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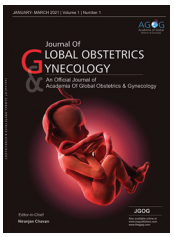
Review Article



Postpartum Hemorrhage: A Never-ending Battle

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ABSTRACT

PPH, the excessive bleeding following childbirth, has been a significant concern throughout human history. The management of PPH has evolved significantly over time, reflecting advances in medical knowledge, technology, and clinical practice. PPH management has evolved and the use of active management of third stage of labour has helped decrease maternal morbidity and mortality. Newer drugs like Carbetocin and inclusion of Tranexa in prevention and management of pph along with new and upcoming concept of PPH bundle care is heralding a new domain of care. The EMOTIVE trial a mulitcentric international trial is also a new cornerstone in PPH management.

Key words: Postpartum, haemorrhage, high-risk obstetrics, bleeding, morbidity, EMOTIVE

HISTORY OF POSTPARTUM HEMORRHAGE (PPH)

PPH, the excessive bleeding following childbirth, has been a significant concern throughout human history. The management of PPH has evolved significantly over time, reflecting advances in medical knowledge, technology, and clinical practice.

Historically, PPH was a leading cause of maternal mortality, particularly in the absence of effective interventions. Ancient medical texts from various cultures, such as Egyptian, Greek, and Indian, document attempts to manage PPH using a range of methods, including herbal remedies, uterine massage, and compression techniques. However, these methods often proved ineffective in controlling severe bleeding.

In the late 19th and early 20th centuries, the discovery of uterotonics, drugs that stimulate uterine contractions, revolutionized the management of PPH. Ergot alkaloids, such as ergometrine, were among the first uterotonics used to control postpartum bleeding. Later, synthetic oxytocin became the primary pharmacological agent for preventing and treating PPH, as it was found to be highly effective in inducing uterine contractions and reducing blood loss.

The development of modern obstetric techniques, such as active management of the third stage of labor (AMTSL), also played a crucial role in reducing the incidence of PPH. The ability to quickly provide blood products, such as packed red blood cells and fresh frozen plasma, has saved countless lives by restoring circulating blood volume and preventing hemorrhagic shock.[1]

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THE MATERNAL MORTALITY RATE

India has been trying to bring down maternal mortality. Moreover, as per the 2021 reports, maternal mortality has decreased up to 99/1,00,000 live births in comparison to 398/1,00,000 live births in 1997–1998.[2] India has adopted the World Health Organization (WHO) sustainable development goals and aims to decrease the maternal mortality ratio (MMR) to 70/1,00,000. To aid in bringing down maternal deaths, it is imperative to shed light on causes leading to maternal mortality. The WHO highlights that the worldwide MMR has decreased greatly, from 342 in the year 2000 to 211 in 2017, decreasing maternal death rates globally, from 451 000 to 295 000 during this period. About 40% of this absolute decline was derived from fewer maternal deaths in India.[3]

ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR

AMTSL is a set of interventions aimed at reducing the risk of PPH by promoting prompt delivery of the placenta and enhancing uterine contraction. This approach contrasts with expectant management, where the placenta is delivered spontaneously without intervention unless there are signs of complications.

AMTSL has become the standard of care in many clinical

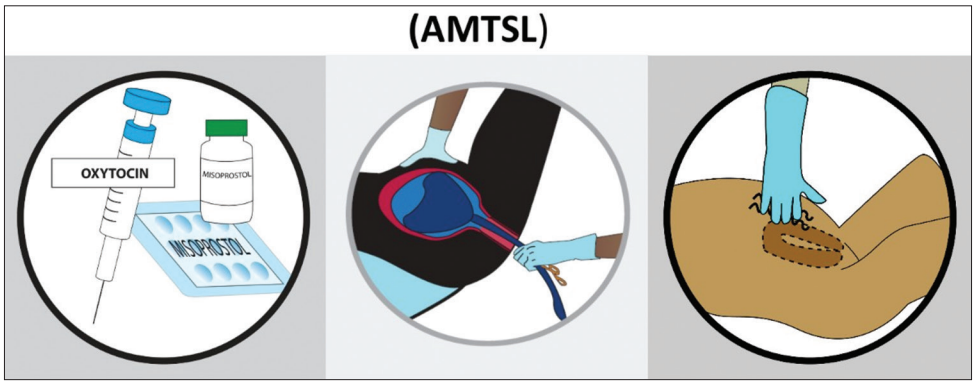


Figure 1: Steps of active management of the third stage of labor

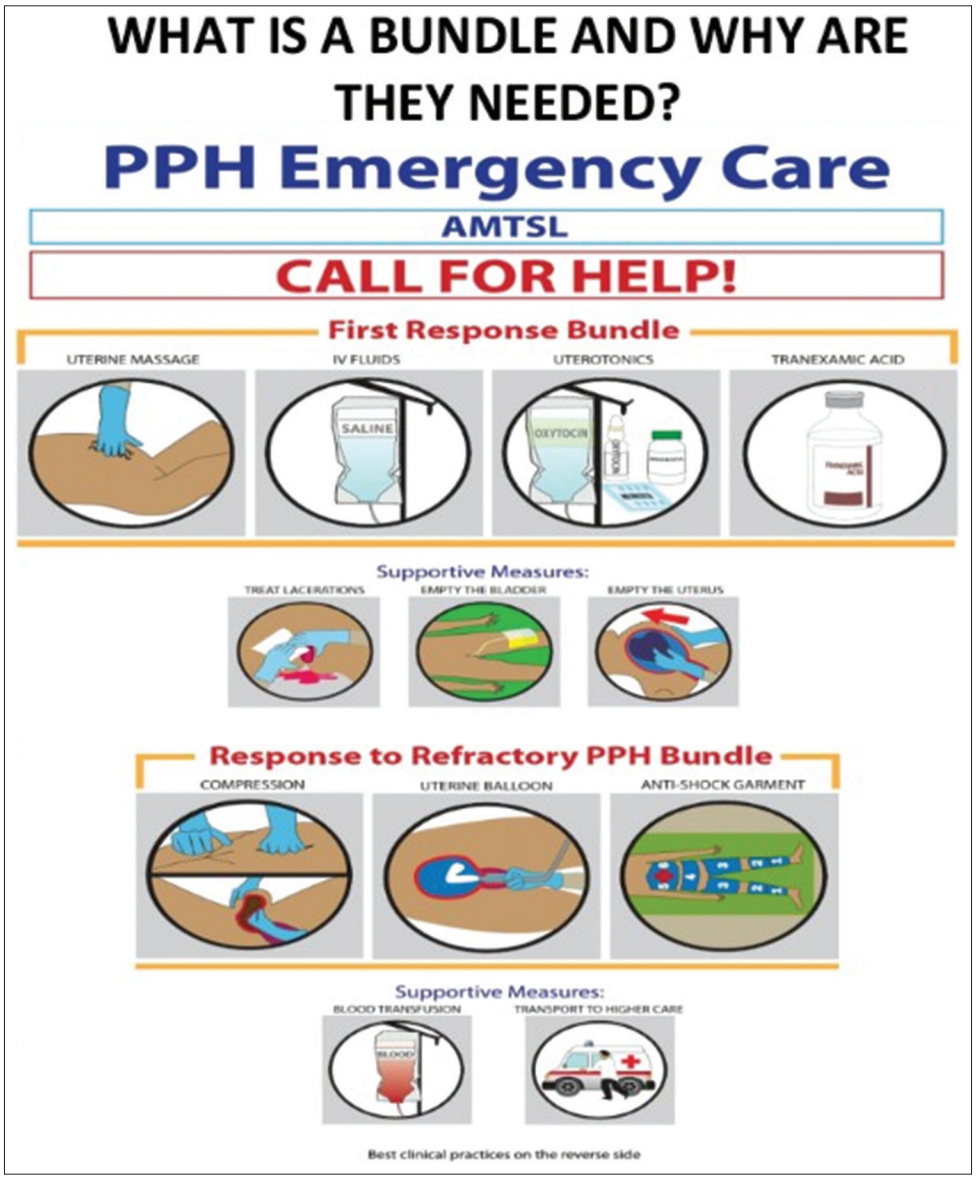


Figure 2: Depicting the postpartum hemorrhage care bundle

settings due to its proven effectiveness in reducing maternal morbidity and mortality associated with PPH.

AMTSL involves three key components [Figure 1]

(1) Administration of a uterotonic agent: A uterotonic drug, such as oxytocin, is administered immediately after the birth of the baby to stimulate uterine contractions and promote placental separation. Oxytocin is the most commonly used uterotonic for this purpose due to its effectiveness and safety profile[4]

(2) Controlled cord traction: After administering the uterotonic, gentle traction is applied to the umbilical cord while simultaneously applying counter-pressure to the uterus. This technique helps to facilitate the expulsion of the placenta by guiding its descent through the birth canal

(3) Uterine massage: Following placental delivery, uterine massage is performed to ensure optimal uterine contraction and prevent excessive bleeding. Massage helps to expel any remaining blood clots from the uterus and promotes uterine tone, reducing the risk of atonic PPH.

The rationale behind AMTSL is to expedite the delivery of the placenta and minimize the time interval between the birth of the baby and placental expulsion. Numerous studies have demonstrated the effectiveness of AMTSL in reducing the risk of PPH compared to expectant management. For example, a Cochrane review published in 2015 analyzed data from 59 trials involving over 87,000 women and found that AMTSL significantly reduced the risk of PPH, severe PPH, and the need for therapeutic interventions such as blood transfusion or surgical procedures.[1]

ANEMIA AND PPH

Anemia increases the heart rate and cardiac output and increases blood loss from bleeding vessels. As hemoglobin falls, aortic hypoxia-sensing cells activate the sympathetic nervous system, increasing heart rate and stroke volume to maintain oxygenation.[5] It also increases blood flow from bleeding vessels due to reduced blood viscosity. Blood viscosity depends on the number (and volume) of red cells in the blood. Blood viscosity falls with decreasing hematocrit and as blood viscosity falls, blood loss increases.[6,7]

Anemic blood clots are more susceptible to fibrinolysis. Red blood cells increase the resistance of fibrin blood clots to fibrinolysis in a dose-dependent manner.[8] Anemia prevents platelet margination and increases bleeding time. In normal flowing blood, red cells are concentrated in the center of the vessel and platelets are concentrated by the wall. This is a laminar flow. If a blood vessel is ruptured the platelets at the wall form a platelet plug. Anemia disrupts laminar flow and increases the bleeding time.[9,10] Anemia (or more specifically iron deficiency) may directly cause uterine atony. Iron is essential for the normal functioning of enzymes with vital cellular functions. It is essential for enzymes and proteins involved in oxidative metabolic processes (e.g., mitochondrial energy metabolism) and are especially important for cells with a high energy demand (cardiomyocytes and skeletal cells). Iron deficiency causes muscle weakness and fatigue. It has also been suggested that anemia might cause uterine atony from impaired uterine oxygenation.[11]

NEWER CONCEPTS: PPH BUNDLE

Bundles are a newer concept in providing optimal, comprehensive healthcare. They are formulated. All evidence are put together, to develop a strategy for dealing with a crucial cause of concern and that works in all health-care settings, in all income countries, and in urban, semi-urban, and rural areas (Figure 2).[12]

Several bundles were tried but the two universally accepted and being intensively researched.

- E-MOTIVE
- PPH EMC Bundle.

WHO E-MOTIVE TRIAL

This was a multi-country, parallel cluster randomized trial with a baseline control phase, along with mixed-methods and health economic evaluations. Published in 2023, it encompassed 80 secondary-level hospitals in Kenya, Nigeria, South Africa, and Tanzania. It aims to evaluate the implementation of early detection and the usage of WHO MOTIVE "first response" treatment for PPH. It aims to explore the clinical, implementational, and resource outcomes.[13]

The EMOTIVE bundle mainly consists of three components [Figure 3].

(1) A strategy for early detection of PPH, triggering the "first response" treatment bundle.

(2) "First response" bundle called "MOTIVE", based on the WHO guideline recommendations and consists of
   (i) Uterine massage
   (ii) Oxytocic drugs
   (iii) Tranexamic acid
   (iv) IV fluids
   (v) Examination and escalation.

(3) An implementation strategy, focusing on simulation-based training, peer-assisted learning, local E-MOTIVE champions, feedback of actionable data to providers, calibrated drape with action line, and MOTIVE emergency kits.

FIGO RECOMMENDATIONS 2022 FOR TREATMENT OF PPH

Intravenous oxytocin is the preferred initial uterotonic medication for managing PPH. If intravenous oxytocin is unavailable or ineffective, alternative options such as intramuscular ergometrine, oxytocin–ergometrine fixed dose, or prostaglandin drugs (including sublingual misoprostol, 800 μg) are recommended. There is insufficient evidence regarding the safety and effectiveness of administering an additional 800-μg dose of misoprostol for treating PPH in women who have already received 600 μg of prophylactic misoprostol orally.[14]

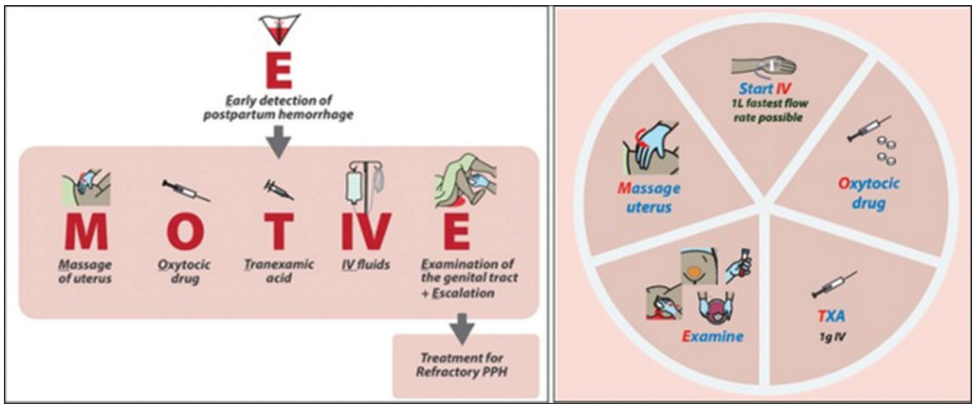
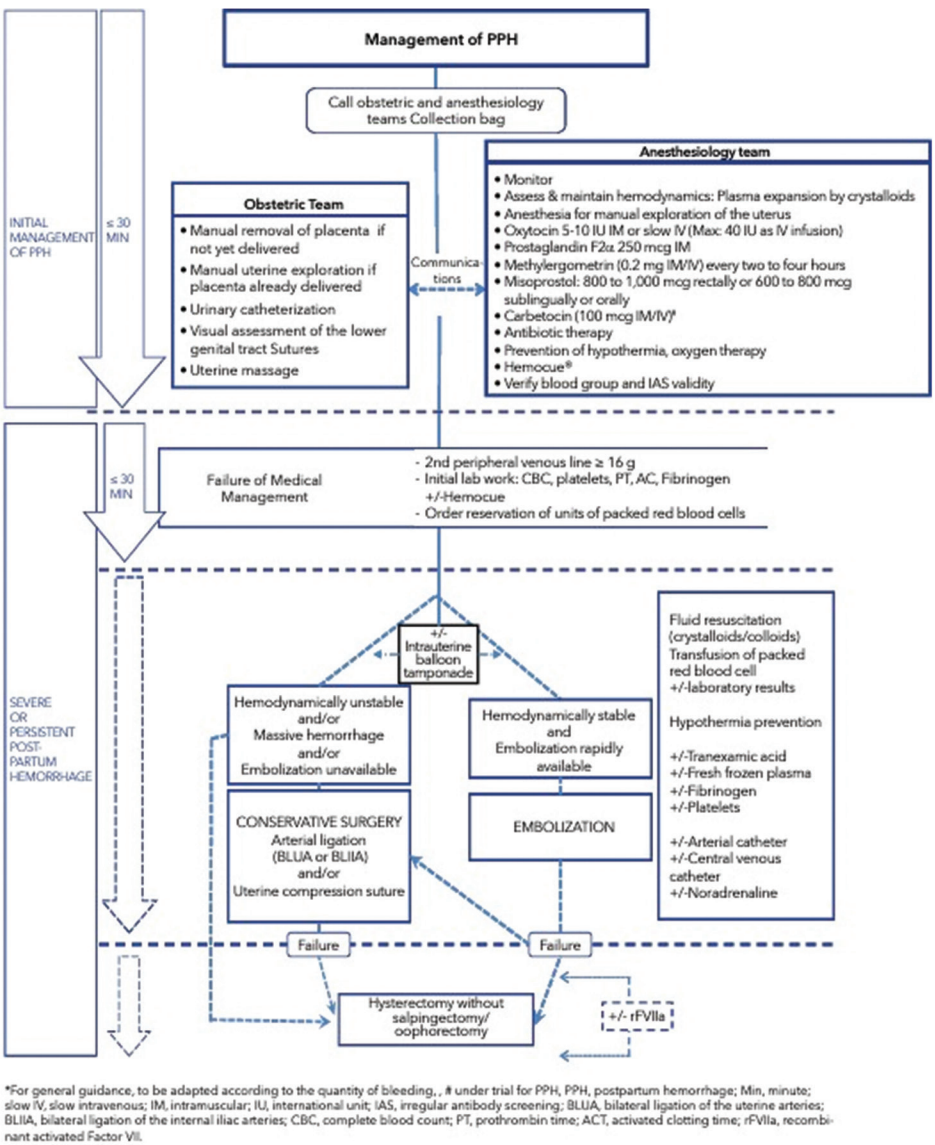


Figure 3: The components of EMOTIVE bundle



*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.

Figure 4: The postpartum hemorrhage guideline put forth by FOGSI

For the initial intravenous fluid resuscitation of women with PPH, isotonic crystalloids are preferred over colloids. Early administration of intravenous tranexamic acid, within 3 h of birth and upon diagnosis of PPH, in addition to standard care, is recommended for women experiencing clinically diagnosed PPH following vaginal or cesarean delivery. Tranexamic acid should be administered at a rate of 1 g (100 mg/mL) intravenously over 10 min, with a second dose of 1 g if bleeding persists after 30 min or if bleeding resumes within 24 h of the first dose. Expanding the use of tranexamic acid for PPH treatment could positively impact health equity and outcomes, particularly for disadvantaged women, especially in low- and middle-income countries.

Uterine massage is recommended as part of PPH treatment. In cases of uterine atony after vaginal birth, bimanual uterine compression or external aortic compression is advised as a temporary measure until appropriate care is available. If uterotonics fail or are unavailable, uterine balloon tamponade is recommended as an effective non-surgical technique, following the exclusion of retained products of conception or uterine rupture.[15] The non-pneumatic anti-shock garment is also recommended as a temporary measure until appropriate care can be provided.[4] However, uterine packing is not recommended for treating PPH due to uterine atony after vaginal birth.

Uterine artery embolization can be considered a conservative management option for PPH if technical resources and skilled personnel are available. If bleeding persists despite conservative interventions, surgical interventions such as compression suture techniques, uterine and hypogastric artery ligation, and hysterectomy are recommended.[16] The primary aim is to halt bleeding before coagulation abnormalities and organ damage occur, with conservative measures attempted initially and more invasive procedures pursued if necessary.

WHO 2020 GUIDELINE ON UMBILICAL VEIN OXYTOCIN

The WHO in 2020 put forth further evidence bolstering its 2012 guideline for the injection of oxytocin in unbiblical veins for retained placenta. Out of the three types of retained placenta, placenta adherents, caused by to failure of the retroplacental myometrium to contract, are most common.

Umbilical vein injection of oxytocin when compared with expectant management or saline injection showed better results with respect to the need for manual removal of the placenta.

NEW DRUGS ON THE BLOCK

(1) Carbetocin:
Carbetocin, a synthetic oxytocin analog, was initially characterized in 1987. It features a half-life of 40 min, approximately 4–10 times longer than oxytocin. On intravenous administration of an optimal dosage of 100 µg, uterine contractions typically commence in <2 min. It is suggested that a single dose of carbetocin may simulate the effects of a 16-h intravenous oxytocin infusion, contributing to heightened uterine tone and diminished risk of PPH in elective cesarean sections[17]

(2) WOMAN Trial 2017 – Tranexamic acid
In this randomized, double-blind, placebo-controlled trial, women aged 16 years and older diagnosed with PPH following either a vaginal birth or cesarean section were recruited from 193 hospitals across 21 countries. Participants were randomly allocated to receive either 1 g of intravenous tranexamic acid or a matching placebo alongside standard care. If bleeding persisted after 30 min or stopped and then resumed within 24 h of the initial dose, a second dose of 1 g of tranexamic acid or placebo could be administered.[18] Tranexamic acid decreases death due to blood loss owing to PPH. No adverse effects have been noted. It is recommended to give tranexamic acid as soon as possible when bleeding ensues or at least within 3 h

(3) Fibrinogen concentrate:
Fibrinogen is one of the best predictors of blood loss. Levels < 1g/l should trigger transfusions. Fibrinogen concentrates are used to decrease the need for transfusion of packed red blood cells, fresh frozen plasma, and platelet concentrates. This, further, decreased the risk associated with transfusion and its reactions.[19]

(4) Recombinant factor VII:
One of the recent and innovative advancements in PPH management involves the utilization of recombinant activated factor VII (rFVIIa), Initially developed for treating bleeding episodes in patients with hemophilia A or B, rFVIIa has found broader application beyond its recognized indications. It has been effectively employed "off-label" on an empirical basis in managing massive PPH. Since its first reported usage almost a decade ago in obstetric hemorrhage, rFVIIa has demonstrated remarkable efficacy and has played a key role in saving numerous lives. Over the past decade, several case reports and series have documented successful PPH management using rFVIIa.[20]

INDIAN CONTRIBUTION: FOGSI GUIDELINES

The Federation of Obstetrics and Gynecology of India put forth its guidelines on the management of PPH in September 2022. They wished to provide clear and crisp guidelines for the management of PPH and to render optimal and respective maternal care (Figure 4).

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