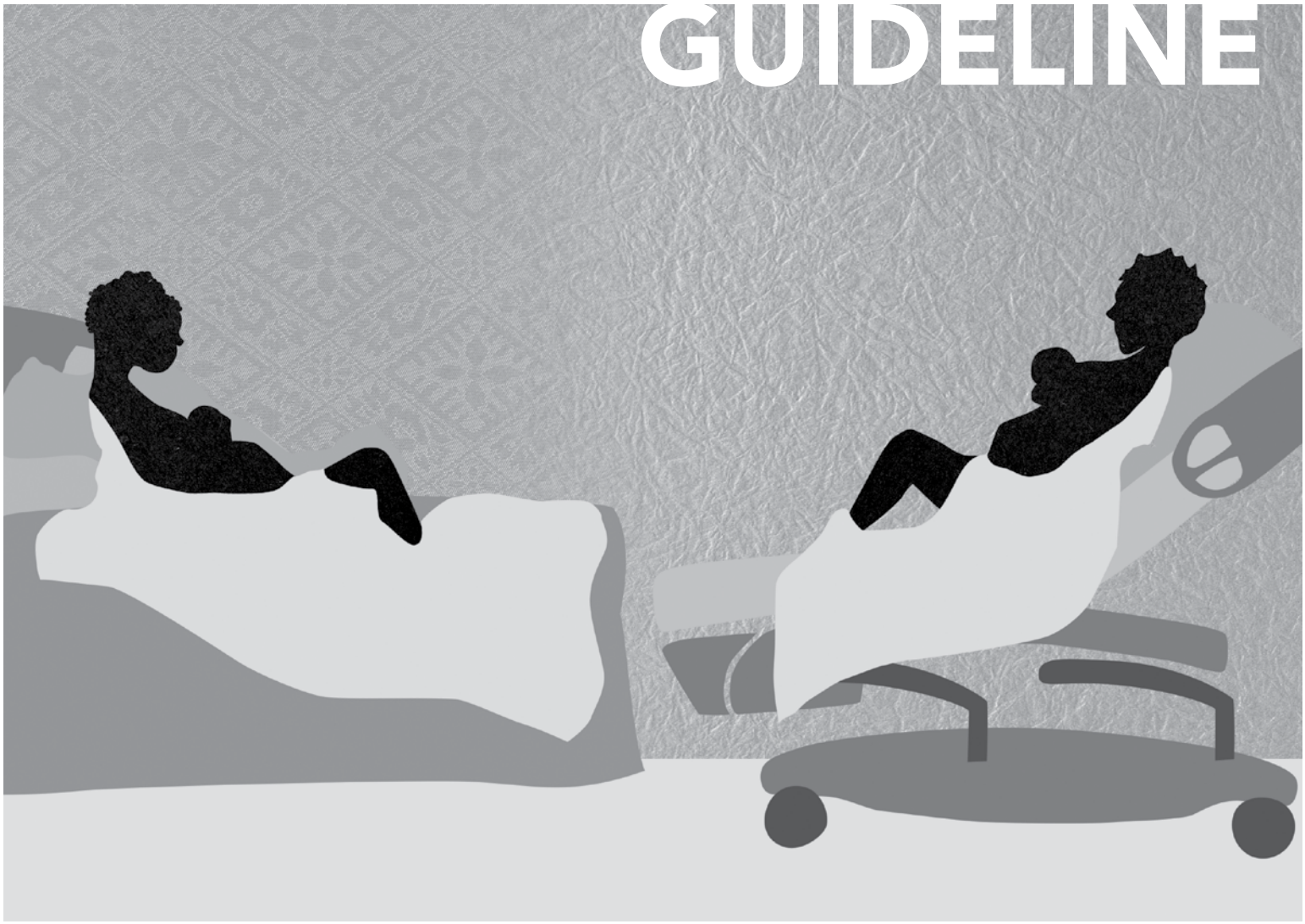
CLINICAL PRACTICE GUIDELINE 17



POSTPARTUM HEMORRHAGE

Association of Ontario Midwives
Delivering what matters.

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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.

TABLE OF CONTENTS

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 at the end of this document. 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)			

GRADE TABLES: Postpartum Hemorrhage

Contents

GRADE Table 1

Active vs expectant management for the prevention of PPH

Question: Should active vs expectant management be used for the prevention of PPH?1

Settings: midwifery units, UK and Ireland

Bibliography: Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990;6(1):3-17. [PubMed: 2182978] Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ 1988;297(6659):1295-300. [PubMed: 3144366] Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351(9104):693-9. [PubMed: 9504513]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Expectant management	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation / collection[2])												
3	randomised trials	very serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	29/2299 (1.3%)	57/2337 (2.4%)	0.34 (0.14 to 0.87)	16 fewer per 1000 (from 3 fewer to 21 fewer)	⊕⊕OO LOW	CRITICAL
								2.6%		17 fewer per 1000 (from 3 fewer to 22 fewer)		
Maternal blood transfusion												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	20/1654 (1.2%)	51/1663 (3.1%)	RR 0.39 (0.24 to 0.66)	19 fewer per 1000 (from 10 fewer to 23 fewer)	⊕⊕OO LOW	CRITICAL
								0.4%		2 fewer per 1000 (from 1 fewer to 3 fewer)		
Manual removal of the placenta												
3	randomised trials	very serious[3]	serious[6]	no serious indirectness	very serious	none	50/2299 (2.2%)	36/2334 (1.5%)	RR 1.76 (0.49 to 6.26)	12 more per 1000 (from 8 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
								1.7%		13 more per 1000 (from 9 fewer to 89 more)		
Blood loss >500mL												
3	randomised	very	no serious	no serious	no serious	none	115/2299	338/2337	RR 0.34	95 fewer per 1000	⊕⊕OO	IMPORTANT

	trials	serious[3]	inconsistency	indirectness	imprecision		(5%)	(14.5%)	(0.27 to 0.44)	(from 81 fewer to 106 fewer)	LOW	
								16.5%		109 fewer per 1000 (from 92 fewer to 120 fewer)		
Mean maternal postpartum Hb, g/L (Better indicated by lower values)												
3	randomised trials	serious[3]	no serious inconsistency[7]	no serious indirectness	no serious imprecision	none	2005	2057	-	MD 5.33 higher (4.78 to 5.87 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Maternal Hb <90-100g/L at 24-48h postpartum												
2[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	134/1387 (9.7%)	255/1345 (19%)	RR 0.53 (0.44 to 0.64)	89 fewer per 1000 (from 68 fewer to 106 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								18.3%		86 fewer per 1000 (from 66 fewer to 102 fewer)		
Therapeutic uterotonic during third stage (or within 24h)												
3	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/2299 (4%)	506/2337 (21.7%)	RR 0.18 (0.14 to 0.23)	178 fewer per 1000 (from 167 fewer to 186 fewer)	⊕⊕OO LOW	IMPORTANT
								21.1%		173 fewer per 1000 (from 162 fewer to 181 fewer)		
dBP >100mmHg between birth and discharge												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	32/2299 (1.4%)	9/2337 (0.39%)	RR 4.1 (1.63 to 10.3)	12 more per 1000 (from 2 more to 36 more)	⊕⊕OO LOW	IMPORTANT
								0.7%		22 more per 1000 (from 4 more to 65 more)		
Vomiting between birth and discharge												
3	randomised trials	serious[3]	serious[6]	no serious indirectness	serious[9]	none	161/2299 (7%)	72/2337 (3.1%)	RR 2.47 (1.36 to 4.48)	45 more per 1000 (from 11 more to 107 more)	⊕OOO VERY LOW	IMPORTANT
								2.2%		32 more per 1000 (from 8 more to 77 more)		
Nausea between birth and discharge												

2[10]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	very serious[9]	none	106/1453 (7.3%)	45/1488 (3%)	RR 6.86 (0.28 to 170.17)	177 more per 1000 (from 22 fewer to 1000 more)	⊕OOO VERY LOW	
								3%		176 more per 1000 (from 22 fewer to 1000 more)		
Headache between birth and discharge												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[9]	none	21/2299 (0.9%)	11/2337 (0.5%)	RR 1.8 (0.87 to 3.72)	4 more per 1000 (from 1 fewer to 13 more)	⊕⊕OO LOW	IMPORTANT
								0.4%		3 more per 1000 (from 1 fewer to 11 more)		
Admission to NICU/special care nursery												
2[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/1594 (4.3%)	84/1613 (5.2%)	RR 0.81 (0.6 to 1.11)	10 fewer per 1000 (from 21 fewer to 6 more)	⊕⊕⊕O MODERATE	IMPORTANT
								5.1%		10 fewer per 1000 (from 20 fewer to 6 more)		
Neonatal jaundice requiring phototherapy or exchange transfusion												
2[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/1562 (4.5%)	78/1580 (4.9%)	RR 0.96 (0.55 to 1.68)	2 fewer per 1000 (from 22 fewer to 34 more)	⊕⊕⊕O MODERATE	IMPORTANT
								4.8%		2 fewer per 1000 (from 22 fewer to 33 more)		
Apgar score <7 at 5 minutes												
1[11]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/846 (0.95%)	8/849 (0.94%)	RR 1 (0.38 to 2.66)	0 fewer per 1000 (from 6 fewer to 16 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0.9%		0 fewer per 1000 (from 6 fewer to 15 more)		
Infant breastfeeding at discharge												
2[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1179/1594 (74%)	1186/1613 (73.5%)	RR 1.01 (0.97 to 1.05)	7 more per 1000 (from 22 fewer to 37 more)	⊕⊕⊕O MODERATE	IMPORTANT
								73.5%		7 more per 1000 (from 22 fewer to 37 more)		

[1] Active management as defined in study protocol: Begley: ergometrine 0.5mg IV immediately after delivery; clamp cord within 30s; CCT once uterus contracted. Prendiville: 5IU oxytocin + 0.5mg ergometrine or 10IU oxytocin immediately after delivery of anterior shoulder; clamp cord within 30s; CCT once uterus contracted. Rogers: administration of prophylactic uterotonic (drug/dose not specified) as soon as possible after delivery of anterior shoulder (within 2m of birth); clamp and cut cord immediately; deliver placenta by CCT or maternal effort.
[2] Begley: blood collected in basin and measured by attending midwife; Prendiville/Rogers: blood loss estimated by attending midwife.
[3] As blinding was not possible, the assessment of many outcomes (particularly subjectively assessed outcomes such as blood loss) could have been influenced by bias. Knowledge of study arm allocation may have also influenced study midwives' decisions to proceed with manual removal of the placenta or administer additional uterotonics. High rates of non-adherence to allocated intervention in expectant management arms of some studies - Prendiville: 47% got full physiologic management package/Rogers: 64% got full expectant management. Prendiville: initial survey of participating midwives (Harding 1989) suggested that participating midwives were largely unfamiliar with physiologic management (only 1/49 survey respondents said they had previously provided third stage care consistent with the study's physiologic management protocol). Cochrane review authors 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. Prendiville: study protocol was modified after 5 months due to higher than anticipated blood loss in physiologic management arm, with a disproportionate amount of hemorrhages occuring in cases in which physiologic management may not have been advisable, leading the study's data monitoring committee to suggest additional exclusion criteria for participation in the study.
[4] Some variation in treatment effects across studies. Potentially attributable to clinical heterogeneity (Begley/Rogers studies included women at low risk of bleeding; Prendiville study initially included women irrespective of risk of bleeding). I^2=60%.
[5] Wide CIs due to small number of events.
[6] Significant heterogeneity across studies.
[7] Statistical measures suggest significant heterogeneity across studies, but likely of very limited clinical significance.
[8] Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ 1988;297(6659):1295-300. [PubMed: 3144366] Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351(9104):693-9. [PubMed: 9504513]
[9] Wide CI noted in Begley trial.
[10] Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990;6(1):3-17. [PubMed: 2182978] Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351(9104):693-9. [PubMed: 9504513]
[11] Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. BMJ 1988;297(6659):1295-300. [PubMed: 3144366]

GRADE Table 1a

Active vs expectant management for the prevention of PPH (women at low risk of PPH)

Question: Should active vs expectant management be used for the prevention of PPH (women at low risk of PPH)?[1,2]

Settings: Midwifery units, UK and Ireland

Bibliography: Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990;6(1):3-17. [PubMed: 2182978] Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351(9104):693-9. [PubMed: 9504513]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Expectant management	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation/collection[3])												
2	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	14/1453 (1%)	31/1488 (2.1%)	RR 0.31 (0.05 to 2.17)	14 fewer per 1000 (from 20 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
								2.6%		18 fewer per 1000 (from 25 fewer to 30 more)		
Maternal blood transfusion												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	2/808 (0.2%)	3/814 (0.4%)	RR 0.69 (0.1 to 4.56)	1 fewer per 1000 (from 3 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
								0.4%		1 fewer per 1000 (from 4 fewer to 14 more)		
Manual removal of the placenta												
2	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[7]	none	34/1453 (2.3%)	14/1488 (0.9%)	RR 4.19 (0.21 to 85.04)	30 more per 1000 (from 7 fewer to 791 more)	⊕OOO VERY LOW	CRITICAL
								1.7%		54 more per 1000 (from 13 fewer to 1000 more)		
Blood loss >500mL (assessed with: visual estimation/collection[3])												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/1453 (4.5%)	186/1488 (12.5%)	RR 0.33 (0.2 to 0.56)	84 fewer per 1000 (from 55 fewer to 100 fewer)	⊕⊕⊕O MODERATE	
								16.5%		111 fewer per 1000		

										(from 73 fewer to 132 fewer)		
Mean maternal postpartum Hb, g/L (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1320	1363	-	MD 5 higher (4.91 to 5.09 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Maternal Hb <90-100g/L at 24-48h postpartum												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	107/702 (15.2%)	204/718 (28.4%)	RR 0.54 (0.44 to 0.66)	131 fewer per 1000 (from 97 fewer to 159 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								18.3%		84 fewer per 1000 (from 62 fewer to 102 fewer)		
Therapeutic uterotonic during third stage (or within 24h)												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/1453 (2.6%)	254/1488 (17.1%)	RR 0.15 (0.11 to 0.21)	145 fewer per 1000 (from 135 fewer to 152 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								21.1%		179 fewer per 1000 (from 167 fewer to 188 fewer)		
dBP >100mmHg between birth and discharge												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	15/1453 (1%)	1/1488 (0.1%)	RR 9.26 (1.7 to 50.51)	6 more per 1000 (from 0 more to 33 more)	⊕⊕OO LOW	IMPORTANT
								0.1%		8 more per 1000 (from 1 more to 50 more)		
Vomiting between birth and discharge												
2	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[7]	none	59/1453 (4.1%)	17/1488 (1.1%)	RR 5.63 (0.69 to 46.08)	53 more per 1000 (from 4 fewer to 515 more)	⊕⊕OO LOW	IMPORTANT
								2.2%		102 more per 1000 (from 7 fewer to 992 more)		
Nausea between birth and discharge												
2	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[7]	none	106/1453 (7.3%)	45/1488 (3%)	RR 6.86 (0.28 to 170.17)	177 more per 1000 (from 22 fewer to 1000 more)	⊕⊕OO LOW	IMPORTANT
								3%		176 more per 1000 (from 22 fewer to 1000		

										more)		
Headache between birth and discharge												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	8/1453 (0.6%)	3/1488 (0.2%)	RR 2.23 (0.62 to 8.08)	2 more per 1000 (from 1 fewer to 14 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0.4%		5 more per 1000 (from 2 fewer to 28 more)		
Admission to NICU/special care nursery												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/748 (2.7%)	20/764 (2.6%)	RR 1.02 (0.55 to 1.88)	1 more per 1000 (from 12 fewer to 23 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								5.1%		1 more per 1000 (from 23 fewer to 45 more)		
Neonatal jaundice requiring phototherapy or exchange transfusion												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/716 (4.5%)	25/731 (3.4%)	RR 1.31 (0.78 to 2.18)	11 more per 1000 (from 8 fewer to 40 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								4.8%		15 more per 1000 (from 11 fewer to 57 more)		
Infant breastfeeding at discharge												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	542/748 (72.5%)	554/764 (72.5%)	RR 1 (0.94 to 1.06)	0 fewer per 1000 (from 44 fewer to 44 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								73.5%		0 fewer per 1000 (from 44 fewer to 44 more)		

[1] Active management as described in study protocol: Begley: ergometrine 0.5mg IV immediately after delivery; clamp cord within 30s; CCT once uterus contracted. Rogers: administration of prophylactic uterotonic (drug/dose not specified) as soon as possible after delivery of anterior shoulder (within 2m of birth); clamp and cut cord immediately; deliver placenta by CCT or maternal effort.

[2] Expectant/physiologic management as described in study protocol: Begley: No routine uterotonic; leave cord attached until pulsation ceases; encourage immediate breastfeeding; upright posture and pushing encouraged after signs of placental seperation; deliver placenta by maternal effort of gentle CCT. Rogers: No routine uterotonic; leave cord unclpaed until pulsation ceased; delivery of placenta by maternal effort.

[3] Begley: blood collected in basin and measured by attending midwife; Rogers: blood loss estimated by attending midwife.

[4] As blinding was not possible, the assessment of many outcomes (particularly subjectively assessed outcomes such as blood loss) could have been influenced by bias. Knowledge of study arm allocation may have also influenced study midwives' decisions to proceed with manual removal of the placenta or administer additional uterotonics. High rates of non-adherence to allocated intervention in expectant management arms of some studies - Rogers: 64% got full expectant management.

[5] Variable estimates of treatment effect.

[6] Wide CIs due to small number of events.

[7] Wide confidence interval in Begley trial.

[8] Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. Lancet 1998;351(9104):693-9. [PubMed: 9504513]

GRADE Table 2a

Active vs mixed management (expectant with immediate cord clamping) for the prevention of PPH

Should active vs mixed management (expectant w/ immediate cord clamping) be used for the prevention of PPH?

Author(s):
Date: 2013-08-13
Question: Should active vs mixed management (expectant w/ immediate cord clamping) be used for the prevention of PPH?[1,2]
Settings: two midwifery units, university hospital, Sweden[3]
Bibliography: Jangsten E, Mattsson LA, Lyckestam I, Hellstrom AL, Berg M. A comparison of active management and expectant management of the third stage of labour: a Swedish randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 2011;118(3):362-9. [PubMed: 21134105]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active	Mixed management (expectant w/ immediate cord clamping)	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: Weighed drape)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/804 (10.2%)	138/817 (16.9%)	RR 0.6 (0.47 to 0.78)	68 fewer per 1000 (from 37 fewer to 90 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								16.9%		68 fewer per 1000 (from 37 fewer to 90 fewer)		
Mean maternal postpartum Hb, g/L (measured with: method unclear; measured 24 hours after delivery; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	810	821	-	MD 2.8 higher (1.43 to 4.17 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Blood loss >500mL (assessed with: Weighed drape)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/804 (9.8%)	156/817 (19.1%)	RR 0.51 (0.4 to 0.66)	94 fewer per 1000 (from 65 fewer to 115 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								19.1%		94 fewer per 1000 (from 65 fewer to 115 fewer)		
Maternal blood transfusion												
1	randomised	serious[4]	no serious	no serious	no serious	none	18/810	23/821	RR 0.79	6 fewer per 1000	⊕⊕⊕O	CRITICAL

	trials		inconsistency	indirectness	imprecision		(2.2%)	(2.8%)	(0.43 to 1.46)	(from 16 fewer to 13 more)	MODERATE	
								2.8%		6 fewer per 1000 (from 16 fewer to 13 more)		
Therapeutic uterotonic during third stage (or within 24h)												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	121/810 (14.9%)	311/821 (37.9%)	RR 0.39 (0.33 to 0.48)	231 fewer per 1000 (from 197 fewer to 254 fewer)	⊕⊕⊕O MODERATE	
								37.9%		231 fewer per 1000 (from 197 fewer to 254 fewer)		
Manual removal of the placenta												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/810 (3.2%)	21/821 (2.6%)	RR 1.25 (0.71 to 2.21)	6 more per 1000 (from 7 fewer to 31 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.6%		6 more per 1000 (from 8 fewer to 31 more)		
Infant birthweight (g) (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	810	821	-	MD 15 higher (28.88 lower to 58.88 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Active management as described in study protocol: cord clamped immediately after birth; 10IU IV oxytocin within 2m; CCT with simultaneous encouragement of pushing; uterine massage after expulsion of placenta.

[2] Expectant [mixed] management as described in study protocol: cord clamped immediately after birth; 2mL IV saline solution administered within 2m; after signs of placental detachment, encouraging woman to push out placenta; uterine massage after delivery of placenta. Early cord clamping was done per hospital routine "to enable blood sampling for blood gas analysis in all newborns."

[3] Administration of prophylactic oxytocin is not routine practice in this setting ("In Sweden it is recommended that all women giving birth vaginally be given an intravenous injection of 10IU of oxytocin as soon as the baby is born. However, the entire AMTSL procedure has not been adopted, and has been questioned by care providers...At the timeof data collection, no strict rules existed for the administration of prophylactic oxytocin to all women after normal childbirth.")

[4] Possibility for selection bias as fewer than 2000 of approximately 11 000 women who gave birth at the units during the study period ended up being recruited to the study -- "not all women were eligible for inclusion because of exclusion criteria, excessive workload at the units or admission in advanced labour." Authors indicate that the study group included a higher proportion of primips than the overall parturient population (57 vs 48%).

GRADE Table 2b

Active management with vs without CCT for prevention of PPH

Question: Should active management with vs without CCT be used for the prevention of PPH?1,2

Settings: high and low-resource settings[3]

Bibliography: Althabe F, Aleman A, Tomasso G, Gibbons L, Vitureira G, Belizan JM, et al. A pilot randomized controlled trial of controlled cord traction to reduce postpartum blood loss. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2009;107(1):4-7. [PubMed: 19541304] Deneux-Tharaux C, Sentilhes L, Maillard F, Closset E, Vardon D, Lepercq J, et al. Effect of routine controlled cord traction as part of the active management of the third stage of labour on postpartum haemorrhage: multicentre randomised controlled trial (TRACOR). BMJ (Clinical research ed.) 2013;346:f1541. [PubMed: 23538918] Gulmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M, et al. Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet 2012;379(9827):1721-7. [PubMed: 22398174]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active management with	Without CCT	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: Weighed drape/graduated collector bag[4])												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1530/13727 (11.1%)	1640/13727 (11.9%)	RR 0.93 (0.87 to 1)	8 fewer per 1000 (from 16 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								5.1%		4 fewer per 1000 (from 7 fewer to 0 more)		
Blood loss >500mL (assessed with: Weighed drape/graduated collector bag[4])												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1706/13727 (12.4%)	1823/13727 (13.3%)	RR 0.94 (0.88 to 0.99)	8 fewer per 1000 (from 1 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								13.7%		8 fewer per 1000 (from 1 fewer to 16 fewer)		
Manual removal of the placenta												
2[5]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	190/13827 (1.4%)	276/13838 (2%)	RR 0.69 (0.57 to 0.83)	6 fewer per 1000 (from 3 fewer to 9 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								3.7%		11 fewer per 1000 (from 6 fewer to 16		

										fewer)		
Maternal blood transfusion												
2[5]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/13824 (0.5%)	71/13838 (0.5%)	RR 0.94 (0.68 to 1.32)	0 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.5%		0 fewer per 1000 (from 2 fewer to 2 more)		
Therapeutic uterotonic during third stage (or within 24h)												
3	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3130/13909 (22.5%)	3252/13920 (23.4%)	RR 0.95 (0.88 to 1.02)	12 fewer per 1000 (from 28 fewer to 5 more)	⊕⊕⊕O MODERATE	IMPORTANT
								20.6%		10 fewer per 1000 (from 25 fewer to 4 more)		
Maternal pain during third stage (assessed with: maternal reporting)												
1[7]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	109/1892 (5.8%)	138/1868 (7.4%)	Co	16 fewer per 1000 (from 1 fewer to 29 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								7.4%		16 fewer per 1000 (from 1 fewer to 29 fewer)		
Cord rupture												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	89/2034 (4.4%)	2/2024 (0.1%)	RR 44.28 (10.92 to 179.58)	43 more per 1000 (from 10 more to 176 more)	⊕⊕OO LOW	IMPORTANT
								0.1%		43 more per 1000 (from 10 more to 179 more)		

[1] Full active management package as described in study protocol -- Althabe: 10IU oxytocin with delivery of anterior shoulder or within 1m delivery; cord clamped once pulsation stops or after 3m; CCT consistent with ICM/FIGO instructions; uterine massage q15m until discharge from delivery ward. Deneux-Tharaux: 5IU IV oxytocin administered and cord clamped and cut within 2m of birth; CCT consistent with ICM/FIGO instructions. Gulmezoglu: 10IU IM oxytocin as soon as possible after birth; cord clamped and cut after contraction (1-3m after delivery); CCT immediately after observation of a contraction; at study sites at which it was common practice,uterine massage performed q15m for up to 2h.

[2] Limited active management package as described in study protocol -- Althabe: 10IU oxytocin with delivery of anterior shoulder or within 1m delivery; cord clamped once pulsation stops or after 3m; placental separation awaited and delivery of placenta by maternal expulsive efforts and gravity; uterine massage q15m until discharge from delivery ward. Deneux-Tharaux: 5IU IV oxytocin administered and cord clamped and cut within 2m of birth; placental delivery by maternal effort afte signs ofplacental separation ("helped by funal pressure or soft tension on the cord") (standard practice in France). Gulmezoglu: 10IU IM oxytocin as soon as possible after birth; cord clamped and cut after contraction (1-3m after delivery); placental delivery with aid of gravity and maternal effort; at study sites at which it was common practice,uterine massage performed q15m for up to 2h.

[3] Althabe: 2 public maternity hospitals, Montevideo, Uruguay; Deneux-Tharaux: 5 university hospitals, France; Gulmezoglu (multicentre): 16 hospitals/health centres in Argentina, Egypt, Kenya, the Philippines, South Africa, Thailand, Uganda

[4] Althabe/Gulmezoglu: weighed drape. Deneux-Tharaux: graduated collector bag
[5] Deneux-Tharaux, Gulmezoglu
[6] Wide CI in Denoux-Tharaux trial due to small number of events.
[7] Deneux-Tharaux
[8] Very wide confidence interval
[9] As blinding was not possible, the assessment of outcomes could have been influenced by bias. Knowledge of study arm allocation may have also influenced study midwives' decisions to proceed with manual removal of the placenta or administer additional uterotonics.

GRADE Table 2c

Active management with vs without CCT for the prevention of PPH in high-resource settings

Should active management with vs without CCT be used for the prevention of PPH in high-resource settings?

Author(s):
Date: 2013-08-13
Question: Should active management with vs without CCT be used for the prevention of PPH in high-resource settings?[1,2]
Settings: France[3]
Bibliography: Deneux-Tharaux C, Sentilhes L, Maillard F, Closset E, Vardon D, Lepercq J, et al. Effect of routine controlled cord traction as part of the active management of the third stage of labour on postpartum haemorrhage: multicentre randomised controlled trial (TRACOR). BMJ (Clinical research ed.) 2013;346:f1541. [PubMed: 23538918]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active management with	Without CCT	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: Graduated collector bag)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/2005 (1.7%)	37/2008 (1.8%)	RR 0.92 (0.58 to 1.46)	1 fewer per 1000 (from 8 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.8%		1 fewer per 1000 (from 8 fewer to 8 more)		
Blood loss >500mL (assessed with: Graduated collector bag)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	196/2005 (9.8%)	206/2008 (10.3%)	RR 0.95 (0.79 to 1.15)	5 fewer per 1000 (from 22 fewer to 15 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								13.7%		7 fewer per 1000 (from 29 fewer to 21 more)		
Manual removal of the placenta												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/2033 (4.2%)	123/2024 (6.1%)	RR 0.69 (0.53 to 0.9)	19 fewer per 1000 (from 6 fewer to 29 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								3.7%		11 fewer per 1000 (from 4 fewer to 17 fewer)		

Maternal blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/2034 (0.6%)	9/2024 (0.4%)	RR 1.33 (0.56 to 3.14)	1 more per 1000 (from 2 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.5%		2 more per 1000 (from 2 fewer to 11 more)		
Therapeutic uterotonic during third stage (or within 24h)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	727/2030 (35.8%)	805/2024 (39.8%)	RR 0.9 (0.83 to 0.97)	40 fewer per 1000 (from 12 fewer to 68 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								20.6%		21 fewer per 1000 (from 6 fewer to 35 fewer)		
Maternal pain during third stage (assessed with: Maternal report)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	109/1892 (5.8%)	138/1868 (7.4%)	RR 0.78 (0.61 to 0.99)	16 fewer per 1000 (from 1 fewer to 29 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								7.4%		16 fewer per 1000 (from 1 fewer to 29 fewer)		
Cord rupture												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	89/2034 (4.4%)	2/2024 (0.1%)	RR 44.28 (10.92 to 179.58)	43 more per 1000 (from 10 more to 176 more)	⊕⊕OO LOW	IMPORTANT
								0.1%		43 more per 1000 (from 10 more to 179 more)		

[1] Full active management package as described in study protocol: 5IU IV oxytocin administered and cord clamped and cut within 2m of birth; CCT consistent with ICM/FIGO instructions.

[2] Limited active management package as described in study protocol 5IU IV oxytocin administered and cord clamped and cut within 2m of birth; placental delivery by maternal effort after signs of placental separation ("helped by funal pressure or soft tension on the cord"). Per authors: "This standard placental expulsion is the usual management in France, as taught in university hospitals and midwifery schools, and it was the routine procedure in the five participating centres before the trial."

[3] 5 university hospitals, care provided by OBs and MWs

[4] Very wide confidence interval

GRADE Table 2d

Active management with vs without uterine massage (before delivery of the placenta) for the prevention of PPH

Question: Should active management with vs without uterine massage (before delivery of the placenta) be used for the prevention of PPH?1,2

Settings: Egypt and South Africa

Bibliography: Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, Hofmeyr GJ. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2010;111(1):32-6. [PubMed: 20599196]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active management with	Without uterine massage (before delivery of the placenta)	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: volume measured after collection in plastic drape/fracture pan)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	3/652 (0.5%)	1/639 (0.2%)	RR 2.94 (0.31 to 28.19)	3 more per 1000 (from 1 fewer to 43 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.2%		4 more per 1000 (from 1 fewer to 54 more)		
Maternal blood transfusion												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	4/637 (0.6%)	4/622 (0.6%)	RR 0.98 (0.25 to 3.89)	0 fewer per 1000 (from 5 fewer to 19 more)	⊕⊕OO Low	CRITICAL
								0.6%		0 fewer per 1000 (from 4 fewer to 17 more)		
Therapeutic uterotonic during third stage (or within 24h)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/638 (3.3%)	20/622 (3.2%)	RR 1.02 (0.56 to 1.87)	1 more per 1000 (from 14 fewer to 28 more)	⊕⊕⊕O MODERATE	IMPORTANT
								3.2%		1 more per 1000 (from 14 fewer to 28 more)		

Manual removal of the placenta												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/655 (2%)	11/634 (1.7%)	RR 1.14 (0.52 to 2.53)	2 more per 1000 (from 8 fewer to 27 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.7%		2 more per 1000 (from 8 fewer to 26 more)		
Maternal Hb <80g/dL at 12-24h postpartum												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	5/191 (2.6%)	8/191 (4.2%)	RR 0.62 (0.21 to 1.88)	16 fewer per 1000 (from 33 fewer to 37 more)	⊕⊕⊕O MODERATE	IMPORTANT
								4.2%		16 fewer per 1000 (from 33 fewer to 37 more)		
Blood loss >500mL												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/652 (6.3%)	22/639 (3.4%)	RR 1.83 (1.1 to 3.03)	29 more per 1000 (from 3 more to 70 more)	⊕⊕⊕⊕ HIGH	
								3.4%		28 more per 1000 (from 3 more to 69 more)		

[1] Active management with uterine massage as described in study protocol: 10IU IM oxytocin as per hospital protocol (with anterior shoulder or after delivery); cord clamped soon after delivery; placenta delivered by CCT after uterine contraction; 30m uterine massage ("manual stimulation of the whole surface of the uterus using steady repetitive movements, as firmly as possible without causing distress to the mother.")

[2] Active management without uterine massage as described in study protocol: 10IU IM oxytocin as per hospital protocol (with anterior shoulder or after delivery); cord clamped soon after delivery; placenta delivered by CCT after uterine contraction.

[3] Wide confidence interval (small number of events)

[4] Small number of events

[5] As blinding was not possible, the assessment of outcomes could have been influenced by bias. Knowledge of study arm allocation may have also influenced study midwives' decisions to proceed with manual removal of the placenta or administer additional uterotonics.

GRADE Table 2e

Active management with vs without uterine massage (after delivery of the placenta) for the prevention of PPH

Question: Should active management with vs without uterine massage (after delivery of the placenta) be used for the prevention of PPH?1,2

Settings: Egypt/South Africa, China[3]

Bibliography: Abdel-Aleem H, Hofmeyr GJ, Shokry M, El-Sonoosy E. Uterine massage and postpartum blood loss. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2006;93(3):238-9. [PubMed: 16678826] Chen M, Chang Q, Duan T, He J, Zhang L, Liu X. Uterine massage to reduce blod loss after vaginal delivery: A randomized controlled trial. Obstetrics and Gynecology 2013;122(2 (part 1)):290-5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active management with	Without uterine massage (after delivery of the placenta)	Relative (95% CI)	Absolute		
Blood loss >400mL (assessed with: weighed drape)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	no serious imprecision	none	143/1170 (12.2%)	144/1170 (12.3%)	RR 0.99 (0.8 to 1.23)	1 fewer per 1000 (from 25 fewer to 28 more)	⊕⊕⊕O MODERATE	IMPORTANT
								12.3%		1 fewer per 1000 (from 25 fewer to 28 more)		
Blood loss >500mL (assessed with: collection in plastic drape)												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	4/98 (4.1%)	8/102 (7.8%)	RR 0.52 (0.16 to 1.67)	38 fewer per 1000 (from 66 fewer to 53 more)	⊕⊕⊕O MODERATE	IMPORTANT
								7.8%		37 fewer per 1000 (from 66 fewer to 52 more)		
Therapeutic uterotonic during third stage (or within 24h)												
2	randomised trials	serious[10]	serious[8]	no serious indirectness	no serious imprecision	none	230/1268 (18.1%)	236/1272 (18.6%)	RR 0.49 (0.09 to 2.57)	95 fewer per 1000 (from 169 fewer to 291 more)	⊕⊕OO LOW	
								21.7%		111 fewer per 1000 (from 197 fewer to		

										341 more)		
Maternal blood transfusion												
2	randomised trials	serious[10]	serious[9]	no serious indirectness	serious[7]	none	7/1268 (0.6%)	9/1272 (0.7%)	RR 0.78 (0.29 to 2.08)	2 fewer per 1000 (from 5 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL
								0.4%		1 fewer per 1000 (from 3 fewer to 4 more)		
Maternal Hb <80g/dL before discharge												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	7/1170 (0.6%)	5/1170 (0.4%)	RR 1.4 (0.45 to 4.4)	2 more per 1000 (from 2 fewer to 15 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0.4%		2 more per 1000 (from 2 fewer to 14 more)		

[1] Active management with uterine massage as described in study protocol -- Abdel-Aleem: 10IU oxytocin; immediate cord clamping; CCT; uterine massage q10m for 60m ("manual stimulation of the whole surface of the uterus using steady repetitive movements, as firmly as can be achieved without causing distress to the mother, till the uterus became contracted"). Chen: 10IU IM oxytocin immediately after delivery of anterior shoulder; cord clamped and cut approx. 1m after birth of neonate; CCT; 30m sustained uterine massage promptly after placental delivery ("massage was performed as follows: finding the uterine fundus, manually stimulating the fundus and the whole body of the uterus using fingers and palms steadily and repititively, and trying not to cause discomfort to the woman").

[2] Active management without uterine massage as described in study protocol -- Abdel-Aleem: 10IU oxytocin; immediate cord clamping; CCT. Chen: 10IU IM oxytocin immediately after delivery of anterior shoulder; cord clamped and cut approx. 1m after birth of neonate; CCT.

[3] Abdel-Aleem: university hospital, Egypt; Chen: four university hospitals, China

[4] Chen

[5] Blood loss >500mL was pre-selected by CPG work group as the outcome of importance.

[6] Abdel-Aleem

[7] Small number of events

[8] Significant heterogeneity across studies.

[9] No explanation was provided

[10] As blinding was not possible, the assessment of outcomes could have been influenced by bias. Knowledge of study arm allocation may have also influenced study midwives' decisions to proceed with manual removal of the placenta or administer additional uterotonics.

GRADE Table 2f

Active management with vs without CCT for the prevention of PPH (observational study)

Date: 2014-11-12
Question: Should active management with vs without CCT be used for the prevention of PPH (obs study)?
Settings: Turkey, Vietnam, Burkina Faso
Bibliography: Sheldon WR, Durocher J, Winikoff B, Blum J, Trussell J. How effective are the components of active management of the third stage of labor? BMC Pregnancy Childbirth. 2013 Feb 21;13:46.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active management with	Without CCT	Relative (95% CI)	Absolute		
Blood loss >500mL												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	205/6897 (3%)	659/3638 (18.1%)	RR 0.16 (0.14 to 0.19)	152 fewer per 1000 (from 147 fewer to 156 fewer)	⊕OOO VERY LOW	IMPORTANT
								18.1%		152 fewer per 1000 (from 147 fewer to 156 fewer)		
Blood loss >700mL												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	99/6897 (1.4%)	117/3638 (3.2%)	RR 0.45 (0.34 to 0.58)	18 fewer per 1000 (from 14 fewer to 21 fewer)	⊕OOO VERY LOW	n/a
								3.2%		18 fewer per 1000 (from 13 fewer to 21 fewer)		

[1] Data collected as part of RCT of oxytocing vs misoprostol for Tx of PPH. Investigators compared outcomes based on third stage mgmt practices routinely used in each setting -- usual practice in one setting (Turkey, Vietnam) compared to usual practice in other settings (Turkey, Vietnam, Burkina Faso) .
[2] Due to study design (usual practice in one setting compared with usual practice in another setting) other differences that existed between sites may have influenced outcomes.

GRADE Table 2g

Expectant management with vs without CCT for the prevention of PPH (observational study)

Author(s):
Date: 2014-11-12
Question: Should expectant management with vs without CCT be used for the prevention of PPH?
Settings: Multicentre (Egypt, Vietnam)
Bibliography: Sheldon WR, Durocher J, Winikoff B, Blum J, Trussell J. How effective are the components of active management of the third stage of labor? BMC Pregnancy Childbirth. 2013 Feb 21;13:46.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Expectant management with	Without CCT	Relative (95% CI)	Absolute		
Blood loss >500mL (assessed with: Calibrated drape)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	204/4014 (5.1%)	302/1832 (16.5%)	RR 0.31 (0.26 to 0.36)	114 fewer per 1000 (from 106 fewer to 122 fewer)	⊕OOO VERY LOW	IMPORTANT
								16.5%		114 fewer per 1000 (from 106 fewer to 122 fewer)		
Blood loss >700mL												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196/4014 (4.9%)	154/1832 (8.4%)	RR 0.58 (0.47 to 0.71)	35 fewer per 1000 (from 24 fewer to 45 fewer)	⊕OOO VERY LOW	
								8.4%		35 fewer per 1000 (from 24 fewer to 45 fewer)		
Mean blood loss (Better indicated by lower values)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4014	1832	-	MD 144 lower (156.14 to 131.86 lower)	⊕OOO VERY LOW	

[1] Data collected as part of RCT of oxytocing vs misoprostol for Tx of PPH. Investigators compared outcomes based on third stage mgmt practices routinely used in each setting -- usual practice in one setting (Egypt) compared to usual practice in another setting (Vietnam) .
[2] Due to study design (usual practice in one setting compared with usual practice in another setting) other differences that existed between sites may have influenced outcomes.

GRADE Table 3

Oxytocin vs no uterotonic for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs no uterotonic for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, Hofmeyr GJ. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. International Journal of Gynecology & Obstetrics 2010;111(1):32–6. De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstetricia et Gynecologica Scandinavica 1996;75:464–8. Jerbi M, Hidar S, Elmoueddeb, Chaieb A, Khairi H. Oxytocin in the third stage of labor. International Journal of Gynecology & Obstetrics 2007;96(3):198–9. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. British Journal of Obstetrics and Gynaecology 1997;104:781–6. Pierre F, Mesnard L, Body G. For a systematic policy of iv oxytocin inducted placenta deliveries in a unit where a fairly active management of third stage of labour is yet applied: results of a controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology 1992;43:131–5. Poeschmann RP, Doesburg WH, Eskes TKAB. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. British Journal of Obstetrics and Gynaecology 1991;98: 528–30.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	No uterotonic	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: volume/weight[5])												
5[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	52/2367 (2.2%)	87/1795 (4.8%)	RR 0.62 (0.44 to 0.87)	18 fewer per 1000 (from 6 fewer to 27 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								8.8%		33 fewer per 1000 (from 11 fewer to 49 fewer)		
PPH >500mL (assessed with: volume/weight[5])												
5[6]	randomised trials	serious[7]	serious[9]	no serious indirectness	no serious imprecision	none	241/2398 (10.1%)	431/1795 (24%)	RR 0.53 (0.38 to 0.74)	113 fewer per 1000 (from 62 fewer to 149 fewer)	⊕⊕OO LOW	IMPORTANT
								31%		146 fewer per 1000 (from 81 fewer to 192 fewer)		
Maternal Hb <90g/L at 24-48h postpartum												
3[10]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/932 (12.2%)	92/713 (12.9%)	RR 0.78 (0.6 to 1)	28 fewer per 1000 (from 52 fewer to 0 more)	⊕⊕⊕O MODERATE	IMPORTANT
								15.4%		34 fewer per 1000 (from 62 fewer to 0 more)		
Blood transfusion												
3[11]	randomised	no serious	no serious	no serious	no serious	none	17/1848	15/1272	RR 0.89 (0.44	1 fewer per 1000 (from 7	⊕⊕⊕⊕	CRITICAL

	trials	risk of bias	inconsistency	indirectness	imprecision		(0.9%)	(1.2%)	to 1.78)	fewer to 9 more)	HIGH	
								1.1%		1 fewer per 1000 (from 6 fewer to 9 more)		
Manual removal of the placenta												
6	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76/2461 (3.1%)	50/1859 (2.7%)	RR 1.26 (0.88 to 1.81)	7 more per 1000 (from 3 fewer to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.2%		3 more per 1000 (from 1 fewer to 10 more)		
Nausa between birth and discharge												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	1/24 (4.2%)	RR 0.29 (0.01 to 6.74)	30 fewer per 1000 (from 41 fewer to 239 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								4.2%		30 fewer per 1000 (from 42 fewer to 241 more)		
Need for therapeutic uterotonics												
4[13]	randomised trials	serious[7]	serious[14]	no serious indirectness	serious[15]	none	95/1879 (5.1%)	148/1295 (11.4%)	RR 0.56 (0.36 to 0.87)	50 fewer per 1000 (from 15 fewer to 73 fewer)	⊕OOO VERY LOW	IMPORTANT
								11.1%		49 fewer per 1000 (from 14 fewer to 71 fewer)		

[1] Abdel-Aleem: 10 IU IM; de Groot: 5 IU IM; Jerbi: 5 IU IV; Nordstrom: 10 IU IV; Pierre: 5 IU IV; Poeschmann 5 IU IM.

[2] Nordstrom, Poeschmann: saline placebo.

[3] Remainder of third stage management (active/expectant) varied by study.

[4] Abdel-Aleem: Egypt, South Africa; de Groot: Netherlands; Jerbi: Tunisia; Nordstrom: Sweden; Pierre: France; Poeschmann: Netherlands.

[5] Abdel-Aleem, Pierre: Blood collected in plastic pans/sheets; de Groot, Nordstrom, Poeschmann: drapes weighed; Jerbi: assessment method not clear.

[6] Abdel-Aleem, de Groot, Nordstroom, Pierre, Poeschmann

[7] Jerbi, Pierre were only quasi-randomized -- participants allocated to study arms sequentially, not randomly. Some trials unblinded

[8] Wide CI observed in Poeschmann trial, attributable to small sample size and low event rate.

[9] More profound treatment effect noted in Pierre trial.

[10] Abdel-Allem, Jerbi, Nordstrom

[11] Abdel-Aleem, de Groot, Nordstrom

[12] Poeschmann 1991

[13] Abdel-Aleem, de Groot, Nordstrom, Poeschmann

[14] I^2=58% and widely varying RRs.

[15] Varying estimates crossing line of no effect.

GRADE Table 3a

Oxytocin vs no uterotonic (high quality RCTs) for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Should Oxytocin vs no uterotonic (high quality RCTs) be used for the third stage of labour?[1,2]
Settings: Abdel-Aleem: Egypt, South Africa; de Groot: Netherlands; Nordstrom: Sweden
Bibliography: Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, Hofmeyr GJ. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. International Journal of Gynecology & Obstetrics 2010;111(1):32–6. De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstetricia et Gynecologica Scandinavica 1996;75:464–8. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. British Journal of Obstetrics and Gynaecology 1997;104:781–6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	No uterotonic (high quality RCTs)	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: measured volume/weighed drapes)												
3	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/1851 (2.3%)	63/1289 (4.9%)	RR 0.71 (0.49 to 1.03)	14 fewer per 1000 (from 25 fewer to 1 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								8.8%		26 fewer per 1000 (from 45 fewer to 3 more)		
PPH >500mL (assessed with: measured volume/weighed drapes)												
3	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	197/1882 (10.5%)	295/1289 (22.9%)	RR 0.61 (0.48 to 0.77)	89 fewer per 1000 (from 53 fewer to 119 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								31%		121 fewer per 1000 (from 71 fewer to 161 fewer)		
Maternal Hb <90g/L at 24-48h postpartum												
2	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/867 (12.2%)	82/648 (12.7%)	RR 0.77 (0.6 to 1.01)	29 fewer per 1000 (from 51 fewer to 1 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								15.4%		35 fewer per 1000 (from 62 fewer to 2 more)		

Blood transfusion												
3	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[5]	none	17/1848 (0.9%)	15/1272 (1.2%)	RR 0.89 (0.44 to 1.78)	1 fewer per 1000 (from 7 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.1%		1 fewer per 1000 (from 6 fewer to 9 more)		
Need for therapeutic uterotonics												
3	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	95/1851 (5.1%)	146/1271 (11.5%)	RR 0.58 (0.36 to 0.92)	48 fewer per 1000 (from 9 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								13.8%		58 fewer per 1000 (from 11 fewer to 88 fewer)		
Manual removal of the placenta												
3	randomised trials	no serious risk of bias[3]	no serious inconsistency	no serious indirectness	serious[5]	none	43/1880 (2.3%)	17/1288 (1.3%)	RR 1.8 (1.03 to 3.15)	11 more per 1000 (from 0 more to 28 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.2%		10 more per 1000 (from 0 more to 26 more)		

[1] Abdel-Aleem: 10 IU IM; de Groot: 5 IU IM; Nordstrom: 10 IU IV

[2] Remainder of third stage management (active/expectant) varied by study.

[3] Abdel-Aleem, de Groot: not blinded

[4] Abdel-Aleem: not blinded.

[5] Small number of events.

GRADE Table 3b

Oxytocin vs no uterotonic - active management for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs no uterotonic - active management for the third stage of labour[1]
Settings: Abdel-Aleem: Egypt, South Africa; Pierre: France
Bibliography: Abdel-Aleem H, Singata M, Abdel-Aleem M, Mshweshwe N, Williams X, Hofmeyr GJ. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. International Journal of Gynecology & Obstetrics 2010;111(1):32–6. Pierre F, Mesnard L, Body G. For a systematic policy of iv oxytocin inducted placenta deliveries in a unit where a fairly active management of third stage of labour is yet applied: results of a controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology 1992;43:131–5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	No uterotonic - active management	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: blood collected in drape/bedpan and measured)												
2	randomised trials	serious[2]	very serious[3]	no serious indirectness	no serious imprecision	none	105/1779 (5.9%)	18%	RR 0.39 (0.22 to 0.72)	110 fewer per 1000 (from 50 fewer to 140 fewer)	⊕OOO VERY LOW	CRITICAL
Blood loss >500mL												
2	randomised trials	serious[2]	very serious[4]	no serious indirectness	no serious imprecision	none	99/1779 (5.6%)	191/1141 (16.7%)	RR 0.38 (0.23 to 0.63)	104 fewer per 1000 (from 62 fewer to 129 fewer)	⊕OOO VERY LOW	IMPORTANT
								0%		-		
Blood transfusion												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/1257 (0.6%)	7/642 (1.1%)	RR 0.58 (0.21 to 1.6)	5 fewer per 1000 (from 9 fewer to 7 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.1%		5 fewer per 1000 (from 9 fewer to 7 more)		
Maternal Hb <90g/L at 24-48h postpartum												
1[5]	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/382 (22.5%)	52/190 (27.4%)	RR 0.82 (0.61 to 1.11)	49 fewer per 1000 (from 107 fewer to 30 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								15.4%		28 fewer per 1000 (from 60 fewer to 17 more)		

Manual removal of the placenta												
2	randomised trials	serious[2]	serious[6]	no serious indirectness	no serious imprecision	none	56/1777 (3.2%)	38/1140 (3.3%)	RR 1.28 (0.65 to 2.55)	9 more per 1000 (from 12 fewer to 52 more)	⊕⊕OO LOW	CRITICAL
								1.2%		3 more per 1000 (from 4 fewer to 19 more)		
Need for therapeutic uterotonics												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/1260 (3.3%)	53/641 (8.3%)	RR 0.39 (0.26 to 0.58)	50 fewer per 1000 (from 35 fewer to 61 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								8.3%		51 fewer per 1000 (from 35 fewer to 61 fewer)		

[1] Abdel-Aleem: 10 IU IM; Pierre: 5 IU IV

[2] Pierre: quasi-randomized, allocation by sequence, not random. Neither trial blinded.

[3] Variation in estimates of effect - Abdel-Aleem: RR 0.53 (0.39-0.74), Pierre: RR 0.29 (0.21-0.41). I^2 = 84%.

[4] Variation in estimates of effect - Abdel-Aleem: RR 0.49 (0.35-0.68), Pierre: RR 0.29 (0.21-0.41). I^2 = 78%.

[5] Abdel-Aleem

[6] Some variation in estimates of effect, though good overlap of CIs. I^2 = 50%.

GRADE Table 3c

Oxytocin vs no uterotonic - expectant management for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs no uterotonic - expectant management for the third stage of labour[1,2]
Settings: Netherlands, Sweden
Bibliography: De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstetricia et Gynecologica Scandinavica 1996;75:464–8. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. British Journal of Obstetrics and Gynaecology 1997;104:781–6. Poeschmann RP, Doesburg WH, Eskes TKAB. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. British Journal of Obstetrics and Gynaecology 1991;98: 528–30.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	No uterotonic - expectant management	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: Blood loss assessed by weighed drape)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/619 (6.6%)	62/654 (9.5%)	RR 0.72 (0.49 to 1.05)	27 fewer per 1000 (from 48 fewer to 5 more)	⊕⊕⊕⊕ HIGH	
								11.2%		31 fewer per 1000 (from 57 fewer to 6 more)		
PPH >500mL (assessed with: Blood loss assessed by weighed drape)												
3	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	136/619 (22%)	240/654 (36.7%)	RR 0.64 (0.49 to 0.84)	132 fewer per 1000 (from 59 fewer to 187 fewer)	⊕⊕⊕⊕ HIGH	
								31%		112 fewer per 1000 (from 50 fewer to 158 fewer)		
Maternal Hb <90g/L at 24-48h postpartum												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/485 (4.1%)	30/458 (6.6%)	RR 0.63 (0.36 to 1.09)	24 fewer per 1000 (from 42 fewer to 6 more)	⊕⊕⊕⊕ HIGH	
								15.4%		57 fewer per 1000 (from 99 fewer to 14 more)		

Blood transfusion												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	9/591 (1.5%)	8/630 (1.3%)	RR 1.3 (0.5 to 3.38)	4 more per 1000 (from 6 fewer to 30 more)	⊕⊕⊕O MODERATE	
								1.1%		3 more per 1000 (from 5 fewer to 26 more)		
Manual removal of the placenta												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	19/619 (3.1%)	11/654 (1.7%)	RR 1.66 (0.81 to 3.41)	11 more per 1000 (from 3 fewer to 41 more)	⊕⊕⊕O MODERATE	
								1.2%		8 more per 1000 (from 2 fewer to 29 more)		
Nausea between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	0/28 (0%)	1/24 (4.2%)	RR 0.29 (0.01 to 6.74)	30 fewer per 1000 (from 41 fewer to 239 more)	⊕⊕OO LOW	
								4.2%		30 fewer per 1000 (from 42 fewer to 241 more)		
Need for therapeutic uterotonics												
3	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	54/619 (8.7%)	95/654 (14.5%)	RR 0.68 (0.41 to 1.12)	46 fewer per 1000 (from 86 fewer to 17 more)		
								13.8%		44 fewer per 1000 (from 81 fewer to 17 more)		

[1] de Groot: 5 IU IM; Nordstrom: 10 IU IV; Poeschmann 5 IU IM.

[2] Nordstrom, Poeschmann - saline placebo

[3] I^2 = 35%. Tight confidence interval around largest study (Nordstrom) - 0.56 (0.46-0.70), wider CIs crossing line of no effect around smaller studies.

[4] Nordstrom

[5] de Groot, Nordstrom

[6] Wide CIs crossing line of no effect

[7] Poeschmann

[8] I^2 = 38% suggests moderate imprecision. Tight CI around large study (Nordstrom) with RR 0.57 (0.39-0.82); wide CIs around smaller studies, with second largest study (de Groot) with RR close to 1 (0.99 (0.55-1.78)).

GRADE Table 3d

Oxytocin vs no uterotonic - expectant mgmt (high quality RCTs) for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Should Oxytocin vs no uterotonic - expectant mgmt (high quality RCTs) be used for the third stage of labour?[1,2]
Settings: Netherlands, Sweden
Bibliography: De Groot ANJA, Van Roosmalen J, Van Dongen PWJ, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta Obstetricia et Gynecologica Scandinavica 1996;75:464–8. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. British Journal of Obstetrics and Gynaecology 1997;104:781–6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	No uterotonic - expectant mgmt (high quality RCTs)	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drapes)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/591 (6.6%)	59/630 (9.4%)	RR 0.73 (0.49 to 1.07)	25 fewer per 1000 (from 48 fewer to 7 more)	⊕⊕⊕⊕ HIGH	
								8.8%		24 fewer per 1000 (from 45 fewer to 6 more)		
PPH >500mL (assessed with: weighed drapes)												
2	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	129/591 (21.8%)	230/630 (36.5%)	RR 0.66 (0.45 to 0.97)	124 fewer per 1000 (from 11 fewer to 201 fewer)	⊕⊕⊕O MODERATE	
								31%		105 fewer per 1000 (from 9 fewer to 171 fewer)		
Maternal Hb <90g/L at 24-48h postpartum												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/485 (4.1%)	30/458 (6.6%)	RR 0.63 (0.36 to 1.09)	24 fewer per 1000 (from 42 fewer to 6 more)	⊕⊕⊕⊕ HIGH	
								15.4%		57 fewer per 1000 (from 99 fewer to 14 more)		

Blood transfusion												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	9/591 (1.5%)	8/630 (1.3%)	RR 1.3 (0.5 to 3.38)	4 more per 1000 (from 6 fewer to 30 more)	⊕⊕⊕O MODERATE	
								1.1%		3 more per 1000 (from 5 fewer to 26 more)		
Need for therapeutic uterotonics												
2	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	54/591 (9.1%)	93/630 (14.8%)	RR 0.71 (0.42 to 1.22)	43 fewer per 1000 (from 86 fewer to 32 more)	⊕⊕⊕O MODERATE	
								13.8%		40 fewer per 1000 (from 80 fewer to 30 more)		
Manual removal of the placenta												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	19/591 (3.2%)	11/630 (1.7%)	RR 1.66 (0.81 to 3.41)	12 more per 1000 (from 3 fewer to 42 more)	⊕⊕OO LOW	
								1.2%		8 more per 1000 (from 2 fewer to 29 more)		

[1] de Groot: 5 IU IM; Nordstrom: 10 IU IV;

[2] Nordstrom: saline placebo

[3] Moderately variable estimates of effect - de Groot RR: 0.83 (0.57-1.22), Nordstrom RR 0.56 (0.46-0.70). I^2 = 67%.

[4] Nordstrom

[5] Wide CIs reflect low event rate.

[6] Moderately variable estimates of effect - de Groot: RR 0.99 (0.55-1.78), Nordstrom: RR 0.57 (0.39-0.82). I^2 = 59%.

[7] de Groot: wide CI around RR reflects small sample size/low event rate (RR 5.47, 0.23-132.66)

GRADE Table 4

Oxytocin vs ergot alkaloids for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs ergot alkaloids for the third stage of labour[1,2]
Settings: varied[3]
Bibliography: de Groot AN, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta obstetricia et gynecologica Scandinavica 1996;75(5):464-8. [PubMed: 8677772] Ilancheran A, Ratnam SS. Effect of oxytocics on prostaglandin levels in the third stage of labour. Gynecologic and obstetric investigation 1990;29(3):177-80. [PubMed: 2358192] Moodie JE, Moir DD. Ergometrine, oxytocin and extradural analgesia. British journal of anaesthesia 1976;48(6):571-4. [PubMed: 952692] Orji E, Agwu F, Loto O, Olaleye O. A randomized comparative study of prophylactic oxytocin versus ergometrine in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2008;101(2):129-32. [PubMed: 18164304] Saito K, Haruki A, Ishikawa H, Takahashi T, Nagase H, Koyama M, et al. Prospective study of intramuscular ergometrine compared with intramuscular oxytocin for prevention of postpartum hemorrhage. The journal of obstetrics and gynaecology research 2007;33(3):254-8. [PubMed: 17578351] Sorbe B. Active pharmacologic management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstetrics and gynecology 1978;52(6):694-7. [PubMed: 310530]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergot alkaloids	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drape/measured volume)												
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/740 (3.1%)	28/876 (3.2%)	RR 1.07 (0.62 to 1.85)	2 more per 1000 (from 12 fewer to 27 more)	⊕⊕⊕O MODERATE	
								2.8%		2 more per 1000 (from 11 fewer to 24 more)		
PPH >500mL (assessed with: mostly weighed drape/measured volume[6])												
5[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	102/1042 (9.8%)	174/1184 (14.7%)	RR 0.76 (0.61 to 0.94)	35 fewer per 1000 (from 9 fewer to 57 fewer)	⊕⊕⊕O MODERATE	
								20%		48 fewer per 1000 (from 12 fewer to 78 fewer)		
Need for therapeutic uterotonics												
3[9]	randomised trials	serious[5]	serious[10]	no serious indirectness	no serious imprecision	none	40/531 (7.5%)	74/636 (11.6%)	RR 0.7 (0.38 to 1.29)	35 fewer per 1000 (from 72 fewer to 34 more)	⊕⊕OO LOW	
								12.3%		37 fewer per 1000 (from 76 fewer to 36 more)		
Blood transfusion												
2[11]	randomised	serious[12]	no serious	no serious	very serious[13]	none	2/234	1/333	RR 3.74 (0.34	8 more per 1000 (from 2	⊕OOO	

	trials		inconsistency	indirectness			(0.9%)	(0.3%)	to 40.64)	fewer to 119 more)	VERY LOW	
								0.3%		8 more per 1000 (from 2 fewer to 119 more)		
Manual removal of the placenta												
4[14]	randomised trials	serious[5]	serious[15]	no serious indirectness	no serious imprecision	none	27/1037 (2.6%)	57/1179 (4.8%)	RR 0.59 (0.29 to 1.17)	20 fewer per 1000 (from 34 fewer to 8 more)	⊕⊕OO LOW	
								3.6%		15 fewer per 1000 (from 26 fewer to 6 more)		
Vomiting between birth and discharge												
2[16]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/453 (2.6%)	132/490 (26.9%)	RR 0.07 (0.02 to 0.25)	251 fewer per 1000 (from 202 fewer to 264 fewer)	⊕⊕⊕O MODERATE	
								39.7%		369 fewer per 1000 (from 298 fewer to 389 fewer)		
Nausea between birth and discharge												
2[16]	randomised trials	serious[12]	serious[17]	no serious indirectness	serious[18]	none	14/453 (3.1%)	136/490 (27.8%)	RR 0.18 (0.06 to 0.53)	228 fewer per 1000 (from 130 fewer to 261 fewer)	⊕OOO VERY LOW	
								5.1%		42 fewer per 1000 (from 24 fewer to 48 fewer)		
Headache between birth and discharge												
2[16]	randomised trials	no serious risk of bias	very serious[19]	no serious indirectness	serious[18]	none	1/453 (0.2%)	56/490 (11.4%)	RR 0.08 (0 to 9.46)	105 fewer per 1000 (from 114 fewer to 967 more)	⊕OOO VERY LOW	
								9.5%		87 fewer per 1000 (from 95 fewer to 804 more)		

[1] de Groot 1996: 5 IU Oxytocin IM; Ilancheran 1990: dose not known; Orji 2008: 10 IU Oxytocin IV; Saito 2007: 5 IU Oxytocin IM; Sorbe 1978: 10 IU Oxytocin IV.

[2] de Groot 1996: oral ergometrine 0.4mg; Ilancheran 1990: dose not known; Orji 2008: ergometrine 0.25mg IV; Saito 2007: methylergometrine 0.2mg IM; Sorbe 1978: ergometrine 0.2mg IV.

[3] de Groot 1996: Netherlands; Ilancheran 1990: Singapore; Orji 2008: Nigeria; Saito 2007: Japan; Sorbe 1978: Sweden.

[4] de Groot 1996; Saito 2007; Sorbe 1978.

[5] Saito 2007 and Sorbe 1978: quasi-randomised trials (Saito: allocation by midwives' shift: Sorbe: allocation by even/odd hospital number). No blinding in any study,

[6] Ilancheran: method of blood loss assessment not clear.

[7] de Groot 1996; Ilancheran 1990; Orji 2008; Saito 2007; Sorbe 1978.

[8] Ilancheran 1990, Saito 2007 and Sorbe 1978: quasi-randomised trials (Ilancheran: randomization sequence note clear or pre-determined; Saito: allocation by midwives' shift; Sorbe: allocation by even/odd hospital number). No blinding in any study.

[9] de Groot 1996; Orji 2008; Saito 2007.

[10] Some heterogeneity of findings not explained by differences in study populations -- all three studies had detailed/consistent exclusion criteria.I^2 = 62%.

[11] de Groot 1996, Saito 2007.

[12] Saito 2007: quasi-randomised trial (allocation by midwives' shift). No blinding in any study

[13] Small number of events in de Groot 1996 with wide CI; no events in Saito 2007.

[14] de Groot 1996; Orji 2008; Saito 2007; Sorbe 1978.

[15] Some heterogeneity of results; I^2 = 40%.

[16] Orji 2008; Saito 2007.

[17] Wide descrepancies in estimates of effect (Orji RR 0.12, 95% CI 0.09-0.19, Saito RR 0.61, 95% CI 0.11-3.23). I^2 = 60%

[18] Discrepancies in estimates of effect, small number of events and wide CI in Saito trial.

[19] Wide descrepancies in estimates of effect (Orji RR 0.01, 95% CI 0.01-0.15, Saito RR 0.60, 95% CI 0.05-6.55). I^2 = 85%

GRADE Table 4a

Oxytocin vs ergot alkaloids (RCTs only) for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs ergot alkaloids (RCTs only) for the third stage of labour[1,2]
Settings: Netherlands (de Groot), Nigeria (Orji)
Bibliography: de Groot AN, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta obstetricia et gynecologica Scandinavica 1996;75(5):464-8. [PubMed: 8677772] Orji E, Agwu F, Loto O, Olaleye O. A randomized comparative study of prophylactic oxytocin versus ergometrine in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2008;101(2):129-32. [PubMed: 18164304]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergot alkaloids (RCTs only)	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drapes)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	7/78 (9%)	12/146 (8.2%)	RR 1.09 (0.45 to 2.66)	7 more per 1000 (from 45 fewer to 136 more)	⊕⊕⊕O MODERATE	
								2.8%		3 more per 1000 (from 15 fewer to 46 more)		
PPH >500mL (assessed with: weighed drape)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/375 (9.9%)	72/449 (16%)	RR 0.82 (0.58 to 1.15)	29 fewer per 1000 (from 67 fewer to 24 more)	⊕⊕⊕⊕ HIGH	
								20%		36 fewer per 1000 (from 84 fewer to 30 more)		
Need for therapeutic uterotonics												
2	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	none	32/375 (8.5%)	51/449 (11.4%)	RR 0.86 (0.43 to 1.74)	16 fewer per 1000 (from 65 fewer to 84 more)	⊕⊕⊕O MODERATE	
								12.3%		17 fewer per 1000 (from 70 fewer to 91 more)		
Blood transfusion												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	2/78 (2.6%)	1/146 (0.7%)	RR 3.74 (0.34 to 40.64)	19 more per 1000 (from 5 fewer to 272 more)	⊕⊕OO LOW	
								0.3%		8 more per 1000 (from 2 fewer to 119 more)		

Manual removal of the placenta												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	13/375 (3.5%)	23/449 (5.1%)	RR 0.6 (0.31 to 1.17)	20 fewer per 1000 (from 35 fewer to 9 more)	⊕⊕⊕O MODERATE	
								3.6%		14 fewer per 1000 (from 25 fewer to 6 more)		
Vomiting between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/297 (4%)	132/303 (43.6%)	RR 0.09 (0.05 to 0.16)	396 fewer per 1000 (from 366 fewer to 414 fewer)	⊕⊕⊕⊕ HIGH	
								39.7%		361 fewer per 1000 (from 333 fewer to 377 fewer)		
Nausea between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/297 (5.1%)	132/303 (43.6%)	RR 0.12 (0.07 to 0.19)	383 fewer per 1000 (from 353 fewer to 405 fewer)	⊕⊕⊕⊕ HIGH	
								5.1%		45 fewer per 1000 (from 41 fewer to 47 fewer)		
Headache between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/297 (0%)	54/303 (17.8%)	RR 0.01 (0 to 0.15)	176 fewer per 1000 (from 151 fewer to 178 fewer)	⊕⊕⊕⊕ HIGH	
								9.5%		94 fewer per 1000 (from 81 fewer to 95 fewer)		

[1] de Groot 1996: 5 IU Oxytocin IM; Orji 2008: 10 IU Oxytocin IV.

[2] de Groot 1996: oral ergometrine 0.4mg; Orji 2008: ergometrine 0.25mg IV.

[3] de Groot 1996

[4] Wide CI reflecting small number of events.

[5] Point estimates on either side of line of no effect, minimal overlap of CIs. I^2 > 60%.

[6] de Groot: Wide CI reflecting small number of events.

[7] Orji 2008.

GRADE Table 4b

Oxytocin vs ergot alkaloids - active management for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs ergot alkaloids - active management for the third stage of labour[1,2]
Settings: Nigeria (Orji 2008), Japan (Saito 2007)
Bibliography: Orji E, Agwu F, Loto O, Olaleye O. A randomized comparative study of prophylactic oxytocin versus ergometrine in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2008;101(2):129-32. [PubMed: 18164304] Saito K, Haruki A, Ishikawa H, Takahashi T, Nagase H, Koyama M, et al. Prospective study of intramuscular ergometrine compared with intramuscular oxytocin for prevention of postpartum hemorrhage. The journal of obstetrics and gynaecology research 2007;33(3):254-8. [PubMed: 17578351]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergot alkaloids - active management	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drape)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	3/156 (1.9%)	1/187 (0.5%)	RR 3.6 (0.38 to 34.23)	14 more per 1000 (from 3 fewer to 178 more)	⊕⊕OO LOW	
								2.8%		73 more per 1000 (from 17 fewer to 930 more)		
PPH >500mL												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/453 (6.4%)	56/490 (11.4%)	RR 0.58 (0.38 to 0.89)	48 fewer per 1000 (from 13 fewer to 71 fewer)	⊕⊕⊕O MODERATE	
								20%		84 fewer per 1000 (from 22 fewer to 124 fewer)		
Need for therapeutic uterotonics												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/453 (5.7%)	53/490 (10.8%)	RR 0.54 (0.34 to 0.85)	50 fewer per 1000 (from 16 fewer to 71 fewer)	⊕⊕⊕O MODERATE	
								12.3%		57 fewer per 1000 (from 18 fewer to 81 fewer)		
Blood transfusion												

1	no methodology chosen					none	0/156 (0%)	0/187 (0%)	not pooled	not pooled		
								0.3%		not pooled		
Manual removal of the placenta												
2	randomised trials	serious[4]	serious[6]	no serious indirectness	serious[5]	none	16/453 (3.5%)	23/490 (4.7%)	RR 0.95 (0.25 to 3.56)	2 fewer per 1000 (from 35 fewer to 120 more)	⊕OOO VERY LOW	
								3.6%		2 fewer per 1000 (from 27 fewer to 92 more)		
Vomiting between birth and discharge												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/453 (2.6%)	132/490 (26.9%)	RR 0.09 (0.05 to 0.16)	245 fewer per 1000 (from 226 fewer to 256 fewer)	⊕⊕⊕⊕ HIGH	
								39.7%		361 fewer per 1000 (from 333 fewer to 377 fewer)		
Nausea between birth and discharge												
2	randomised trials	serious[4]	serious[7]	no serious indirectness	serious[5]	none	17/453 (3.8%)	136/490 (27.8%)	RR 0.22 (0.05 to 1.03)	216 fewer per 1000 (from 264 fewer to 8 more)		
								5.1%		40 fewer per 1000 (from 48 fewer to 2 more)		
Headache between birth and discharge												
2	randomised trials	serious[4]	serious[7]	no serious indirectness	serious[5]	none	1/453 (0.2%)	56/490 (11.4%)	RR 0.08 (0 to 9.46)	105 fewer per 1000 (from 114 fewer to 967 more)	⊕OOO VERY LOW	
								9.5%		87 fewer per 1000 (from 95 fewer to 804 more)		

[1] Orji 2008: 10 IU Oxytocin IV; Saito 2007: 5 IU Oxytocin IM.

[2] Orji 2008: ergometrine 0.25mg IV; Saito 2007: methylergometrine 0.2mg IM.

[3] Saito 2007.

[4] Saito 2007: quasi-randomised trial (allocation by midwives' shift).

[5] Wide CI reflecting small number of events.

[6] Non-significant point estimates on both sides of line of no effect, minimal overlap of CIs; I^2 = 57%.

[7] Divergent point estimates, minimal overlap of CIs; I^2 > 70%.

GRADE Table 4c

Oxytocin vs ergot alkaloids - expectant management for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin vs ergot alkaloids - expectant management for the third stage of labour[1,2]
Settings: Netherlands (de Groot 1997), Sweden (Sorbe 1978)
Bibliography: de Groot AN, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta obstetricia et gynecologica Scandinavica 1996;75(5):464-8. [PubMed: 8677772] Sorbe B. Active pharmacologic management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstetrics and gynecology 1978;52(6):694-7. [PubMed: 310530]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin	Ergot alkaloids - expectant management	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drape/measured volume)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/584 (3.4%)	27/689 (3.9%)	RR 0.99 (0.56 to 1.75)	0 fewer per 1000 (from 17 fewer to 29 more)	⊕⊕⊕O MODERATE	
								2.8%		0 fewer per 1000 (from 12 fewer to 21 more)		
PPH >500mL												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/584 (12.5%)	117/689 (17%)	RR 0.84 (0.65 to 1.09)	27 fewer per 1000 (from 59 fewer to 15 more)	⊕⊕⊕O MODERATE	
								20%		32 fewer per 1000 (from 70 fewer to 18 more)		
Need for therapeutic uterotonics												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/78 (17.9%)	21/146 (14.4%)	RR 1.25 (0.67 to 2.31)	36 more per 1000 (from 47 fewer to 188 more)	⊕⊕⊕⊕ HIGH	
								12.3%		31 more per 1000 (from 41 fewer to 161 more)		

Blood transfusion												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	2/78 (2.6%)	1/146 (0.7%)	RR 3.74 (0.34 to 40.64)	19 more per 1000 (from 5 fewer to 272 more)	⊕⊕OO LOW	
								0.3%		8 more per 1000 (from 2 fewer to 119 more)		
Manual removal of the placenta												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/584 (1.9%)	34/689 (4.9%)	RR 0.36 (0.19 to 0.71)	32 fewer per 1000 (from 14 fewer to 40 fewer)	⊕⊕⊕O MODERATE	
								3.6%		23 fewer per 1000 (from 10 fewer to 29 fewer)		

[1] de Groot 1996: 5 IU Oxytocin IM; Sorbe 1978: 10 IU Oxytocin IV.

[2] de Groot 1996: oral ergometrine 0.4mg; Sorbe 1978: ergometrine 0.2mg IV.

[3] Sorbe 1978: quasi-randomised trial (allocation by even/odd hospital number). No blinding,

[4] de Groot 1996

[5] Wide CI reflecting small number of events

GRADE Table 4d

Oxytocin (IM) vs ergot alkaloids for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin (IM) vs ergot alkaloids for the third stage of labour[1,2]
Settings: Netherland (de Groot), Japan (Saito)
Bibliography: de Groot AN, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled trial of oral ergometrine to reduce postpartum hemorrhage. Acta obstetricia et gynecologica Scandinavica 1996;75(5):464-8. [PubMed: 8677772] Saito K, Haruki A, Ishikawa H, Takahashi T, Nagase H, Koyama M, et al. Prospective study of intramuscular ergometrine compared with intramuscular oxytocin for prevention of postpartum hemorrhage. The journal of obstetrics and gynaecology research 2007;33(3):254-8. [PubMed: 17578351]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin (IM)	Ergot alkaloids	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: weighed drape)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	10/234 (4.3%)	13/333 (3.9%)	RR 1.28 (0.56 to 2.94)	11 more per 1000 (from 17 fewer to 76 more)	⊕⊕OO LOW	
								2.8%		8 more per 1000 (from 12 fewer to 54 more)		
PPH >500mL (assessed with: weighed drape)												
2	randomised trials	serious[3]	serious[5]	no serious indirectness	no serious imprecision	none	42/234 (17.9%)	92/333 (27.6%)	RR 0.71 (0.44 to 1.13)	80 fewer per 1000 (from 155 fewer to 36 more)	⊕⊕OO LOW	
								20%		58 fewer per 1000 (from 112 fewer to 26 more)		
Need for therapeutic uterotonics												
2	randomised trials	serious[3]	serious[6]	no serious indirectness	no serious imprecision	none	22/234 (9.4%)	44/333 (13.2%)	RR 0.74 (0.25 to 2.19)	34 fewer per 1000 (from 99 fewer to 157 more)	⊕⊕OO LOW	
								12.3%		32 fewer per 1000 (from 92 fewer to 146 more)		
Blood transfusion												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious	none	2/234 (0.9%)	1/333 (0.3%)	RR 3.74 (0.34 to 40.64)	8 more per 1000 (from 2 fewer to 119 more)	⊕⊕OO LOW	
								0.3%		8 more per 1000 (from 2 fewer to 119 more)		

Manual removal of the placenta												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[7]	none	5/234 (2.1%)	4/333 (1.2%)	RR 1.75 (0.44 to 6.94)	9 more per 1000 (from 7 fewer to 71 more)	⊕⊕OO LOW	
								3.6%		27 more per 1000 (from 20 fewer to 214 more)		
Vomiting between birth and discharge												
1[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/156 (0%)	0/187 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								39.7%		not pooled		
Nausea between birth and discharge												
1[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	2/156 (1.3%)	4/187 (2.1%)	RR 0.6 (0.11 to 3.23)	9 fewer per 1000 (from 19 fewer to 48 more)	⊕⊕OO LOW	
								5.1%		20 fewer per 1000 (from 45 fewer to 114 more)		
Headache between birth and discharge												
1[8]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/156 (0.6%)	2/187 (1.1%)	RR 0.6 (0.05 to 6.55)	4 fewer per 1000 (from 10 fewer to 59 more)	⊕⊕OO LOW	
								9.5%		38 fewer per 1000 (from 90 fewer to 527 more)		

[1] de Groot 1996: 5 IU Oxytocin IM; Saito 2007: 5 IU Oxytocin IM.

[2] de Groot 1996: oral ergometrine 0.4mg; Saito 2007: methylergometrine 0.2mg IM.

[3] Saito 2007: quasi-randomised trial (allocation by midwives' shift).

[4] Wide CI due to small number of events in Saito trial.

[5] Some variation in point estimates. I^2 = 57%.

[6] Significant variation in point estimates (on either side of line of no effect). I^2 = 79%.

[7] Wide CI due to small number of events.

[8] Saito 2007.

GRADE Table 4e

Oxytocin (IV) vs ergot alkaloids for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Oxytocin (IV) vs ergot alkaloids for the third stage of labour[1,2]
Settings: Singapore (Orji), Nigeria (Orji), Sweden (Sorbe)
Bibliography: Ilancheran A, Ratnam SS. Effect of oxytocics on prostaglandin levels in the third stage of labour. Gynecologic and obstetric investigation 1990;29(3):177-80. [PubMed: 2358192] Orji E, Agwu F, Loto O, Olaleye O. A randomized comparative study of prophylactic oxytocin versus ergometrine in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2008;101(2):129-32. [PubMed: 18164304] Sorbe B. Active pharmacologic management of the third stage of labor. A comparison of oxytocin and ergometrine. Obstetrics and gynecology 1978;52(6):694-7. [PubMed: 310530]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxytocin (IV)	Ergot alkaloids	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL) (assessed with: measured volume)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/506 (2.6%)	15/543 (2.8%)	RR 0.93 (0.45 to 1.94)	2 fewer per 1000 (from 15 fewer to 26 more)	⊕⊕⊕O MODERATE	
								2.8%		2 fewer per 1000 (from 15 fewer to 26 more)		
PPH >500mL												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	60/808 (7.4%)	82/851 (9.6%)	RR 0.78 (0.57 to 1.07)	21 fewer per 1000 (from 41 fewer to 7 more)	⊕⊕OO LOW	
								20%		44 fewer per 1000 (from 86 fewer to 14 more)		
Need for therapeutic uterotonics												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/297 (6.1%)	30/303 (9.9%)	RR 0.61 (0.35 to 1.07)	39 fewer per 1000 (from 64 fewer to 7 more)	⊕⊕⊕⊕ HIGH	
								12.3%		48 fewer per 1000 (from 80 fewer to 9 more)		
Manual removal of the placenta												
2[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/803 (2.7%)	53/846 (6.3%)	RR 0.44 (0.26 to 0.76)	35 fewer per 1000 (from 15 fewer to 46 fewer)	⊕⊕⊕O MODERATE	
								3.6%		20 fewer per 1000 (from 9 fewer to 27 fewer)		

Vomiting between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/297 (4%)	132/303 (43.6%)	RR 0.09 (0.05 to 0.16)	396 fewer per 1000 (from 366 fewer to 414 fewer)	⊕⊕⊕⊕ HIGH	
								39.7%		361 fewer per 1000 (from 333 fewer to 377 fewer)		
Nausea between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/297 (5.1%)	132/303 (43.6%)	RR 0.12 (0.07 to 0.19)	383 fewer per 1000 (from 353 fewer to 405 fewer)	⊕⊕⊕⊕ HIGH	
								5.1%		45 fewer per 1000 (from 41 fewer to 47 fewer)		
Headache between birth and discharge												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/297 (0%)	54/303 (17.8%)	RR 0.01 (0 to 0.15)	176 fewer per 1000 (from 151 fewer to 178 fewer)	⊕⊕⊕⊕ HIGH	
								9.5%		94 fewer per 1000 (from 81 fewer to 95 fewer)		

[1] Ilancheran 1990: dose not known; Orji 2008: 10 IU Oxytocin IV; Sorbe 1978: 10 IU Oxytocin IV.

[2] Ilancheran 1990: dose not known; Orji 2008: ergometrine 0.25mg IV; Sorbe 1978: ergometrine 0.2mg IV.

[3] Sorbe 1978.

[4] Sorbe 1978: quasi-randomised trial (allocation by even/odd hospital number). No blinding,

[5] Ilancheran 1990, Sorbe 1978: quasi-randomised trials (Ilancheran: randomization sequence note clear or pre-determined; Sorbe: allocation by even/odd hospital number). No blinding in any study.

[6] Wide CI reflecting small number of participants/events in Ilancheran trial.

[7] Orji 2008.

[8] Orji 2008, Sorbe 1978.

GRADE Table 5

Syntometrine vs oxytocin for the third stage of labour

Author(s):
Date: 2013-11-13
Question: Should syntometrine vs oxytocin be used for the third stage of labour?[1,2]
Settings: Varied[3]
Bibliography: Choy CM, Lau WC, Tam WH, Yuen PM. A randomised controlled trial of intramuscular syntometrine and intravenous oxytocin in the management of the third stage of labour. BJOG : an international journal of obstetrics and gynaecology 2002;109(2):173-7. [PubMed: 11905429] Khan GQ, John IS, Chan T, Wani S, Hughes AO, Stirrat GM. Abu Dhabi third stage trial: oxytocin versus Syntometrine in the active management of the third stage of labour. European journal of obstetrics, gynecology, and reproductive biology 1995;58(2):147-51. [PubMed: 7774741] McDonald SJ, Prendiville WJ, Blair E. Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of third stage of labour. BMJ (Clinical research ed.) 1993;307(6913):1167-71. [PubMed: 8251842] Mitchell GG, Elbourne DR. The Salford Third Stage Trial. Oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage of labor. The Online journal of current clinical trials 1993;Doc No 83:[2305 words; 32 paragraphs]. [PubMed: 8306013] Rashid M, Clark A, Rashid MH. A randomised controlled tiral comparing the efficacy of intramuscular syntometrine and intravenous syntocinon, in preventing postpartum haemorrhage. J Obstet Gynaecol 2009 Jul;29(5):396-401. [Other: ; PubMed: 19603316] Yuen PM, Chan NS, Yim SF, Chang AM. A randomised double blind comparison of Syntometrine and Syntocinon in the management of the third stage of labour. British journal of obstetrics and gynaecology 1995;102(5):377-80. [PubMed: 7612530]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Syntometrine	Oxytocin	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/4312 (2.1%)	120/4328 (2.8%)	RR 0.78 (0.6 to 1.02)	6 fewer per 1000 (from 11 fewer to 1 more)	⊕⊕⊕⊕ HIGH	
								1.6%		4 fewer per 1000 (from 6 fewer to 0 more)		
PPH >500mL												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	393/4312 (9.1%)	468/4328 (10.8%)	RR 0.79 (0.63 to 0.98)	23 fewer per 1000 (from 2 fewer to 40 fewer)	⊕⊕⊕⊕ HIGH	
								6.3%		13 fewer per 1000 (from 1 fewer to 23 fewer)		
Manual removal of the placenta												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	113/4311 (2.6%)	118/4328 (2.7%)	RR 0.98 (0.71 to 1.33)	1 fewer per 1000 (from 8 fewer to 9 more)	⊕⊕⊕⊕ HIGH	
								1.2%		0 fewer per 1000 (from 3 fewer to 4 more)		
Blood transfusion												
5[4]	randomised	no serious	no serious	no serious	no serious	none	55/4074	38/4093	RR 1.44 (0.95	4 more per 1000 (from 0	⊕⊕⊕⊕	

	trials	risk of bias	inconsistency	indirectness	imprecision		(1.4%)	(0.9%)	to 2.18)	fewer to 11 more)	HIGH	
								0.9%		4 more per 1000 (from 0 fewer to 11 more)		
Elevated dBP (assessed with: defined variably)												
5[4]	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	none	72/4077 (1.8%)	36/4095 (0.9%)	RR 2.05 (0.92 to 4.57)	9 more per 1000 (from 1 fewer to 31 more)	⊕⊕OO LOW	
								1.4%		15 more per 1000 (from 1 fewer to 50 more)		
Vomiting												
4[7]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	serious[9]	none	377/3061 (12.3%)	67/3083 (2.2%)	RR 3.77 (1.69 to 8.43)	60 more per 1000 (from 15 more to 161 more)	⊕⊕OO LOW	
								0.7%		19 more per 1000 (from 5 more to 52 more)		
Nausea												
4[7]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	499/3061 (16.3%)	138/3083 (4.5%)	RR 2.18 (1.08 to 4.41)	53 more per 1000 (from 4 more to 153 more)	⊕⊕⊕O MODERATE	
								2.1%		25 more per 1000 (from 2 more to 72 more)		
Nausea and/or vomiting												
4	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	874/3737 (23.4%)	198/3749 (5.3%)	RR 2.99 (1.65 to 5.43)	105 more per 1000 (from 34 more to 234 more)	⊕⊕⊕O MODERATE	
								1.8%		36 more per 1000 (from 12 more to 80 more)		
Need for additional uterotonics												
4[7]	randomised trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecision	none	432/3066 (14.1%)	500/3085 (16.2%)	RR 0.92 (0.69 to 1.22)	13 fewer per 1000 (from 50 fewer to 36 more)	⊕⊕⊕O MODERATE	
								12%		10 fewer per 1000 (from 37 fewer to 26 more)		
Apgar score 6 or under at 5 minutes												
2[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/2729 (1.8%)	48/2739 (1.8%)	RR 1 (0.67 to 1.49)	0 fewer per 1000 (from 6 fewer to 9 more)	⊕⊕⊕⊕ HIGH	
								2%		0 fewer per 1000 (from 7 fewer to 10 more)		
Jaundice												

2[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	453/2729 (16.6%)	466/2739 (17%)	RR 0.98 (0.87 to 1.1)	3 fewer per 1000 (from 22 fewer to 17 more)	⊕⊕⊕⊕ HIGH	
								15%		3 fewer per 1000 (from 20 fewer to 15 more)		
No breastfeeding at discharge												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	252/1713 (14.7%)	235/1727 (13.6%)	RR 1.08 (0.92 to 1.27)	11 more per 1000 (from 11 fewer to 37 more)	⊕⊕⊕⊕ HIGH	
								13.6%		11 more per 1000 (from 11 fewer to 37 more)		
Admission to NICU												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	317/1713 (18.5%)	309/1727 (17.9%)	RR 1.03 (0.9 to 1.19)	5 more per 1000 (from 18 fewer to 34 more)	⊕⊕⊕⊕ HIGH	
								17.9%		5 more per 1000 (from 18 fewer to 34 more)		

[1] All studies: syntometrine 1mL IM

[2] Choy 2002: oxytocin 10 IU IV; Khan 1995: oxytocin 10 IU IM; McDonald 1993: oxytocin 10 IU IM; Mitchell 1993: oxytocin 5 IU IM; Rashid 2009: oxytocin 10 IU IV; Yuen 1995: oxytocin 10 IU IM.

[3] Choy 2002: Hong Kong; Khan 1995: UAE; McDonald 1993: Australia; Mitchell 1993: UK; Rashid 2009: Saudi Arabia; Yuen 1995: Hong Kong.

[4] Outcome not included in Mitchell 1993.

[5] Widely varying point estimates. May reflect different Dx criteria.

[6] Wide CIs around point estimates, may reflect small number of events in some studies.

[7] Outcome not included in Mitchell 1993, Khan 1995.

[8] Some variation in point estimates. I^2 > 50%.

[9] Wide CI.

[10] Point estimates w/ small CIs on either side of line of no effect. I^2 = 69%.

[11] Khan 1995, McDonald 1993.

[12] McDonald 1993

GRADE Table 6

Carbetocin vs syntometrine for the third stage of labour

Author(s):
Date: 2013-11-11
Question: Carbetocin vs syntometrine for the third stage of labour[1,2]
Settings: Asia[3]
Bibliography: Askar AA, Ismail MT, El-Ezz AA, Rabie NH. Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. Archives of gynecology and obstetrics 2011;284(6):1359-65. [PubMed: 21336835] Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. BJOG : an international journal of obstetrics and gynaecology 2006;113(12):1459-64. [PubMed: 17176279] Nirmala K, Zainuddin AA, Ghani NA, Zulkifli S, Jamil MA. Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery. The journal of obstetrics and gynaecology research 2009;35(1):48-54. [PubMed: 19215547] Su LL, Rauff M, Chan YH, Mohamad Suphan N, Lau TP, Biswas A, et al. Carbetocin versus syntometrine for the third stage of labour following vaginal delivery--a double-blind randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 2009;116(11):1461-6. [PubMed: 19538418]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Syntometrine	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL)												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	1/455 (0.2%)	3/455 (0.7%)	RR 0.52 (0.09 to 2.97)	3 fewer per 1000 (from 6 fewer to 13 more)	⊕⊕⊕O MODERATE	
								0.7%		3 fewer per 1000 (from 6 fewer to 14 more)		
Blood loss >500mL												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/515 (2.7%)	14/515 (2.7%)	RR 0.96 (0.44 to 2.09)	1 fewer per 1000 (from 15 fewer to 30 more)	⊕⊕⊕⊕ HIGH	
								2.1%		1 fewer per 1000 (from 12 fewer to 23 more)		
Need for additional uterotonics												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/515 (11.5%)	71/515 (13.8%)	RR 0.84 (0.59 to 1.19)	22 fewer per 1000 (from 57 fewer to 26 more)	⊕⊕⊕⊕ HIGH	
								15.9%		25 fewer per 1000 (from 65 fewer to 30 more)		
Blood transfusion												
3[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	6/455 (1.3%)	3/455 (0.7%)	RR 1.83 (0.49 to 6.83)	5 more per 1000 (from 3 fewer to 38 more)	⊕⊕⊕O MODERATE	
								0.8%		7 more per 1000 (from		

										4 fewer to 47 more)		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/515 (2.1%)	54/515 (10.5%)	RR 0.22 (0.12 to 0.41)	82 fewer per 1000 (from 62 fewer to 92 fewer)	⊕⊕⊕⊕ HIGH	
								8.3%		65 fewer per 1000 (from 49 fewer to 73 fewer)		
Nausea												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/515 (3.3%)	71/515 (13.8%)	RR 0.25 (0.15 to 0.41)	103 fewer per 1000 (from 81 fewer to 117 fewer)	⊕⊕⊕⊕ HIGH	
								9.1%		68 fewer per 1000 (from 54 fewer to 77 fewer)		
Headache												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/515 (3.7%)	23/515 (4.5%)	RR 0.83 (0.46 to 1.49)	8 fewer per 1000 (from 24 fewer to 22 more)	⊕⊕⊕⊕ HIGH	
								1.7%		3 fewer per 1000 (from 9 fewer to 8 more)		
Uterine or abdominal pain												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/305 (7.2%)	39/305 (12.8%)	RR 0.56 (0.35 to 0.92)	56 fewer per 1000 (from 10 fewer to 83 fewer)	⊕⊕⊕⊕ HIGH	
								10.8%		48 fewer per 1000 (from 9 fewer to 70 fewer)		
Facial flushing												
3[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/455 (1.8%)	17/455 (3.7%)	RR 0.53 (0.23 to 1.22)	18 fewer per 1000 (from 29 fewer to 8 more)	⊕⊕⊕⊕ HIGH	
								3.3%		16 fewer per 1000 (from 25 fewer to 7 more)		
Shivering												
1[7]	randomised	no serious	no serious	no serious	no serious	none	2/150	6/150	RR 0.33	27 fewer per 1000 (from 37 fewer to 25	⊕⊕⊕⊕	

	trials	risk of bias	inconsistency	indirectness	imprecision		(1.3%)	(4%)	(0.07 to 1.63)	more)	HIGH	
								4%		27 fewer per 1000 (from 37 fewer to 25 more)		
Mean diff Hb (g/L) (Better indicated by lower values)												
2	no methodology chosen					none	210	210	-	MD 0.1 lower (0.17 to 0.03 lower)		
BP at or above 140/90 immediately after delivery												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/270 (1.5%)	8/270 (3%)	RR 0.5 (0.15 to 1.64)	15 fewer per 1000 (from 25 fewer to 19 more)	⊕⊕⊕⊕ HIGH	
								3%		15 fewer per 1000 (from 25 fewer to 19 more)		
BP at or above 140/90 30m after delivery												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/270 (0%)	16/270 (5.9%)	RR 0.06 (0.01 to 0.44)	56 fewer per 1000 (from 33 fewer to 59 fewer)	⊕⊕⊕⊕ HIGH	
								6%		56 fewer per 1000 (from 34 fewer to 59 fewer)		
BP at or above 140/90 60m after delivery												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/270 (0%)	13/270 (4.8%)	RR 0.07 (0.01 to 0.54)	45 fewer per 1000 (from 22 fewer to 48 fewer)	⊕⊕⊕⊕ HIGH	
								4.9%		46 fewer per 1000 (from 23 fewer to 49 fewer)		

[1] All studies: 100 mcg IM

[2] All studies: 1mL IM

[3] Askar 2011: Kuwait; Leung 2006: Hong Kong; Nirmala 2009: Malaysia; Su 2009: Singapore.

[4] Outcomes not included in Nirmala 2009,

[5] Wide CI due to small number of events.

[6] Askar 2011, Leung 2006, Su 2009.

[7] Leung 2006.

[8] Askar 2011, Leung 2006.

GRADE Table 6a

Carbetocin vs syntometrine for the third stage of labour (women at low risk of PPH)

Author(s):
Date: 2013-11-11
Question: Should Carbetocin vs syntometrine be used for the third stage of labour (women at low risk of PPH)?[1,2]
Settings: Asia[3]
Bibliography: Askar AA, Ismail MT, El-Ezz AA, Rabie NH. Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. Archives of gynecology and obstetrics 2011;284(6):1359-65. [PubMed: 21336835] Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. BJOG : an international journal of obstetrics and gynaecology 2006;113(12):1459-64. [PubMed: 17176279] Su LL, Rauff M, Chan YH, Mohamad Suphan N, Lau TP, Biswas A, et al. Carbetocin versus syntometrine for the third stage of labour following vaginal delivery--a double-blind randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 2009;116(11):1461-6. [PubMed: 19538418]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbetocin	Syntometrine	Relative (95% CI)	Absolute		
Severe PPH (blood loss >1000mL)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	1/455 (0.2%)	3/455 (0.7%)	RR 0.52 (0.09 to 2.97)	3 fewer per 1000 (from 6 fewer to 13 more)	⊕⊕⊕O MODERATE	
								0.7%		3 fewer per 1000 (from 6 fewer to 14 more)		
Blood loss >500mL												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	11/455 (2.4%)	8/455 (1.8%)	RR 1.32 (0.51 to 3.4)	6 more per 1000 (from 9 fewer to 42 more)	⊕⊕⊕O MODERATE	
								2.1%		7 more per 1000 (from 10 fewer to 50 more)		
Need for additional uterotonics												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/455 (12.3%)	62/455 (13.6%)	RR 0.9 (0.64 to 1.26)	14 fewer per 1000 (from 49 fewer to 35 more)	⊕⊕⊕⊕ HIGH	
								15.9%		16 fewer per 1000 (from 57 fewer to 41 more)		
Blood transfusion												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	6/455 (1.3%)	3/455 (0.7%)	RR 1.83 (0.49 to 6.83)	5 more per 1000 (from 3 fewer to 38 more)	⊕⊕⊕O MODERATE	
								0.8%		7 more per 1000 (from		

										4 fewer to 47 more)		
Vomiting												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/455 (2.4%)	52/455 (11.4%)	RR 0.22 (0.12 to 0.41)	89 fewer per 1000 (from 67 fewer to 101 fewer)	⊕⊕⊕⊕ HIGH	
								8.3%		65 fewer per 1000 (from 49 fewer to 73 fewer)		
Nausea												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/455 (3.7%)	70/455 (15.4%)	RR 0.24 (0.15 to 0.41)	117 fewer per 1000 (from 91 fewer to 131 fewer)	⊕⊕⊕⊕ HIGH	
								9.1%		69 fewer per 1000 (from 54 fewer to 77 fewer)		
Headache												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	17/455 (3.7%)	22/455 (4.8%)	RR 0.78 (0.42 to 1.43)	11 fewer per 1000 (from 28 fewer to 21 more)	⊕⊕⊕O MODERATE	
								1.7%		4 fewer per 1000 (from 10 fewer to 7 more)		
Uterine or abdominal pain												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	22/305 (7.2%)	39/305 (12.8%)	RR 0.56 (0.35 to 0.92)	56 fewer per 1000 (from 10 fewer to 83 fewer)	⊕⊕⊕O MODERATE	
								10.8%		48 fewer per 1000 (from 9 fewer to 70 fewer)		
Facial flushing												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	8/455 (1.8%)	17/455 (3.7%)	RR 0.53 (0.23 to 1.22)	18 fewer per 1000 (from 29 fewer to 8 more)	⊕⊕⊕O MODERATE	
								3.3%		16 fewer per 1000 (from 25 fewer to 7 more)		
Shivering												
1[7]	randomised	no serious	no serious	no serious	serious[4]	none	2/150	6/150	RR 0.33	27 fewer per 1000	⊕⊕⊕O	

	trials	risk of bias	inconsistency	indirectness			(1.3%)	(4%)	(0.07 to 1.63)	(from 37 fewer to 25 more)	MODERATE	
								4%		27 fewer per 1000 (from 37 fewer to 25 more)		
Mean diff Hb (g/L) (Better indicated by lower values)												
1	no methodology chosen					none	150	150	-	MD 0.1 lower (0.37 lower to 0.17 higher)		
BP at or above 140/90 immediately after delivery												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	4/270 (1.5%)	8/270 (3%)	RR 0.5 (0.15 to 1.64)	15 fewer per 1000 (from 25 fewer to 19 more)	⊕⊕⊕O MODERATE	
								3%		15 fewer per 1000 (from 25 fewer to 19 more)		
BP at or above 140/90 30m after delivery												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	0/270 (0%)	16/270 (5.9%)	RR 0.06 (0.01 to 0.44)	56 fewer per 1000 (from 33 fewer to 59 fewer)		
								6%		56 fewer per 1000 (from 34 fewer to 59 fewer)		
BP at or above 140/90 60m after delivery												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	0/270 (0%)	13/270 (4.8%)	RR 0.07 (0.01 to 0.54)	45 fewer per 1000 (from 22 fewer to 48 fewer)	⊕⊕⊕O MODERATE	
								4.9%		46 fewer per 1000 (from 23 fewer to 49 fewer)		

[1] All studies: 100mcg IM.

[2] All studies: 1ml IM.

[3] Askar 2011: Kuwait; Leung 2006: Hong Kong; Su 2009: Singapore.

[4] Wide CIs due to small number of events.

[5] Askar 2011, Su 2009.

[6] No explanation was provided

[7] Leung 2006.

[8] Askar 2011, Leung 2006.

GRADE Table 7

Carboprost vs other injectable uterotonics

Author(s):
Date: 2013-12-11
Question: Should carboprost vs other injectable uterotonic be used for the third stage of labour?[1,2]
Settings: Egypt, India[3]
Bibliography: Abdel-Aleem H, Abol-Oyoun EM, Moustafa SA, Kamel HS, Abdel-Wahab HA. Carboprost trometamol in the management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 1993;42(3):247-50. Chua S, Chew SL, Yeoh CL, Roy AC, Ho LM, Selamat N, et al. A randomized controlled study of prostaglandin 15-methyl F2 alpha compared with syntometrine for prophylactic use in the third stage of labour. The Australian & New Zealand journal of obstetrics & gynaecology 1995;35(4):413-6. Kushtagi P, Verghese LM. Evaluation of two uterotonic medications for the management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2006;94(1):47-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carboprost	Other injectable uterotonic	Relative (95% CI)	Absolute		
Blood loss >500mL (assessed with: volume measured objectively)												
2[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	7/181 (3.9%)	5/184 (2.7%)	RR 1.39 (0.45 to 4.23)	11 more per 1000 (from 15 fewer to 88 more)	⊕⊕OO LOW	
								2.3%		9 more per 1000 (from 13 fewer to 74 more)		
Need for therapeutic uterotonics												
1[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	1/54 (1.9%)	1/58 (1.7%)	RR 1.07 (0.07 to 16.75)	1 more per 1000 (from 16 fewer to 272 more)	⊕OOO VERY LOW	
								1.7%		1 more per 1000 (from 16 fewer to 268 more)		
Manual removal of the placenta												
1[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	1/54 (1.9%)	0/58 (0%)	RR 3.22 (0.13 to 77.34)	-	⊕OOO VERY LOW	
								0%		-		
Mean postpartum Hb (g/L) (Better indicated by higher values)												
1[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108	107	-	MD 0 higher (0.27 lower to 0.27 higher)	⊕⊕⊕O MODERATE	

Nausea												
1[12]	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	serious[9]	none	1/73 (1.4%)	1/77 (1.3%)	RR 1.05 (0.07 to 16.55)	1 more per 1000 (from 12 fewer to 202 more)	⊕⊕OO LOW	
								1.3%		1 more per 1000 (from 12 fewer to 202 more)		
Vomiting												
2	randomised trials	serious[b]	very serious[14]	no serious indirectness	very serious[15]	none	16/181 (8.8%)	8/184 (4.3%)	RR 2.43 (0.1 to 60.24)	62 more per 1000 (from 39 fewer to 1000 more)	⊕OOO VERY LOW	
								3.9%		56 more per 1000 (from 35 fewer to 1000 more)		
Headache												
1[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[9]	none	0/108 (0%)	2/107 (1.9%)	RR 0.2 (0.01 to 4.08)	15 fewer per 1000 (from 19 fewer to 58 more)	⊕⊕OO LOW	
								1.9%		15 fewer per 1000 (from 19 fewer to 59 more)		
Abdominal pain												
2[16]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	serious[9]	none	12/127 (9.4%)	2/135 (1.5%)	RR 4.49 (1.14 to 17.61)	52 more per 1000 (from 2 more to 246 more)	⊕⊕OO LOW	
								1.7%		59 more per 1000 (from 2 more to 282 more)		
Diarrhea												
2[16]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	serious[9]	none	18/127 (14.2%)	1/135 (0.7%)	RR 12.03 (2.29 to 63.21)	82 more per 1000 (from 10 more to 461 more)	⊕⊕OO LOW	
								0.9%		99 more per 1000 (from 12 more to 560 more)		
Fever (>/= 38 degrees C)												
1[f]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[18]	none	0/54 (0%)	0/58 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								0%		not pooled		

[1] Abdel-Aleem 1993: Carboprost trometamol 0.25mg IM. Chua 1995: Carbroprost trometamol 0.125mg IM. Kushtagi 2006: Carboprost tromethamine 0.125mg IM.

[2] Abdel-Aleem 1993: Methylergometrine maleate 0.2mg IV. Chua 1995: Syntometrine 0.5mg IM. Kushtagi 2006: Methylergometrine 0.2mg IV.

[3] Abdel-Aleem 1993: Egypt, women w/vaginal deliveries considered to be at low risk of PPH. Exclusion criteria: labour<2/>24h, MgSO4 use, Hx PPH, APH, chroioamnionities, multiple pregnancy, episiotomoy. Chua 1995: Singapore, women with SVDs. Exclusion criteria: multiple pregnancy, antenatal complications. Kushtagi 2006: India, women with low-risk deliveries.

[4] Abdel-Aleem 1993, Kushtagi 2006.

[5] Abdel-Aleem 1993, Kushnagi 2006: While neither trial involved blinding, most outcomes (including blood loss) were objectively assessed. Randomization methods were not well-described in either study. In both studies, not all primary outcomes were reported.
[6] No events in Abdel-Aleem 1993; small number of events in Kushnagi 2006.
[7] Chua 1995.
[8] Not clear if blinding. Randomization methodology not well-explained. Small number of women (2.6%) exluded from study post-randomization. Not all primary outcomes were reported.
[9] Small number of events. Large CI crossing line of no effect.
[10] Kushtagi 2006.
[11] Kushnagi 2006: no blinding, though most outcomes (including blood loss) were objectively assessed. Randomization methods were not well-described and not all primary outcomes were reported.
[12] Abdel-Aleem 1993.
[13] Abde-Aleem 1993: no blinding, though most outcomes (including blood loss) were objectively assessed. Randomization methods were not well-described and not all primary outcomes were reported.
[14] Divergent point estimates on either side of line of no effect. Minimal overlap of confidence intervals. I^2 = 87%.
[15] Very wide CIs.
[16] Abdel-Aleem 1993, Chua 1995.
[17] Abdel-Aleem 1993, Chua 1995: While neither trial involved blinding, most outcomes (including blood loss) were objectively assessed. Randomization methods were not well-described in either study. In both studies, not all primary outcomes were reported.
[18] No events.

GRADE Table 8

Oral misoprostol vs oxytocin

Author(s):
Date: 2013-12-11
Question: Should oral misoprostol (any dose) vs oxytocin be used for the third stage of labour?[1,2,3]
Settings: Varied[4]
Bibliography: Baskett TF, Persad VL, Clough HJ, Young DC. Misoprostol versus oxytocin for the reduction of postpartum blood loss. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2007;97(1):2-5. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358(9283):689-95. Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2001;75(3):235-41. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour. British journal of obstetrics and gynaecology 1999;106(4):304-8. Oboro VO, Tabowei TO. A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2003;23(1):13-6. Parsons SM, Walley RL, Crane JM, Matthews K, Hutchens D. Oral misoprostol versus oxytocin in the management of the third stage of labour. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2006;28(1):20-6. Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG : an international journal of obstetrics and gynaecology 2000;107(9):1111-5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol (any dose)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: varied methods (estimation + quantification)[5])												
7	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	411/10839 (3.8%)	288/10665 (2.7%)	RR 1.38 (1.18 to 1.62)	10 more per 1000 (from 5 more to 17 more)	⊕⊕⊕⊕ HIGH	
								2%		8 more per 1000 (from 4 more to 12 more)		
Blood loss >500mL (assessed with: varied methods (estimation + quantification)[5])												
6[8]	randomised trials	no serious risk of bias[6]	serious[9]	no serious indirectness	serious[10]	none	1929/10527 (18.3%)	1342/10353 (13%)	RR 1.14 (0.81 to 1.6)	18 more per 1000 (from 25 fewer to 78 more)	⊕⊕OO LOW	
								7.8%		11 more per 1000 (from 15 fewer to 47 more)		
Need for additional uterotonics												
7	randomised	no serious	serious[9]	no serious	no serious	none	1664/10816	1219/10641	RR 1.17	19 more per 1000 (from 3 fewer to 48	⊕⊕⊕O	

	trials	risk of bias[11]		indirectness	imprecision		(15.4%)	(11.5%)	(0.97 to 1.42)	more)	MODERATE	
								10.8%		18 more per 1000 (from 3 fewer to 45 more)		
Blood transfusion												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	75/10777 (0.7%)	101/10601 (1%)	RR 0.74 (0.55 to 1)	2 fewer per 1000 (from 4 fewer to 0 more)	⊕⊕⊕O MODERATE	
								0.4%		1 fewer per 1000 (from 2 fewer to 0 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
1[12]	randomised trials	no serious risk of bias[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	225	225	-	MD 0.1 higher (0.23 lower to 0.43 higher)	⊕⊕⊕⊕ HIGH	
Manual removal of the placenta												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/10830 (2.4%)	253/10656 (2.4%)	RR 1 (0.84 to 1.18)	0 fewer per 1000 (from 4 fewer to 4 more)	⊕⊕⊕⊕ HIGH	
								0.8%		0 fewer per 1000 (from 1 fewer to 1 more)		
Nausea												
6[8]	randomised trials	no serious risk of bias	serious[14]	no serious indirectness	no serious imprecision	none	100/10489 (1%)	60/10318 (0.6%)	RR 1.23 (0.7 to 2.15)	1 more per 1000 (from 2 fewer to 7 more)	⊕⊕⊕O MODERATE	
								1.9%		4 more per 1000 (from 6 fewer to 22 more)		
Vomiting												
6[8]	randomised trials	no serious risk of bias	serious[14]	no serious indirectness	serious[15]	none	86/10499 (0.8%)	45/10338 (0.4%)	RR 1.37 (0.71 to 2.65)	2 more per 1000 (from 1 fewer to 7 more)	⊕⊕OO LOW	
								1.3%		5 more per 1000 (from 4 fewer to 21 more)		
Diarrhea												
6[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[15]	none	56/10481 (0.5%)	16/10311 (0.2%)	RR 2.86 (1.24 to 6.62)	3 more per 1000 (from 0 more to 9 more)	⊕⊕⊕O MODERATE	
								0.2%		4 more per 1000 (from 0 more to 11 more)		

Shivering												
7	randomised trials	no serious risk of bias	very serious[16]	no serious indirectness	serious[17]	none	2201/10824 (20.3%)	622/10647 (5.8%)	RR 3.9 (2.34 to 6.52)	169 more per 1000 (from 78 more to 322 more)	⊕OOO VERY LOW	
								5.7%		165 more per 1000 (from 76 more to 315 more)		
Fever (>/= 38 degrees C)												
5[18]	randomised trials	no serious risk of bias	serious[19]	no serious indirectness	very serious[20]	none	638/10396 (6.1%)	86/10220 (0.8%)	RR 6.26 (2.17 to 18.07)	44 more per 1000 (from 10 more to 144 more)	⊕OOO VERY LOW	
								0.4%		21 more per 1000 (from 5 more to 68 more)		

[1] Baskett 2007: Misoprostol 400mg PO (tablet). Gulmezoglu 2001: Misoprostol 600mcg PO (tablet). Kundodyiwa 2001: Misoprostol 400mcg PO (tablet). Lumbiganon 1999: Misoprostol 400mcg PO (tablet) or misoprostol 600mcg PO (tablet) (three arms of study). Oboro 2003: Misoprostol 600mcg dissolved in 50mL water PO. Parsons 2006: Misoprostol 800 mcg PO (tablet). Walley 2000: Misoprostol 400mcg dissolved in 50mL water PO. Parenteral placebo (saline) used in all trials but Parsons 2006.

[2] Baskett 2007: Oxytocin 5 IU IV. Gulmezoglu 2001: Oxytocin 10 IU IV or IM. Kundodyiwa 2001: Oxytocin 10 IU IM. Lumbiganon 1999: Oxytocin 10 IU IV. Oboro 2003: Oxytocin 10 IU IM. Parsons 2006: Oxytocin 10 IU IM. Walley 2000: Oxytocin 10 IU IM. Oral placebo used in all trials but Parsons 2006.

[3] Baskett 2007: other components of AMTSL used. Gulmezoglu 2001: other components of AMTSL used. Kundodyiwa 2001: other management of third stage not described. Lumbiganon 1999: other components of AMTSL used. Oboro 2003: management of third stage involved CCT, no other details. Parsons 2006: other components of AMTSL used. Walley 2000: other components of AMTSL used.

[4] Baskett 2007: Canada / exclusion criteria: CD, multiple pregnancies, placenta previa or abruption, coagulation disorders,asthma. Gulmezoglu 2001: Argentina, China, Egypt, Ireland, Nigeria, S. Africa, Switzerland, Thailand, Vietnam / exclusion criteria: fever at admit, severe asthma, bleeding disorders, CS. Kundodyiwa 2001: Zimbabwe / exclusion criteria:Hx of PPH, APH, DIC, coagulation disorders, CS, multiple pregnancies, Hx asthma, other contraindications to misoprostol or oxytocin. Lumbiganon 1999: Thailand, S. Africa / exclusion criteria: asthma, planned CS. Oboro 2003: Nigeria / exclusion crietia: CS, risk factors for PPH. Parsons 2006: Ghana / high and low risk VDs. Walley 2000: Ghana / exclusion criteria: grand multiparity, multiple pregnancies, GA <32w, HDP ir HELLP, polyhadramnios, Hx PPH, coagulation disorders, precipitous labour, chorioamnionities, oxytocin induction or augmentation.

[5] Baskett 2007: estimate based on visual assessment plus volume of blood collected in kidney dish. Gulmezoglu 2001: collected blood plus gauze measured by volume; linens weighed in some study locations. Kundodyiwa 2001: volume plus weight of linens. Lumbiganon 1999: volume of blood plus small gauze pads; other linens not included. Oboro 2003: visual estimation. Parsons 2006: visual estimation. Walley 2000: estimate based on visual assessment.

[6] All studies but Parsons 2006 were double-blinded (oral/parenteral placebos used). While estimation of blood loss was based on subjective methods of assessement in some of the studies included, providers and outcome assessors were blinded -- mis-estimation of blood loss is thus likely to be distributed randomly between study arms. Good randomization/allocation concealment methods across all studies, with few post-randomization exclusions or loss to follow-up.

[7] Small number of events in all but one large study (Gulmezoglu 2001).

[8] Gulmezoglu 2001, Kundodyiwa 2001, Lumbiganon 1999, Oboro 2003, Parsons 2006, Walley 2000.

[9] Widely variable point estimates on both sides of line of no effect. I^2>50%.

[10] Three studies (Orobo 2003, Parsons 2006, Walley 2000) involved a very small number of events.

[11] Authors of Baskett 2007 attribute high rates of additional uterotonic use (159/311 in misoprostol arm, 126/311 in oxytocin arm) to most women having IV lines in place during labour -- threshold for bolus oxytocin administration was therefore low.

[12] Parsons 2006.

[13] While this study (Parsons 2006) was not blinded, this outcome is unlikely to be affected by knowledge of study arm allocation.

[14] Variable point estimates on either line of no effect. I^2~40%. Strongest effect (RR ~2-3) noted in largest study (Gulmezoglu 2001).

[15] Small number of events.

[16] Widely variable point estimates w/ minimal overlap of CIs. I^2>90%.

[17] Very wide CIs in some trials included.
[18] Baskett 2007,Gulmezoglu 2001, Kundodyiwa 2001, Lumbaginon 1999, Oboro 2003.
[19] Variable point estimates. I^2>70%.
[20] No explanation was provided

GRADE Table 8a

Oral misoprostol (800mcg) vs oxytocin

Author(s):
Date: 2013-12-11
Question: Oral misoprostol (800mcg) vs oxytocin for the third stage of labour[1,2,3]
Settings: Ghana / included women at high and low risk of PPH
Bibliography: Parsons SM, Walley RL, Crane JM, Matthews K, Hutchens D. Oral misoprostol versus oxytocin in the management of the third stage of labour. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2006;28(1):20-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol (800mcg)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	0/225 (0%)	0/225 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								2%		not pooled		
Blood loss >500mL (assessed with: visual estimation)												
1[4]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	0/225 (0%)	5/225 (2.2%)	RR 0.09 (0.01 to 1.63)	20 fewer per 1000 (from 22 fewer to 14 more)	⊕⊕OO LOW	
								7.8%		71 fewer per 1000 (from 77 fewer to 49 more)		
Need for additional uterotonics												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/225 (7.1%)	21/225 (9.3%)	RR 0.76 (0.41 to 1.42)	22 fewer per 1000 (from 55 fewer to 39 more)	⊕⊕⊕O MODERATE	
								10.8%		26 fewer per 1000 (from 64 fewer to 45 more)		
Blood transfusion												
1	randomised	serious[6]	no serious	no serious	serious[5]	none	1/222	2/221	RR 0.5 (0.05	5 fewer per 1000 (from	⊕⊕OO	

	trials		inconsistency	indirectness			(0.5%)	(0.9%)	to 5.45)	9 fewer to 40 more)	LOW	
								0.4%		2 fewer per 1000 (from 4 fewer to 18 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	225	225	-	MD 0.1 higher (0.23 lower to 0.43 higher)	⊕⊕⊕⊕ HIGH	
Manual removal of the placenta												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	0/225 (0%)	0/225 (0%)	not pooled	not pooled	⊕⊕OO LOW	
								0.8%		not pooled		
Nausea												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	2/223 (0.9%)	4/222 (1.8%)	RR 0.5 (0.09 to 2.69)	9 fewer per 1000 (from 16 fewer to 30 more)	⊕⊕OO LOW	
								1.9%		9 fewer per 1000 (from 17 fewer to 32 more)		
Vomiting												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	1/221 (0.5%)	4/224 (1.8%)	RR 0.25 (0.03 to 2.25)	13 fewer per 1000 (from 17 fewer to 22 more)	⊕⊕OO LOW	
								1.3%		10 fewer per 1000 (from 13 fewer to 16 more)		
Diarrhea												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	5/221 (2.3%)	0/218 (0%)	RR 10.85 (0.6 to 195.06)	-	⊕⊕OO LOW	
								0.2%		20 more per 1000 (from 1 fewer to 388 more)		
Shivering												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	180/223 (80.7%)	8/223 (3.6%)	RR 22.5 (11.36 to 44.56)	771 more per 1000 (from 372 more to 1000 more)	⊕⊕⊕O MODERATE	
								5.7%		1000 more per 1000 (from 591 more to 1000		

										more)		
Fever (>/= 38 degrees C)												
1	no methodology chosen					none	-	-	not pooled	not pooled		
								0.4%		not pooled		

[1] Parsons 2006: Misoprostol 800 mcg PO (tablet). No blinding/placebo.

[2] Parsons 2006: Oxytocin 10 IU IM. No blinding/placebo.

[3] Third stage otherwise managed actively.

[4] As study was not blinded and blood loss was visually estimated, knowledge of study arm allocation may have influenced providers' estimates of blood loss.

[5] Small number of events and wide CI.

[6] Study was not blinded. Knowledge of study arm allocation may have influenced providers' decision-making around therapeutic interventions (use of add'l uterotonics, blood transfusion, manual removal of placenta, etc.).

GRADE Table 8b

Oral misoprostol (600mcg) vs oxytocin

Author(s):
Date: 2013-12-11
Question: Oral misoprostol (600mcg) vs oxytocin for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358(9283):689-95. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour. British journal of obstetrics and gynaecology 1999;106(4):304-8. Oboro VO, Tabowei TO. A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2003;23(1):13-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol (600mcg)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: varied methods (estimation/quantification)[5])												
3	randomised trials	no serious risk of bias[6]	serious[7]	no serious indirectness	no serious imprecision	none	374/9660 (3.9%)	276/9677 (2.9%)	RR 1.04 (0.48 to 2.23)	1 more per 1000 (from 15 fewer to 35 more)	⊕⊕⊕O MODERATE	
								2%		1 more per 1000 (from 10 fewer to 25 more)		
Blood loss >500mL (assessed with: varied methods (estimation/quantification)[5])												
3	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	serious[8]	none	1841/9659 (19.1%)	1301/9676 (13.4%)	RR 1.2 (0.76 to 1.9)	27 more per 1000 (from 32 fewer to 121 more)	⊕⊕OO LOW	
								7.8%		16 more per 1000 (from 19 fewer to 70 more)		
Need for additional uterotonics												
3	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	no serious imprecision	none	1447/9671 (15%)	1057/9677 (10.9%)	RR 1.09 (0.71 to 1.66)	10 more per 1000 (from 32 fewer to 72 more)	⊕⊕⊕O MODERATE	
								10.8%		10 more per 1000 (from 31 fewer to 71 more)		
Blood transfusion												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/9667 (0.7%)	97/9675 (1%)	RR 0.74 (0.55 to 1.01)	3 fewer per 1000 (from 5 fewer to 0 more)	⊕⊕⊕⊕	

								0.4%		1 fewer per 1000 (from 2 fewer to 0 more)	HIGH	
Manual removal of the placenta												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	224/9671 (2.3%)	225/9677 (2.3%)	RR 0.95 (0.67 to 1.35)	1 fewer per 1000 (from 8 fewer to 8 more)	⊕⊕⊕O MODERATE	
								0.8%		0 fewer per 1000 (from 3 fewer to 3 more)		
Nausea												
3	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	serious[8]	none	86/9673 (0.9%)	45/9681 (0.5%)	RR 1.47 (0.64 to 3.34)	2 more per 1000 (from 2 fewer to 11 more)	⊕⊕OO LOW	
								1.9%		9 more per 1000 (from 7 fewer to 44 more)		
Vomiting												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	78/9673 (0.8%)	35/9681 (0.4%)	RR 1.9 (0.97 to 3.72)	3 more per 1000 (from 0 fewer to 10 more)	⊕⊕⊕O MODERATE	
								1.3%		12 more per 1000 (from 0 fewer to 35 more)		
Diarrhea												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	46/9673 (0.5%)	10/9681 (0.1%)	RR 4.37 (2.24 to 8.55)	3 more per 1000 (from 1 more to 8 more)	⊕⊕⊕O MODERATE	
								0.2%		7 more per 1000 (from 2 more to 15 more)		
Shivering												
3	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	no serious imprecision	none	1817/9673 (18.8%)	526/9681 (5.4%)	RR 3.32 (2.61 to 4.24)	126 more per 1000 (from 87 more to 176 more)	⊕⊕⊕O MODERATE	
								5.7%		132 more per 1000 (from 92 more to 185 more)		
Fever (>/= 38 degrees C)												
3	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	serious[8]	none	577/9644 (6%)	85/9653 (0.9%)	RR 4.55 (1.96 to 10.59)	31 more per 1000 (from 8 more to 84 more)	⊕⊕OO LOW	
								0.4%		14 more per 1000 (from 4 more to 38 more)		

[1] Gulmezoglu 2001: Misoprostol 600mcg PO (tablet). Lumbiganon 1999: Misoprostol 400mcg PO (tablet) or misoprostol 600mcg PO (tablet) (three arms of study). Oboro 2003: Misoprostol 600mcg dissolved in 50mL water PO.
[2] Gulmezoglu 2001: Oxytocin 10 IU IV or IM. Lumbiganon 1999: Oxytocin 10 IU IV. Oboro 2003: Oxytocin 10 IU IM.
[3] Gulmezoglu 2001, Lumbaginon 1999: other components of AMTSL used. Oboro 2003: management of third stage involved CCT, no other details.
[4] Gulmezoglu 2001: Argentina, China, Egypt, Ireland, Nigeria, S. Africa, Switzerland, Thailand, Vietnam / exclusion criteria: fever at admit, severe asthma, bleeding disorders, CS. Lumbiganon 1999: Thailand, S. Africa / exclusion criteria: asthma, planned CS. Oboro 2003: Nigeria / exclusion crietia: CS, risk factors for PPH.
[5] Gulmezoglu 2001: collected blood plus gauze measured by volume; linens weighed in some study locations. Lumbiganon 1999: volume of blood plus small gauze pads; other linens not included. Oboro 2003: visual estimation.
[6] All studies were double-blinded (oral/parenteral placebos used). While estimation of blood loss was based on subjective methods of assessement in some of the studies included, providers and outcome assessors were blinded -- mis-estimation of blood loss is thus likely to be distributed randomly between study arms. Good randomization/allocation concealment methods across all studies, with few post-randomization exclusions or loss to follow-up.
[7] Divergent point estimates on either line of no effect. I^2>70%.
[8] Small number of events in smaller studies (Lumbaginon 1999, Oboro 2003) w/ wide CIs.
[9] Divergent point estimates. I^2>50%.

GRADE Table 8c

Oral misoprostol (400mcg) vs oxytocin

Author(s):
Date: 2013-12-11
Question: Oral misoprostol (400mcg) vs oxytocin for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Baskett TF, Persad VL, Clough HJ, Young DC. Misoprostol versus oxytocin for the reduction of postpartum blood loss. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2007;97(1):2-5. Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2001;75(3):235-41. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO Collaborative Trial of Misoprostol in the Management of the Third Stage of Labour. British journal of obstetrics and gynaecology 1999;106(4):304-8. Walley RL, Wilson JB, Crane JM, Matthews K, Sawyer E, Hutchens D. A double-blind placebo controlled randomised trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG : an international journal of obstetrics and gynaecology 2000;107(9):1111-5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol (400mcg)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: varied methods (estimation/quantification)[5])												
4	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/954 (3.9%)	25/963 (2.6%)	RR 1.48 (0.9 to 2.45)	12 more per 1000 (from 3 fewer to 38 more)	⊕⊕⊕⊕ HIGH	
								2%		10 more per 1000 (from 2 fewer to 29 more)		
Blood loss >500mL (assessed with: varied methods (estimation/quantification)[5])												
3	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	serious[7]	none	88/643 (13.7%)	88/652 (13.5%)	RR 1.03 (0.79 to 1.34)	4 more per 1000 (from 28 fewer to 46 more)	⊕⊕⊕O MODERATE	
								7.8%		2 more per 1000 (from 16 fewer to 27 more)		
Need for additional uterotonics												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	201/920 (21.8%)	169/939 (18%)	RR 1.15 (0.86 to 1.54)	27 more per 1000 (from 25 fewer to 97 more)	⊕⊕⊕⊕ HIGH	
								10.8%		16 more per 1000 (from 15 fewer to 58 more)		
Blood transfusion												
4	randomised	no serious	no serious	no serious	serious[8]	none	2/888	2/905	RR 1.09 (0.16	0 more per 1000 (from	⊕⊕⊕O	

	trials	risk of bias	inconsistency	indirectness			(0.2%)	(0.2%)	to 7.4)	2 fewer to 14 more)	MODERATE	
								0.4%		0 more per 1000 (from 3 fewer to 26 more)		
Manual removal of the placenta												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	33/934 (3.5%)	36/954 (3.8%)	RR 0.93 (0.59 to 1.48)	3 fewer per 1000 (from 15 fewer to 18 more)	⊕⊕⊕O MODERATE	
								0.8%		1 fewer per 1000 (from 3 fewer to 4 more)		
Nausea												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	12/593 (2%)	12/615 (2%)	RR 1.06 (0.48 to 2.33)	1 more per 1000 (from 10 fewer to 26 more)	⊕⊕⊕O MODERATE	
								1.9%		1 more per 1000 (from 10 fewer to 25 more)		
Vomiting												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	7/605 (1.2%)	7/633 (1.1%)	RR 1.09 (0.39 to 3.04)	1 more per 1000 (from 7 fewer to 23 more)	⊕⊕⊕O MODERATE	
								1.3%		1 more per 1000 (from 8 fewer to 27 more)		
Diarrhea												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	5/587 (0.9%)	6/612 (1%)	RR 0.99 (0.14 to 6.88)	0 fewer per 1000 (from 8 fewer to 58 more)	⊕⊕⊕O MODERATE	
								0.2%		0 fewer per 1000 (from 2 fewer to 12 more)		
Shivering												
4	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	serious[10]	none	204/928 (22%)	113/943 (12%)	RR 2.25 (1.18 to 4.31)	150 more per 1000 (from 22 more to 397 more)	⊕⊕OO LOW	
								5.7%		71 more per 1000 (from 10 more to 189 more)		
Fever (>/= 38 degrees C)												
3	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	serious[11]	none	61/749 (8.1%)	7/766 (0.9%)	RR 8.79 (0.29 to 269.8)	71 more per 1000 (from 6 fewer to 1000 more)		
								0.4%		31 more per 1000 (from		

										3 fewer to 1000 more)		

[1] Baskett 2007: Misoprostol 400mg PO (tablet). Kundodyiwa 2001: Misoprostol 400mcg PO (tablet). Lumbiganon 1999: Misoprostol 400mcg PO (tablet) or misoprostol 600mcg PO (tablet) (three arms of study). Walley 2000: Misoprostol 400mcg dissolved in 50mL water PO. Parenteral placebo (saline) used in all trials.

[2] Baskett 2007: Oxytocin 5 IU IV. Kundodyiwa 2001: Oxytocin 10 IU IM. Lumbiganon 1999: Oxytocin 10 IU IV. Walley 2000: Oxytocin 10 IU IM. Oral placebo used in all trials.

[3] Baskett 2007, Lumbaginon 1999, Walley 2000: other components of AMTSL used. Kundodyiwa 2001: other management of third stage not described.

[4] Baskett 2007: Canada / exclusion criteria: CD, multiple pregnancies, placenta previa or abruption, coagulation disorders,asthma. Kundodyiwa 2001: Zimbabwe / exclusion criteria:Hx of PPH, APH, DIC, coagulation disorders, CS, multiple pregnancies, Hx asthma, other contraindications to misoprostol or oxytocin. Lumbiganon 1999: Thailand, S. Africa / exclusion criteria: asthma, planned CS. Oboro 2003: Nigeria / exclusion crietia: CS, risk factors for PPH. Walley 2000: Ghana / exclusion criteria: grand multiparity, multiple pregnancies, GA <32w, HDP ir HELLP, polyhadramnios, Hx PPH, coagulation disorders, precipitous labour, chorioamnionities, oxytocin induction or augmentation.

[5] Baskett 2007: estimate based on visual assessment plus volume of blood collected in kidney dish. Kundodyiwa 2001: volume plus weight of linens. Lumbiganon 1999: volume of blood plus small gauze pads; other linens not included. Walley 2000: estimate based on visual assessment.

[6] All studies were double-blinded (oral/parenteral placebos used). While estimation of blood loss was based on subjective methods of assessement in some of the studies included, providers and outcome assessors were blinded -- mis-estimation of blood loss is thus likely to be distributed randomly between study arms. Good randomization/allocation concealment methods across all studies, with few post-randomization exclusions or loss to follow-up.

[7] Very few events in one study (Walley 2000), with wide CI.

[8] Small number of events, wide CIs.

[9] Divergent point estimates and limited overlap of CIs. I^2>80%.

[10] Very wide CI noted in Baskett 2007.

[11] Very wide CIs.

GRADE Table 9

Rectal misoprostol vs oxytocin

Author(s):
Date: 2013-12-11
Question: Rectal misoprostol (any dose) vs oxytocin for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2001;73(1):1-6. Karkanis SG, Caloia D, Salenieks ME, Kingdom J, Walker M, Meffe F, et al. Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2002;24(2):149-54. Nasr A, Shahin AY, Elsamman AM, Zakherah MS, Shaaban OM. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2009;105(3):244-7. Parsons SM, Walley RL, Crane JM, Matthews K, Hutchens D. Rectal misoprostol versus oxytocin in the management of the third stage of labour. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2007;29(9):711-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal misoprostol (any dose)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: varied methods (estimation/quantification)[5])												
2[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	0/540 (0%)	2/563 (0.4%)	RR 0.35 (0.04 to 3.32)	2 fewer per 1000 (from 3 fewer to 8 more)	⊕⊕OO LOW	
								0.4%		3 fewer per 1000 (from 4 fewer to 9 more)		
Blood loss >500mL (assessed with: varied methods (estimation/quantification)[9])												
3[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/797 (3.8%)	33/820 (4%)	RR 0.92 (0.52 to 1.62)	3 fewer per 1000 (from 19 fewer to 25 more)	⊕⊕⊕O MODERATE	
								4.4%		4 fewer per 1000 (from 21 fewer to 27 more)		
Need for therapeutic uterotonics												
4	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/913 (4.7%)	50/933 (5.4%)	RR 0.89 (0.56 to 1.42)	6 fewer per 1000 (from 24 fewer to 23 more)	⊕⊕⊕O MODERATE	
								5.3%		6 fewer per 1000 (from 23 fewer to 22 more)		
Blood transfusion												

4	randomised trials	serious[12]	serious[13]	no serious indirectness	serious[14]	none	11/907 (1.2%)	10/930 (1.1%)	RR 1.07 (0.26 to 4.5)	1 more per 1000 (from 8 fewer to 38 more)	⊕OOO VERY LOW	
								0.9%		1 more per 1000 (from 7 fewer to 31 more)		
Manual removal of the placenta												
1[15]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[14]	none	0/110 (0%)	6/113 (5.3%)	RR 0.08 (0 to 1.39)	49 fewer per 1000 (from 53 fewer to 21 more)	⊕⊕OO LOW	
								5.3%		49 fewer per 1000 (from 53 fewer to 21 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
2[16]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	477	477	-	MD 0 higher (0.16 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH	
Nausea												
3[17]	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	serious[14]	none	10/574 (1.7%)	10/583 (1.7%)	RR 1.04 (0.35 to 3.06)	1 more per 1000 (from 11 fewer to 35 more)	⊕⊕OO LOW	
								1.9%		1 more per 1000 (from 12 fewer to 39 more)		
Vomiting												
4	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	serious[14]	none	15/899 (1.7%)	12/917 (1.3%)	RR 1.29 (0.6 to 2.75)	4 more per 1000 (from 5 fewer to 23 more)	⊕⊕OO LOW	
								1.4%		4 more per 1000 (from 6 fewer to 24 more)		
Headache												
1[15]	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	serious[14]	none	9/105 (8.6%)	4/110 (3.6%)	RR 2.36 (0.75 to 7.42)	49 more per 1000 (from 9 fewer to 233 more)	⊕⊕OO LOW	
								3.6%		49 more per 1000 (from 9 fewer to 231 more)		
Abdominal pain												
1[15]	randomised	serious[18]	no serious	no serious	serious[14]	none	12/105	13/110	RR 0.97 (0.46	4 fewer per 1000 (from	⊕⊕OO	

	trials		inconsistency	indirectness			(11.4%)	(11.8%)	to 2.02)	64 fewer to 121 more)	LOW	
								11.8%		4 fewer per 1000 (from 64 fewer to 120 more)		
Diarrhea												
2[19]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	none	6/580 (1%)	7/595 (1.2%)	RR 0.89 (0.24 to 3.29)	1 fewer per 1000 (from 9 fewer to 27 more)	⊕⊕⊕O MODERATE	
								1.3%		1 fewer per 1000 (from 10 fewer to 30 more)		
Shivering												
4	randomised trials	serious[18]	serious[20]	no serious indirectness	serious[21]	none	245/898 (27.3%)	68/917 (7.4%)	RR 4.47 (1.55 to 12.93)	257 more per 1000 (from 41 more to 885 more)	⊕OOO VERY LOW	
								7.3%		253 more per 1000 (from 40 more to 871 more)		
Fever (>/= 38 degrees C)												
1[15]	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/107 (18.7%)	12/112 (10.7%)	RR 1.74 (0.9 to 3.39)	79 more per 1000 (from 11 fewer to 256 more)	⊕⊕⊕O MODERATE	
								10.7%		79 more per 1000 (from 11 fewer to 256 more)		

[1] Bugalho 2001: Misoprostol 400mcg dissolved in 5mL saline and delivered as microenema. Karkanis 2002: Misoprostol 400mcg PR given after delivery of placenta. Nasr 2009: Misoprostol 800mcg PR. Parsons 2007: Misoprostol 800mcg PR. Parenteral placebo also used in Bugalho 2001 and Nasr 2009.

[2] Bugalho 2001: oxytocin 10 IU IM. Karkanis 2002: Oxytocin 5-10 IU IV or IM. Nasr 2009: Oxytocin 5 IU in 5mL Ringer's lactate (IV or IM?). Parsons 2007: Oxytocin 10 IU IM. Rectal placebo used in Bugalho 2001 (saline microenema) and Nasr 2009.

[3] Bugalho 2001, Karkanis 2002: third stage management not described. Nasr 2009, Parsons 2007: other components of AMTSL package used.

[4] Bugalho 2001: Mozambique / uncomplicated VDs at 30-42w GA, exclusion criteria: induction, augmentation. Karkanis 2002: Toronto / exclusion criteria: parity >6, GA <32w, clotting disorders or anticoagulant therapy, Hx PPH, Hx CS. Nasr 2009: Egypt, singleton SVDs / exclusion criteria: contraindications to misoprostol or oxytocin use, Hx of PPH, APH, bleeding, anticoagulant Tx, HDP. Parsons 2007: Ghana / exclusion criteria: contraindications to prostaglandin use; women with RFs for PPH were included in trial but RFs were recorded.

[5] Bugalho 2001: blood collected in pan and measured. Parsons 2007: Blood loss estimated visually.

[6] Bugalho 2001, Parsons 2007.

[7] Parsons 2007: providers were not blinded and blood loss was estimated visually; knowledge of study arm allocation may therefore have influenced estimates of blood loss. The findings of Bugalho 2001 are at less risk of bias, as providers were were blinded to study arm allocation and blood loss was quantified.

[8] Small number of events and wide confidence intervals.

[9] Bugalho 2001: blood collected in pan and measured. Nasr 2009 and Parsons 2007: Blood loss estimated visually.

[10] Bugalho 2001, Nasr 2009, Parsons 2007.

[11] Parsons 2007: providers were not blinded and blood loss was estimated visually; knowledge of study arm allocation may therefore have influenced estimates of blood loss. The findings of Bugalho 2001 are at less risk of bias, as providers were were blinded to study arm allocation and blood loss was quantified. Nasr 2009: while blood loss was subjectively assessed, providers were blinded to study arm allocation, so misestimation of blood loss is likely to be randomly distributed between groups.

[12] Karkanis 2002 and Parsons 2007: as providers were not blinded, knowledge of study arm allocation may have influenced providers' decision-making around therapeutic uterotonic use, blood transfusion, manual removal of placenta.
[13] Divergent point estimates and limited overlap of CIs. I^2=45%.
[14] Small number of events and wide CIs.
[15] Karkanis 2002.
[16] Nasr 2009, Parsons 2007.
[17] Karkanis 2002, Nasr 2009, Parsons 2007.
[18] Karkanis 2002 and Parsons 2007: as providers were not blinded, knowledge of study arm allocation may have influenced interpretation and/or reporting of side effects of uterotonic use.
[19] Bugalho 2001, Nasr 2009.
[20] Divergent point estimates and limited overlap of CIs. I^2=86%.
[21] Wide CIs in some trials.

GRADE Table 9a

Rectal misoprostol (800mcg) vs oxytocin

Author(s):
Date: 2013-12-11
Question: Rectal misoprostol (800mcg) vs oxytocin for the third stage of labour[1,2,3]
Settings: Egypt, Ghana[4]
Bibliography: Nasr A, Shahin AY, Elsamman AM, Zakherah MS, Shaaban OM. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2009;105(3):244-7. Parsons SM, Walley RL, Crane JM, Matthews K, Hutchens D. Rectal misoprostol versus oxytocin in the management of the third stage of labour. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2007;29(9):711-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal misoprostol (800mcg)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/217 (0%)	1/224 (0.4%)	RR 0.34 (0.01 to 8.4)	3 fewer per 1000 (from 4 fewer to 33 more)	⊕⊕OO LOW	
								0.4%		3 fewer per 1000 (from 4 fewer to 30 more)		
Blood loss >500mL (assessed with: visual estimation)												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	20/474 (4.2%)	18/481 (3.7%)	RR 1.02 (0.4 to 2.58)	1 more per 1000 (from 22 fewer to 59 more)	⊕⊕OO LOW	
								4.4%		1 more per 1000 (from 26 fewer to 70 more)		
Need for therapeutic uterotonics												
2	randomised trials	serious[9]	serious[10]	no serious indirectness	serious[7]	none	15/480 (3.1%)	23/481 (4.8%)	RR 0.76 (0.25 to 2.28)	11 fewer per 1000 (from 36 fewer to 61 more)	⊕OOO VERY LOW	
								5.3%		13 fewer per 1000 (from 40 fewer to 68 more)		
Blood transfusion												
2	randomised	serious[9]	serious[10]	no serious	serious[7]	none	9/474	9/478	RR 0.76 (0.08	5 fewer per 1000 (from	⊕OOO	

	trials			indirectness			(1.9%)	(1.9%)	to 7.13)	17 fewer to 115 more)	VERY LOW	
								0.9%		2 fewer per 1000 (from 8 fewer to 55 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	477	477	-	MD 0 higher (0.16 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH	
Nausea												
2	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[7]	none	2/469 (0.4%)	5/473 (1.1%)	RR 0.43 (0.08 to 2.39)	6 fewer per 1000 (from 10 fewer to 15 more)	⊕⊕OO LOW	
								1.9%		11 fewer per 1000 (from 17 fewer to 26 more)		
Vomiting												
2	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[7]	none	7/471 (1.5%)	7/470 (1.5%)	RR 1.01 (0.35 to 2.9)	0 more per 1000 (from 10 fewer to 28 more)	⊕⊕OO LOW	
								1.4%		0 more per 1000 (from 9 fewer to 27 more)		
Diarrhea												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	6/257 (2.3%)	5/257 (1.9%)	RR 1.2 (0.37 to 3.88)	4 more per 1000 (from 12 fewer to 56 more)	⊕⊕⊕O MODERATE	
								1.3%		3 more per 1000 (from 8 fewer to 37 more)		
Shivering												
2	randomised trials	serious[11]	serious[10]	no serious indirectness	serious[7]	none	96/470 (20.4%)	2/470 (0.4%)	RR 30.74 (0.8 to 1187.86)	127 more per 1000 (from 1 fewer to 1000 more)	⊕OOO VERY LOW	
								7.3%		1000 more per 1000 (from 15 fewer to 1000 more)		

[1] Nasr 2009: Misoprostol 800mcg PR. Parsons 2007: Misoprostol 800mcg PR. Parenteral placebo also used in Nasr 2009.

[2] Nasr 2009: Oxytocin 5 IU in 5mL Ringer's lactate (IV or IM?). Parsons 2007: Oxytocin 10 IU IM. Rectal placebo used in Nasr 2009.

[3] Nasr 2009, Parsons 2007: other components of AMTSL package used.

[4] Nasr 2009: Egypt, singleton SVDs / exclusion criteria: contraindications to misoprostol or oxytocin use, Hx of PPH, APH, bleeding, anticoagulant Tx, HDP. Parsons 2007: Ghana / exclusion criteria: contraindications to prostaglandin use; women with RFs for PPH were included in trial but RFs were recorded.

[5] Parsons 2007

[6] Parsons 2007: providers were not blinded and blood loss was estimated visually; knowledge of study arm allocation may therefore have influenced estimates of blood loss.

[7] Small number of events and wide CIs.
[8] Parsons 2007: providers were not blinded and blood loss was estimated visually; knowledge of study arm allocation may therefore have influenced estimates of blood loss. Nasr 2009: while blood loss was subjectively assessed, providers were blinded to study arm allocation, so misestimation of blood loss is likely to be randomly distributed between groups.
[9] Parsons 2007: providers were not blinded; knowledge of study arm allocation may have influenced decision-making around use of additional uterotonics, blood transfusion, manual removal of placenta.
[10] Divergent point estimates and limited overlap of confidence intervals. I^2>50%.
[11] Parsons 2007: providers were not blinded; knowledge of study arm allocation may have influenced assessment and/or reporting of known side effects.
[12] Nasr 2009.

GRADE Table 9b

Rectal misoprostol (400mcg) vs oxytocin

Author(s):
Date: 2013-12-11
Question: Rectal misoprostol (400mcg) vs oxytocin for the third stage of labour[1,2,3]
Settings: Mozambique, Canada[4]
Bibliography: Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum hemorrhage. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2001;73(1):1-6. Karkanis SG, Caloia D, Salenieks ME, Kingdom J, Walker M, Meffe F, et al. Randomized controlled trial of rectal misoprostol versus oxytocin in third stage management. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2002;24(2):149-54.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal misoprostol (400mcg)	Oxytocin	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: volume collected in pan)												
1[5]	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/323 (0%)	1/339 (0.3%)	RR 0.35 (0.01 to 8.56)	2 fewer per 1000 (from 3 fewer to 22 more)	⊕⊕⊕O MODERATE	
								0.4%		3 fewer per 1000 (from 4 fewer to 30 more)		
Blood loss >500mL (assessed with: volume collected in pan)												
1[5]	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/323 (3.1%)	15/339 (4.4%)	RR 0.7 (0.32 to 1.53)	13 fewer per 1000 (from 30 fewer to 23 more)	⊕⊕⊕⊕ HIGH	
								4.4%		13 fewer per 1000 (from 30 fewer to 23 more)		
Need for therapeutic uterotonics												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/433 (6.5%)	27/452 (6%)	RR 1.07 (0.66 to 1.75)	4 more per 1000 (from 20 fewer to 45 more)	⊕⊕⊕O MODERATE	
								5.3%		4 more per 1000 (from 18 fewer to 40 more)		
Blood transfusion												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	2/433 (0.5%)	1/452 (0.2%)	RR 2.1 (0.19 to 23.04)	2 more per 1000 (from 2 fewer to 49 more)	⊕⊕OO LOW	
								0.9%		10 more per 1000 (from		

										7 fewer to 198 more)		
Manual removal of the placenta												
1[9]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	0/110 (0%)	6/113 (5.3%)	RR 0.08 (0 to 1.39)	49 fewer per 1000 (from 53 fewer to 21 more)	⊕⊕OO LOW	
								5.3%		49 fewer per 1000 (from 53 fewer to 21 more)		
Nausea												
1[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[7]	none	8/105 (7.6%)	5/110 (4.5%)	RR 1.68 (0.57 to 4.96)	31 more per 1000 (from 20 fewer to 180 more)	⊕⊕OO LOW	
								1.9%		13 more per 1000 (from 8 fewer to 75 more)		
Vomiting												
2	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[7]	none	8/428 (1.9%)	5/447 (1.1%)	RR 1.67 (0.56 to 5.01)	7 more per 1000 (from 5 fewer to 45 more)	⊕⊕OO LOW	
								1.4%		9 more per 1000 (from 6 fewer to 56 more)		
Headache												
1[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[7]	none	9/105 (8.6%)	4/110 (3.6%)	RR 2.36 (0.75 to 7.42)	49 more per 1000 (from 9 fewer to 233 more)	⊕⊕OO LOW	
								3.6%		49 more per 1000 (from 9 fewer to 231 more)		
Abdominal pain												
1[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/105 (11.4%)	13/110 (11.8%)	RR 0.97 (0.46 to 2.02)	4 fewer per 1000 (from 64 fewer to 121 more)	⊕⊕⊕O MODERATE	
								11.8%		4 fewer per 1000 (from 64 fewer to 120 more)		
Diarrhea												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	0/323 (0%)	2/338 (0.6%)	RR 0.21 (0.01 to 4.34)	5 fewer per 1000 (from 6 fewer to 20 more)	⊕⊕⊕O MODERATE	
								1.3%		10 fewer per 1000 (from 13 fewer to 43 more)		
Shivering												
2	randomised	serious[10]	no serious	no serious	no serious	none	149/428	66/447	RR 2.36	201 more per 1000	⊕⊕⊕O	

	trials		inconsistency	indirectness	imprecision		(34.8%)	(14.8%)	(1.82 to 3.05)	(from 121 more to 303 more)	MODERATE	
								7.3%		99 more per 1000 (from 60 more to 150 more)		
Fever (>/= 38 degrees C)												
1[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/107 (18.7%)	12/112 (10.7%)	RR 1.74 (0.9 to 3.39)	79 more per 1000 (from 11 fewer to 256 more)	⊕⊕⊕O MODERATE	
								10.7%		79 more per 1000 (from 11 fewer to 256 more)		

[1] Bugalho 2001: Misoprostol 400mcg dissolved in 5mL saline and delivered as microenema. Karkanis 2002: Misoprostol 400mcg PR given after delivery of placenta. Parenteral placebo also used in Bugalho 2001.

[2] Bugalho 2001: oxytocin 10 IU IM. Karkanis 2002: Oxytocin 5-10 IU IV or IM. Rectal placebo used in Bugalho 2001 (saline microenema).

[3] Bugalho 2001, Karkanis 2002: third stage management not described.

[4] Bugalho 2001: Mozambique / uncomplicated VDs at 30-42w GA, exclusion criteria: induction, augmentation. Karkanis 2002: Toronto / exclusion criteria: parity >6, GA <32w, clotting disorders or anticoagulant therapy, Hx PPH, Hx CS.

[5] Bugalho 2001

[6] Findings of Bugalho 2001 are at low risk of bias, as providers were were blinded to study arm allocation and blood loss was quantified.

[7] Small number of events and wide CI.

[8] As Karkanis 2002 was not blinded, knowledge of study arm allocation may have influenced providers' decision-making around use of therapeutic uterotonics, blood transfusion or manual removal of the placenta. Findings of Bugalho 2001 are at less risk of bias, as providers were were blinded to study arm allocation and blood loss was quantified.

[9] Karkanis 2002

[10] As Karkanis 2002 was not blinded, knowledge of study arm allocation may have influenced interpretation and/or recording of side effects of uterotonic use.

GRADE Table 10

Oral misoprostol vs other injectable uterotonic

Author(s):
Date: 2013-12-11
Question: Oral misoprostol vs other injectable uterotonic for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. British journal of obstetrics and gynaecology 1999;106(10):1066-70. Enakpene CA, Morhason-Bello IO, Enakpene EO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor. The journal of obstetrics and gynaecology research 2007;33(6):810-7. Garg P, Batra S, Gandhi G. Oral misoprostol versus injectable methylergometrine in management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2005;91(2):160-1. Ng PS, Chan AS, Sin WK, Tang LC, Cheung KB, Yuen PM. A multicentre randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labour. Human reproduction (Oxford, England) 2001;16(1):31-5. Ng PS, Lai CY, Sahota DS, Yuen PM. A double-blind randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labor. Gynecologic and obstetric investigation 2007;63(1):55-60.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol	Other injectable uterotonic	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation)												
3[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	8/1304 (0.6%)	5/1309 (0.4%)	RR 1.53 (0.52 to 4.5)	2 more per 1000 (from 2 fewer to 13 more)	⊕⊕OO LOW	
								0.4%		2 more per 1000 (from 2 fewer to 14 more)		
Blood loss >500mL (assessed with: visual estimation[8])												
5	randomised trials	serious[6]	serious[9]	no serious indirectness	no serious imprecision	none	100/1832 (5.5%)	105/1834 (5.7%)	RR 0.99 (0.4 to 2.47)	1 fewer per 1000 (from 34 fewer to 84 more)	⊕⊕OO LOW	
								5.1%		1 fewer per 1000 (from 31 fewer to 75 more)		
Need for therapeutic uterotonics												
5	randomised trials	serious[6]	serious[9]	no serious indirectness	no serious imprecision	none	328/1830 (17.9%)	259/1832 (14.1%)	RR 1.28 (0.65 to 2.52)	40 more per 1000 (from 49 fewer to 215 more)	⊕⊕OO LOW	
								13.6%		38 more per 1000 (from 48 fewer to 207 more)		

Blood transfusion												
3[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	24/1304 (1.8%)	21/1309 (1.6%)	RR 1.14 (0.63 to 2.05)	2 more per 1000 (from 6 fewer to 17 more)	⊕⊕OO LOW	
								1.6%		2 more per 1000 (from 6 fewer to 17 more)		
Manual removal of the placenta												
4[10]	randomised trials	serious[6]	serious[9,11]	no serious indirectness	no serious imprecision	none	34/1736 (2%)	41/1741 (2.4%)	RR 0.72 (0.31 to 1.68)	7 fewer per 1000 (from 16 fewer to 16 more)	⊕⊕OO LOW	
								3.5%		10 fewer per 1000 (from 24 fewer to 24 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	177	-	MD 0 higher (0.33 lower to 0.33 higher)	⊕⊕⊕⊕ HIGH	
Nausea												
5	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/1823 (4.6%)	119/1835 (6.5%)	RR 0.71 (0.55 to 0.92)	19 fewer per 1000 (from 5 fewer to 29 fewer)	⊕⊕⊕O MODERATE	
								9%		26 fewer per 1000 (from 7 fewer to 41 fewer)		
Vomiting												
5	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/1823 (3%)	103/1835 (5.6%)	RR 0.55 (0.37 to 0.83)	25 fewer per 1000 (from 10 fewer to 35 fewer)	⊕⊕⊕O MODERATE	
								11.3%		51 fewer per 1000 (from 19 fewer to 71 fewer)		
Diarrhea												
3[13]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	3/710 (0.4%)	3/709 (0.4%)	RR 1 (0.21 to 4.84)	0 fewer per 1000 (from 3 fewer to 16 more)	⊕⊕OO LOW	
								0%		-		
Headache												

4[10]	randomised trials	serious[6]	serious[9]	no serious indirectness	no serious imprecision	none	100/1723 (5.8%)	151/1735 (8.7%)	RR 0.63 (0.17 to 2.34)	32 fewer per 1000 (from 72 fewer to 117 more)	⊕⊕OO LOW	
								10.3%		38 fewer per 1000 (from 85 fewer to 138 more)		
Shivering												
4[14]	randomised trials	serious[6]	serious[15]	no serious indirectness	no serious imprecision	none	442/1390 (31.8%)	152/1403 (10.8%)	RR 3.06 (1.88 to 4.99)	223 more per 1000 (from 95 more to 432 more)	⊕⊕OO LOW	
								9.9%		204 more per 1000 (from 87 more to 395 more)		
Fever (>/= 38 degrees C)												
4[14]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/1404 (11.2%)	23/1409 (1.6%)	RR 6.37 (4.16 to 9.73)	88 more per 1000 (from 52 more to 143 more)	⊕⊕⊕O MODERATE	
								2.1%		113 more per 1000 (from 66 more to 183 more)		

[1] Amant 1999: Misoprostol 600mcg PO. Enakpene 2007: Misoprostol 400mcg PO. Garg 2005: Misoprostol 600mcg PO. Ng 2001: Misoprostol 600mcg PO. Ng 2007: MIsoprostol 400mcg PO. Parenteral placebos used in all trials but Garg 2005 and Ng 2001.

[2] Amant 1999: Methylergometrine 0.2mg IV. Enakpene 2007: Methylergometrine 0.5mg IM. Garg 2005: Methylergometrine 0.2mg IV. Ng 2001: Syntometrine 1mL (oxytocin 5IU + ergometrine 0.5mg) IM. Ng 2007: Syntometrine 2mL (oxytocin 10IU + ergometrine 1mg) IM. Oral placebos used in all trials but Garg 2005 and Ng 2001.

[3] Amant 1999: Thirds stage management by AMTSL with uterine massage. Enakpene 2007: AMTSL. Garg 2005: Early cord clamping; no mention of CCT or uterine massage. Ng 2001: CCT. Ng 2007: AMTSL.

[4] Amant 1999: Belgium / exclusion criteria: CS,HDP, GA <32w, IUFD, IBD, CVD, sepsis, uterine abnormalities, contraindications to misoprostol/ergometrine use. Enakpene 2007: Nigeria / exclusion criteria:contraindications to misoprostol/ergometrine use (HDP, CVD, Hx anemia, athsma, renal or hepatic disorders, allergies) or indications for prophylactic oxytocin use (grand multiparity, polyhadramnios, Hx PPH, fibroids). Garg 2005: India / singleton VDs. Ng 2001: Hon Kong / singleton VDs. Ng 2007: China / exclusion criteria: fibroids, polyhadramnios, IUGR, Hx PPH, contraindications to misoprostol/syntometrine use (asthma, HDP, CVD) or indications for prophylactic oxytocin.

[5] Amant 1999, Ng 2001, Ng 2007.

[6] Knowledge of study arm allocation may have influenced providers' estimates of blood loss-related outcomes in non-blinded studies (Garg 2005 and Ng 2001). Knowledge of study arm allocation may have also biased clinicians' interpretation and/or recording of side effects and/or decision-making around interventions (uterotonic Tx, blood transfusion, manual removal).

[7] Small number of events and wide CI(s).

[8] Enakpene 2007: blood loss estimated based on volume of blood collected in pans, weight of linens, and clinician estimates.

[9] Divergent point estimates on both sides of line of no effect. I^2>85%.

[10] Amant 1999, Enakpene 2007, Ng 2001, Ng 2007.

[11] Divergent point estimates on both sides of line of no effect. I^2>50%.

[12] Ng 2007.

[13] Enakpene 2007, Garg 2005, Ng 2007.

[14] Amant 1999, Garg 2005, Ng 2001, Ng 2007.

[15] Divergent point estimates. I^2>85%.

GRADE Table 10a

Oral misoprostol (600mcg) vs other injectable uterotonic

Author(s):
Date: 2013-12-11
Question: Oral misoprostol (600mcg) vs other injectable uterotonic for the third stage of labour[1,2,3]
Settings: Varied[4]
Bibliography: Amant F, Spitz B, Timmerman D, Corremans A, Van Assche FA. Misoprostol compared with methylergometrine for the prevention of postpartum haemorrhage: a double-blind randomised trial. British journal of obstetrics and gynaecology 1999;106(10):1066-70. Enakpene CA, Morhason-Bello IO, Enakpene EO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor. The journal of obstetrics and gynaecology research 2007;33(6):810-7. Garg P, Batra S, Gandhi G. Oral misoprostol versus injectable methylergometrine in management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2005;91(2):160-1. Ng PS, Chan AS, Sin WK, Tang LC, Cheung KB, Yuen PM. A multicentre randomized controlled trial of oral misoprostol and i.m. syntometrine in the management of the third stage of labour. Human reproduction (Oxford, England) 2001;16(1):31-5. Ng PS, Lai CY, Sahota DS, Yuen PM. A double-blind randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labor. Gynecologic and obstetric investigation 2007;63(1):55-60.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral misoprostol (600mcg)	Other injectable uterotonic	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: visual estimation)												
2[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	6/1126 (0.5%)	4/1132 (0.4%)	RR 1.43 (0.42 to 4.8)	2 more per 1000 (from 2 fewer to 13 more)	⊕⊕OO LOW	
								0.4%		2 more per 1000 (from 2 fewer to 15 more)		
Blood loss >500mL (assessed with: visual estimation)												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76/1222 (6.2%)	54/1225 (4.4%)	RR 1.41 (1 to 1.98)	18 more per 1000 (from 0 more to 43 more)	⊕⊕⊕O MODERATE	
								5.1%		21 more per 1000 (from 0 more to 50 more)		
Need for therapeutic uterotonics												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	254/1220 (20.8%)	155/1223 (12.7%)	RR 1.64 (1.37 to 1.97)	81 more per 1000 (from 47 more to 123 more)	⊕⊕⊕O MODERATE	
								13.6%		87 more per 1000		

										(from 50 more to 132 more)		
Blood transfusion												
2[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	16/1126 (1.4%)	17/1132 (1.5%)	RR 0.95 (0.48 to 1.86)	1 fewer per 1000 (from 8 fewer to 13 more)	⊕⊕OO LOW	
								1.6%		1 fewer per 1000 (from 8 fewer to 14 more)		
Manual removal of the placenta												
2[5]	randomised trials	serious[6]	serious[8]	no serious indirectness	serious[7]	none	8/1126 (0.7%)	17/1132 (1.5%)	RR 0.57 (0.13 to 2.57)	6 fewer per 1000 (from 13 fewer to 24 more)	⊕OOO VERY LOW	
								3.5%		15 fewer per 1000 (from 30 fewer to 55 more)		
Nausea												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/1213 (4.9%)	87/1226 (7.1%)	RR 0.71 (0.53 to 0.95)	21 fewer per 1000 (from 4 fewer to 33 fewer)	⊕⊕⊕O MODERATE	
								9%		26 fewer per 1000 (from 5 fewer to 42 fewer)		
Vomiting												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/1213 (3.8%)	71/1226 (5.8%)	RR 0.66 (0.47 to 0.93)	20 fewer per 1000 (from 4 fewer to 31 fewer)	⊕⊕⊕O MODERATE	
								11.3%		38 fewer per 1000 (from 8 fewer to 60 fewer)		
Diarrhea												
1[9]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	3/100 (3%)	3/100 (3%)	RR 1 (0.21 to 4.84)	0 fewer per 1000 (from 24 fewer to 115 more)	⊕⊕OO LOW	
								0%		-		
Headache												
2[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/1113 (8.2%)	95/1126 (8.4%)	RR 0.97 (0.74 to 1.28)	3 fewer per 1000 (from 22 fewer to 24 more)	⊕⊕⊕O	

								10.3%		3 fewer per 1000 (from 27 fewer to 29 more)	MODERATE	
Shivering												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	407/1212 (33.6%)	150/1226 (12.2%)	RR 2.55 (1.74 to 3.76)	190 more per 1000 (from 91 more to 338 more)	⊕⊕⊕O MODERATE	
								9.9%		153 more per 1000 (from 73 more to 273 more)		
Fever (>/= 38 degrees C)												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/1226 (12.2%)	23/1232 (1.9%)	RR 6.26 (3.94 to 9.92)	98 more per 1000 (from 55 more to 167 more)	⊕⊕⊕O MODERATE	
								2.1%		110 more per 1000 (from 62 more to 187 more)		

[1] Amant 1999: Misoprostol 600mcg PO. Garg 2005: Misoprostol 600mcg PO. Ng 2001: Misoprostol 600mcg PO. Placebos used in Amant 1999.

[2] Amant 1999: Methylergometrine 0.2mg IV. Garg 2005: Methylergometrine 0.2mg IV. Ng 2001: Syntometrine 1mL (oxytocin 5IU + ergometrine 0.5mg) IM. Oral placebos used in Amant 1999.

[3] Amant 1999: Thirds stage management by AMTSL with uterine massage. Garg 2005: Early cord clamping; no mention of CCT or uterine massage. Ng 2001: CCT.

[4] Amant 1999: Belgium / exclusion criteria: CS,HDP, GA <32w, IUFD, IBD, CVD, sepsis, uterine abnormalities, contraindications to misoprostol/ergometrine use. Garg 2005: India / singleton VDs. Ng 2001: Hon Kong / singleton VDs.

[5] Amant 1999, Ng 2001.

[6] Knowledge of study arm allocation may have influenced providers' estimates of blood loss-related outcomes in non-blinded studies (Garg 2005 and Ng 2001). Knowledge of study arm allocation may have also biased clinicians' interpretation and/or recording of side effects and/or decision-making around interventions (uterotonic Tx, blood transfusion, manual removal).

[7] Small number of events and wide CI(s).

[8] Divergent point estimates, limited overlap of CIs. I^2>60%.

[9] Garg 2005.

GRADE Table 10b

Oral misoprostol (400mcg) vs other injectable uterotonic

Author(s):
Date: 2013-12-11
Question: Oral misoprostol (400mcg) vs other injectable uterotonic for the third stage of labour[1,2,3]
Settings: Nigeria, China[4]
Bibliography: Enakpene CA, Morhason-Bello IO, Enakpene EO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor. The journal of obstetrics and gynaecology research 2007;33(6):810-7. Ng PS, Lai CY, Sahota DS, Yuen PM. A double-blind randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labor. Gynecologic and obstetric investigation 2007;63(1):55-60.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral misoprostol (400mcg)**	**Other injectable uterotonic**	**Relative (95% CI)**	**Absolute**		
Blood loss >1000mL (assessed with: visual estimation)												
1[5]	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	serious[7]	none	2/178 (1.1%)	1/177 (0.6%)	RR 1.99 (0.18 to 21.74)	6 more per 1000 (from 5 fewer to 117 more)	⊕⊕⊕O MODERATE	
								0.4%		4 more per 1000 (from 3 fewer to 83 more)		
Blood loss >500mL												
2	randomised trials	no serious risk of bias[6]	serious[8]	no serious indirectness	no serious imprecision	none	24/610 (3.9%)	51/609 (8.4%)	RR 0.54 (0.04 to 7.4)	39 fewer per 1000 (from 80 fewer to 536 more)	⊕⊕⊕O MODERATE	
								5.1%		23 fewer per 1000 (from 49 fewer to 326 more)		
Need for therapeutic uterotonics												
2	randomised trials	no serious risk of bias	very serious[8]	no serious indirectness	no serious imprecision	none	74/610 (12.1%)	104/609 (17.1%)	RR 0.83 (0.21 to 3.34)	29 fewer per 1000 (from 135 fewer to 400 more)	⊕⊕OO LOW	
								13.6%		23 fewer per 1000 (from 107 fewer to 318 more)		

Blood transfusion												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	8/178 (4.5%)	4/177 (2.3%)	RR 1.99 (0.61 to 6.49)	22 more per 1000 (from 9 fewer to 124 more)	⊕⊕⊕O MODERATE	
								1.6%		16 more per 1000 (from 6 fewer to 88 more)		
Manual removal of the placenta												
2	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	no serious imprecision	none	26/610 (4.3%)	24/609 (3.9%)	RR 0.89 (0.3 to 2.65)	4 fewer per 1000 (from 28 fewer to 65 more)	⊕⊕⊕O MODERATE	
								3.5%		4 fewer per 1000 (from 24 fewer to 58 more)		
Hb at 24-48h postpartum (g/L) (Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	177	-	MD 0 higher (0.33 lower to 0.33 higher)	⊕⊕⊕⊕ HIGH	
Nausea												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/610 (3.8%)	32/609 (5.3%)	RR 0.72 (0.43 to 1.21)	15 fewer per 1000 (from 30 fewer to 11 more)	⊕⊕⊕⊕ HIGH	
								9%		25 fewer per 1000 (from 51 fewer to 19 more)		
Vomiting												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/610 (1.3%)	32/609 (5.3%)	RR 0.23 (0.06 to 0.85)	40 fewer per 1000 (from 8 fewer to 49 fewer)	⊕⊕⊕⊕ HIGH	
								11.3%		87 fewer per 1000 (from 17 fewer to 106 fewer)		
Diarrhea												
2	randomised trials					none	0/610 (0%)	0/609 (0%)	not pooled	not pooled		

								0%		not pooled		
Headache												
2	randomised trials	no serious risk of bias	very serious[8]	no serious indirectness	very serious[7]	none	9/610 (1.5%)	56/609 (9.2%)	RR 0.28 (0 to 90.89)	66 fewer per 1000 (from 92 fewer to 1000 more)	⊕OOO VERY LOW	
								10.3%		74 fewer per 1000 (from 103 fewer to 1000 more)		
Shivering												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	35/178 (19.7%)	2/177 (1.1%)	RR 17.4 (4.25 to 71.25)	185 more per 1000 (from 37 more to 794 more)	⊕⊕OO LOW	
								9.9%		1000 more per 1000 (from 322 more to 1000 more)		
Fever (>/= 38 degrees C)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	7/178 (3.9%)	0/177 (0%)	RR 14.92 (0.86 to 259.21)	-	⊕⊕⊕O MODERATE	
								2.1%		292 more per 1000 (from 3 fewer to 1000 more)		

[1] Enakpene 2007: Misoprostol 400mcg PO. Ng 2007: Misoprostol 400mcg PO. Parenteral placebos used.

[2] Enakpene 2007: Methylergometrine 0.5mg IM. Ng 2007: Syntometrine 2mL (oxytocin 10IU + ergometrine 1mg) IM. Oral placebos used.

[3] AMTSL in both trials.

[4] Enakpene 2007: Nigeria / exclusion criteria:contraindications to misoprostol/ergometrine use (HDP, CVD, Hx anemia, athsma, renal or hepatic disorders, allergies) or indications for prophylactic oxytocin use (grand multiparity, polyhadramnios, Hx PPH, fibroids). Ng 2007: China / exclusion criteria: fibroids, polyhadramnios, IUGR, Hx PPH, contraindications to misoprostol/syntometrine use (asthma, HDP, CVD) or indications for prophylactic oxytocin.

[5] Ng 2007.

[6] While blood loss was visually estimated in both trials, blinding should ensure that any mis-estimation of blood loss is distributed equally across groups.

[7] Small number of events and wide CI(s).

[8] Widely divergent point estimates on either side of line of no effect. I^2>90%.

[9] No explanation was provided

GRADE Table 11

Rectal misoprostol vs other injectable uterotonic (syntometrine)

Author(s):
Date: 2013-12-11
Question: Rectal misoprostol (400mcg) vs other injectable uterotonic for the third stage of labour[1,2,3]
Settings: South Africa/Jamaica[4]
Bibliography: Bamigboye AA, Merrell DA, Hofmeyr GJ, Mitchell R. Randomized comparison of rectal misoprostol with Syntometrine for management of third stage of labor. Acta obstetricia et gynecologica Scandinavica 1998;77(2):178-81. Harriott J, Christie L, Wynter S, DaCosta V, Fletcher H, Reid M. A randomized comparison of rectal misoprostol with syntometrine on blood loss in the third stage of labour. The West Indian medical journal 2009;58(3):201-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal misoprostol (400mcg)	Other injectable uterotonic	Relative (95% CI)	Absolute		
Blood loss >500mL (assessed with: visual estimation)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	2/231 (0.9%)	1/233 (0.4%)	OR 2.03 (0.18 to 22.5)	4 more per 1000 (from 4 fewer to 84 more)	⊕⊕OO LOW	
								0.4%		4 more per 1000 (from 3 fewer to 79 more)		
Blood transfusion												
1[8]	randomised trials	[9]				none	0/70 (0%)	0/70 (0%)	not pooled	not pooled		
								0%		not pooled		
Manual removal of the placenta												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/70 (0%)	1/70 (1.4%)	RR 0.33 (0.01 to 8.04)	10 fewer per 1000 (from 14 fewer to 101 more)	⊕⊕OO LOW	
								1.4%		9 fewer per 1000 (from 14 fewer to 99 more)		
Nausea												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/70 (0%)	3/70 (4.3%)	RR 0.14 (0.01 to 2.72)	37 fewer per 1000 (from 42 fewer to 74 more)	⊕⊕OO LOW	
								4.3%		37 fewer per 1000 (from		

										43 fewer to 74 more)		
Vomiting												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/70 (0%)	1/70 (1.4%)	RR 0.33 (0.01 to 8.04)	10 fewer per 1000 (from 14 fewer to 101 more)	⊕⊕OO LOW	
								1.4%		9 fewer per 1000 (from 14 fewer to 99 more)		
Shivering												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	11/70 (15.7%)	6/70 (8.6%)	RR 1.83 (0.72 to 4.68)	71 more per 1000 (from 24 fewer to 315 more)	⊕⊕OO LOW	
								8.6%		71 more per 1000 (from 24 fewer to 316 more)		

[1] Bamigboye 1998: Misoprostol 400mcg PR. Harriot 2009: Misoprostol 400mcg PR.

[2] Bamigboye 1998: Syntometrine 1mL (5IU oxytocin + 0.5mg ergometrine) IM. Harriott 2009: Syntometrine 1mL (5IU oxytocin + 0.5mg ergometrine) IM.

[3] AMTSL used in both trials.

[4] Bamigboye 1998: South Africa / Participating women considered to be 'at low risk for PPH but exclusion criteria not described". Harriot 2009: Jamaica / Exclusion criteria: Hx PPH, Hx CS, HDP, IUFD, sepsis/fever, APH, anemia.

[5] Bamigboye 1998.

[6] Participating clinicians do not appear to have been blinded, estimation of blood loss may have been influenced by knowledge of study arm allocation (particularly in Bamigboye 1998, where blood loss was visually estimated). Knowledge of study arm allocation may also have influenced clinicians' management decisions (blood tranfusion, manual removal of the placenta) or interpretation/recording of uterotonic side effects.

[7] Small number of events and wide CI.

[8] Harriot 2009.

[9] No explanation was provided

GRADE Table 12

Sublingual misoprostol vs other injectable uterotonic (ergometrine)

Author(s):
Date: 2013-12-11
Question: Should Sublingual misoprostol (any dose) vs other injectable uterotonic be used for the third stage of labour?[1,2,3]
Settings: India[4]
Bibliography: Vaid A, Dadhwal V, Mittal S, Deka D, Misra R, Sharma JB, et al. A randomized controlled trial of prophylactic sublingual misoprostol versus intramuscular methyl-ergometrine versus intramuscular 15-methyl PGF2alpha in active management of third stage of labor. Archives of gynecology and obstetrics 2009;280(6):893-7. Vimala N, Mittal S, Kumar S, Dadhwal V, Mehta S. Sublingual misoprostol versus methylergometrine for active management of the third stage of labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2004;87(1):1-5.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual misoprostol (any dose)	Other injectable uterotonic	Relative (95% CI)	Absolute		
Blood loss >1000mL (assessed with: volume/weight)												
1[5]	randomised trials					none	0/60 (0%)	0/60 (0%)	not pooled	not pooled		
								0%		not pooled		
Blood loss >500mL (assessed with: volume/weight)												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	10/126 (7.9%)	12/127 (9.4%)	RR 1.08 (0.2 to 5.84)	8 more per 1000 (from 76 fewer to 457 more)	⊕⊕OO LOW	
								9%		7 more per 1000 (from 72 fewer to 436 more)		
Need for therapeutic uterotonics												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/126 (11.1%)	17/127 (13.4%)	RR 0.87 (0.37 to 2.02)	17 fewer per 1000 (from 84 fewer to 137 more)	⊕⊕⊕O MODERATE	
								13%		17 fewer per 1000 (from 82 fewer to 133 more)		

Blood transfusion												
1[5]	randomised trials	[6]				none	0/60 (0%)	0/60 (0%)	not pooled	not pooled		
								0%		not pooled		
Maternal Hb at 24-48h postpartum (Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	67	-	MD 0 higher (0.68 lower to 0.68 higher)	⊕⊕⊕⊕ HIGH	
Manual removal of the placenta												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	0/60 (0%)	1/60 (1.7%)	RR 0.33 (0.01 to 8.02)	11 fewer per 1000 (from 17 fewer to 117 more)	⊕⊕OO LOW	
								1.7%		11 fewer per 1000 (from 17 fewer to 119 more)		
Nausea												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	6/66 (9.1%)	1/67 (1.5%)	RR 6.09 (0.75 to 49.22)	76 more per 1000 (from 4 fewer to 720 more)	⊕OOO VERY LOW	
								1.5%		76 more per 1000 (from 4 fewer to 723 more)		
Vomiting												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	8/66 (12.1%)	1/67 (1.5%)	RR 8.12 (1.04 to 63.14)	106 more per 1000 (from 1 more to 927 more)	⊕OOO VERY LOW	
								1.5%		107 more per 1000 (from 1 more to 932 more)		
Abdominal pain												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/66 (3%)	0/67 (0%)	RR 5.07 (0.25 to 103.73)	-	⊕OOO VERY LOW	
								0%		-		
Diarrhea												

1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/66 (1.5%)	0/67 (0%)	RR 3.04 (0.13 to 73.42)	-	⊕OOO VERY LOW	
								0%		-		
Shivering												
1[8]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	29/66 (43.9%)	4/67 (6%)	RR 7.36 (2.74 to 19.78)	380 more per 1000 (from 104 more to 1000 more)	⊕⊕OO LOW	
								6%		382 more per 1000 (from 104 more to 1000 more)		
Fever (>/= 38 degrees C)												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	17/126 (13.5%)	0/127 (0%)	RR 18.17 (2.47 to 133.87)	-	⊕OOO VERY LOW	
								0%		-		

[1] Vaid 2009: Misoprostol 400mcg SL. Vimala 2004: Misoprostol 400mcg SL.

[2] Vaid 2009: Methylergometrine 0.2mg IM. Vimala 2004: Methylergometrine 0.2mg IV.

[3] AMTSL used in both trials.

[4] Vaid 2009: India, women with induced or spontaneous VDs >32w GA / exclusion criteria: parity>/=5, multiple gestation, HELLP or HDP, polyhadramnios, coagulation disorders, Hx asthma or drug allergy, CVD, renal disease, epilepsy, anemia. Vimala 2004: India, low risk women.

[5] Vimala 2004.

[6] As neither study was blinded, providers' decision-making around therapeutic interventions (uterotonic Tx, blood transfusion, manual removal of the placenta) and interpretation/recording of side effects may have been influenced by knowledge of study arm allocation.

[7] Small number of events and wide CI(s).

[8] Vaid 2009.

GRADE Table 13

Misoprostol vs oxytocin for treatment of PPH (no AMTSL)

Author(s):
Date: 2014-01-09
Question: Should misoprostol vs oxytocin be used for the treatment of PPH (no AMTSL)?[1,2]
Settings: Ecuador, Egypt, Vietnam[3]
Bibliography: Winikoff B, Dabash R, Durocher J, Darwish E, Nguyen TN, Leon W, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet 2010;375(9710):210-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin	Relative (95% CI)	Absolute		
Active bleeding controlled within 20m (assessed with: blood collected in drape)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	440/488 (90.2%)	468/490 (95.5%)	RR 0.94 (0.91 to 0.98)	57 fewer per 1000 (from 19 fewer to 86 fewer)	⊕⊕⊕⊕ HIGH	
								95.5%		57 fewer per 1000 (from 19 fewer to 86 fewer)		
Time to active bleeding controlled (min) (measured with: blood collected in drape; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	488	490	-	MD 1.6 higher (0.67 to 2.53 higher)	⊕⊕⊕⊕ HIGH	
Additional blood loss >/= 300mL (assessed with: blood collected in drape)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/488 (30.1%)	83/490 (16.9%)	RR 1.78 (1.4 to 2.26)	132 more per 1000 (from 68 more to 213 more)	⊕⊕⊕⊕ HIGH	
								16.9%		132 more per 1000 (from 68 more to 213 more)		
Additional blood loss >/= 500mL (assessed with: blood collected in drape)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/488 (10.9%)	20/490 (4.1%)	RR 2.66 (1.62 to 4.38)	68 more per 1000 (from 25 more to 138 more)	⊕⊕⊕⊕ HIGH	
								4.1%		68 more per 1000 (from 25 more to 139 more)		
Additional blood loss >/= 1000mL (assessed with: blood collected in drape)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	5/488 (1%)	3/490 (0.61%)	RR 1.67 (0.4 to 6.96)	4 more per 1000 (from 4 fewer to 36 more)	⊕⊕⊕O MODERATE	
								0.6%		4 more per 1000 (from 4 fewer to 36 more)		
Total blood loss (mL) (measured with: blood collected in drape; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	488	490	-	MD 74 higher (39.92 to 108.08 higher)	⊕⊕⊕⊕ HIGH	
Additional blood loss after treatment (mL) (measured with: blood collected in drape; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	488	490	-	MD 54 higher (31.42 to 76.58 higher)	⊕⊕⊕⊕ HIGH	
Additional uterotonic drug												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/488 (12.5%)	31/490 (6.3%)	RR 1.98 (1.31 to 2.99)	62 more per 1000 (from 20 more to 126 more)	⊕⊕⊕⊕ HIGH	
								6.3%		62 more per 1000 (from 20 more to 125 more)		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/488 (8.4%)	26/490 (5.3%)	RR 1.58 (0.98 to 2.55)	31 more per 1000 (from 1 fewer to 82 more)	⊕⊕⊕⊕ HIGH	
								5.3%		31 more per 1000 (from 1 fewer to 82 more)		
Hb at discharge (measured with: at discharge; when possible >12h after IV fluids; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	447	464	-	MD 3 lower (4.82 to 1.18 lower)	⊕⊕⊕⊕ HIGH	
Hysterectomy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/488 (0%)	0/490 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE	
								0%		not pooled		
Fluids and/or plasma expanders												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	89/488 (18.2%)	47/490 (9.6%)	RR 1.9 (1.37 to 2.65)	86 more per 1000 (from 35 more to 158 more)	⊕⊕⊕⊕ HIGH	
								9.6%		86 more per 1000 (from 36 more to 158 more)		

Exploration under anesthesia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	99/488 (20.3%)	90/490 (18.4%)	RR 1.1 (0.85 to 1.43)	18 more per 1000 (from 28 fewer to 79 more)	⊕⊕⊕⊕ HIGH	
								18.4%		18 more per 1000 (from 28 fewer to 79 more)		
Bimanual compression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	294/488 (60.2%)	283/490 (57.8%)	RR 1.04 (0.94 to 1.16)	23 more per 1000 (from 35 fewer to 92 more)	⊕⊕⊕⊕ HIGH	
								57.8%		23 more per 1000 (from 35 fewer to 92 more)		
Shivering												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	229/488 (46.9%)	82/490 (16.7%)	RR 2.8 (2.25 to 3.49)	301 more per 1000 (from 209 more to 417 more)	⊕⊕⊕⊕ HIGH	
								16.7%		301 more per 1000 (from 209 more to 416 more)		
Fever (any)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	217/488 (44.5%)	27/490 (5.5%)	RR 8.07 (5.52 to 11.8)	390 more per 1000 (from 249 more to 595 more)	⊕⊕⊕⊕ HIGH	
								5.5%		389 more per 1000 (from 249 more to 594 more)		
Fever >/= 40 degrees C												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	66/488 (13.5%)	0/490 (0%)	RR 133.54 (8.29 to 2151.28)	-		
								0%		-		
Nausea (assessed with: questionnaire at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/488 (10%)	41/490 (8.4%)	RR 1.2 (0.81 to 1.78)	17 more per 1000 (from 16 fewer to 65 more)	⊕⊕⊕⊕ HIGH	
								8.4%		17 more per 1000 (from 16 fewer to 66 more)		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	24/488 (4.9%)	7/490 (1.4%)	RR 3.44 (1.5 to 7.92)	35 more per 1000 (from 7 more to 99 more)	⊕⊕⊕O MODERATE	
								1.4%		34 more per 1000 (from 7		

										more to 97 more)		
Fainting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	4/488 (0.8%)	4/490 (0.8%)	RR 1 (0.25 to 3.99)	0 fewer per 1000 (from 6 fewer to 24 more)	⊕⊕⊕O MODERATE	
								0.8%		0 fewer per 1000 (from 6 fewer to 24 more)		
Diarrhea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	2/488 (0.4%)	2/490 (0.4%)	RR 1 (0.14 to 7.1)	0 fewer per 1000 (from 4 fewer to 25 more)	⊕⊕⊕O MODERATE	
								0.4%		0 fewer per 1000 (from 3 fewer to 24 more)		
Intolerable shivering (assessed with: reported by participant - questionnaire at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	55/488 (11.3%)	1/490 (0.2%)	RR 55.23 (7.67 to 397.48)	111 more per 1000 (from 14 more to 809 more)	⊕⊕OO LOW	
								16.7%		1000 more per 1000 (from 1000 more to 1000 more)		
Intolerable fever (assessed with: reported by participant - questionnaire at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	45/488 (9.2%)	0/490 (0%)	RR 91.37 (5.64 to 1479)	-	⊕⊕OO LOW	
								5.5%		1000 more per 1000 (from 255 more to 1000 more)		
Intolerable nausea (assessed with: reported by participant - questionnaire at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/488 (0%)	0/490 (0%)	-	-	⊕⊕⊕O MODERATE	
								8.4%		84 fewer per 1000 (from 84 fewer to 84 fewer)		
Intolerable vomiting (assessed with: reported by participant - questionnaire at discharge)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	1/488 (0.2%)	0/490 (0%)	RR 3.01 (0.12 to 73.76)	-	⊕⊕⊕⊕ HIGH	
								1.4%		28 more per 1000 (from 12 fewer to 1000 more)		
Intolerable fainting (assessed with: reported by participant - questionnaire at discharge)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/488 (0%)	0/490 (0%)	-	-	⊕⊕⊕O MODERATE	
								0.8%		8 fewer per 1000 (from 8 fewer to 8 fewer)		
Intolerable diarrhea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	0/488 (0%)	0/490 (0%)	-	-	⊕⊕⊕O MODERATE	
								0.4%		4 fewer per 1000 (from 4 fewer to 4 fewer)		

[1] Misoprostol 800mcg SL plus IV placebo

[2] Oxytocin 40IU in 1000mL IV solution over 15m plus SL placebo

[3] Inclusion criteria: Dx of primary PPH based on measured blood loss >700mL (978 of 9348 women with blood loss measured following VD). Exclusion criteria: allergy/contraindication to PG use, uterotonics in labour, non-atonic PPH, CS. AMTSL not used in routinely in study settings. No routine oxytocin induction/augmentation.

[4] Small number of events.

[5] No events

[6] Small number or no events in control group, very wide CI.

GRADE Table 14

Misoprostol vs oxytocin for treatment of PPH (following AMTSL)

Author(s):
Date: 2014-01-09
Question: Should misoprostol vs oxytocin be used for the treatment of PPH (following AMTSL)?[1,2]
Settings: Varied [3]
Bibliography: Blum J, Winikoff B, Raghavan S, Dabash R, Ramadan MC, Dilbaz B, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. Lancet 2010;375(9710):217-23.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin	Relative (95% CI)	Absolute		
Active bleeding controlled within 20m												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	363/407 (89.2%)	360/402 (89.6%)	RR 1 (0.95 to 1.04)	0 fewer per 1000 (from 45 fewer to 36 more)	⊕⊕⊕⊕ HIGH	
								89.6%		0 fewer per 1000 (from 45 fewer to 36 more)		
Time to active bleeding controlled (min) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	407	402	-	MD 0.2 higher (1.84 lower to 2.24 higher)	⊕⊕⊕⊕ HIGH	
Additional blood loss >/= 300mL (assessed with: collected in drape and volume measured)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	139/407 (34.2%)	123/402 (30.6%)	RR 1.12 (0.91 to 1.36)	37 more per 1000 (from 28 fewer to 110 more)	⊕⊕⊕⊕ HIGH	
								30.6%		37 more per 1000 (from 28 fewer to 110 more)		
Additional blood loss >/= 500mL (assessed with: collected in drape and volume measured)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/407 (14.3%)	53/402 (13.2%)	RR 1.08 (0.76 to 1.53)	11 more per 1000 (from 32 fewer to 70 more)	⊕⊕⊕⊕ HIGH	
								13.2%		11 more per 1000 (from 32 fewer to 70 more)		
Additional blood loss >/= 1000mL (assessed with: collected in drape and volume measured)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	11/407 (2.7%)	3/402 (0.7%)	RR 3.62 (1.02 to 12.88)	20 more per 1000 (from 0 more to 89 more)	⊕⊕⊕O MODERATE	
								0.8%		21 more per 1000 (from 0 more to 95 more)		
Total blood loss (measured with: collected in drape and volume measured; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	407	402	-	MD 27 higher (11.86 lower to 65.86 higher)	⊕⊕⊕⊕ HIGH	
Additional blood loss after treatment (measured with: collected in drape and volume measured; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	407	402	-	MD 27 higher (4.56 lower to 58.56 higher)	⊕⊕⊕⊕ HIGH	
Additional uterotonic drug												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/407 (9.8%)	46/402 (11.4%)	RR 0.86 (0.58 to 1.28)	16 fewer per 1000 (from 48 fewer to 32 more)	⊕⊕⊕⊕ HIGH	
								11.4%		16 fewer per 1000 (from 48 fewer to 32 more)		
Blood transfusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/407 (5.9%)	18/402 (4.5%)	RR 1.32 (0.73 to 2.39)	14 more per 1000 (from 12 fewer to 62 more)	⊕⊕⊕⊕ HIGH	
								4.5%		14 more per 1000 (from 12 fewer to 63 more)		
Hb at discharge (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	383	384	-	MD 1 lower (2.91 lower to 0.91 higher)	⊕⊕⊕⊕ HIGH	
Hysterectomy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	4/407 (1%)	2/402 (0.5%)	RR 1.98 (0.36 to 10.72)	5 more per 1000 (from 3 fewer to 48 more)	⊕⊕⊕O MODERATE	
								0.5%		5 more per 1000 (from 3 fewer to 49 more)		
Exploration under anesthesia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/407 (9.1%)	22/402 (5.5%)	RR 1.66 (1 to 2.76)	36 more per 1000 (from 0 more to 96 more)	⊕⊕⊕⊕ HIGH	
								5.5%		36 more per 1000 (from 0		

										more to 97 more)		
Bimanual compression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/407 (9.6%)	31/402 (7.7%)	RR 1.24 (0.79 to 1.95)	19 more per 1000 (from 16 fewer to 73 more)	⊕⊕⊕⊕ HIGH	
								7.7%		18 more per 1000 (from 16 fewer to 73 more)		
Shivering												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/407 (37.3%)	59/402 (14.7%)	RR 2.54 (1.95 to 3.32)	226 more per 1000 (from 139 more to 340 more)	⊕⊕⊕⊕ HIGH	
								14.7%		226 more per 1000 (from 140 more to 341 more)		
Fever (any) (assessed with: min. temperature not defined)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/407 (21.6%)	59/402 (14.7%)	RR 1.47 (1.09 to 1.99)	69 more per 1000 (from 13 more to 145 more)	⊕⊕⊕⊕ HIGH	
								14.7%		69 more per 1000 (from 13 more to 146 more)		
Fever >/= 40 degrees C												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	5/407 (1.2%)	1/402 (0.2%)	RR 4.94 (0.58 to 42.08)	10 more per 1000 (from 1 fewer to 102 more)	⊕⊕⊕O MODERATE	
								0.3%		12 more per 1000 (from 1 fewer to 123 more)		
Nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/407 (14.5%)	69/402 (17.2%)	RR 0.84 (0.61 to 1.16)	27 fewer per 1000 (from 67 fewer to 27 more)	⊕⊕⊕⊕ HIGH	
								17.2%		28 fewer per 1000 (from 67 fewer to 28 more)		
Vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/407 (4.7%)	10/402 (2.5%)	RR 1.88 (0.88 to 3.99)	22 more per 1000 (from 3 fewer to 74 more)	⊕⊕⊕⊕ HIGH	
								2.5%		22 more per 1000 (from 3 fewer to 75 more)		
Fainting or feeling faint												
1	randomised	no serious	no serious	no serious	no serious	none	58/407	58/402	RR 0.99 (0.71	1 fewer per 1000 (from	⊕⊕⊕⊕	

	trials	risk of bias	inconsistency	indirectness	imprecision		(14.3%)	(14.4%)	to 1.38)	42 fewer to 55 more)	HIGH	
								14.4%		1 fewer per 1000 (from 42 fewer to 55 more)		
Diarrhea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	5/407 (1.2%)	3/402 (0.7%)	RR 1.65 (0.4 to 6.84)	5 more per 1000 (from 4 fewer to 44 more)	⊕⊕⊕O MODERATE	
								0.8%		5 more per 1000 (from 5 fewer to 47 more)		

[1] Misoprostol 800mcg SL plus IV placebo.

[2] Oxytocin 40IU in 1000mL IV solution over 15m plus SL placebo.

[3] Trial sites at five hospitals in Burkina Faso, Egypt, Turkey, Vietnam. Management of third stage w/ ocytocin routine in all settings.

[4] Small number of events

GRADE Table 15

Misoprostol vs oxytocin and ergometrine for treatment of PPH

Author(s):
Date: 2014-01-09
Question: Should misoprostol vs oxytocin and ergometrine be used for the treatment of PPH?[1,2,3]
Settings: South Africa[4]
Bibliography: Lokugamage AU, Sullivan KR, Niculescu I, Tigere P, Onyangunga F, El Refaey H, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. Acta obstetricia et gynecologica Scandinavica 2001;80(9):835-9.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol	Oxytocin and ergometrine	Relative (95% CI)	Absolute		
Active bleeding controlled within 20m (assessed with: varied[5])												
1	randomised trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/32 (93.8%)	21/32 (65.6%)	RR 1.43 (1.09 to 1.86)	282 more per 1000 (from 59 more to 564 more)	⊕⊕⊕⊕ HIGH	
								65.6%		282 more per 1000 (from 59 more to 564 more)		
Additional uterotonic drug												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/32 (6.3%)	11/32 (34.4%)	RR 0.18 (0.04 to 0.76)	282 fewer per 1000 (from 83 fewer to 330 fewer)	⊕⊕⊕⊕ HIGH	
								34.4%		282 fewer per 1000 (from 83 fewer to 330 fewer)		
Hysterectomy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	0/32 (0%)	0/32 (0%)	-	-	⊕⊕⊕O MODERATE	
								0.5%		5 fewer per 1000 (from 5 fewer to 5 fewer)		

[1] Misoprostol 800mcg PR plus IV placebo.
[2] Syntometrine IM 1 ampoule (5IU oxytocin + 500mcg ergometrine maleate) plus syntocinon (10IU oxytocin in 500mL normal saline) plus rectal placebo.
[3] Inclusion criteria: Dx of PPH w/in 24 hours of VD or CS based on >500ml estimated blood loss + poorly contracted uterus. Women w/ HTN, CVD, asthma, other contraindications to prostaglandin use excluded from study.

[4] Teaching hospitals, S. Africa. AMTSL used for some women (equal amount in each arm of study); not clear what drug(s) used for AMTSL.
[5] Blood loss assessed visually.
[6] While blood loss was assessed visually, providers were blinded to treatment arm. Research doctor running study aware of treatment allocation, therefore detection bias possible.
[7] Small number of events.

GRADE Table 16

Misoprostol as adjunct to standard treatment for PPH

Author(s):
Date: 2014-01-09
Question: Should misoprostol as adjunct to standard treatment be used for for PPH?[1,2]
Settings: Varied[3]
Bibliography: Hofmeyr GJ, Ferreira S, Nikodem VC, Mangesi L, Singata M, Jafta Z, et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]. BMC pregnancy and childbirth 2004;4(1):16. Walraven G, Dampha Y, Bittaye B, Sowe M, Hofmeyr J. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology 2004;111(9):1014-7. Widmer M, Blum J, Hofmeyr GJ, Carroli G, Abdel-Aleem H, Lumbiganon P, et al. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. Lancet 2010;375(9728):1808-13. Zuberi NF, Durocher J, Sikander R, Baber N, Blum J, Walraven G. Misoprostol in addition to routine treatment of postpartum hemorrhage: a hospital-based randomized-controlled trial in Karachi, Pakistan. BMC pregnancy and childbirth 2008;8:40.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Misoprostol as adjunct to standard treatment	Control	Relative (95% CI)	Absolute		
Additional blood loss >500mL (within 1h) (assessed with: collected in pan/sheet and volume/weight measured)												
4	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	121/930 (13%)	138/950 (14.5%)	RR 0.8 (0.55 to 1.15)	29 fewer per 1000 (from 65 fewer to 22 more)	⊕⊕⊕⊕ HIGH	
								13.2%		26 fewer per 1000 (from 59 fewer to 20 more)		
Additional blood loss >1000mL (within 1h) (assessed with: collected in pan/sheet and volume/weight measured)												
3[5]	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/901 (1.3%)	14/918 (1.5%)	RR 0.88 (0.41 to 1.91)	2 fewer per 1000 (from 9 fewer to 14 more)	⊕⊕⊕⊕ HIGH	
								1.3%		2 fewer per 1000 (from 8 fewer to 12 more)		
Blood transfusion												
4	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	139/928 (15%)	150/949 (15.8%)	RR 0.95 (0.77 to 1.17)	8 fewer per 1000 (from 36 fewer to 27 more)	⊕⊕⊕⊕ HIGH	

								15.6%		8 fewer per 1000 (from 36 fewer to 27 more)		
Use of additional uterotonics												
3[5]	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	254/895 (28.4%)	271/910 (29.8%)	RR 0.96 (0.84 to 1.1)	12 fewer per 1000 (from 48 fewer to 30 more)	⊕⊕⊕⊕ HIGH	
								28.3%		11 fewer per 1000 (from 45 fewer to 28 more)		
Postpartum Hb <60g/L or blood transfusion (assessed with: at 12-24 hours post-delivery)												
2[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/189 (16.9%)	29/197 (14.7%)	RR 1.15 (0.73 to 1.83)	22 more per 1000 (from 40 fewer to 122 more)	⊕⊕⊕⊕ HIGH	
								14.7%		22 more per 1000 (from 40 fewer to 122 more)		
Postpartum Hb <80g/L or blood transfusion (assessed with: at or within 24h post-delivery)												
2[7]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	164/815 (20.1%)	176/833 (21.1%)	RR 1.01 (0.74 to 1.38)	2 more per 1000 (from 55 fewer to 80 more)	⊕⊕⊕O MODERATE	
								25.6%		3 more per 1000 (from 67 fewer to 97 more)		
Hysterectomy and/or ICU admission												
4	randomised trials	no serious risk of bias[4]	serious	no serious indirectness	serious[9]	none	11/930 (1.2%)	12/951 (1.3%)	RR 0.95 (0.23 to 3.94)	1 fewer per 1000 (from 10 fewer to 37 more)	⊕⊕OO LOW	
								0.7%		0 fewer per 1000 (from 5 fewer to 21 more)		
Shivering (any) at or within 1h												
4	randomised trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecision	none	556/928 (59.9%)	270/948 (28.5%)	RR 2.24 (1.72 to 2.91)	353 more per 1000 (from 205 more to 544 more)	⊕⊕⊕O MODERATE	
								17.7%		219 more per 1000 (from 127 more to 338 more)		

Shivering (severe) at or within 1h												
2[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	80/733 (10.9%)	7/749 (0.9%)	RR 11.64 (5.41 to 25.03)	99 more per 1000 (from 41 more to 225 more)	⊕⊕⊕O MODERATE	
								0.5%		53 more per 1000 (from 22 more to 120 more)		
Nausea (any) at or within one hour												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/812 (6.2%)	42/830 (5.1%)	RR 1.22 (0.82 to 1.82)	11 more per 1000 (from 9 fewer to 41 more)	⊕⊕⊕⊕ HIGH	
								6.2%		14 more per 1000 (from 11 fewer to 51 more)		
Nausea (severe) at or within one hour												
2[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	2/733 (0.3%)	1/749 (0.1%)	RR 2.04 (0.19 to 22.41)	1 more per 1000 (from 1 fewer to 29 more)	⊕⊕OO LOW	
								0.1%		1 more per 1000 (from 1 fewer to 21 more)		
Fever at or within one hour												
4	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/926 (37.3%)	120/948 (12.7%)	RR 2.91 (2.42 to 3.5)	242 more per 1000 (from 180 more to 316 more)	⊕⊕⊕⊕ HIGH	
								9.6%		183 more per 1000 (from 136 more to 240 more)		
Vomiting at or within one hour												
2[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	38/733 (5.2%)	17/749 (2.3%)	RR 2.29 (1.3 to 4.01)	29 more per 1000 (from 7 more to 68 more)	⊕⊕⊕O MODERATE	
								2.7%		35 more per 1000 (from 8 more to 81 more)		
Diarrhea at or within one hour												
2[11]	randomised	no serious	no serious	no serious	serious[9]	none	2/733	3/749	RR 0.68	1 fewer per 1000	⊕⊕⊕O	

	trials	risk of bias	inconsistency	indirectness			(0.3%)	(0.4%)	(0.11 to 4.05)	(from 4 fewer to 12 more)	MODERATE	
								0.2%		1 fewer per 1000 (from 2 fewer to 6 more)		

[1] Hofmeyr: oxytocic + 1000mcg misoprostol (200 mcg PO, 400 mcg buccal/SL, 400mcg PR) or oxytocic + oral/SL/rectal placebo. Walraven: ocytocic + 600mcg misoprostol (200mcg PO,400mcg SL) or oxytocic + oral/SL placebo. Widmer: oxytocin 10 IU IM or IV + 600mcg misoprostol SL or ocytocin 10 IU IM or IV and placebo. Zuberi: oxytocin IV + 600mcg misoprostol SL or oxytocin IV + placebo

[2] Criteria for enrollment in trial - Hofmeyr: "more than expected bleeding" at least 10m after delivery, thought to be attributed to uterine atony. Walraven: measured blood loss 500mL or more within 1 hour of birth, attributed to uterine atony. Widmer: clinical Dx of PPH suspected to be due to uterine atony. Zuberi: measured blood loss of 500mL or more within one hour of birth, attributable to uterine atony.

[3] Hofmeyr: South Africa. Walraven: Gambia. Widmer: Argentina, Egypt, South Africa, Thailand, Vietnam. Zuberi: Pakistan. AMTSL routine in all settings. Hofmeyr: oxytoxin 10 IU or syntometrine 1 ampoule. Walraven: oxytoxin 10 IU or syntometrine 1 ampoule. Widmer: mostly (98%) oxytocin. Zuberi: oxytoxin 10 IU or 10 IU oxytocin + 0.4mg ergometrine.

[4] Double-blinding in all studies, adequate allocation concealment. Small number (6/250) women excluded from final analysis in Hofmeyr b/c it was unclear whether they'd been given treatment or placebo.

[5] Hofmeyr, Walraven, Widmer.

[6] Hofmeyr, Walraven.

[7] Hofmeyr, Widmer.

[8] Limited overlap of confidence intervals. I^2>50%.

[9] Small number of events, wide CIs.

[10] No explanation was provided

[11] Widmer, Zuberi.

GRADE table 17:

Tranexamic acid vs placebo for the third stage of labour

Author(s):
Date: 2015-07-16
Question: Should Tranexamic acid vs placebo be used for the third stage of labour?[1]
Settings: Turkey, Iran
Bibliography: Gungorduk K, Asıcıoğlu O, Yildirım G, Ark C, Tekirdağ Aİ, Besimoglu B. Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study. Am J Perinatol 2012 Sep 21;30(5):407-13; Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, Shirdel M. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol. 2015 Feb;55(1).

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Placebo	Relative (95% CI)	Absolute		
Blood loss >500mL (assessed with: weighed drape)												
2	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[3]	no serious imprecision	none	13/280 (4.6%)	30/279 (10.8%)	RR 0.43 (0.23 to 0.8)	61 fewer per 1000 (from 22 fewer to 83 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								15.9%		91 fewer per 1000 (from 32 fewer to 122 fewer)		
Blood loss >/= 1000 mL												
2	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[3]	no serious imprecision	none	2/280 (0.7%)	7/279 (2.5%)	RR 0.28 (0.06 to 1.36)	18 fewer per 1000 (from 24 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
								2.8%		20 fewer per 1000 (from 26 fewer to 10 more)		
Need for add'l uterotonic												
2	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[3]	no serious imprecision	none	9/280 (3.2%)	26/279 (9.3%)	RR 0.35 (0.16 to 0.72)	61 fewer per 1000 (from 26 fewer to 78 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								10.2%		66 fewer per 1000 (from 29 fewer to 86 fewer)		
Hb at 24h post delivery (mg/L) (Better indicated by higher values)												
1[4]	randomised trials	no serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220	219	-	MD 6 higher (3.8 to 8.2 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Nausea												
2	randomised trials	serious[2,5]	no serious inconsistency	serious[3]	serious[6]	none	35/280 (12.5%)	12/279 (4.3%)	RR 2.83 (1.52 to 5.25)	79 more per 1000 (from 22 more to 183 more)	⊕OOO VERY LOW	IMPORTANT
								4.3%		79 more per 1000 (from 22 more to 183 more)		
Diarrhea												
1[4]	randomised trials	serious[2,5]	no serious inconsistency	no serious indirectness	serious[7]	none	16/220 (7.3%)	4/219 (1.8%)	RR 3.98 (1.35 to 11.72)	54 more per 1000 (from 6 more to 196 more)	⊕⊕OO LOW	IMPORTANT
								1.8%		54 more per 1000 (from 6 more to 193 more)		
Dizziness (assessed with: method unclear [5])												
1[8]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[7]	none	2/60 (3.3%)	0/60 (0%)	RR 5 (0.25 to 102)	-	⊕OOO VERY LOW	IMPORTANT
								0%		-		
Fever (not defined)												
1[4]	randomised trials	serious[2,5]	no serious inconsistency	no serious indirectness	serious[7]	none	3/220 (1.4%)	2/219 (0.91%)	RR 1.49 (0.25 to 8.85)	4 more per 1000 (from 7 fewer to 72 more)	⊕⊕OO LOW	IMPORTANT
								0.9%		4 more per 1000 (from 7 fewer to 71 more)		
Headache												
1[4]	randomised trials	serious[2,5]	no serious inconsistency	no serious indirectness	serious[7]	none	7/220 (3.2%)	11/219 (5%)	RR 0.63 (0.25 to 1.6)	19 fewer per 1000 (from 38 fewer to 30 more)	⊕⊕OO LOW	IMPORTANT
								5%		19 fewer per 1000 (from 38 fewer to 30 more)		
Shivering												
1[4]	randomised trials	serious[2,5]	no serious inconsistency	no serious indirectness	serious[7]	none	7/220 (3.2%)	4/219 (1.8%)	RR 1.74 (0.52 to 5.87)	14 more per 1000 (from 9 fewer to 89 more)	⊕⊕OO LOW	IMPORTANT
								1.8%		13 more per 1000 (from 9 fewer to 88 more)		
Vomiting (assessed with: method unclear [5])												
1[4]	randomised trials	serious[2,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/220 (13.6%)	14/219 (6.4%)	RR 2.13 (1.16 to 3.91)	72 more per 1000 (from 10 more to 186 more)	⊕⊕⊕O MODERATE	IMPORTANT
								6.4%		72 more per 1000 (from 10 more to 186 more)		

[1] Gungorduk 2013: 1g/10mL TXA in 20mL 5% glucose. All participants given standard AMTSL: 10 IU oxytocin within 2m of bith, early cord clamping, CCT. Mirghafouvand 2015: 1g TXA dissolved in 5mL distilled water. All participants given 10 IU oxytocin in 500mL NS over 20m; other aspects of third stage mgmt not clear.

[2] Gungorduk 2013: labelling of IV bags may have made providers aware of study arm allocation -- possibility of bias, particularly w/ subjectively assessed outcomes (e.g. add'l uterotonic and possible drug side effects. Mirghafourvand 2015: based on study protocol, the lead researcher may have been aware of study arm allocation -- possibility of bias w/ subjectively assessed outcomes.

[3] Mirghafourvand 2015: High episiotomy rates noted across study -- both groups 87%.

[4] Gungorduk 2013

[5] Gongorduk 2013: unclear at what point which side effects were assessed -- some assessment occured after unblinding. Possibility for differential assessment based on whether study arm allocation was known.

[6] Wide confidence intervals due to small number of events in one study (Mirghafourand 2015).

[7] Wide confidence interval due to small number of events

[8] Mirghafourvand 2015

GRADE Table 18:

Tranexamic acid as adjunct to standard treatment for the treatment of PPH

Author(s):
Date: 2015-08-12
Question: TXA as adjunct to standard treatment for the treatment of PPH[1,2]
Settings:
Bibliography: Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, Mandelbrot L, Tillouche N, Fontaine S, Le Goueff F, Depret-Mosser S, Vallet B; EXADELI Study Group. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care 2011;15(2):R117.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA as adjunct to standard treatment	Control	Relative (95% CI)	Absolute		
Development of severe PPH (as defined in protocol) (assessed with: composite variable developed by researchers[3])												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	27/77 (35.1%)	37/74 (50%)	RR 0.7 (0.48 to 1.03)	150 fewer per 1000 (from 260 fewer to 15 more)	⊕⊕OO LOW	
								50%		150 fewer per 1000 (from 260 fewer to 15 more)		
Persistent bleeding at 30m after randomization												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	28/77 (36.4%)	40/74 (54.1%)	RR 0.67 (0.47 to 0.97)	178 fewer per 1000 (from 16 fewer to 286 fewer)	⊕⊕OO LOW	
								54.1%		179 fewer per 1000 (from 16 fewer to 287 fewer)		
Hemoglobin drop >40g/L (assessed with: Hb following delivery compared with last antenatal Hb measurement)												
1	randomised trials	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	19/77 (24.7%)	32/74 (43.2%)	RR 0.57 (0.36 to 0.91)	186 fewer per 1000 (from 39 fewer to 277 fewer)	⊕⊕⊕O MODERATE	
								43.2%		186 fewer per 1000 (from 39 fewer to 276 fewer)		
PRBC transfusion in first 6w postpartum												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	13/77 (16.9%)	20/74 (27%)	RR 0.62 (0.34 to 1.16)	103 fewer per 1000 (from 178 fewer to 43 more)	⊕⊕OO LOW	
								27%		103 fewer per 1000 (from 178 fewer to 43 more)		
ICU admission												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	3/77 (3.9%)	5/74 (6.8%)	RR 0.58 (0.14 to 2.33)	28 fewer per 1000 (from 58 fewer to 90 more)	⊕⊕OO LOW	
								6.8%		29 fewer per 1000 (from 58 fewer to 90 more)		
DVT												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[5]	2/77 (2.6%)	1/74 (1.4%)	RR 1.92 (0.18 to 20.75)	12 more per 1000 (from 11 fewer to 267 more)	⊕OOO VERY LOW	
								1.4%		13 more per 1000 (from 11 fewer to 276 more)		
Nausea/vomiting												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[5]	12/77 (15.6%)	1/74 (1.4%)	RR 11.53 (1.54 to 86.49)	142 more per 1000 (from 7 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT
								1.4%		147 more per 1000 (from 8 more to 1000 more)		
All non-severe side effects												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[5]	18/77 (23.4%)	4/74 (5.4%)	RR 4.32 (1.54 to 12.18)	179 more per 1000 (from 29 more to 604 more)	⊕OOO VERY LOW	
								5.4%		179 more per 1000 (from 29 more to 604 more)		

[1] Participants allocated to treatment arm received 4gg tranexamic acid (TXA) in 50mL saline over 1 hr, then 1g TXA/h over 6 hours. All participants received standard Tx for PPH: oxytocin 30 IU over 30m and 500mcg of sulprostone if no effect from oxytocin, bladder catherization, genital tract exam, exploration of uterus and manual removal of placenta as required.

[2] Participants were randomized into study if PPH >800mL and other inclusion criteria met (>18yo, no hemostatic abnormalities or Hx of VTE or epilepsy, consent to participate).

[3] Development of severe PPH was defined as: peripartum Hb decrease >40g/L; transfusion of 4 or more units of packed RBCs; invasive hemostatic intervenion (e.g. arterial embolization or surgical intervention); death.

[4] Researchers describe study as being "partially blind" - study arm allocation was known to anesthetists who administered TXA but not communicated to participants or obstetricians, midwives or nurses. Clinicians providing direct care to participants would have been aware of presence of IV in participants allocated to TXA arm of study.

[5] Protocol for study registered only after study completion and publication of results occured many years after study completion. (per Cochrane review: Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2014 Feb 13;2:CD003249.)

[6] Wide confidence interval due to small number of events