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RESEARCH ARTICLE

General obstetrics

Postpartum haemorrhage in high-resource settings: Variations in clinical management and future research directions based on a comparative study of national guidelines

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Abstract

Objective: To compare guidelines from eight high-income countries on prevention and management of postpartum haemorrhage (PPH), with a particular focus on severe PPH.

Design: Comparative study.

Setting: High-resource countries.

Population: Women with PPH.

Methods: Systematic comparison of guidance on PPH from eight high-income countries.

Main outcome measures: Definition of PPH, prophylactic management, measurement of blood loss, initial PPH-management, second-line uterotonics, non-pharmacological management, resuscitation/transfusion management, organisation of care, quality/methodological rigour.

Conclusions: Our study highlights areas where strong evidence is lacking. There is need for a universal definition of (severe) PPH. Consensus is required on how and when to quantify blood loss to identify PPH promptly. Future research may focus on timing and sequence of second-line uterotonics and non-pharmacological interventions and how these impact maternal outcome. Until more data are available, different transfusion strategies will be applied. The use of clear transfusion-protocols are nonetheless recommended to reduce delays in initiation. There is a need for a collaborative effort to develop standardised, evidence-based PPH guidelines.

Results: Definitions of (severe) PPH varied as to the applied cut-off of blood loss and incorporation of clinical parameters. Dose and mode of administration of prophylactic uterotonics and methods of blood loss measurement were heterogeneous. Recommendations on second-line uterotonics differed as to type and dose. Obstetric management diverged particularly regarding procedures for uterine atony. Recommendations on transfusion approaches varied with different thresholds for blood transfusion and supplementation of haemostatic agents. Quality of guidelines varied considerably.

KEYWORDS
clinical guidelines, obstetric haemorrhage, postpartum haemorrhage

1 | INTRODUCTION

Severe postpartum haemorrhage (PPH) is an important cause of severe maternal outcome in high-income countries. Although the maternal mortality ratio (MMR) due to PPH has been decreasing in several high-income countries, it remains among the leading causes of maternal mortality.[1-5] Reasons for the decrease in MMR are hypothesised to include implementation of national and local audit processes, simulation training, skills and drills training, and development of national evidence-based clinical practice guidelines (CPG).[3,6,7]

Most high-income countries have established CPGs for PPH, which are generally available in the local language to make these accessible to all practitioners. Although CPGs often refer to the same scientific literature, the care context in each country may substantially impact interpretation and translation into local guidance. Also, expert opinion is influenced considerably by country-specific practices.[8]

Earlier comparisons of guidelines on the prevention and management of PPH pointed out the urgent need for more robust research into the clinical management of more severe forms of PPH.[9,10] Comparing the recommended management of severe PPH is particularly important, as several countries have reported an increasing incidence of severe PPH and PPH-related severe morbidity, whereas other countries have reported a decline.[11-14]

The primary aim of this study was to compare national guidance for the management of PPH, with a particular focus on severe PPH, with regard to the applied definitions of (severe) PPH, prophylactic and initial management of PPH, second-line uterotonics and non-pharmacological management after first-line treatment fails, resuscitation and transfusion management and organisation of maternity care for PPH. Our study may inform future research agendas around (severe) PPH management and provide new insights to policy makers, health professionals and researchers.

2 | METHODS

In November 2021, we selected eight national CPGs from high-income countries about the prevention and management of PPH in English, French, Dutch, German or Italian. The guidelines were sourced directly through the websites of these eight professional societies. As we were particularly interested in guidance used in high-resource settings, we did not include the guideline of the World Health Organization (WHO) and International Federation of Gynaecology and Obstetrics (FIGO), which we hypothesised to be used mostly in low- and middle-income countries.[15,16]

We included the most recent updates of the guidelines of the following professional societies (Table S1):

- French College of Gynaecologists and Obstetricians (CNGOF);[17]
- The Dutch 'Nederlandse Vereniging voor Obstetrie en Gynaecologie' (NVOG);[18]
- German Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Austrian Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) and Swiss Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe SGGG);[19]
- Royal College of Obstetricians and Gynaecologists (RCOG);[20]
- American College of Obstetricians and Gynecologists (ACOG);[21]
- Italian Sistema Nazionale Linee Guida (SNLG);[22]
- Society of Obstetricians and Gynaecologists of Canada (SOGC)[23]
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).[24]

To compare these guidelines, we extracted the following information from each: (a) definitions of (severe) PPH, (b) prophylactic measures; haemorrhage risk assessment/prophylactic uterotonic/controlled cord traction/early cord clamping/manual removal of placenta in the absence of bleeding, (c) measurement of blood loss, (d) initial management of PPH; choice and timing of first line uterotonic/uterine massage/emptying bladder/performance and timing of manual uterine exploration/performance and timing of assessment of the genital tract, (e) choice and timing of second-line uterotonics (defined as uterotonics applied when the first type of uterotonic is found to fail in stopping the bleeding); injectable prostaglandins/oxytocin agonists/misoprostol/ergots alkaloids, (f) choice and timing of non-pharmacological management; intrauterine tamponade/transcatheter arterial embolisation/surgical vascular ligation/placement of compression sutures/peripartum hysterectomy, (g) composition of resuscitation and transfusion management; fluid replacement therapy/transfusion therapy/coagulation screening/fibrinogen/recombinant activated factor VII/tranexamic acid/cell salvage, and (h) factors related to organisation of care; clinical leadership/transfer of patients/patient surveillance/documentation/obstetric simulation training and other PPH-related training.

Guideline selection was done by PdV/TvdA. Relevant information for each item was summarised into tables by PdV and reviewed by TvdA/CD-T. All data were checked for accuracy by the entire group of authors and summarised in Tables 1–4 and Tables S1–S3.

The quality and methodological rigour of the guidelines were independently assessed by three authors (PdV, TvdA, CD-T) with the Appraisal of Guidelines for Research & Evaluation instrument (Agree II).[25] All guidelines were assessed on twenty-three items divided by six domains: scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; editorial independence. For each item in these domains, seven values can be given in a range from 1 (strongly disagree) to 7 (strongly agree). Domain scores were calculated as the sum of all the scores of the individual items in a domain and scaled in percentages of the maximum possible score for that domain. If

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TABLE 1 Definition postpartum haemorrhage: severe postpartum haemorrhage.

Organisation	PPH/severe PPH	Definition
CNGOF	PPH	Blood loss ≥500 ml after birth regardless route of delivery
	Severe PPH	Blood loss ≥1000 ml after birth regardless of the route of delivery
RCOG	PPH	The loss of ≥500 ml of blood from the genital tract within 24 hours of the birth of a baby
	Severe PPH	Moderate: 1000–2000 ml blood loss Severe: >2000 ml blood loss
ACOG	PPH	Cumulative blood loss ≥1000 ml accompanied by signs or symptoms of hypovolaemia within 24 hours after the birth process (includes intrapartum loss) regardless of the route of delivery
	Severe PPH	No definition
NVOG	PPH	Blood loss of ≥1000 ml regardless of mode of birth
	Severe PPH	No definition
DGGG/OEGGG/SGGG	PPH	Blood loss of ≥500 ml following vaginal delivery Blood loss of ≥1000 ml following caesarean section
	Severe PPH	No definition
SNLG	PPH	Blood loss of ≥500 ml regardless of route of delivery
	Severe PPH	Blood loss ≥1000 ml regardless of the route of delivery *Controlled major obstetric haemorrhage*: controlled blood loss, with compromised maternal condition requiring careful monitoring *Persistent major obstetric haemorrhage*: persistent severe blood loss and/or signs of shock with life-threatening maternal condition
SOGC	PPH	Traditionally the definition of PPH has been blood loss in excess of 500 ml after vaginal delivery and in excess of 1000 ml after abdominal delivery. For clinical purposes, any blood loss that has the potential to produce haemodynamic instability should be considered to be PPH
	Severe PPH	No definition
RANCZOG	PPH	Blood loss of ≥500 ml despite route of delivery
	Severe PPH	Blood loss with signs of haemodynamic compromise regardless of the estimated volume of blood loss

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CNGOF, French College of Gynaecologists and Obstetricians; DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; ml, millilitres; OEGGG, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe; PPH, postpartum haemorrhage; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCOG, Royal College of Obstetricians and Gynaecologists; SGGG, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe; SNLG, Italian Sistema Nazionale Linee Guida; SOGC, Society of Obstetricians and Gynaecologists of Canada.

an item was considered 'non-judgeable', it was not included in this calculation. High-quality guidelines were, after consensus between PdV, TvdA and CDT, those with an overall domain score >75%.

No patients were involved in the development of this research.

3 | RESULTS

3.1 | Definition PPH and severe PPH

Most countries (6/8) define PPH as blood loss of ≥500 ml. Two guidelines define PPH according to mode of birth with a cut-off of ≥500 ml after vaginal birth and ≥1000 ml after caesarean section (Table 1). Italy/USA also include the physiological response to bleeding in their definition. The Netherlands/ USA define PPH as blood loss over 1000 ml, with 3/8 guidelines considering this by definition to be *severe* PPH. Only half of the guidelines provide a definition of *severe* PPH.

Only in the UK guideline is PPH classified as mild (≥500 ml), moderate (1000–2000 ml) or major blood loss (≥2000 ml).

3.2 | Prophylactic management of PPH

In total, 7/8 guidelines mention a haemorrhage-related risk assessment to anticipate early treatment of PPH or guide discussion on the most appropriate site of birth (Table 2). The correction of prenatal anaemia is mentioned in 5/8 guidelines, but Italy is the only country specifying *when* to screen during pregnancy.

In the case of a vaginal birth, all guidelines recommend a prophylactic bolus of oxytocin for active management of the third stage of labour but the route of administration (intramuscular versus intravenous) and the dose (3–10 IU) vary between guidelines.

In the case of a caesarean section, carbetocin is proposed as an alternative prophylactic uterotonic in 3/8 guidelines. The use of oxytocin per slow infusion in different doses in

TABLE 2 Prophylactic management postpartum haemorrhage.

	CNGOF	NVOG	RCOG	ACOG	DGGG/OEGGG/SGGG	SNLG	SOGC	RANZCOG
Haemorrhage risk assessment	PPH risk factors are not globally predictive. In women at risk for PPH, multidisciplinary discussion of the site of birth is necessary and must take into account the nature of the risk and the speed of access to blood products Prenatal anaemia: iron supplementation	Recommended to anticipate early treatment. Prenatal anaemia: not specified	Recommended. Care plans must be modified when risk factors for PPH arise. Women with known risk factors for PPH should only be delivered in a hospital with a blood bank on site. Prenatal anaemia: to be investigated and treated appropriately	Not recommended. Vigilance is needed in all patients, even in those first thought to be low risk. Prenatal anaemia: not specified	Recommended. Prenatal anaemia: anaemia (<9 g/dl) is considered a risk factor to be assessed antenatally	Recommended Women at risk of PPH (listed) are referred to appropriate healthcare facilities. Vigilance and early PPH-diagnosis are recommended in all care settings as many PPH cases do not present identifiable highrisk factors Prenatal anaemia: every woman should be screened for anaemia at 28 and 33–37 weeks of pregnancy	All parturient women are at risk for PPH. Extra risk factors should be recognised (they are listed) to take appropriate action Prenatal anaemia: not specified	Recommended. All women should birth in a unit with rapid access to blood and blood products. In women at risk of PPH, appropriate management should be initiated antenatally and intrapartum Prenatal anaemia: to be corrected
Prophylactic uterotonic	VB: Oxytocin, 5 or 10 IU IIM or a slow IV. Women at cardiovascular risk: very slow IV administration for longer than 5 min to limit haemodynamic effects CS: Oxytocin: slow IV 5–10 IU. Routine maintenance treatment by an IV infusion can be performed as long as it does not exceed 10 IU/hour	Oxytocin. In low-risk patients: 5 IU IM or slow IV CS or women at increased risk of haemorrhage: 5 IU slow IV followed by 10 IU/4 hours	Oxytocin, 10 IU IM. Women at increased risk of PPH: Ergometrine 500 mcg + oxytocin 5 IU in 1 ml (Syntometrine) may be used in the absence of hypertension CS: oxytocin 5 IU by slow IV injection	Oxytocin, dilute intravenous infusion (bolus 10 IU) or 10 IU IM	VB Oxytocin, 3–5 IU slow IV infusion. CS: Oxytocin, 3–5 IU slow IV infusion or carbetocin 100 mcg by short infusion or slow IV infusion	Oxytocin, recommended, 10 IU IM, followed by slow IV infusion of 8–10 UI/hour in isotonic solution for 2–4 h in case of PPH high risk women. CS: oxytocin 3–5 IU by slow IV injection, followed by slow. IV infusion of 8–10 IU/hour in isotonic solution for 2–4 hours	VB: Oxytocin, 10 IU IM, or 5 to 10 IU IV/1 to 2 minutes or IV infusion 20–40 IU in 1000 ml, (150 ml/hour) Women at increased risk of PPH: Carbetocin 100 μg IM Ergonovine 0.2 mg and misoprostol, 600–800 μg, oral, sublingual, or rectal when oxytocin is not available CS: carbetocin, 100 mcg IV bolus/1 minute	Oxytocin, dose or route of administration not mentioned. Syntometrine may reduce the need for additional uterotonics and other PPH interventions CS: Carbetocin has been shown to be equivalent to oxytocin bolus with oxytocin infusion for reducing PPH

TABLE 2 (Continued)

	CNGOF	NVOG	RCOG	ACOG	DGGG/OEGGG/SGGG	SNLG	SOGC	RANZCOG
Controlled cord traction	Not recommended	Recommended	Recommended	Recommended	Not recommended	Recommended for CS. VB: only after administration of oxytocin, umbilical cord clamping and signs of placental detachment	Recommended	Recommended
Early cord clamping	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Recommended only for fetal indication	Recommended only for fetal indication	Not specified
Manual removal of placenta in case of placenta retention in the absence of bleeding	30–60 minutes after birth	30–60 minutes after birth. If blood loss <500 ml, VP normal and operating theatre immediately available, it can be considered to wait 60 minutes	Not specified	Not specified	Not specified	30–60 minutes after birth	30–45 minutes after birth	Not specified

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CNGOF, French College of Gynaecologists and Obstetricians; CS, caesarean section; DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; IM, intramuscular; IU, international unit; IV, intravenous; mg, milligram; min, minutes; ml, millilitres; OEGGG, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe; PPH, postpartum haemorrhage; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCOG, Royal College of Obstetricians and Gynaecologists; SGGG, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe; SNLG, Italian Sistema Nazionale Linee Guida; SOGC, Society of Obstetricians and Gynaecologists of Canada; VB, vaginal birth; VP, vital parameters; mcg, microgram.

TABLE 3 Initial management postpartum haemorrhage.

	CNGOF	NVOG	RCOG	ACOG	DGGG/OEGGG/SGGG	SNLG	SOGC[a]	RANZCOG[a]
First-line uterotonic	Oxytocin 5–10 IU slow IV or IM followed by a maintenance infusion of 5–10 IU/hour for 2 hours (Maximum 40 IU) Timing: within 30 minutes after onset PPH	Oxytocin 40 IU slow IV, followed by oxytocin infusion 2.5 IE/4 hours. Timing: not specified	Oxytocin 5 IU IM. Oxytocin infusion (40 IU in 500 mL isotonic crystalloids at 125 ml/hour) unless fluid restriction is necessary Timing: not specified	Oxytocin, 10 IU IM or 10–40 IU in 1000-ml continuous infusion. Timing: not specified	10–40 IU oxytocin in 500–1000 mL saline as a continuous infusion (dose depends on the clinical situation, particularly the impact on uterine tone). Timing: not specified	5 IU oxytocin slow IV or Ergometrin 2 × 0.2 mg IM or 5 IU IV or 5 IU oxytocin IV combined with ergometrin 0.2 mg IM followed by oxytocin infusion 10 IU for 2 hours Timing: not specified	10 IU IM oxytocin. 5 IU IV push 20 to 40 IU in 250 ml of normal saline, infused IV at an hourly rate of 500–1000 ml Timing: not specified	5 IU slow IV (if already administered for 3rd stage management, a repeat dose may be given) Oxytocin 40 IU IV infusion/4 hoursTiming: not specified
Measurement of blood loss	Collector bag. Start: in case of overt PPH	Weigh blood loss. Start: immediately after birth in case of women at high risk of PPH or if blood loss is superior to what is normal	Blood collection drapes for vaginal deliveries and weighing of swabs. Clinical signs and assessment should be included in the assessment of blood loss Start: not specified	Collector bag and/or weighing. Start: Immediately after the infant's birth (before delivery of placenta)	Weigh blood loss. Collect all blood-soaked pads, bedding, linens and significant coagulum Start: not specified	Blood collection drapes for vaginal deliveries and weighing of swabs Symptoms, clinical signs of hypovolaemia and degree of shock should be included in the assessment of blood loss Start: once minor PPH has been diagnosed	Clinical markers (signs and symptoms) rather than a visual estimation of blood loss Start: not specified	Weigh blood loss. Start: not specified
Uterine massage	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
Emptying bladder	Recommended	Not specified	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended

TABLE 3 (Continued)

	CNGOF	NVOG	RCOG	ACOG	DGGG/OEGGG/SGGG	SNLG	SOGC[a]	RANZCOG[a]
Manual uterine exploration	Recommended Timing: within 30 minutes after PPH diagnosis	Not specified	Recommended Timing: not specified	Retention of placental tissue can be identified by bedside ultrasound or manual examination Timing: when PPH exceeds expecting volumes	Only when retention of placental tissue is suspected after ultrasound or examination of the placenta Timing: once PPH initiates	Recommended Timing: as soon as first and second-line uterotonics do not appear to be effective	Recommended Timing: not specified	Recommended for all cases of persistent haemorrhage Timing: in case of persistent haemorrhage
Assessment of the genital tract	Recommended. Timing: within 30 minutes after PPH diagnosis	Not specified	Recommended Timing: not specified	Recommended Timing: when PPH exceeds expecting volumes	Recommended Timing: once PPH initiates	Recommended Timing: as soon as first and second-line uterotonics do not appear to be effective	Recommended Timing: not specified	Recommended Timing: not specified

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CNGOF, French College of Gynaecologists and Obstetricians; DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; IM, intramuscular; IU, international units; IV, intravenous; mg, milligram; min, minutes; ml, millilitres; OEGGG, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe; PPH, postpartum haemorrhage; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCOG, Royal College of Obstetricians and Gynaecologists; SGGG, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe; SNLG, Italian Sistema Nazionale Linee Guida; SOGC, Society of Obstetricians and Gynaecologists of Canada.

[a]Do not distinguish between first- and second-line uterotonics. Together with the uterotonics mentioned in Table 4, these uterotonics are all part of the 'additional' uterotonics that can be given in case of established PPH.

TABLE 4 Second-line uterotonics for postpartum haemorrhage.

	CNGOF	NVOG	RCOG	ACOG	DGGG/OEGGG/SGGG	SNLG	SOGC[a]	RANZCOG[a]
Misoprostol	Not recommended if oxytocin available	Not recommended. Misoprostol is only effective in the absence of any other uterotonic	800 μg sublingually Timing: not specified	600–1000 mcg orally, sublingual or rectally Timing: not specified	Not recommended due to presence of other more effective uterotonics	Not recommended due to presence of other more effective uterotonics	400–800 mcg oral or sublingual or 800–1000 mcg rectally Timing: not specified	1000 mg rectally. Timing: not specified
Injectable prostaglandins	Sulprostone maximum 500 mcg in 500 ml/hour Timing: within 30 min of PPH diagnosis, should oxytocin be ineffective	Sulprostone 500 mcg/30 min, maintenance dose 60–120 mcg/hour Timing: not specified	Carboprost tromethamine 0.25 mg IM every 15 minutes, maximum of 8 doses. Timing: not specified	Carboprost tromethamine 0.25 mg IM every 15–90 minutes, maximum 8 doses. Timing: not specified	Sulprostone 500 μg in 500 mL, 100 ml/hour, maximum of 500 ml/hour. Maintenance dose: 100 ml/hour. Timing: immediately once first-line uterotonics appear not to be effective	Sulprostone 0.50 mg IV in 250 mL; 0.1–0.4 mg/hour, maximum 1.5 mg/24 hours. Timing: immediately once first-line uterotonics appear not to be effective	Carboprost tromethamine 0.25 IM or intramyometrially, every 15 minutes to a maximum of 2 mg (8 doses) Timing: not specified	Carboprost tromethamine 0.25 mg IM every 15 min to max 2.0 mg (8 doses). Intramyometrially 0.5 mg Timing: not specified
Oxytocin agonist	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Carbetocin 100 mcg IM or IV over 1 minute Timing: not specified	Not recommended
Ergot alkaloids	Not recommended given the range of serious cardiovascular side effects	Ergometrine 0.2 mg IV or IM Timing: not specified	Ergometrine 0.5 mg IV or IM Timing: not specified	Methylergonovine 0.2 mg IM every 2–4 hours Timing: not specified	Not recommended given the range of serious side effects and the fact that better alternatives are available	Ergometrine 0.2 mg IM (2×) Timing: immediately once first-line uterotonics appear not to be effective	Ergonovine 0.25 mg IM or IV, can be repeated every 2 hours Timing: not specified	Ergometrine 0.25 mg by IV or IM, can be repeated up to a max of 1.0 mg Timing: not specified

Note: Reported side effects – misoprostol: diarrhoea, abdominal pain, nausea and vomiting, shivering and pyrexia; carboprost tromethamine: vomiting, abdominal pain, diarrhoea and bronchospasm; sulprostone: nausea, vomiting and diarrhoea; carbetocin: side effect profile similar to oxytocin, which is not significantly worse than placebo for common side-effects such as nausea and vomiting;[25,49] ergot alkaloids: hypertension, pain after birth, nausea and vomiting.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CNGOF, French College of Gynaecologists and Obstetricians; DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; IM, intramuscular; IU, international units; IV, intravenous; min, minutes; ml, millilitres; OEGGG, Österreichische Gesellschaft für Gynäkologie und Geburtshilfe; PPH, postpartum haemorrhage; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCOG, Royal College of Obstetricians and Gynaecologists; SGGG, Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe; SNLG, Italian Sistema Nazionale Linee Guida; SOGC, Society of Obstetricians and Gynaecologists of Canada; mcg, microgram.

[a]Do not distinguish between first- and second-line uterotonics. Together with the uterotonics mentioned in Table 3, these uterotonics are all part of the 'additional' uterotonics that can be given in case of established PPH.

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addition to the standard prophylactic injection of oxytocin is recommended in 3/8 guidelines.

Controlled cord traction is not recommended in the French or the German guidelines, and removal of the placenta (in the absence of bleeding) is mentioned in only half of the guidelines, in which case recommendations vary from proceeding to manual removal within 30 to 60 minutes after birth.

3.3 | Measuring blood loss

Different recommendations exist on how to measure blood loss, varying from collector bags (1/8), weighing of blood loss (3/8) or a combination of both (3/8) (Table 2). The Canadian guideline states that rather than relying on visual estimation, clinical markers (signs and symptoms) should be used. The additional use of clinical markers to assess severity of PPH has also been suggested in Italy/UK. Timing of blood loss quantification is specified in 3/8 guidelines either immediately after the infant's birth (UK) or in the case of overt PPH (France).

3.4 | Initial management

Although there is consensus to use oxytocin as the first-line uterotonic for PPH management, in addition to the prophylaxis dose once PPH ensues, recommended dosages, timing and route of administration vary (Table 3). Australia/New Zealand and Canada do not make a distinction between first-line and second-line uterotonics and do not specify which uterotonic is first choice. There is consensus among the guidelines to empty the bladder and perform uterine massage. Indication and timing of manual uterine exploration and examination of the genital tract vary.

3.5 | Second-line uterotonics

All guidelines recommend one or several types of second-line uterotonics after failure of oxytocin as a first-line agent for the initial treatment of PPH (Table 4). France, Italy and the German-speaking countries specify *when* second-line uterotonics should be administered during the course of PPH. Although most guidelines recommend the use of multiple second-line uterotonics, the sequence in which these should be given is only specified in the British guideline.

Notable variations about the use of second-line uterotonics included:

- Injectable prostaglandins are recommended in all guidelines either in the form of sulprostone or carboprost tromethamine. Administration regimens of sulprostone vary between guidelines, whereas these are uniform for carboprost tromethamine. The French specify the administration of sulprostone within 30 minutes of onset of PPH should oxytocin be ineffective or earlier if bleeding is severe.
- Oxytocin agonists are only recommended as the second-line uterotonic of choice for the management of PPH in the Canadian guideline.
- Half of the guidelines recommend misoprostol either rectally or sublingually, whereas the other half do not recommend misoprostol at all as a second-line agent if oxytocin is available, stating there is insufficient data to support superiority of adding misoprostol to using oxytocin alone.
- Ergot alkaloids are recommended in 6/8 guidelines either as ergometrine or methylergometrine, but are not recommended by the French and the German-speaking countries in view of serious side effects and other available alternatives.

3.6 | Non-pharmacologic management of severe PPH

The French guideline defines specific management strategies for each mode of birth. Four of eight guidelines adapt management strategies according to the aetiology of PPH (Table S2).

Uterine tamponade is recommended in all guidelines after failure of second-line uterotonics and different options to perform uterine tamponade are specified such as intrauterine balloon tamponade (by different devices), vaginal packing and inserting gauzes coated with a haemostatic agent into the uterus. Two guidelines stress not ruling out other therapeutic options, suggesting uterine tamponade should be seen as a 'bridging' measure to accomplish brief haemostasis while preparing the patient for more invasive definite interventions.

Transcatheter arterial embolisation after vaginal birth is recommended by 7/8 guidelines when second-line uterotonics fail and before resorting to surgical procedures such as compression sutures, pelvic artery ligation or hysterectomy, the timing of which are found to be dependent on the patient's haemodynamic status (3/8). Only the German guideline recommends transcatheter arterial embolisation as a last resort after surgical treatment has been exhausted. The UK underlines the logistical limits of transcatheter arterial embolisation where 'the equipment or an interventional radiologist may not be available'.

Surgical procedures that may contribute to avoiding hysterectomy and preserve a woman's fertility are compression sutures and vascular ligation. Both options are recommended by all guidelines, with variations with regard to the time frame in which these procedures should be performed. Some guidelines specify which type of compression suture can be applied (5/8). Half recommend involving a senior obstetrician-gynaecologist or vascular surgeon when vascular ligation of the internal iliac artery is considered.

All guidelines urge that emergency peripartum hysterectomy should be performed in time to prevent death but

recommendations vary with regard to the surgical approach being a subtotal or total hysterectomy. Three of eight guidelines advise involving a second senior clinician in the decision and performance of peripartum hysterectomy, in light of its high complication rate.

3.7 | Resuscitation and transfusion management of PPH and severe PPH

Resuscitation management is an essential part of the management of (severe) including hemodynamically guided fluid replacement, transfusion therapy and pharmacological therapy (Table S3).

- Volume replacement therapy by crystalloids is mentioned in 6/8 CPGs as having to start as soon as PPH is diagnosed.

Recommendations on transfusion of red blood cells and fresh frozen plasma are either ratio-based (3/8) or laboratory guided (4/8).

- Most guidelines (6/8) recommend platelet transfusion with transfusion thresholds varying between 50×10^9/l to 1000×10^9/l during ongoing PPH.

- Half the guidelines recommend the use of point-of-care clotting tests. The French and British guidelines mention bedside testing for haemoglobin.
- Thresholds for supplementation of fibrinogen vary between 1.5 and 2.5 g/l and only the US guideline does not recommend substituting fibrinogen. Most guidelines recommend the use of fibrinogen, the UK guideline recommends cryoprecipitate and the Italian guideline proposes three alternatives: FFP, fibrinogen or cryoprecipitate.
- Tranexamic acid (TXA) is recommended in half of the guidelines and timing and dose are similar. The UK guideline recommends the use of prophylactic TXA in women during caesarean sections with an increased risk of PPH.
- We found consensus among the guidelines that rFVIIa should only be used in case of life-threatening haemorrhage, due to its high cost, questionable efficacy and possible risks of adverse thrombo-embolic events.
- Cell salvage is mentioned in 5/8 guidelines in women at high risk of (severe) PPH, e.g. women refusing allogenous blood transfusion or placenta accreta spectrum. For patients refusing blood transfusion, only Italy and USA recommend a formal informed consent signed by the patient and her physician to document the products and alternatives that she is willing to accept or decline. None of the guidelines provides specific guidance on prevention and management of PPH in these women.

3.8 | Factors related to organisation of care

All guidelines refer to organisational aspects concerning the management of severe PPH, such as patient surveillance and documentation of the course of PPH on specific monitoring charts (Table S4). Most guidelines recommend a multidisciplinary approach to severe PPH with the presence of a senior obstetrician and anaesthesiologist. Guidelines mentioning transfers between hospitals for transcatheter arterial embolisation or admission into an intensive care unit (3/8) stress this should only be considered in haemodynamically stable patients.

Multidisciplinary simulation trainings are recommended by half of the guidelines. Italy recommends the implementation of surgical skills trainings for compression sutures and/or vessel ligation.

3.9 | Appraisal of clinical practice guidelines

According to the appraisal of the guidelines by the AGREE II criteria, the Italian, French and UK guidelines can be considered high-quality guidelines (overall domain rate >75%; Figure S1). The Italian guideline was attributed the highest overall score (93%), and the Dutch and Canadian guidelines obtained the lowest scores (57.0%). Domains that generally scored low were editorial independence (43%) and applicability (48%). Half of the guidelines failed to provide easily identifiable and interpretable recommendations.

4 | DISCUSSION

Our comparative study of eight national guidelines on the management of PPH brings to light five crucial issues.

First, there is no consensus on the definition of (severe) PPH, hampering international collaborations. Most guidelines refer to the 2012 WHO PPH definition: >500 ml of blood loss, regardless mode of birth.[15] The use of a definition according to mode of birth, historically based on the average blood loss, which appeared to be higher in caesarean sections, seems rather illogical given that the woman's response to bleeding is independent from the mode of birth.[26] ACOG has incorporated clinical parameters to express the physiological response to bleeding, allowing for a more universal approach to PPH.[27-30] Defining the severity of PPH may guide clinicians as to when to escalate management. The Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis recommends to also define *massive* PPH. Such a definition may provide guidance as to when to proceed to invasive treatment and initiate massive transfusion protocols.[31] Currently, only the UK has implemented such a definition.

We advocate for the use of a universal consensus definition for (severe) PPH, taking into account the physiological response to bleeding. This may contribute to a common understanding and may help arrive at guidance for the timing of escalating to more advanced clinical management.

Secondly, guidelines are conflicting with regard to prevention of PPH. Despite recent evidence that intravenous administration of oxytocin is more effective than

intramuscular administration in preventing PPH during vaginal birth without any additional safety concerns, most guidelines still recommend the intramuscular route.[32,33] Variations in recommendations regarding blood loss measurements to diagnose PPH can probably be explained by the lack of evidence supporting one method over another.[34] Although measurements seem to be more accurate than visual estimation alone, no difference has been reported in terms of maternal outcome. Moreover, measuring blood loss can be time-consuming, contributing to delays in PPH management.[34-36] The addition of clinical parameters may provide an earlier warning of (severity) of PPH.[35] Variations as to when to start blood loss quantification may contribute to differences in the incidence of (severe) PPH among countries highlighting the need for consensus.

There is no consensus on how and when to quantify blood loss in order to identify PPH promptly. The incorporation of clinical parameters such as the bleeding rate may result in earlier detection of (severity) of haemorrhage, reducing delay in PPH management. Future studies might focus on the timing of initiation of blood loss measurement and how this relates to the timing of interventions to manage PPH.

Thirdly, recommendations vary on how to manage more severe forms of PPH. There is controversy about a possible association between the (simultaneous) use of sulprostone and ergot alkaloids on one hand and severe cardiovascular side effects on the other.[37-40] Most guidelines do not provide guidance on the sequence in which second-line uterotonics should be administered and we did not find any data investigating the use of multiple uterotonics regarding maternal outcome. After failure of intrauterine tamponade, guidance diverges about when to proceed to transcatheter arterial embolisation or surgical procedures. The literature does not provide high-level evidence as to the ideal sequence of these interventions.[41-50]

Variations in recommendations on how to manage more severe forms of PPH highlight areas that require a stronger evidence-base, such as the use of multiple second-line uterotonics and timing and sequence of non-pharmacological interventions.

Fourthly, there is no consensus on transfusion approaches, and the timing of and indication for haemostatic agents, reflecting the lack of high-quality evidence in obstetric patients. Although goal-directed transfusion has been related to improved outcomes in other contexts, its use is limited when blood loss is massive, explaining the increased interest in point-of-care testing.[51-53] Although there seems to be consensus to maintain platelet levels above 50×10^9/l, the trigger to initiate supplementation in order to maintain platelet levels above this cut-off remains unclear, explaining the reported differences in our study. There is no evidence that fibrinogen should be administered preemptively, but supplementation of levels <2 g/dl with fibrinogen concentrate or cryoprecipate may reduce the risk of severe PPH.[54-56] The absence of recommendations on the use of tranexamic acid in half of the guidelines could be explained by the fact these have not been revised after publication of new evidence on the use of tranexamic acid in early-stage PPH.[57-60] Even in absence of high-level evidence, the presence of a clear local or national protocol on transfusion management has been related to improved outcome.[61-64]

Until more data are available, different transfusion strategies are likely to be applied by clinicians. To reduce delays in administration of blood products, use of a local or national transfusion protocol is highly recommended. More trials are necessary to compare fixed ratio and goal-directed transfusion therapy in obstetric patients.

Fifthly, we report variations in the quality of the guidelines and interpretations of available evidence. Guidelines may vary based on cultural, historical and local factors. For instance, road networks and transportation play a vital role in decision-making in some CPGs, for instance in recommendations around transcatheter arterial embolisation.[65,66]Bundling a selection of existing recommendations in PPH care-bundles, such as proposed by ACOG, can improve implementation of guidelines.[67]

There is a need for a collaborative effort to develop standardised, evidence-based CPGs for high-resource settings with clear guidance on how these recommendations should be applied in various contexts.

Main strengths of our study are the systematic and detailed comparison of eight guidelines in different languages with emphasis on severe PPH as well as the international panel of authors and the quality appraisal of the guidelines. Limitations are that we did not review all high-income countries. Although there are some similarities between our study and the recently published FIGO guideline, our results remain relevant as they provide additional information about the definitions of (severe) PPH used in different guidelines, as well as the differences in guidance for transfusion/resuscitation management and organisation of care, both of which are crucial elements in PPH management. Moreover, we included guidance from other high-income countries that were not included in the FIGO guideline. Where the FIGO review mainly focuses on best available evidence on prevention and management in low-resource settings, our focus is on high-income settings, which might explain the different research agendas proposed.

In conclusion, considerable variations among guidelines exist with regard to the definition, diagnosis and management of (severe) PPH. These discrepancies, which may reflect differences in care context and 'obstetric culture', highlight areas where strong evidence is lacking and may inform future research agendas. There is need for a collaborative effort to develop a high-quality, standardised, evidence-based guideline and clinical practice algorithm for high-resource settings.

AUTHOR CONTRIBUTIONS

PdV/TvdA/CD-T developed the study design. The assessment of the guidelines was performed by PdV/TvdA. Quality of guidelines was appraised by PdV/TvdA/CD. Relevant

information for each item was summarised into tables by PdV and reviewed by TvdA/CD. All data were checked for accuracy by all the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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