PPH Prevention and Management:
Updated PPH Guidelines

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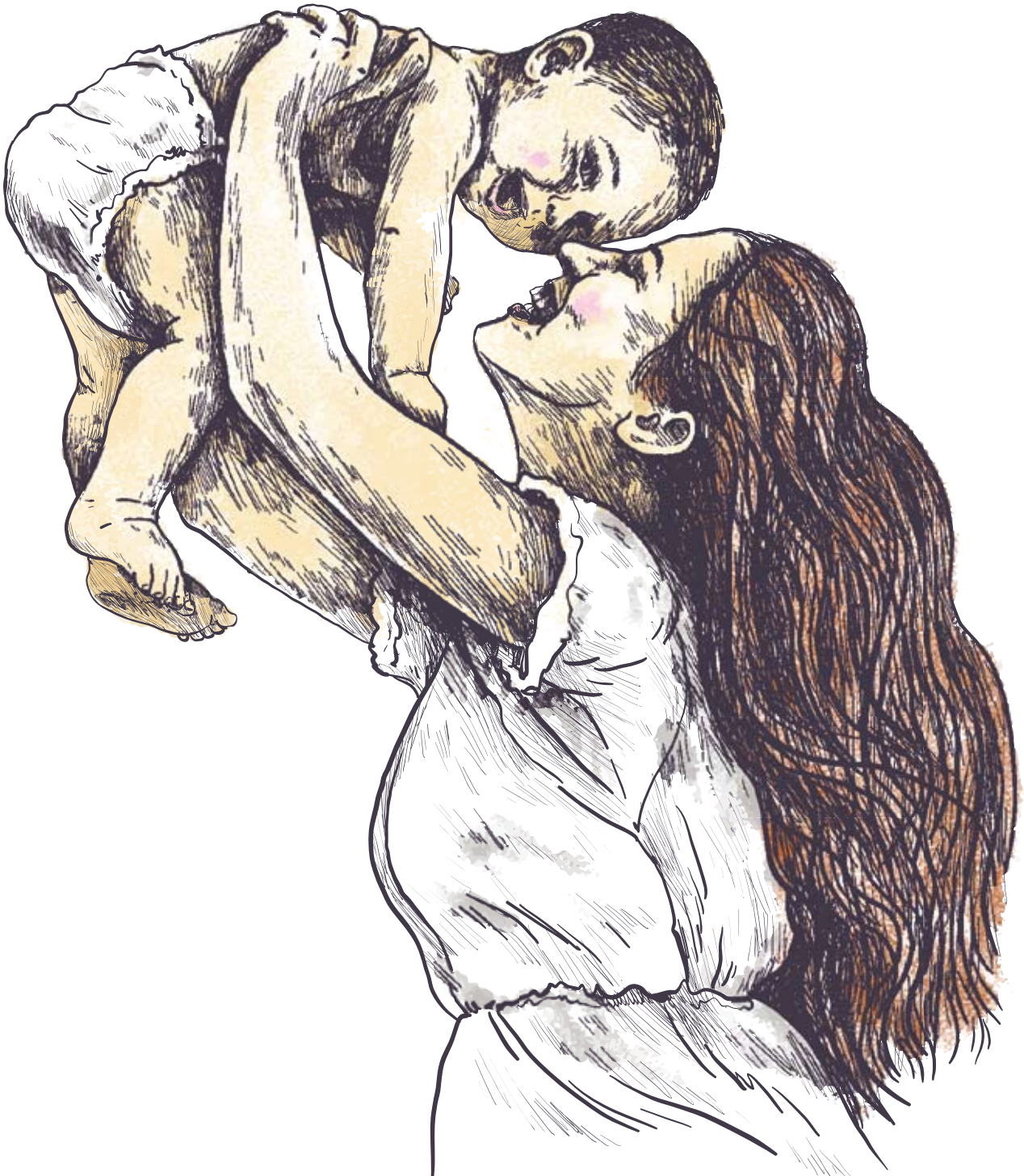

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PPH Prevention and Management:
Updated PPH Guidelines

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Dear Friends,

India is a diverse cultural country with unique advantages and challenges. Of the medical challenges this vast country faces, prevention and management of Postpartum Hemorrhage (PPH) stands out because of the impact it has both on the women and their newborn, healthcare system, and the families.

Interventions to treat PPH generally proceed from less to more invasive and include compression techniques, medications, procedures, and surgeries. PPH management varies significantly according to available resources.

FOGSI has taken upon itself to create an updated guideline with experts from the country with support and guidance from key dignitaries from FIGO. I appreciate and thank the efforts of all the experts in creating the guideline.

S. Shantha Kumari

Dr. S. Shantha Kumari
President, FOGSI 2022

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INTRODUCTION

Maternal mortality is the death of a woman from complications during pregnancy, irrespective of the duration and site of pregnancy, childbirth, or within 42 days of termination of pregnancy, excluding accidental or incidental causes. Maternal mortality is understood through the Maternal Mortality Ratio (MMR), which is the number of deaths per 100,000 live births.[1]

About 20% of maternal deaths are reported in South Asia. Among the countries in South Asia with the highest maternal deaths (35000 maternal deaths) estimated globally in 2017, India accounted for 12% of global maternal mortality, trailing Nigeria (23%). Postpartum hemorrhage (PPH) is the most common cause of maternal death worldwide.[2] In India, the leading cause of maternal death is the obstetric hemorrhage, which as been reported in 47% of the cases and this number could be higher in poorer states.[3] A critical step towards preventing maternal mortality is timely diagnosis and management of PPH, which is underdiagnosed in primary care facilities in India.[4]

As per the latest data from World Health Organization (WHO) and United Nations Children's Fund (UNICEF) (2017), India accounts for 12% of world maternal deaths. In March 2022, the Special Bulletin on MMR–released by the Registrar General of India showed a 10-point decline in MMR, from 113 in 2016–18 to 103 in 2017–19.[5]

PURPOSE OF THE UPDATED GUIDELINES

- To reduce maternal mortality and a maternal near miss, particularly due to PPH
- The universal approach to clinical management at all levels of settings
- Clear guidelines for PPH management at each level of facility and community to provide optimum and respectful maternity care
- Promoting non-clinical components and strengthening referral protocol
- Adding new uterotonics which are evidence-based in a medical protocol like carbetocin
- Adding evidence-based other drugs such as tranexamic acid to the medical management
- Adding mechanical methods such as uterine balloon tamponades (UBT) and non-pneumatic anti-shock garment (NASG)
- Adding the new surgical/other evidence-based techniques, National/ International
- Reducing the global burden of PPH

EPIDEMIOLOGY

PPH is the most common cause of maternal death, accounting for about 35% of all maternal deaths worldwide. The incidence of PPH is 2%–4% after vaginal delivery and 6% after a cesarean section.[2] In 2017, estimated 24 million children were born and about 35,000 mothers died

during childbirth or shortly thereafter, giving a maternal mortality rate of 145 every 100 000 live births. This rate represented 12% of global maternal deaths.[3]

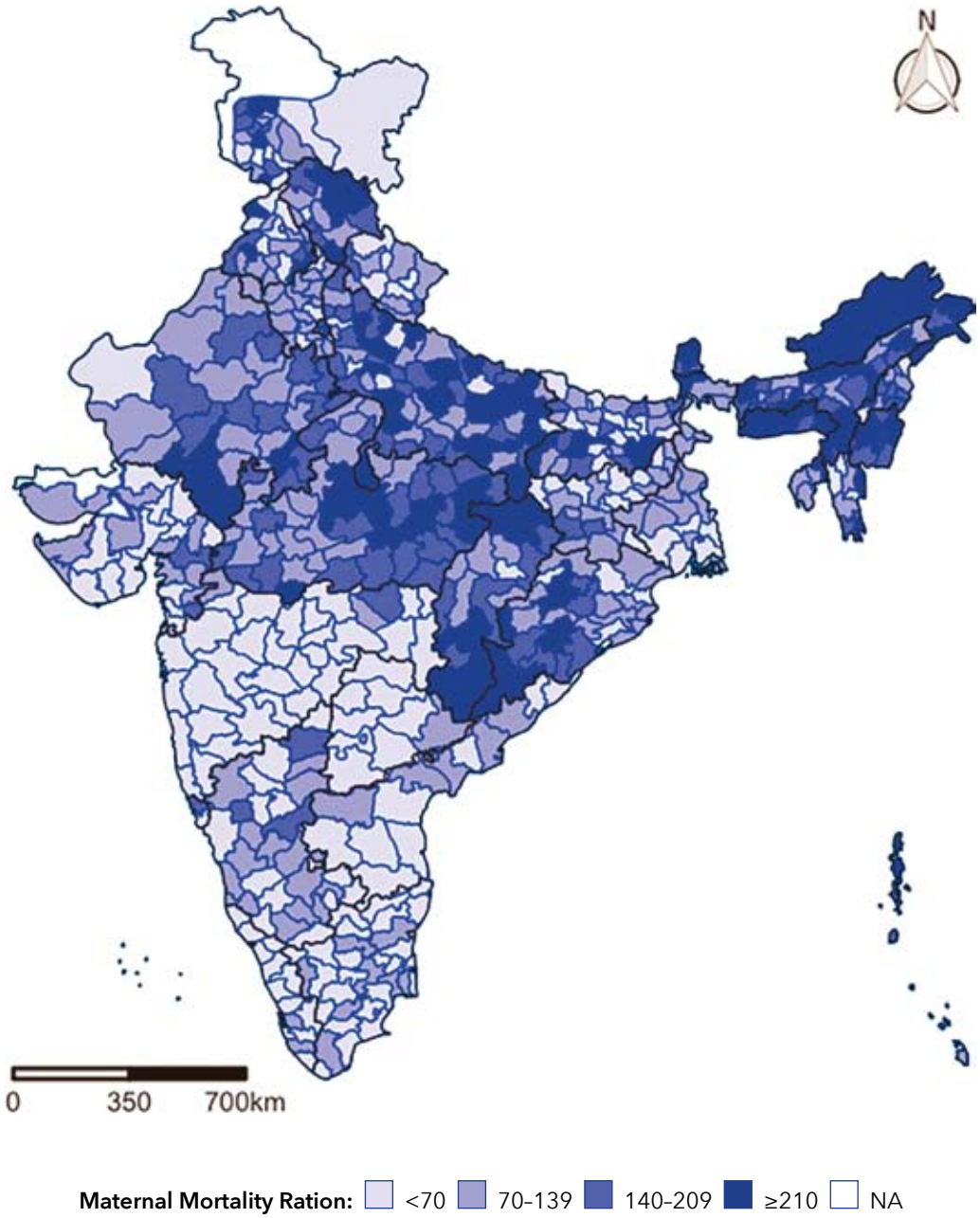
As per the Sample Registration System (SRS) report by Registrar General of India (RGI) for the last three years, Maternal Mortality Ratio (MMR) of India has declined over the years to 103 per 100,000 in 2017–19 from 113 per 100,000 in 2016–18.[6] The overall state based maternal mortality ratio is provided in Table 1.[6]

Table 1. Maternal Mortality Ratio (MMR), Maternal Mortality Rate and life time risk; India, Empowered Action Group (EAG) and Assam, South and other states, 2017–19

India and Major states	MMR	95% CI	Material mortality rate	Lifetime risk
India	**103**	**(94-113)**	**6.5**	**0.2%**
Assam	205	(125–285)	31.0	0.5%
Bihar	130	(88–171)	12.8	0.4%
Jharkhand	61	(13–108)	4.7	0.2%
Madhya Pradesh	163	(117–209)	14.7	0.5%
Chhattisgarh	160	(70–249)	11.8	0.4%
Odisha	136	(85–188)	8.5	0.3%
Rajasthan	141	(94–189)	12.2	0.4%
Uttar Pradesh	167	(126–208)	14.7	0.5%
Uttarakhand	101	(51–152)	6.4	0.2%
EAG AND ASSAM SUBTOTAL	**145**	**(128-162)**	**11.6**	**0.4%**
Andhra Pradesh	58	(21–95)	3.2	0.1%
Telangana	56	(12–101)	3.1	0.1%
Karnataka	83	(45–120)	4.3	2.2%
Kerala	30	(2–58)	1.4	0.1%
Tamil Nadu	58	(27–89)	3.0	0.1%
SOUTH SUBTOTAL	**59**	**(43-75)**	**3.1**	**0.1%**
Gujarat	70	(38–103)	5.0	0.2%
Haryana	96	(47–144)	7.1	0.2%
Maharashtra	38	(14–63)	2.1	0.1%
Punjab	114	(46–182)	6.0	0.2%
West Bengal	109	(68–151)	5.5	0.2%
Other states	77	(55–99)	4.0	0.1%
OTHER SUBTOTAL	**79**	**(65-93)**	**4.4**	**0.2%**

For the first time, using triangulation of routine records of maternal deaths under the Health Management Information System (HMIS), Census of India, and SRS, Maternal Mortality Ratio (MMR) for all districts of India is provided in Figure 1. The findings suggest that 70% of districts (448 out of 640 districts) in India have reported MMR above 70 deaths. The HMIS suggests that about 6 states (and two union territories) and 128 districts have MMR above 200.

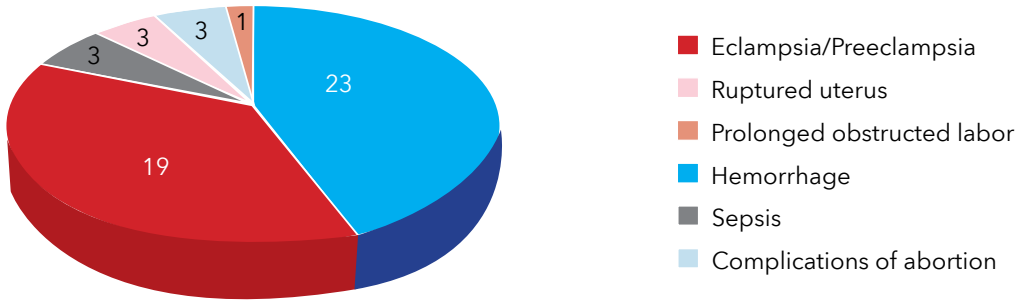
Figure 1. Geographical pattern of maternal mortality ratio by 640 districts in India, HMIS



Goli S, Puri P, Salve PS, Pallikadavath S, James KS (2022) Estimates and correlates of district-level maternal mortality ratio in India. PLOS Glob Public Health 2(7): e0000441.

The six leading, major, or direct causes of maternal mortality are shown in Figure 2.[7]

Figure 2. Causes of maternal mortality



PPH rate of approximately 12% in rural areas of India where expectant management of labor is practiced.[8] PPH can occur in 5.8% of women in their first pregnancy. The risk of a first PPH in a second or third pregnancy is 4%–5%. Risk of recurrence of PPH in a subsequent pregnancy is up to 15%. About 54%–93% of maternal deaths due to obstetric hemorrhage are preventable when standardized and multidisciplinary programmes are implemented.[9]

Most deaths due to severe PPH seem to occur during the first 24 hours after birth. The transition of hemorrhage from the compensated to the decompensated stage is rapid and easily overlooked. Hence, prediction, early recognition, and intervention are crucial for lowering the risk of severe PPH or improving its clinical outcomes.[10]

DEFINITION

The definition of PPH is based on the amount of blood loss after birth. According to the WHO, PPH is defined as a blood loss of more than 500 mL from the genital tract after vaginal delivery. However, 500 mL is selected as a cut-off, which is also considered normal postpartum blood loss. The most recent WHO definitions of PPH (2012), for vaginal births, PPH is defined as blood loss >500 mL, and severe PPH is defined as loss of >1000 mL. In cases of cesarean birth, PPH is defined as blood loss more than 1000 ml.[11]

According to the American College of Obstetricians and Gynecologists (ACOG), the definition of PPH is cumulative blood loss more than or equal to 1000 ml that is associated with signs or symptoms reflecting hypovolemia within the first 24 hours of the birthing process.[12] Despite meticulous estimation of blood loss in cases of PPH, careful observation of clinical signs is also vital. Low systolic blood pressure, tachycardia, and a raised respiratory rate have been historically used as signs of hypovolemia.[13]

ETIOLOGY AND RISK FACTORS

Pregnancy itself is a risk factor for PPH; every pregnancy can result in PPH. It is important to identify the risk factors and prophylactically prevent PPH. The risk factors for PPH are provided by Hoveyda et al, which are modified to suit the Indian population in Table 2.[14]

Table 2. Risk factors for postpartum hemorrhage

Maternal issues	
• Teenage pregnancy • Elderly primigravida • Multiparity and Grand multiparity (> 4) • Inadequate prenatal visits • Low socioeconomic status • Previous postpartum hemorrhage • Previous uterine surgeries • Uterine malformations • Fibroid uterus • Previous cesarean section • Previous instrumental delivery • Anemia • Thrombocytopenia • Diabetes	• Cardiac dysfunction • Hypertensive disorders • Thyroid dysfunction • ART pregnancy • Renal and liver disorders • Respiratory disorders • Anticoagulant therapy • Viral infections, dengue • Inherited and acquired coagulopathies • Hemoglobinopathies • Metabolic syndrome • Post-bariatric surgery • Pregnancy after renal transplant • Multifetal gestation
Intrapartum	
• Induction and augmentation of labor • Precipitate labor and prolonged labor • Obstructed labor • The arrest of labor in the second stage • Trial of labor after cesarean (TOLAC)/ vaginal birth after cesarean (VBAC) • Placenta previa • Placenta accreta syndrome • Chorio angioma	• Instrumental deliveries • Cesarean section • In-coordinate uterine action (hypotonic & hypertonic) • Prolonged rupture of the membrane (PROM/PPORM) • Chorioamnionitis • Placenta abruption • Arteriovenous malformations
Postpartum	
• Genital tract trauma • Retained placenta • Retained placental tissues	• Uterine inversion, uterine rupture • Subinvolution • Puerperal sepsis
Fetal issues	
• Polyhydramnios • Large-for-gestational-age fetus • Fetal macrosomia (birth weight greater than 8 lb, 13 oz [4,000 g]) • Congenitally malformed fetus	
Placental issues	
• Placenta previa • Placenta abruption • Placenta accreta • AV malformations • Chorio angioma • Placental abnormalities (battle door placenta, vasa previa etc)	

Risk assessment tool

Performing prenatal risk assessment and planning is highly recommended. Early identification and management preparation for patients will enable better outcomes. The patients with two or more medium risk factors should be considered as high risk.[15] Table 3 provides the risk categories.[15]

Table 3. Risk category: Admission

Low risk	Medium risk	High risk
• No previous uterine incision • Singleton pregnancy • No medical disorder • No known bleeding disorder • No history of PPH • Optimal hemoglobin	• Induction of labor (with oxytocin) or Cervical ripening • Multiple gestations • >4 previous vaginal birth • Prior cesarean birth or prior uterine incision • Large uterine fibroids • History of one previous PPH • Family history in first-degree relatives who experienced PPH (known or unknown etiology with possible coagulopathy) • Chorioamnionitis • Fetal demise • Polyhydramnios	• Has two or more medium-risk actors • Active bleeding is more than a "bloody show" • Suspected placenta accrete or percreta • Placenta previa, low-lying placenta • Known coagulopathy • History of more than one previous PPH • Hematocrit <30 and other risk factors • Platelets <100,000/mm^3

PATHOPHYSIOLOGY

Physiology of uterine contractions

Understanding the physiology of the uterus during the term and preterm parturition is significant to making strategies to control uterine function and clinical problems related to labor. For normal labor at term, the biochemical changes in the cervical connective tissue precede uterine contractions and cervix dilatation. Parturition involves two main steps:[16]

- A long conditioning phase
- A short secondary phase (active labor)

The "Conditioning" step leads to softening of the cervix. In the myometrium, the preparatory process involves changes in transduction mechanisms and synthesis of several proteins including connexins, ion channels, and receptors for uterotonics, see Table 4. The down-regulation of nitric oxide leads to the withdrawal of uterine relaxation.[16]

Uterine atony

Most of the physiological processes in the third stage of labor remain unclear. However, primary PPH due to uterine atony occurs when the relaxed myometrium fails to constrict the blood vessels, causing hemorrhage. As up to one-fifth of maternal cardiac output (1000 ml/min) enters

Table 4. Changes in the uterus (myometrium), cervix, and fetal membranes[16]			
	Major changes		**Successful labor**
Uterus	↑ Coupling ↑ Ion channels ↑ Receptors ↓ No system	↑ Conductivity ↑ Excitability ↓ Relaxation	Reinforcement of contraction
	|---	**37 weeks to term** ---|	
Cervix	↑ Inflammatory response ↑ Collagenolys	↑ Ripening	Dilatation
	|---	**37 weeks to term** ---|	
Fetal membrane	↑ ECM degradation	↓ Tissue integrity	Rupture
	|---	**37 weeks to term** ---|	
Steps	Initiation	Conditioning (preparation)	Active labor

the uteroplacental circulation at term, PPH can lead to a severe loss of blood within a short time. Uterine atony is responsible for 75%–90% of primary PPH, and 20% of all primary PPH is due to traumatic causes (including obstetric lacerations, uterine inversion, and uterine rupture).[17] Atonic PPH is a recognized complication and, even if a cesarean section is performed, severe intraoperative bleeding is a significant risk.[17]

The lower segment as an implantation site

In placenta previa and placenta previa accreta, the placental bed is in the lower segment. The presence of lower-segment implantation makes hemorrhage and placental retention much more likely. There are indications that the anatomical and physiological limitations of the lower segment are linked to the etiology of pathological bleeding.[17]

In placenta previa, the placental site is located in an abnormally low position. In lower segment implantation, the muscle around the placental bed is inadequate for the task of postpartum contraction/retraction, and thus hemorrhage is initiated.[16]

THE 4 T'S: TONE, TISSUE, TRAUMA, THROMBIN

The causes of PPH as related to abnormalities of one or more of four basic processes 'the four Ts': tone, trauma, tissue, and thrombin.

Tone/abnormality of uterine contraction

Uterine atony is the most common cause of PPH (80%). Patients with an overly distended uterus (twins, macrosomia, or hydramnios) is also at risk. Others causes include intraamniotic infection and functional/ anatomic distortion of the uterus.

Tissue (retained product of conception)

Retained placenta (failure of the placenta to deliver within 30 minutes of birth) occurs in 3%–5% of the cases. Retained products of conception or invasive attachments of the placenta to the uterine wall (accreta, percreta, or increta) can cause massive PPH. PPH has also been linked to blood clots and cotyledons.

Trauma [at genital tract]

About 10%–15% women experience trauma, including cervix, vagina, perineum laceration, and hematomas resulting from birth, can cause significant blood loss. A careful inspection of these areas should be performed, and repair of trauma should be done. Uterine rupture and uterine inversion have also been associated with PPH.

Thrombin [abnormality of coagulation]

Coagulation disorders are a rare cause of PPH, reported in 1% to 2% of the cases.

CLINICAL FEATURES

A quick history and general physical examination along with an abdominal examination, speculum and vaginal examination, and examination of the placenta will help to identify the probable cause.

Table 5. Finding and probable diagnosis in case of PPH

Findings in case of PPH	Probable diagnosis
Relaxed flabby uterus	Atonic PPH
Contracted uterus with bleeding	Traumatic PPH
Undelivered placenta/ partial expulsion of placental tissue/ Incomplete placenta	Partial or total retained placenta
Non-palpable fundus of the uterus	Inversion of uterus
Contracted uterus along with absence of trauma or retained placental tissues, failure of medical treatment	Disseminated intravascular coagulation (DIC)

ASSESSMENT AND DIAGNOSIS

An accurate assessment of blood loss continues to be challenging in the care of women in labor and delivery. Clinicians are prone to either underestimate or overestimate maternal blood loss (Figure 3). Underestimation can be particularly problematic as it delays the diagnosis of PPH, increasing maternal morbidity and mortality.[13]

The diagnosis of PPH is based on the patient's physical assessment and the clinician's clinical judgment. Initial evaluation of the patient should include a rapid assessment of the patient's status and risk factors. Maternal postpartum hemorrhage risk assessment is conducted antenatally, at the time of admission, and during labor or the postpartum period.[18]

Figure 3. Visual estimation of blood loss

Solid sanitary towel
30 ml

Incontinence pad
250 ml

Full kidney dish
500 ml

Saturated small swab (10x10 cm)
60 ml

Saturated swab (45x45 cm)
350 ml

Blood spilling on bed
500 ml

Saturated sanitary towel
100 ml

Floor spill (100 cm diameter)
350 ml

Blood spilling to floor
500 ml

Clinical signs or symptoms of blood loss, such as tachycardia and hypotension, may be masked in some cases. If these signs are present, there should be a concern for considerable blood volume loss (> 25% of total blood volume). For patient safety, a continuous assessment of vital signs and estimation of total blood loss is an important factor.[19] Patient examination at the time of hemorrhage can help to identify the probable cause of bleeding.

Table 6. Clinical signs and symptoms

	Stage 1	Stage 2	Stage 3	Stage 4
Blood loss (%)	<15	15–30	30–40	>40
Blood loss (cm^3)	<750	750–1500	1500–2000	>2000
Pulse rate	<100	>100	>120	>140
Respiratory rate	14–20	20–30	30–40	>35
Blood pressure	Normal	Decreased	Decreased	Decreased
Mental state	Normal/slightly anxious	Mild anxiety	Confusion and lathargy	Confusion

Modified shock index

The modified shock index is a bedside assessment defined as Heart rate (HR) to mean blood pressure (MAP), with a normal range of 0.5 to 0.7 in healthy adults.

Table 7. Shock index to mortality rates

	Shock index	Mortality rate	Blood products
No shock	<0.6	10.9% mortality	1 unit
Mild shock	≥0.6 to < 1.0		2.8 units
Moderate shock	≥1.0 to < 1.4		9.9 units
Severe shock	≥ 1.4	39.8% motrality	11.4 units

Method used to estimate the MAP: **MAP = DP + 1/3(SP – DP)** or **MAP = DP + 1/3(PP)**

*DP: diastolic blood pressure, MAP: mean blood pressure; PP: pulse pressure; SP: systolic blood pressure.

The common finding with uterine atony includes soft, boggy, or non-contracted uterus. Manual examination for any retained placental tissue should be followed by bedside ultrasound.

Uterine inversion presents as a mass with palpation of the fundal wall in the cervix or lower uterine segment. It is often linked to excessive traction on the umbilical cord or an abnormally adherent placenta.[19]

- A rapid assessment of the genital tract for hematomas, lacerations, or signs of uterine rupture should be performed.
- The amount of blood loss can be measured by using BRASS-V drape/or other blood collection receptacle. However, clinical conditions should always be kept in mind.

INVESTIGATIONS AND THEIR INTERPRETATION

Investigation for the diagnosis of PPH[20,21]

- Hemoglobin and HCT –fall in HB and hematocrit, (may not be initially low)
- Bed side tests: Bleeding time, clotting time, clot observation test
- Coagulation profile may be deranged in hemorrhage
  - » Bleeding time (BT) increased
  - » Clotting Time (CT) increased
  - » Platelet count (PC) decreased
  - » Prothrombin time (PT) increased
  - » International normalized ratio (INR) increased in coagulopathy
  - » Serum fibrinogen decreased or normal
  - » D-Dimers increased
- Serum electrolytes may or may not be altered

- Renal parameters: Blood urea, serum creatinine elevated in renal failure, and hemolysis
- Serum Lactate: Elevated in sepsis
- Serum calcium, magnesium and potassium: Can be low in hemorrhage
- Ultrasound: Retained placenta, adherent placenta, inversion, rupture
- Thromboelastogram (TEG): Wherever available and feasible
- Arterial blood gas analysis and its interpretation
- Frequency of investigations: As per the clinical situation

Blood investigations[12]

Table 8. Summary of blood loss thresholds and vital sign changes for diagnosis of postpartum hemorrhage (PPH) according to Internaltionl clinical guidelines

Guidelines	Vaginal/cesarean delivery	Vital signs	Comments
International Federation of Gynecology and Obstetrics	Loss >500 mL/>1000 mL	For clinical purposes, any blood loss that has the potential to produce hemodynamic instability should be considered a PPH	Clinical estimates of blood loss are often inaccurate
American College of Obstetricians and Gynecologists	Cumulative blood loss ≥ 1000 mL, regardless of route of delivery	Signs or symptoms of hypovolemia; important to recognize that the signs or symptoms of considerable blood loss is substantial	Excess of 500 mL after vaginal delivery is an alert; when postpartum bleeding exceeds expected volumes (500 mL in a vaginal delivery or 1000 mL in a cesarean delivery), a careful and through evaluation should be undertaken
Royal College of Obstetricians and Gynaecologists	Estimated blood loss of 500–1000 mL (minor PPH) and >1000 mL (major PPH) with no clinical signs of shock	Pulse and blood pressure normal until blood loss exceeds 1000 mL; tachycardia, tachypnea slight fall in systolic blood pressure with blood loss of 1000–1500 mL; > 1500 mL systolic blood pressure < 80 mmHg, worsening tachycardia, tachypnea, and altered mental state	A blood loss of >40% of total blood volume (approximately 2800 mL) is generally regarded as "life-threatening"
Society of Obstetricians and Gynaecologists of Canada	Loss >500 mL/>1000 mL	Any blood loss that has the potential to produce hemodynamic instability should be considered PPH	The amount of blood loss required to cause hemodynamic instability depend on the preexisting condition of the woman
Royal Australian and New Zealand college of Obstetricians and Gynaecologists	Estimated blood loss 500 mL; severe PPH after blood loss of 1000 mL	Clinical signs of shock or tachycardia, which incudes an accurate appraisal of blood loss (both concealed and revealed), assessment of the mother	It is important to consider both the patient's previous hemoglobin level and her total blood volume for the assessment of the severity of PPH

PREVENTION OF PPH

Preparedness

Table 9. Preparedness to prevent PPH	
Pregnant woman	• Birth preparedness and complication readiness for pregnant women, family members and service providers. • Adequate antenatal check-ups and investigations
Heath Care Provider	• Adequate number • Skilled and with updated knowledge • Emergency Response Team (ERT) with team division
Facility readiness	• Traffic signal approach for Triage – Green, Yellow, and Red • Adequate infrastructure • Appropriate equipments, instruments and consumables • PPH kit, Crash kit trolley • Appropriate medications such as all uterotonics, tranexamic acid • Special requirements for uterine balloon tamponade and non-pneumatic anti-shock garment (NASG), suction cannula and trans-vaginal uterine artery clamps • Blood and blood products availability • PPH Checklist and debriefing forms
Protocols and procedures	• Partography mandatory • Cardio tocography in high risk situations (if available) • Active management of third stage of labor in all cases • Use of safe birthing checklist and surgical safety checklist

Anticipate, prevent, perform

- Risk assessment (detailed history, clinical evaluation, relevant investigations)
- Optimal prenatal care
- Correction of anemia, nutritional management
- Management of medical conditions (multidisciplinary approach for optimization of the condition)

PREVENTION OF PPH: ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOR (AMTSL)

After childbirth, blood loss and other clinical parameters should be closely monitored.[22] There is insufficient evidence to recommend quantification of blood loss over clinical estimation.

Preventing PPH can reduce the number of women who die or suffer each year due to excessive bleeding associated with pregnancy. Most incidences of PPH are preventable. Several conditions can predispose a woman to hemorrhage. However, 90% of women have no risk factors. As a result, every woman must have access to a skilled birth attendant (SBA), who can manage labour and childbirth to minimize risk.[22] Routine active management is superior to expectant management in terms of blood loss, postpartum hemorrhage, and other serious complications of the third stage of labor. Active management should be the routine management of choice for women expecting to deliver a baby in a maternity hospital.[23]

Several Cochrane reviews have reported on the prophylaxis for the third stage of labor for women delivering vaginally.[24-27] According to these review studies, the risk of PPH can be reduced with both active management and the use of prophylactic uterotonics in the third stage of labor. The AMTSL involves the use of interventions (including the use of uterotonics, early clamping of the umbilical cord, and controlled cord traction) to expedite delivery of the placenta to reduce blood loss. In expectant management, signs of placental separation are awaited, and the placenta is delivered spontaneously. According to a Cochrane systematic review, for women at mixed levels of risk of bleeding, active management resulted in a reduction in the average risk of maternal primary hemorrhage at the time of birth (more than 1000 mL; average risk ratio [RR] 0.34, 95% CI 0.14–0.87) and maternal Hb less than 9 g/dL following birth (average RR 0.50, 95% CI 0.30–0.83).[28]

- All the three steps AMTSL should only be done by SBA/trained staff.
    i. Administration of uterotonics after delivery of baby
    ii. Delayed cord clamping
    iii. Controlled cord traction
- AMTSL is a prophylactic intervention recommended by WHO. The prevention of PPH in AMTSL, over the years. consists of: 1) Giving uterotonic immediately after baby is born, 2) Controlled cord tension, and 3) uterine massage. The three procedures can be combined in one step of care with the administration of uterotonics, as it increases uterine contraction immediately after delivery.[29] All women giving birth should be offered uterotonics after cesarean or vaginal delivery of the baby for PPH prevention.
- Oxytocin IV injection has been the the uterotonic of choice for AMTSL over the years. Oxytocin (10 IU, IM) is the preferred uterotonic based on studies on the safety and effectiveness of uterotonics.
- If oxytocin is not available, room temperature stable carbetocin (100 mcg IM/IV), or methylergometrine (0.2 mg IV/IM), or misoprostol (800 to 1,000 mcg rectally or 600 to 800 mcg sublingually or orally) can be the first-line choices.
- Caution should be exercised when opting for ergot derivatives (methylergometrine) for the prevention of PPH as these drugs have clear contraindications in women with hypertensive disorders. Thus, it is probably safer to avoid the use of ergot derivatives in unscreened populations.
- If a skilled attendant is not present, and oxytocin is not available (such as at an unattended home birth), administer 600 mcg of oral misoprostol. Women delivering without a skilled attendant also need uterotonic for PPH prevention, so oral misoprostol should be given by a community health worker who is present.

- Delayed cord clamping (performed after 1 to 3 minutes after birth) is still recommended for all births to reduce newborn anemia while beginning essential newborn care at the same time.
- The uterus is palpated abdominally, and when it is contracted (this happens in 1 to 3 minutes of administration of uterotonics), controlled cord traction is done to deliver the placenta.
- Control Cord Traction (CCT) is not recommended in situations where SBA is not available.
- Suture any perineal or labial tears/ episiotomy quickly.
- Continue to palpate the uterus frequently to see that it stays firm (contracted).
- Help the mother to feed and care for her baby.

OVERVIEW OF UTEROTONICS (POST-DELIVERY)

Drug	Dosage	Action	Side effects	Contraindication
Oxytocin	10U IM/IV	Onset: 1–3 mins Lasts: 10–15 mins	Minimal	• Allergic to oxytocin • Cardiac dysfunction (to minimize risk of volume overload) • Obstructed labour • Grand multiparity (relative contraindication)
Methylergometrine	0.2mg IV/IM	Onset: 2–7 mins Lasts: 2–4 hours	Nausea, vomiting, headache, hypertension	• Hypertension • Cardiac disease
Prostaglandin F2α	250mcg IM	Onset: 1–2 mins Lasts: 15–20 mins	Vomiting, diarrhea, bronchospasm	• Bronchial asthma
Misoprostol	800 to 1,000 mcg rectally or 600 to 800 mcg sublingually or orally	Onset: 3–5 mins Peak: 20–30 mins Lasts: <75 mins	Shivering, rise in temperature	• Pre-existing cardiovascular disease
Carbetocin room temperature stable	100 mcg IV/IM	• Rapid onset of action (within 2 minutes for both IV and IM administration) • Long half-life, and prolonged duration of action (60 min for a single IV injection, 120 min for an IM injection)	Generally well tolerated, Vomiting, abdominal pain, headache, tremor, dizziness, chest pain	• Serious cardiovascular disorders • In women with hepatic or renal disorders • Epilepsy • Hypersensitivity to carbetocin, oxytocin or any of the excipients according to the composition • Pregnancy and labour before the delivery of the infant • Must not be used in induction of labour

CARBETOCIN: AN UPDATE

- Carbetocin is the carba analog that has prolonged activity and a long half-life due to deamination. which protects carbetocin from aminopeptidase cleavage, and its lipophilicity.
- Carbetocin is a newer long-acting synthetic analogue of oxytocin with agonist properties.[30]
- Carbetocin is available as room temperature formulation in India.

Pharmacokinetics

- After IV administration, the tetanic contraction have a mean time (± SD) of 1.2 ± 0.5 min and last for 6.9 ± 2.1 min, followed by rhythmic contraction for 60 ± 18 min.
- After IM administration, the onset is 1.9 ± 0.6 min, with tetanic contractions lasting for 11.3 ± 3 min, followed by rhythmic contractions for 119 ± 69 min.

Clinical efficacy

Elbohoty et al compared carbetocin with oxytocin versus misoprostol in women with cesarean delivery. In the study, the need for further uterotonics was 5 (6%, lowest, p= 0.004), 11 (13%), and 20 (22%) in women receiving carbetocin, oxytocin 10 IU/mL injection, and misoprostol respectively. The prevention of uterine atony: carbetocin comparable with oxytocin [RR = 0.41 (95% CI, 0.14 to 1.25)] and superior to misoprostol [RR = 0.21 (95% CI, 0.07 to 0.58)]. Additional uterotonics were needed less frequently by patients treated with carbetocin. Carbetocin was comparable to oxytocin and superior to misoprostol in the prevention of uterine atony following an elective cesarean delivery.[30] In a double-blinded randomized control trial, researchers compared the uterotonic effect of room temperature stable carbetocin 100 mcg with IV 10 IU oxytocin in 300 patients undergoing cesarean delivery. Carbetocin was superior to oxytocin in reducing the need for additional uterotonic agents by 12% and non-inferior to oxytocin for blood transfusion 3.5%, without any clinically significant change in blood pressure or pulse rate.[31]

An international WHO-sponsored trial of a room-temperature stable formulation of carbetocin versus oxytocin (the CHAMPION trial) was published in 2018, showing carbetocin was non-inferior to oxytocin in preventing blood loss of at least 500 mL. Non-inferiority was not shown for the outcome of a blood loss of at least 1000 mL; however, the trial was underpowered for this outcome.[32]

In December 2018, WHO updated the its recommendations on uterotonics for the prevention of PPH and recommended the use of room temperature stable carbetocin (100 mg, IM/IV) for the prevention of PPH for all births in contexts where its cost is comparable to that of other effective uterotonics. This recommendation was based on the evidence extracted from the updated Cochrane NMA of the seven uterotonic options.[33]

In another study, carbetocin 100 µg/mL was compared with misoprostol 800 µg for prevention of PPH in low-risk women in third stage labor. Researchers observed that the carbetocin

group had significantly less blood loss ($p<0.001$), a shorter third-stage ($p<0.001$), and less need for additional uterotonics ($p=0.013$) or uterine massage ($p=0.007$). Both drugs were hemodynamically safe. Hemoglobin levels after delivery were comparable between the two groups ($p=0.475$). Adverse effects were more common in the misoprostol group ($p<0.001$). Carbetocin was a better alternative to misoprostol for active management of the third stage of labor; it reduced blood loss and the use of additional uterotonic drugs.[34]

As per a meta-analysis of randomized control trials (RCT), carbetocin has been associated with a low incidence of adverse effects similar to oxytocin and is at least as effective as syntometrine. Hence, it can become an alternative uterotonic agent for the prevention of PPH.[35] In an RCT, researchers demonstrated that a single IM carbetocin injection prevented PPH in women at risk when compared to a continuous oxytocin IV infusion.[36] The room-temperature carbetocin is recommended as a molecule of choice for the prevention of PPH.

The stability of carbetocin as room-temperature formulation has been verified at 30^0 C for 3 years, at 40^0 C for 6 months, at 50^0 C for 3 months and at 60^0 C for 1 month.[37]

ROLE OF TRANEXAMIC ACID IN MANAGEMENT OF PPH

Tranexamic acid is an antifibrinolytic agent that blocks lysine-binding sites on plasminogen molecules. It reduces bleeding-related mortality in women with PPH especially when administered soon after delivery. According to the RCTs thus far reported for PPH prevention after C-section deliveries, women who received tranexamic acid had significantly less postpartum blood loss and no increase in severe adverse effects. The WHO recommends that women with PPH receive an IV of 1 g tranexamic acid soon after giving birth, followed by a second dose if bleeding continues after 30 min or restarts within 24 h after the first dose. Urgent treatment is critical, and tranexamic acid is most effective when given early; evidence suggests there is no benefit when the drug is given more than 3 hours after bleeding onset.[38]

A multicenter, double-blind, RCT with two parallel groups including 4,524 women who had cesarean deliveries before or during labor, at a term ≥34 weeks were administered tranexamic intravenously just after birth. According to the study, tranexamic acid is a promising candidate for preventing PPH after birth in these women.[39]

MANAGEMENT OF PPH: ZERO HOUR, MEDICAL (NEW RECOMMENDATIONS), MECHANICAL, AND SURGICAL MANAGEMENT

Zero hour checklist

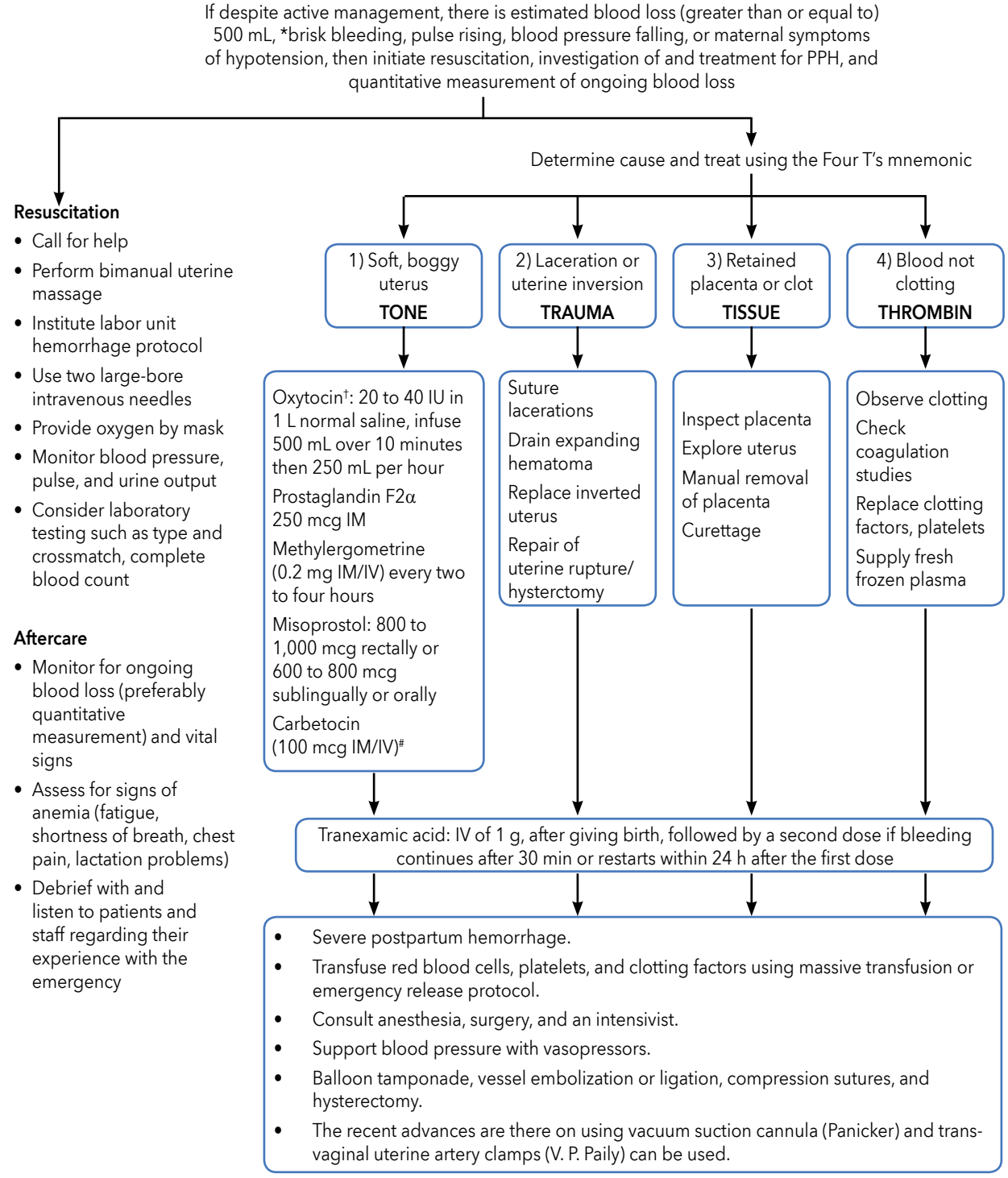
- Once a woman has been assessed to have PPH, call the Emergency Response Team (ERT) for help.

- Initial resuscitation with ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach is to be done.
- IV access with two wide bore cannula #14/16
- Blood sample for investigations to be collected and adequate blood and blood products to be arranged.
- Catheterization is mandatory.
- The vitals- Shock Index must be recorded.
- Quick history and rapid initial assessment

CLINICAL AND PHARMACOLOGICAL MANAGEMENT

- Ensure the cause by palpating the uterus for atony.
- In cases of uterine atony, the primary response is to do uterine massage, bimanual uterine compression, aortic compression, and administer uterotonics.
- Tranexemic acid injection: 1gm IV to be given immediately (within 3 hours of PPH) and repeat another 1 gm IV after 30 minutes if PPH persists.
- If the uterus has contracted, inspect for genital tract trauma. If detected, appropriate intervention should be taken.
- Evaluate for blood coagulation abnormalities.
- If patient is still bleeding and goes in refractory PPH then, uterine balloon tamponade to be done and NASG to be placed.
- In cases of lower level health facilities, transfer and appropriate referral to be done.
- In level II and level III settings, if women is still bleeding, she can be taken for surgical compression sutures, uterine artery ligation (stepwise devascularization), uterine artery embolization, and hysterectomy.

Clinical and pharmacological management of PPH (modified flowchart)[40]

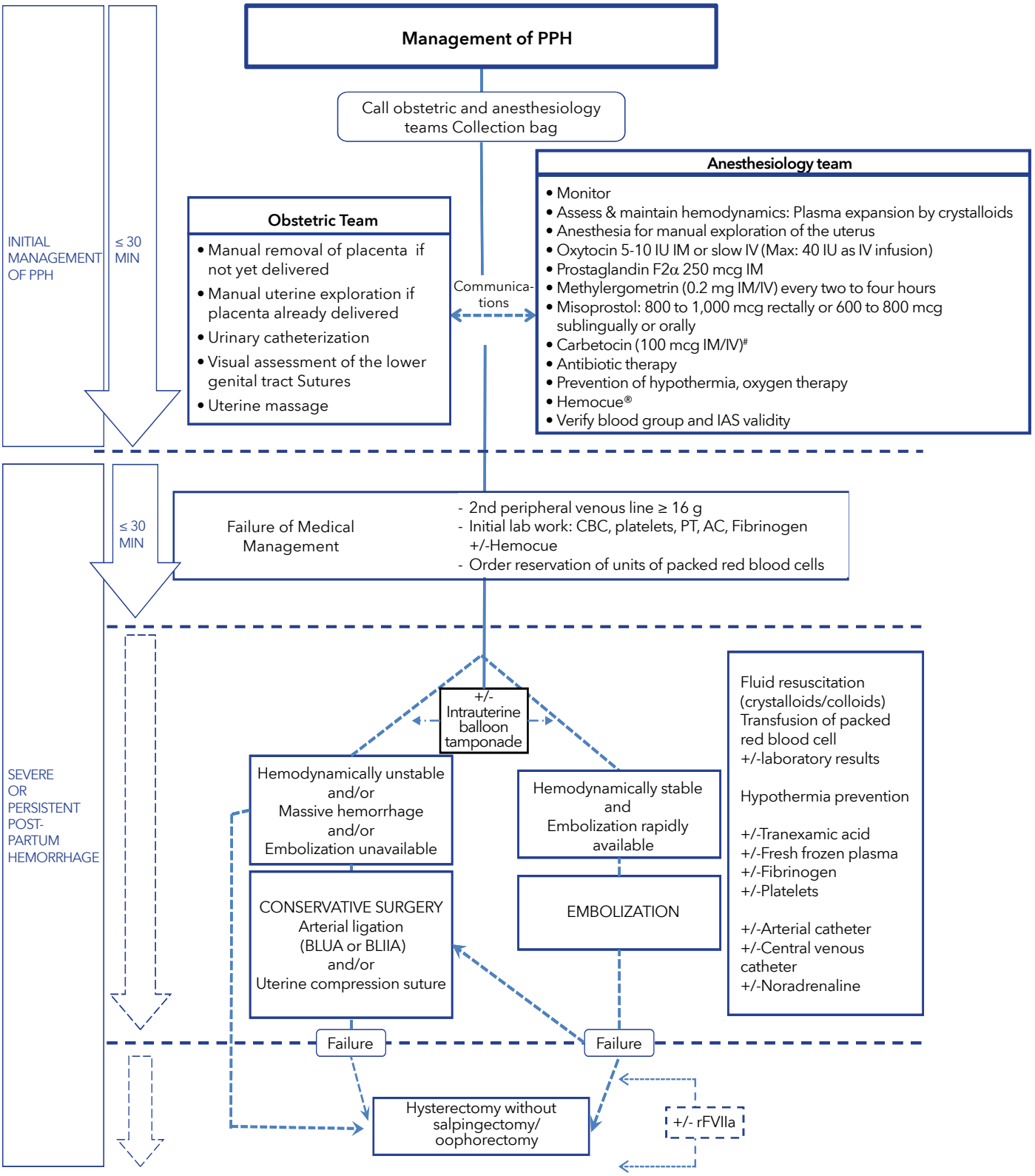


*–The American College of Obstetricians and Gynecologists defines early postpartum hemorrhage as blood loss of 1,000 mL or more accompanied by signs and symptoms of hypovolemia; cumulative blood loss of 500 to 999 mL alone should trigger increased supervision and potential interventionsas clinically indicated.

†–Oxytocin should be used as a first-line agent, with other agents added only if needed to control hemorrhage.

Under trial for PPH.

Algorithm for management of PPH[39]



*For general guidance, to be adapted according to the quantity of bleeding, , # under trial for PPH, PPH, postpartum hemorrhage; Min, minute; slow IV, slow intravenous; IM, intramuscular; IU, international unit; IAS, irregular antibody screening; BLUA, bilateral ligation of the uterine arteries; BLIIA, bilateral ligation of the internal iliac arteries; CBC, complete blood count; PT, prothrombin time; ACT, activated clotting time; rFVIIa, recombinant activated Factor VII.

SPECIAL CIRCUMSTANCES

It is recommended that awareness and individualization of management be used in special situations such as multifetal pregnancy, VBAC, and other high-risk pregnancies. There is little evidence on best practices in these situations.[41]

- In cases of multifetal pregnancy, all fetuses must be delivered prior to the administration of oxytocic drugs to avoid intrauterine asphyxia.
- Methylergometrine should not be given to women with hypertension, cardiac disease, severe anemia, and Rh-negative mothers.
- Injectable prostaglandins can be used in special situations where women at are at high risk of PPH. However, it should not be given to women with bronchial asthma and heart disease.
- Misoprostol is a synthetic analogue of prostaglandin E_1 (PGE_1) and is safe for women with bronchial asthma and heart disease.
- In obese, nulliparous women undergoing emergency cesarean delivery, a single 100 mcg IV carbetocin infusion is more effective than IV oxytocin infusion for maintaining adequate uterine tone and preventing postpartum bleeding.[42]
- Carbetocin is as effective as oxytocin in the prevention of PPH in women with severe preeclampsia but without any association with the development of oliguria or hypertension.

MANAGEMENT FOR DELAYED PPH

Hemorrhage between 24 hours and 6 weeks postpartum is termed "delayed PPH." Common causes include retention of placental tissue and/or membranes and infection leading to endometritis, endomyometritis, and parametritis. Bleeding can be sudden and profound, resulting in rapid cardiovascular collapse.[30] Septic shock may also be present due to infection. The investigations in these cases are similar to atonic PPH; however, some additional investigations of septic foci to isolate organisms for culture and antibiotic sensitivity are mandatory. These cases may have early features of DIC, so a blood coagulation profile should be done earlier.

The main stay of management include:

- Resuscitation and fluid therapy.
- Broad spectrum intravenous antibiotic therapy (to cover gram positive, gram negative, and anaerobes) according to the hospital antibiotic policy. It can be changed according to the culture report and antibiotic sensitivity pattern.
- Evacuation of the uterus/surgical management for any septic foci.
- Individualized surgical procedure may be adopted depending on the case.

- Uterotonics and tranexamic acid may be needed.
- Blood and blood products may be given depending on the haemoglobin and coagulation profile.

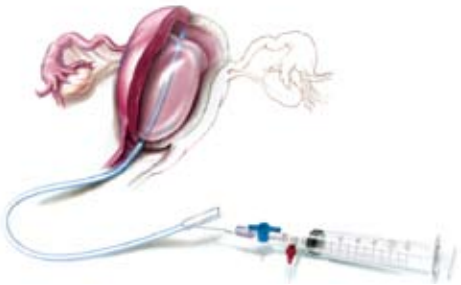
MECHANICAL AND SURGICAL METHODS OF MANAGEMENT OF REFRACTORY PPH

- Bi-manual compression
- Uterine balloon tamponade
- Aortic compression

Uterine tamponade

A systemic review and meta-analysis have reported that the overall pooled success rate of uterine balloon tamponade (Figure 4) in the treatment of PPH was 85.9%. Women with PPH due to uterine atony and placenta previa had a higher success rate than those with placenta accreta spectrum or retained products of conception. The frequency of complications due to the use of uterine balloon tamponade is low and has no adverse consequences on subsequent reproductive function.[43,44]

Figure 4. Uterine balloon tamponade



Non-pneumatic anti shock garment (NASG)

The NASG is a unique, low-technology, life-saving first-aid device made of neoprene and Velcro, that is used on women with obstetric hemorrhage (Figure 5). It can be applied by anyone, even those with very little medical training. The NASG has a unique role in hemorrhage and shock management because it is meant to be used with, not instead of, other technologies. Currently, it is the only tool that aids in stabilizing pulse and blood pressure after a woman has gone into shock from a obstetric hemorrhage.

Figure 5. Non-pneumatic anti-shock garment

Surgical management and radiological methods, along with blood and blood product transfusions

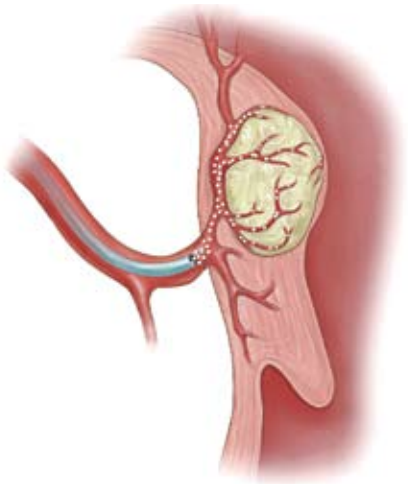
The surgery for controlling PPH should be used immediately after the failure of drug therapy, preferably within the "golden hour". In the surgical treatment of PPH, vascular ligation, and uterine compression sutures must precede hysterectomy. The main technique of vascular ligation is bilateral uterine artery occlusion, although progressive devascularization techniques may optimize the surgical approach. The effectiveness of surgical treatment of PPH increases with the use of uterine compression sutures and vascular ligation.[45]

Damage control surgery is indicated when the patient with PPH is already in the lethal triad and definitive interruption of bleeding is not possible or requires excessive time.[46]

Uterine artery embolization

Usually, uterine artery or internal iliac artery embolization is done. The arteries are catheterized and embolized with polyvinyl alcohol particles 150-300 micron in size. The blood flow of vessels will be arrested, giving similar effect of the ligation of vessels (Figure 6). The polyvinyl alcohol particles are usually reabsorbed in 10 days, and recanulation of the vessels is possible. Advantages include: high success rate, low C/c, fertility is preserved, and very useful when surgery is difficult. The side effects of uterine artery embolization are endometritis, uterine synechiae, and uterine wall necrosis.

Figure 6. Uterine artery embolization



NON CLINICAL COMPONENT PPH MANAGEMENT

1. System Integration

- Mapping and linkage of low-resource centres with tertiary care centres to minimize morbidity and mortality due to PPH.

2. Facility readiness

- Availability of PPH KIT
- Emergency response team
- Availability of transport

3. Team work and communication with referral protocol

- Constitution of emergency response team along with clear alarm system
- Clear roles and responsibility of team members (in-charge, associates, supplier, and informer)
- Obstetric erills and simulation on PPH
- Evaluate performance for continued improvement through a debrief
- Continuous evaluation of competency (skill & knowledge) of staff
- Group discussions/brainstorming session/team building exercises
- Respectful maternity care/empathy
- Timely information to family
- Knowledge of dedicated helpline numbers
- Feedback system

- Information Education Communication (IEC) Material for advocacy among beneficiary and Family on PPH
- Clear understanding of what can be managed at the facility as per preparedness
- List of high risk which needs to be referred
- Documentation and equipment required for referral
- Trained personnel should take care during transport
- Timely information to higher facility
- List of higher level facility along with contact details
- Well-equipped ambulance for proper referral
- Clear roles and responsibility of each Health Care Worker during referral

4. Quality improvement

- Need to focus on quality improvement along with quality assurance – It should be a continuous process
- Identification of problem and find solution by the team
- Data recording and Analysis
- Standard data management (LR & case sheets)
- Monthly/quarterly review of data of key PPH related indicators
- Maternal death and maternal near miss data review
- Inventory management system for PPH kit

5. Advocacy

- The various models should be tested for PPH management . Whichever model is successful should be replicated in different settings to reduce morbidity and mortality due to PPH.

UPDATES AND RECENT ADVANCES IN PPH MANAGEMENT

EMOTIVE trial

E-MOTIVE is a multi-country, parallel cluster randomized trial with a baseline control phase, along with mixed-methods and health economic evaluations. The trial is conducted to evaluate the implementation of early detection and the use of the WHO MOTIVE 'first response' treatment bundle for PPH on clinical, implementation, and resource use outcomes.

This focus on implementation considers what it would take to support roll-out and implementation of the E-MOTIVE bundle. This trial therefore aims to maximize internal validity with future scalability, and implementation of the E-MOTIVE bundle in routine practice, if proven to be effective.[47]

PPH management using PPH emergency care using bundle approach

The WHO technical group 2017- Global Health Initiative for PPH EMC using bundle approach and the FIGO initiative – PPH working Group

Overview of experience implementing the PPH emergency care using a bundle approach training package components:

- Non-clinical components:
  - » System integration – Helplines
  - » Team work
  - » Facility readiness
  - » Advocacy- GOI, GOM, Partner's forum, Brazil, Colombia
  - » Quality improvements
- Clinical components:
  - » Zero-hour management - the first response bundle
  - » Refractory PPH
  - • Supportive care

PANIKER'S suction canula for PPH management

Any vacuum suction cannula system for atonic PPH works on the following principle. After insertion of the cannula into the uterine cavity, when negative pressure is applied, soft cervical tissues get sucked into the small holes of the cervical portion of the cannula and become adherent (Figure 7).[48]

Figure 7. PANIKER'S suction canula

Champion 1

Heat-stable carbetocin was noninferior to oxytocin for the prevention of blood loss of at least 500 mL or the use of additional uterotonic agents. Noninferiority was not shown for the outcome of a blood loss of at least 1000 mL; low event rates for this outcome reduced the power of the trial.[49]

TRAAP 1

TRAAP 1, a multicenter, double-blind, randomized, controlled trial, included 4079 women who underwent randomization and 3891 had a vaginal delivery. Women randomized to the tranexamic acid group had a lower rate of provider-assessed clinically significant postpartum hemorrhage than those in the placebo group (7.8% vs. 10.4%; relative risk, 0.74; 95% CI, 0.61 to 0.91; p=0.004; p=0.04 after adjustment for multiple comparisons post hoc) and also received additional uterotonic agents less often (7.2% vs. 9.7%; relative risk, 0.75; 95% CI, 0.61 to 0.92; p=0.006; adjusted p=0.04). Among women with vaginal deliveries who received prophylactic oxytocin, the use of tranexamic acid reduced the rate of PPH of at least 500 ml that was significantly low compared to PPH rates with placebo.[50]

TRAAP 2

In a multicenter, double-blind, randomized, controlled trial, of the 4551 women who underwent randomization, 4431 underwent cesarean delivery, 4153 (93.7%) of them had primary outcome data available. Among women who underwent cesarean delivery and received prophylactic uterotonic agents, tranexamic acid treatment resulted in a significantly lower incidence of calculated estimated blood loss greater than 1000 mL or red-cell transfusion by day 2 than placebo.[51]

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