenta following birth) has seen increased interest in high-resource settings in recent years. (204) Reported effects of placentophagy include prevention of postpartum depression, increased milk production and reduction of postpartum bleeding, though health benefits and risks have not been well studied in humans. (204–206) A recent literature review identified 49 articles on the topic of placentophagy published between 1950-2014; no peer reviewed empirical studies exploring the effects of human placentophagy were found. A study testing the oxytocic effects of dried sheep placenta in uterine tissue from guinea pigs, rats and cats produced inconclusive findings. (204)

SUMMARY STATEMENT

- No research was found on the effects of placentophagy as a treatment for PPH or potential PPH-related sequelae (e.g., iron deficiency anemia, postpartum depression, breastfeeding outcomes).

How does PPH affect future pregnancies?

Evidence strongly supports increased risk of PPH in the next birth after primary PPH. The incidence of PPH in a second consecutive pregnancy has been reported as 14.8 to 18%. For women who experienced PPH in 2 consecutive pregnancies, the incidence of PPH in a third pregnancy has been reported as 21.7% to 26.6%. (48,49,207)

A large population-based prospective cohort study examined the records of 538 332 primiparous women in the Swedish Medical Birth Register from 1997-2009 to develop a model for predicting risk of recurrent PPH in a subsequent pregnancy. Researchers found that risk of recurrence was highest for PPH of the same subtype as the first PPH (retained placenta, atony, lacerations, or severe), but risk was also substantially higher for PPH recurrence from any etiology (Table 7). Compared to women with no history of PPH, women with one or 2 previous PPH experienced rates of PPH that was threefold and sixfold higher, respectively. Researchers state that "PPH recurrence risk cannot be explained by known PPH risk factors." (49)

TABLE 7: PPH RECURRENCE IN VAGINAL DELIVERIES

Pregnancy history of PPH		PPH recurrence in vaginal deliveries			
		Any PPH		Recurrent PPH of same specific type	
First pregnancy	Type of previous PPH	%	RR (95%CI)	%	RR (95%CI)
No PPH		3.7	1.0		
PPH	Any	14.2	3.8 (3.6-4.0)		
	Retained placenta	18.3	4.9 (4.6-5.2)	12.0	10.4 (9.5-11.4)
	Atony	12.8	3.4 (3.2-3.7)	7.0	4.0 (3.6-4.4)
	Lacerations	12.6	3.4 (3.0-3.8)	1.7	7.8 (5.5-10.9)
	Severe (> 1000 mL)	18.8	5.0 (4.6-5.5)	4.2	9.1 (7.4-11.3)

Source: (49)

For women who had severe PPH requiring pelvic artery embolization (PAE), the risk of placenta accreta in a subsequent pregnancy is significantly higher compared to women with primary PPH who did not receive this intervention. In a cohort of 103 cases of PPH requiring PAE and 189 cases of PPH not requiring PAE, there was a significantly higher rate of placenta accreta in a subsequent pregnancy in the the PAE group (23.5 % vs. 0%,
p = .04). (208)

SUMMARY STATEMENTS

- Prior PPH significantly increases the risk for a subsequent PPH in future pregnancy.
- Approximately 1 in 7 women with a prior PPH and 1 in 4 with 2 prior PPH will experience another PPH > 1000 mL.
- Recurrence risk is highest for the same subtype of PPH, but risk is also increased for all etiologies.
- Clients who underwent pelvic artery embolization for a previous PPH are at increased risk of placenta accreta in future pregnancy.

CLIENT EXPERIENCES OF PPH

Perspectives and needs of clients and families who experienced PPH

Compared to acute clinical management of PPH, there is less information available to guide midwives in providing care to meet the physical and emotional needs of clients who are recovering from significant postpartum blood loss. (209)

There are conflicting conclusions around the likelihood of long-term emotional effects of PPH, but most research evidence points to at least some women experiencing lasting psychological effects. (31,32,210–217) Women who have had PPH may experience ongoing nightmares, fear, and anxiety. (210) In one study, 40% of participants who experienced a severe PPH had lasting psychological problems, including strong fear of recurrence that impacted family planning. (213)

Research involving women diagnosed with PPH found post-traumatic stress disorder (PTSD) rates of 5% at 2 months postpartum and 3% at 4 months postpartum, suggesting that clients who have PPH are at the high end of the normal range for PTSD in the postpartum population. (215)

A study assessing long-term psychological impacts of severe PPH found that some women reported that their partners had emotional impacts from the intrapartum and postpartum periods. (213)

Considerations for 'debriefing' clients and families following PPH

In qualitative studies, clients and their partners have reported wanting more information both during and after the PPH. (214–216) In one study, researchers noted a debriefing should include "information about what happened and, if possible, an explanation of why it happened; information about implications for future pregnancies including risk of recurrence; consideration of, and attention to, possible emotional sequelae; and strategies to assist with postpartum physical recovery." (215)

An important aspect of postpartum care for clients who have experienced PPH may be discussing the event with the client, partner and possibly others who were present at the birth, as well as offering the client an opportunity for counselling if such resources are available in the community. (210,212) For more information on Ontario midwifery client experiences of PPH, see the AOM resource: *Midwifery Client Experiences of Postpartum Hemorrhage* (209), as well as the client-directed resource: *Life after postpartum hemorrhage: Recovering from the unexpected.* (218)

Practice points for communication during and following PPH

The best practices listed in Figure 1 have the potential to lessen the negative emotional and psychological impacts of PPH. (209,219,220)

FIGURE 1: PRACTICE POINTS FOR COMMUNICATION DURING AND FOLLOWING PPH

DURING PPH

- Explain and support an informed choice process, even during an emergency.
- Manage emergency situations in a calm and skilled manner.
- Include family members in decision-making during an emergency situation.
- Provide information to reassure support people during anxious waiting.

TRANSFER IN HOSPITAL

- Provide continuity of care during transfers, if possible e.g., midwives riding in the ambulance/starting IVs.
- Advocate for clients' emotional and physical needs, e.g., have a private room away from other new families.
- Facilitate access to baby for clients who require intensive care (or vice versa).
- Facilitate client being updated with their baby's progress through photos or regular updates if they cannot be with them.
- Support breastfeeding, or breast milk expression, even if clients are in intensive care.
- Keep baby skin-to-skin during the management of PPH, if possible.

COMMUNICATION

- Ensure good communication with all health professionals involved during the emergency.
- Help clients and families understand what is happening.
- Ensure good communication afterwards to help clients make sense of the experience.

FOLLOW-UP

- Offer the client and support people the opportunity to discuss the events of their birth, and review their charts/clinical notes. Flexible timing for these meetings is important—some clients are ready before others.

POSTNATAL SUPPORT

- Advocate for support from client's primary care team after discharge. The ability to debrief and check in is important as clients recover and get back to normal life.
- Offer or refer for counseling to address long-lasting mental health impacts.

SUMMARY OF RECOMMENDATIONS

1. Midwives should consider any significant postpartum loss of blood that causes signs and symptoms of hypovolemic shock or hemodynamic instability to be a postpartum hemorrhage.

   Strong recommendation; no evidence available.

2. Midwives should continue to visually estimate and document postpartum blood loss.

   Weak recommendation; no evidence available.

   These recommendations recognize that effects of blood loss vary by individual and support individualized care. They recognize midwives' ability to assess effects of blood loss and the need for timely decision-making. Documentation of blood loss permits retrospective assessment and informs immediate and ongoing client care. Accurate blood loss estimation contributes to midwifery data collection and research.

3. Identification of risk factors for PPH should occur in an ongoing manner throughout the course of antenatal and intrapartum care. Midwives should consider risk factors in an informed choice discussion about options for management of the third stage of labour and choice of birthplace.

   Strong recommendation; moderate-quality evidence.

   This recommendation recognizes continuity of care and the ability of the midwife to identify emerging risk factors for PPH.

4. The risks and benefits of physiologic management compared with active management should be discussed with all clients as part of an informed choice discussion. This discussion should address:

   - how risk factors, if present, may increase the client's risk of PPH and impact considerations about choice of birth place; and
   - the client's values and preferences.

   This discussion, including the client's choice, should be appropriately documented in the client's chart.

   Strong recommendation; low-quality evidence.

   This recommendation recognizes the client as the primary decision-maker. This recommendation recognizes that presence of one or more risk factors is not necessarily predictive of PPH, and that the original trials of active management may be interpreted differently in a low-risk population.

5. When active management is chosen for the prevention of PPH, midwives should:

   - Use oxytocin as the uterotonic.
   - Once pulsation stops, clamp and cut the cord.
   - Use controlled cord traction to deliver the placenta.

   Strong recommendation; moderate-quality evidence.

   This recommendation recognizes a large body of research recognizing the effectiveness of oxytocin at preventing blood loss with minimal side-effects compared to other uterotonics for active management, the neonatal benefits of delayed cord clamping, and the modest clinical benefit of controlled cord traction.

6. When physiologic management is chosen, midwives should:

   - Await signs of placental separation and monitor for excessive blood loss.
   - Refrain from clamping or cutting the umbilical cord until pulsation stops or the placenta has delivered.
   - Allow the placenta to be born spontaneously with maternal effort or gravity.
   - Encourage immediate skin-to-skin contact with infant, early breastfeeding and other measures that may encourage the release and uptake of oxytocin.

   Strong recommendation; low-quality evidence.

   This recommendation recognizes the physiology of normal birth. More research is needed to identify the most effective aspects of physiologic care in the third stage of labour.

7. Midwives may offer controlled cord traction to clients choosing physiologic management.

   Weak recommendation; very low-quality evidence

   This recommendation recognizes observational data that associates a reduction in PPH > 700 mL with the use of controlled cord traction without a prophylactic uterotonic as well as randomized trials that show a slight reduction in blood loss > 500 mL, duration of the third stage, and manual removal of the placenta with use of controlled cord traction during active management of the third stage.

8. Uterine massage is not recommended for the prevention of PPH. Postpartum assessment of fundal tone is recommended.

   Strong recommendation; low-quality evidence.

   This recommendation recognizes the importance of identifying uterine atony. Available research does not support the routine use of uterine massage after prophylactic oxytocin has been administered. There is no evidence available on the use of uterine massage where no prophylactic uterotonic has been administered.

9. Midwives should use oxytocin as the first line uterotonic for the treatment of PPH due to uterine atony.

   Strong recommendation; moderate-quality evidence.

   No high-quality research has shown superior efficacy of any uterotonic drug vs oxytocin in settings where it is available. The CMO requires that midwives carry at least 2 uterotonics: oxytocin plus 1 additional drug. The comparative effectiveness of uterotonics for treatment of PPH is identified as a research gap.

10. Available research does not clearly support the use of one particular uterotonic over another for second-line treatment of primary PPH due to uterine atony (ergot alkaloids, prostaglandins and carbetocin). Midwives should choose their second-line uterotonic based on clinical context.

    Strong recommendation; very low-quality evidence.

    Access to each drug may vary by community. In the absence of clear evidence, midwives should use their clinical experience, community standards, and the clinical context of the client and birth to guide second-line uterotonic use.

11. Midwives should consider the use of uterine balloon tamponade for PPH that is unresponsive to uterotonics, and where transport to hospital is necessary.

    Weak recommendation; very low-quality evidence.

    This recommendation recognizes the growing body of literature supporting the use of UBT at all care levels and for all obstetric providers. It acknowledges that midwives attend births in the community and that use of UBT for intractable uterine atony is a potentially life-saving measure. It also recognizes the need for midwives to access the training and equipment needed to safely and effectively use UBT devices, when appropriate, for PPH unresponsive to other interventions.

12. For clients who refuse blood and blood products, midwives should discuss possible increased risks of morbidity and mortality following severe PPH. Midwives should develop or facilitate a plan of care in the event of severe PPH, where blood or blood products would normally be recommended.

    Strong recommendation; very low-quality evidence.

    This recommendation recognizes the degree of potential risk for clients who refuse blood products. It also values the importance of respectful care and interprofessional collaboration to provide client access to options available in the community.

13. Midwives should review with all clients:

    - Normal postpartum blood loss in the immediate postpartum period (within the first 24 hours).
    - How to estimate postpartum blood loss and recognize signs and symptoms that may be indicative of shock or hemodynamic instability.
    - How to contact the midwife and access urgent care when necessary**.**

    Strong recommendation; no evidence available.

    This recommendation is based on expert opinion. It recognizes the skill of midwives in providing health information to clients and normalizes care provided in the community setting.

14. Midwives should offer oral iron supplementation to clients with Hb < 100 g/L ideally measured at ≥ 48 hours postpartum, or to clients who have experienced PPH and who have signs and symptoms of iron deficiency anemia. Normal postpartum blood loss in the immediate postpartum period (within the first 24 hours).

    Weak recommendation; low-quality evidence.

    This recommendation recognizes the lack of high-quality evidence on the clinical effectiveness of treating postpartum iron deficiency anemia.

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APPENDICES

APPENDIX A: DEFINITIONS OF PPH USED IN GUIDELINES

SOURCE	
"Traditional" definition	Blood loss > 500 mL after vaginal delivery Blood loss > 1000 mL after caesarean section
Society of Obstetricians and Gynaecologists of Canada (7)	"Clinically, any blood loss that has the potential to produce hemodynamic instability should be considered PPH. The amount of blood loss required…will depend on the pre-existing condition of the woman."
World Health Organization (19)	Blood loss ≥ 500 mL within 24 hours of birth Severe PPH: Blood loss ≥ 1000 mL within 24 hours of birth
Royal College of Obstetricians and Gynaecologists (U.K.) (10)	Minor: blood loss 500-1000 mL without signs of clinical shock Major: blood loss > 1000 mL with signs of clinical shock or continued bleeding
American College of Obstetrics and Gynecology (221)	"There is no single, satisfactory definition of postpartum hemorrhage."
Expert panel, 2011 (11)	"Persistent (ongoing) PPH is active bleeding > 1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage."
Varney's Midwifery (222)	"In clinical practice, postpartum hemorrhage is a subjective assessment of an estimated blood loss that threatens hemodynamic stability." PPH categorized as compensated, mild, moderate and severe depending on the amount of blood loss and signs of its consequences.
Myles Textbook for Midwives (223)	"…Any blood loss, however small, that adversely effects the mother's condition constitutes a PPH… In addition, if the measured loss reaches 500 mL, it must be treated as a PPH, irrespective of maternal condition."
Secondary PPH (21)	"any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally";"after five days post-delivery, the use of more than five pads a day";"increased bleeding after bleeding had decreased or stopped";"any increase in use of pads by two or more after it was less or none";"passing fresh or clotted blood more than 3 days postpartum"

APPENDIX B: WHO RECOMMENDATIONS FOR PREVENTION AND TREATMENT OF PPH (2012)

1. The use of uterotonics for the prevention of PPH during the third stage of labour is recommended for all births. (Strong recommendation, moderate-quality evidence)

2. Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH. (Strong recommendation, moderate-quality evidence)

3. In settings where oxytocin is unavailable, the use of other injectable uterotonics (if appropriate ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol (600 µg) is recommended. (Strong recommendation, moderate-quality evidence)

4. In settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 µg PO) by community health care workers and lay health workers is recommended for the prevention of PPH. (Strong recommendation, moderate-quality evidence)

5. In settings where skilled birth attendants are available, CCT is recommended for vaginal births if the care provider and the parturient woman regard a small reduction in blood loss and a small reduction in the duration of the third stage of labour as important (Weak recommendation, high-quality evidence)

6. In settings where skilled birth attendants are unavailable, CCT is not recommended. (Strong recommendation, moderate-quality evidence)

7. Late cord clamping (performed after 1 to 3 minutes after birth) is recommended for all births while initiating simultaneous essential newborn care. (Strong recommendation, moderate-quality evidence)

8. Early cord clamping (<1 minute after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation. (Strong recommendation, moderate-quality evidence)

9. Sustained uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin. (Weak recommendation, low-quality evidence)

10. Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women. (Strong recommendation, very-low-quality evidence)

11. Oxytocin (IV or IM) is the recommended uterotonic drug for the prevention of PPH in caesarean section. (Strong recommendation, moderate-quality evidence)

12. Controlled cord traction is the recommended method for removal of the placenta in caesarean section. (Strong recommendation, moderate-quality evidence)

13. Intravenous oxytocin alone is the recommended uterotonic drug for the treatment of PPH. (Strong recommendation, moderate-quality evidence)

14. If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed dose, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended. (Strong recommendation, low-quality evidence)

15. The use of isotonic crystalloids is recommended in preference to the use of colloids for the initial intravenous fluid resuscitation of women with PPH. (Strong recommendation, low-quality evidence)

16. The use of tranexamic acid is recommended for the treatment of PPH if oxytocin and other uterotonics fail to stop bleeding or if it is thought that the bleeding may be partly due to trauma. (Weak recommendation, moderate-quality evidence)

17. Uterine massage is recommended for the treatment of PPH. (Strong recommendation, very low-quality evidence)

18. If women do not respond to treatment using uterotonics, or if uterotonics are unavailable, the use of intrauterine balloon tamponade is recommended for the treatment of PPH due to uterine atony. (Weak recommendation, very-low-quality evidence)

19. If other measures have failed and if the necessary resources are available, the use of uterine artery embolization is recommended as a treatment for PPH due to uterine atony. (Weak recommendation, very-low-quality evidence)

20. If bleeding does not stop in spite of treatment using uterotonics and other available conservative interventions (e.g. uterine massage, balloon tamponade), the use of surgical interventions is recommended. (Strong recommendation, very-low-quality evidence)

21. The use of bimanual uterine compression is recommended as a temporizing measure until appropriate care is available for the treatment of PPH due to uterine atony after vaginal delivery. (Weak recommendation, very-low-quality evidence)

22. The use of external aortic compression for the treatment of PPH due to uterine atony after vaginal birth is recommended as a temporizing measure until appropriate care is available. (Weak recommendation, very-low-quality evidence)

23. The use of non-pneumatic anti-shock garments is recommended as a temporizing measure until appropriate care is available. (Weak recommendation, low-quality evidence)

24. The use of uterine packing is not recommended for the treatment of PPH due to uterine atony after vaginal birth. (Weak recommendation, very-low-quality evidence)

25. If the placenta is not expelled spontaneously, the use of IV/IM oxytocin (10 IU) in combination with controlled cord traction is recommended. (Weak recommendation, very-low-quality evidence)

26. The use of ergometrine for the management of retained placenta is not recommended as this may cause tetanic uterine contractions which may delay the expulsion of the placenta. (Weak recommendation, very-low-quality evidence)

27. The use of prostaglandin E2 alpha (dinoprostone or sulprostone) for the management of retained placenta is not recommended. (Weak recommendation, very-low-quality evidence)

28. A single dose of antibiotics (ampicillin or first-generation cephalosporin) is recommended if manual removal of the placenta is practised. (Weak recommendation, very-low-quality evidence)

Source: (19)

APPENDIX C: DRUGS IN THE MIDWIFERY PHARMACOPEIA FOR MANAGEMENT OF PPH

The choice of the most appropriate uterotonic drug will depend on evaluation of risks and benefits of the following (224):

1. Complications associated with and likelihood of excessive blood loss.
2. Maternal morbidity associated with side-effects of uterotonic.
3. The resources of the setting and community standards.
4. Clinical circumstances (i.e. suspected or confirmed low-lying placenta, if hemorrhage is occurring with the placenta delivered or not, presence of hypertension, etc.).

	Dose	Route	Onset of action	Maximum Dose
Oxytocin	10 IU	IM	• IM: 2 to 3 minutes • IV: instantaneous • duration: approximately 60 minutes • Half-life: 3 minutes (225)	• Not more than 3 L of IV fluids containing oxytocin (19)
First line drug for PPH	5-10 IU	IV (by slow injection over 1-2 minutes)*		
	20-40 IU in 1000 mL crystalloid solution	IV infusion Initially wide open and then dosage adjusted according to response (225)		
Mechanism of action	• Acts on oxytocin receptors of smooth muscle to stimulate the upper uterine segment to contract rhythmically. (225) • Response depends on threshold of excitability. (225,226)			
Side-effects	• Water intoxication with large volumes, prolonged infusion (headache, nausea and vomiting, abdominal pain, lethargy, drowsiness, unconsciousness, grand mal type seizures). • Hypotension, tachycardia, ECG changes (following rapid IV administration of concentrated solutions). (225,226)			
Contraindications	N/A			
Other notes	* Rapid IV bolus of undiluted oxytocin may result in relaxation of vascular smooth muscle leading to hypotension (227), so slow push IV is recommended, over 1 to 2 minutes. (228)			

	Dose	Route	Onset of action	Max Dose
Ergonovine maleate **Second or third line drug for PPH due to uterine atony (if no contra-indications)**	0.2 or 0.25 mg	IM (preferred) or IV *(Compendium of Pharmaceuticals and Specialties* recommends diluting IV doses with 5 mL normal saline and to give over 1 minute) (226)	• IM: 2 to 5 minutes, lasting 3 hours • IV: 1 minute IV, lasting 45 minutes • Half-life: 30 minutes • (225,226)	Can be repeated q 2 hours (228)
Mechanism of action	• Stimulates contractions of uterine and vascular smooth muscle (vasoconstrictor). (226) • Administration of ergonovine results in a sustained tonic uterine contraction by stimulating the myometrial α-adrenergic receptors: both upper and lower uterine segments are stimulated to contract (229)			
Side-effects	• Nausea and vomiting, hypertension, diarrhea, dizziness, abdominal pain. (226)			
Contraindications	• Preeclampsia, eclampsia or hypertension (226) • If client is using certain drugs used to treat HIV (protease inhibitors, non-nucleoside reverse transcriptase inhibitors. (230)			
Other notes	• Ergonovine maleate is a naturally occurring ergoline derivative; from a fungus that contaminates rye and wheat. (224) • Methylergonovine is a synthetic analogue of ergonovine. (231) • Ergonovine maleate is considered second choice to oxytocin (from research on prevention of PPH and extrapolated to treatment of PPH) due to increased risk of maternal side-effects and possible increased incidence of need for manual removal of the placenta. (228) This recommendation comes despite research showing that a combination of oxytocin and ergonovine (syntometrine) has decreased risk of PPH (OR 0.82, 95% CI 0.71-0.95) compared to oxytocin alone. (232) • Inconsistent evidence exists with regards to the risk of retained placenta with use of ergot alkaloids compared with no use of uterotonics. A Cochrane review identified 2 studies examining this risk, one study found a weak association between use of ergot alkaloids and retained placenta, whereas the other study did not. (233) Another Cochrane review comparing the risks of retained placenta when ergonovine was used compared with other uterotonics found no difference in rates of manual removal (232) • Storage and stability: must be refrigerated (2°C to 8°C). Protect from light. (226)			

	Dose	Route	Onset of action	Max Dose
Carboprost tromethamine (Hemabate) **Second or third line drug for PPH (or if other drugs are unavailable or contraindicated)**	0.25 mg	IM, intramyometrial (IMM)	• IM: peak plasma concentration at 15 minutes • IMM: peak plasma concentration at 5 minutes (225)	May be repeated q 15 minutes, up to a maximum dose of 2 mg (8 doses) (226)
Mechanism of action	• Carboprost tromethamine is a synthetic 15-methyl analogue of $PGF_2\alpha$, a prostaglandin and a potent stimulator of myometrial contractility. (234) • Prostaglandins have vasoactive effects and affect platelet function. (226) • Carboprost is a smooth muscle stimulant and stimulates the GI tract (which may cause vomiting and diarrhea). (226)			
Side-effects	• Nausea, vomiting, diarrhea, abdominal pain, pyrexia, bronchospasm. (225,235)			
Contraindications	• Asthma			
Other notes	• Carboprost should be considered as a second or third-line uterotonic agent in management of PPH due to uterine atony, which has been unresponsive to oxytocin and ergonovine (if there are not contraindications for use). (225,235) • Storage: keep refrigerated (between 2˚C to 8˚C) (226)			

	Dose	Route	Onset of action	Max Dose
Misoprostol **Second or third line drug for PPH (or if other drugs are unavailable or contra-indicated)**	200-400 µg *	PO or SL	Faster onset PO duration: ~2 h SL duration: ~3 h	Do not exceed 800 µg (19)
	400-800 µg **	PR	Longer onset PR duration: ~4 h (236)	
Mechanism of action	• Synthetic prostaglandin E1 analogue. Interacts with prostanoid receptors on uterus causing uterine contraction. (237) • May be administered orally, sublingually, vaginally or rectally, but vaginal route not recommended for treatment of active PPH, as tablets may be expelled with blood. • The rectal route has a longer duration and slower onset, compared with faster onset and shorter duration of effect with oral or SL routes. (228)			
Side-effects	• Pyrexia (most common), chills (32%-57% women), nausea and vomiting (usually resolves within 2-6 hours), diarrhea (usually resolves in 1 day) (238) • Side-effects increase with dose. (239) • Pyrexia more common in oral doses exceeding 600 µg. (239,240)			
Contraindications	N/A			
Other notes	* The SOGC CPG recommends a dose of 600-800 µg PO or SL ** The SOGC recommends a dose of 800-1000 µg PR • Most trials have examined use of misoprostol for prevention, rather than treatment of active PPH. The dose that has been most commonly used in prevention trials is an oral dose of 600 µg. Meta-analysis of direct and adjusted indirect comparisons of 400 µg to 600 µg doses suggest that 400 µg dose has similar efficacy and fewer side-effects. (239) For this reason, lower dosages were recommended for use in this manual. • Off-label use: misoprostol is not approved by Health Canada for treatment of PPH (registered for the prevention and treatment of gastric ulcers). (226,228) • Due to limited evidence showing the safety and efficacy of misoprostol for treatment of PPH, WHO recommends that health-care providers continue to use all available standard methods for PPH treatment first and to use misoprostol when other methods are not available or have failed. (238) • No evidence was found contraindicating use of misoprostol to manage PPH following vaginal birth after caesarean, and it is thought to be safe for use as an induction agent for termination of pregnancy in women with a history of one previous CS. (241) The risk of uterine rupture associated with use of misoprostol in the postpartum periods is likely minimal as the uterus is not distended and the lower uterine segment is not as thin the intrapartum or prenatal period. • Misoprostol may be used following acute PPH to ensure ongoing uterine tone over the early postpartum period. • Storage and stability: Inexpensive, stable at room temperature.			

	Dose	Route	Onset of action	Max Dose
Carbetocin **Third line drug for PPH (or if other drugs are unavailable or contraindicated)**	100 µg	IM IV (over 1 minute (228)	2 minutes IM Half-life: 30 to 60 min (4-8 times longer than oxytocin) (242)	Single dose
Mechanism of action	• Long-acting synthetic oxytocin analogue, stimulates rhythmic contractions of the uterus (243). Produces tetanic contractions that last for 11 minutes, followed by rhythmic contractions for 2 hours when given IM. (242)			
Side-effects	• Feeling of warmth, headache, nausea and vomiting, hypotension, flushing, pruritis. (243)			
Contraindications	N/A			
Other notes	• Carbetocin has not been well studied in trials to date. Studies have focused on use for prevention of PPH, largely in women undergoing elective CS. Minimal research evidence has been accumulated to date on the use of this oxytocin analogue following vaginal birth. (242) • Carbetocin has been compared favourably with ergonovine and oxytocin, for use in the prevention of PPH. (224) • A Cochrane review concluded that there is insufficient evidence that carbetocin is as effective as other uterotonics in preventing PPH and should not be used as a first-line agent before other uterotonic agents. (242) • Theoretically, carbetocin should be more potent and longer acting than oxytocin, however, it has not yet been shown to be preferable to other uterotonics. More research is needed. (243) • Storage and stability: keep refrigerated (between 2°C to 8°C). (226)			