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# ROLE OF CARBETOCIN IN POSTPARTUM HEMORRHAGE

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***Dear FOGSIANs,***

*Carbetocin, a synthetic peptide hormone, belongs to the class of oxytocin receptor agonist. Its primary function is to mimic the effects of oxytocin, a hormone naturally produced in the body. Oxytocin plays a vital role in childbirth, as it stimulates uterine contractions and promotes the release of breast milk. In obstetrics, ensuring a safe and healthy delivery for both the mother and the baby is of utmost importance. It is estimated that postpartum hemorrhage (PPH) accounts for approximately one-quarter of all maternal deaths worldwide. Therefore, finding effective measures to prevent and treat PPH is crucial.*

*Carbetocin has emerged as a game-changer in this regard. Extensive research and clinical trials have demonstrated its efficacy in reducing the risk of PPH. Unlike oxytocin, which requires refrigeration and intravenous administration, Carbetocin can be administered through a simple intramuscular injection, making it more accessible and easier to use, especially in resource-limited settings.*

*Furthermore, Carbetocin has a favorable safety profile with minimal side effects. Its use is not associated with adverse cardiovascular effects, which were sometimes observed with other uterotonic agents. This makes it a reliable and safer alternative, ensuring the well-being of both mother and baby during the critical moments of childbirth.*

*The implications of Carbetocin extend far beyond individual patients. By reducing the incidence of PPH, it can alleviate the burden on healthcare systems and contribute to the global effort to reduce maternal mortality rates.*

*Therefore, we should embrace this medical advancement, ensuring a brighter and healthier future for mothers and their newborns.*

**Best wishes!**

HDPai

Dr. Hrishikesh Pai

President, FOGSI 2023

# ROLE OF CARBETOCIN IN POSTPARTUM HEMORRHAGE

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# ROLE OF CARBETOCIN
## in postpartum hemorrhage

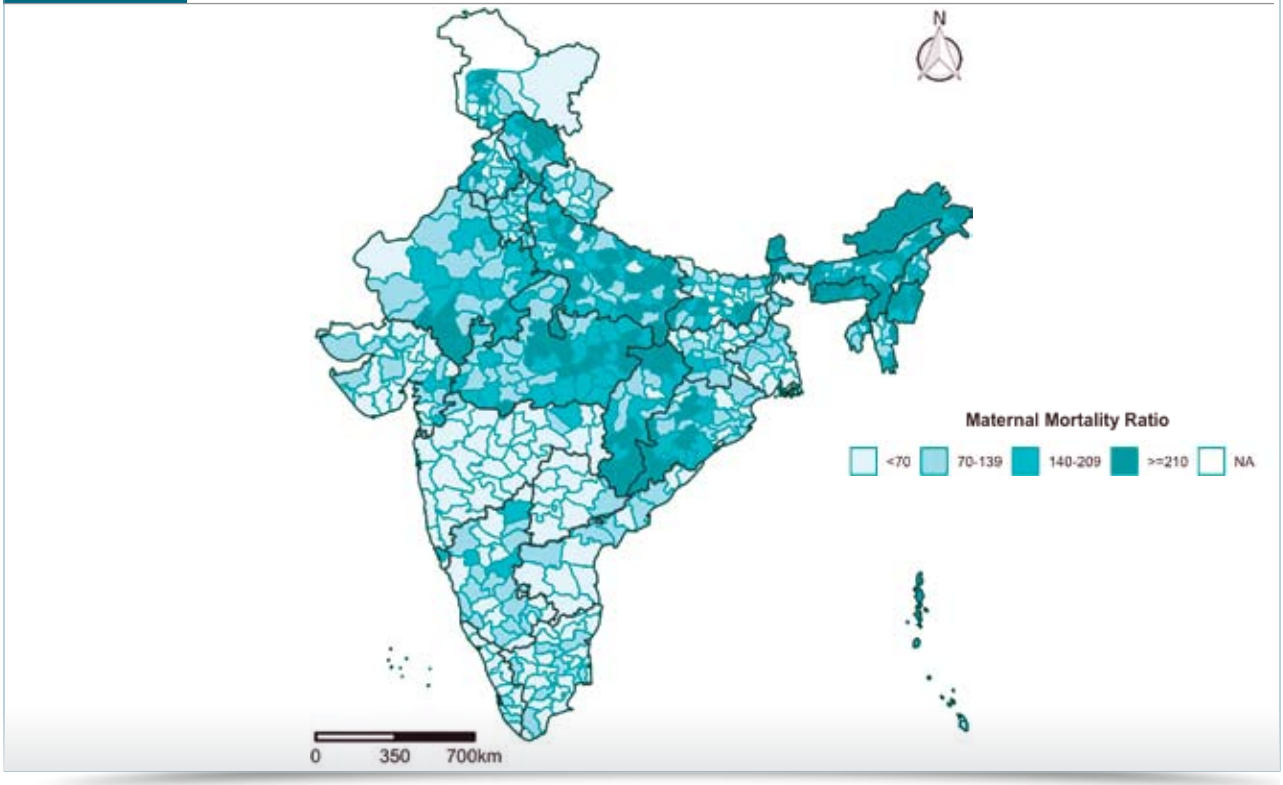
## Definition

The amount of blood loss after birth is used to define postpartum hemorrhage (PPH). The World Health Organization (WHO) defines PPH as blood loss of more than 500 mL from the genital tract following vaginal delivery. However, a cut-off of 500 mL is also considered normal postpartum blood loss. According to the most recent WHO definitions of PPH (2012), PPH is defined as blood loss of >500 mL for vaginal births, while severe PPH is defined as as blood loss exceeding 1000 mL. For cesarean births, PPH is defined as blood loss of more than 1000 mL.[1]

## Maternal mortality statistics

PPH accounts for about 35% of maternal deaths worldwide. The incidence of PPH is 2% to 4% after vaginal delivery and 6% after cesarean section.[2] From 1997–1998 to 2020, India's maternal mortality rate (MMR) decreased from 398 per 100,000 live births to 99 per 100,000. Between 1997 and 2020, there were approximately 1.30 million maternal deaths, with an estimated 23,800 in 2020. Most of these deaths occurred in poorer states (63%) and among women aged 20-29.[3] Figure 1 presents the MMR for all districts in India.[4]

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



## Risk factors

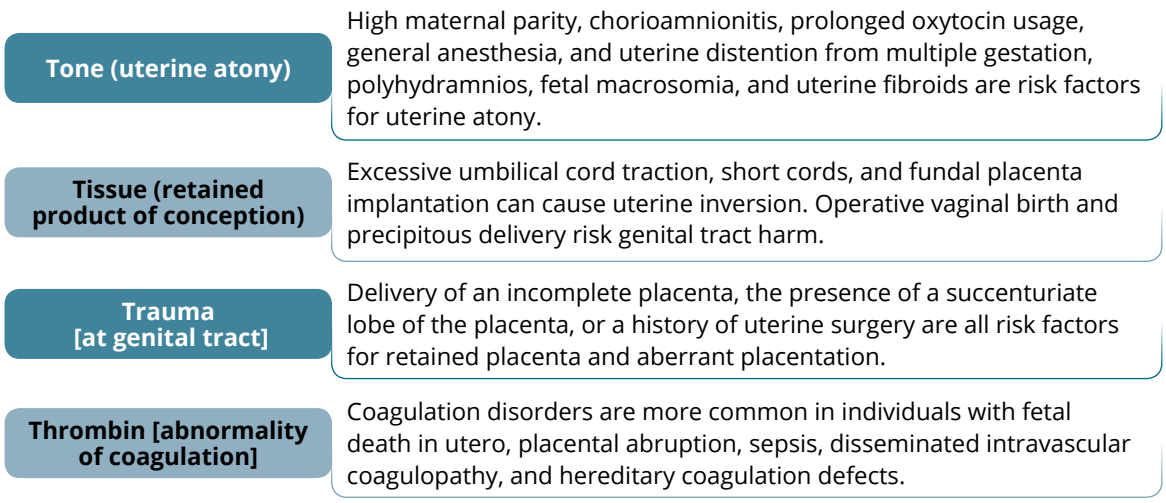
Pregnancy itself is a risk factor for PPH, as every pregnancy carries the potential risk of PPH. The risk factors for PPH, as provided by Hoveyda et al., have been modified to suite the Indian population, as shown in Table 1.[5]

**Table 1.** Risk factors for postpartum hemorrhage

| | |
|---|---|
| **1. Maternal issues** | |
| Teenage pregnancy, elderly primigravida, multiparity and grand multiparity (> 4). | Thyroid dysfunction |
| Illiteracy, inadequate prenatal visits, low socio-economic status | |
| Previous postpartum hemorrhage | ART pregnancy |
| Previous uterine surgeries | Renal and liver disorders |
| Uterine malformations | Respiratory disorders |
| Obesity | Anticoagulant therapy |
| Fibroid uterus | Viral infections, dengue |
| Previous cesarean section | Inherited and acquired coagulopathies, hemoglobinopathies |
| Previous instrumental delivery | Metabolic syndrome |
| Anemia | Post-bariatric surgery |
| Thrombocytopenia | Pregnancy after renal transplant |
| Diabetes | Multifetal gestation |
| Cardiac dysfunction | |
| Hypertensive disorders | |
| **Intrapartum** | |
| Induction and augmentation of labor | Instrumental deliveries<br>Cesarean section |
| Precipitate labor and prolonged labor | In-coordinate Uterine action (Hypotonic & Hypertonic) |
| Obstructed labor | Prolonged rupture of membrane (PROM/PPORM) |
| Arrest of labor in the second stage | Chorioamnionitis |
| VBAC/TOLAC | |
| Placenta previa | Placenta abruption |
| Placenta accreta syndrome | Arteriovenous malformations |
| Chorio angioma | Placental abnormalities such as succenturiate, battle door placenta, vasa previa etc |
| **Postpartum** | |
| Genital tract trauma | Uterine inversion, uterine rupture |
| Retained placenta | Subinvolution |
| Retained placental tissues | Puerperal sepsis |
| **2. Fetal issues** | |
| • Polyhydramnios | |
| • Large-for-gestational-age fetus | |
| • Fetal macrosomia (birth weight greater than 8 lb, 13 oz [4,000 g]) | |
| • Congenitally malformed fetus | |
| **3. Placental issues** | |
| • Polyhydramnios | |
| • Large-for-gestational-age fetus | |
| • Fetal macrosomia (birth weight greater than 8 lb, 13 oz [4,000 g]) | |
| • Congenitally malformed fetus | |

ART: Assisted reproductive technology; TOLAC: trial of labor after cesarean; vaginal birth after cesarean (VBAC).

**Figure 2.** Etiology of post-partum hemorrhage[9]




## Etiology and mechanism of PPH

Risk factors for PPH depend on the etiology of the hemorrhage.[6] The "Four T's" can be used to identify and address the four most common causes of PPH (uterine atony [Tone]; laceration, hematoma, inversion, rupture [Trauma]; retained tissue or invasive placenta [Tissue]; and coagulopathy [Thrombin]), as shown in Figure 2.[7]

## Symptoms and signs

The most prominent symptom of PPH is vaginal bleeding after delivery. The bleeding is usually a slow trickle from the vagina. Low systolic blood pressure, tachycardia, and an increased respiratory rate have traditionally been used to diagnose hypovolemia. Occasionally, the bleeding is concealed as a vulvovaginal or wide ligament hematoma (collection of blood outside blood vessels). In extreme cases, anemia as well as signs of shock caused by decreased blood volume, known as hypovolemic shock can occur. In severe situations, low blood pressure and a rapid heart rate are observed.[8] The clinical findings in hypovolemia are listed in Table 2.[9]

## Diagnosis of PPH

Patient status and risk factors should be assessed quickly at the initial evaluation. If postpartum women have tachycardia and hypotension, they may be losing more than 25% of their blood volume. PPH patients must be monitored for vital signs and total blood loss.[7]

**Table 2.** Clinical findings in obstetric hemorrhage[9]

| Blood Volume Loss | Blood Pressure (systolic) | Symptoms and Signs | Degree of Shock |
|---|---|---|---|
| 500–1000 mL (10%–15%) | Normal | Palpitations, tachycardia, dizziness | Compensated |
| 1000–1500 mL (15%–25%) | Slight fall (80–100 mmHg) | Weakness, tachycardia, sweating | Mild |
| 1500–2000 mL (25%–35%) | Moderate fall (70–80 mmHg) | Restlessness, pallor, oliguria | Moderate |
| 2000–3000 mL (35%–50%) | Marked fall (50–70 mmHg) | Collapse, air hunger, anuria | Severe |

Examining the patient during a hemorrhage can help determine the likely source of the bleeding by focusing on the patient's risk factors. A rapid examination of the entire genital area for lacerations, hematomas, or signs of uterine rupture is recommended. The evaluation may include a physical exam, placental tissue extraction or bedside ultrasonography.[7]

Laboratory testing can be ordered in cases of PPH to aid in the evaluation and management of the patient. Preparing for a blood transfusion may require a type and screen or crossmatch. Hemoglobin, hematocrit, and platelets can be checked periodically. If disseminated intravascular coagulation (DIC) is suspected, coagulation tests and fibrinogen will be beneficial.[7]

## Prevention of PPH

The risk of PPH can be reduced with both active management and the use of prophylactic uterotonics in the third stage of labor. All three steps of Active Management of the Third Stage of Labor (AMTSL) should only be done by healthcare provider.[10]

- Administration of prophylactic uterotonics at the time of delivery
- Delayed cord clamping
- Controlled cord traction

The majority of PPH deaths can be prevented with the use of prophylactic uterotonics during the third stage of labor through well-timed and suitable management. All women giving birth should be offered uterotonics after delivery of the baby to prevent PPH (Table 3).[10] **The Federation of Obstetric and Gynaecological Societies of India (FOGSI) recommends administration of uterotonic agent within one minute of delivery, after ruling out the presence of second fetus.**[11]

**Table 3.** Existing molecules used for PPH prevention[11]

| Drug | Dosage | Action | Side effects | Contraindications |
|---|---|---|---|---|
| Oxytocin | 10 U IM/IV | Onset: 1–3 mins<br>Lasts: 10–15 mins | Minimal | • Allergic to oxytocin<br>• Cardiac dysfunction (to minimize risk of volume overload)<br>• Obstructed labour<br>• Grand multiparity (relative contraindication) |
| Methylergometrine | 0.2 mg IV/IM | Onset: 2–7 mins<br>Lasts: 2–4 mins | Nausea, vomiting, headache, hypertension | • Hypertension<br>• Cardiac disease |
| Prostaglandin F2α | 250 mcg IM | Onset: 1–2 mins<br>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<br>Peak: 20–30 mins<br>Lasts: <75 mins | | • None |
| Tranexamic acid[12,13] | 1 gm IV to be given immediately (within 3 hours of PPH) and repeat | Onset: 5 to 15 mins<br>Half-life: 2 hours | Seizures, headaches, backache, abdominal pain, nausea, vomiting, diarrhea, fatigue, pulmonary embolism, deep vein thrombosis, and visual disturbances | • Known allergy to TXA, intracranial bleeding, known defective color vision, history of venous or arterial thrombo-embolism, or active thrombo-embolic disease |

## Need for newer molecules

Carbetocin and Oxytocin are uterotonics listed in the Essential Medicines List by the World Health Organization.[14] Reports have shown that the use of intravenous crystalloid solutions such as oxytocin can lead to fluid accumulation and trigger cerebral or pulmonary edema.[15]

The usual dose of oxytocin requires intravenous administration over extended periods during and after the third stage of labor to prevent bleeding episodes, which lead to complications. Oxytocin can cause water retention and intoxication (confusion, convulsions, and coma). When administered as a bolus, it may lead to an increase in heart rate and a decrease in mean arterial blood pressure.[15]

Additional concerns include need for repeat dosing. Consequently, the use of oxytocin during AMTSL is associated with certain risks.[15] Therefore, it is important to have varied options and newer molecules to reduce the risk of PPH.

## Advantages of Carbetocin to existing uterotonics

- Carbetocin is a long-acting synthetic analog of oxytocin with a half-life of approximately 40 minutes,15 which is reported to be about 4 to 10 times longer than that of oxytocin.[10]
- Carbetocin demonstrates a bioavailability of 80% and achieves peak plasma levels in <30 minutes after intramuscular injection.[10]
- Intravenous administration of carbetocin can produce tetanic uterine contractions lasting for six minutes followed by more rhythmic ones for approximately an hour.[15]
- Studies have shown that the use of carbetocin reduces the need to manually explore the uterine cavity for persistent bleeding.[15]
- Another advantage of carbetocin is its tolerance to heat and does not require the cold-chain transport and storage that is needed for oxytocin use, making it a possible alternative for countries where it is problematic to maintain the cold chain.[10]
- Carbetocin is available as a room-temperature formulation in India, Table 4.[11]

**Table 4.** Carbetocin in PPH

| Drug | Dosage | Action | Side-effects | Contraindication |
|---|---|---|---|---|
| Carbetocin room temperature stable[11] | 100 mcg IV/IM | Rapid onset of action (within 2 minutes for both IV and IM administration), the long half-life, and prolonged duration of action (60 min for a single IV injection, 120 min for an IM injection) | Vomiting, abdominal pain, headache, tremor, dizziness, chest pain | • Pregnancy and labor before delivery of the infant<br>• Must not be used for induction of labor:<br>» In women with serious cardiovascular disorders<br>» In women with hepatic or renal disorders<br>» Epilepsy<br>» Hypersensitivity to carbetocin, oxytocin or any of the excipients according to the composition |

## Carbetocin vs. other molecules for PPH prevention

The Carbetocin Haemorrhage Prevention (CHAMPION) trial was an international, a WHO sponsored study was conducted at 23 hospitals (sites) across 10 countries, including India. Researchers compared heat-stable carbetocin with oxytocin for the prevention of PPH during the third stage of labor in women giving birth vaginally. The study found that intramuscular injections of heat-stable carbetocin (at a dose of 100 µg) were non-inferior to oxytocin (at a dose of 10 IU) administered immediately after vaginal birth in preventing blood loss of at least 500 mL. Non-inferiority was not demonstrated for the outcome of blood loss of at least 1000 mL; however, the trial was underpowered for this outcome.[16]

A secondary analysis of the WHO CHAMPION trial evaluated the association between the third stage of labor duration and blood loss in the sub cohort of women from the CHAMPION trial receiving AMTSL. Around 10,040 women were analyzed. There was a steep rise in blood loss during the first 10 minutes of the third stage, with more gradual increase thereafter. This trend was observed for both oxytocin and heat-stable carbetocin and the difference in the trends for both drugs were not statistically significant (p value=0.2070). Therefore, a positive association was observed between postpartum blood loss and third stage of labor duration with either uterotonic.[17]

Another study showed that carbetocin is a better alternative to misoprostol for AMTSL. Pregnant women admitted for vaginal delivery were randomized to receive either carbetocin (100 µg/mL) intravenously or misoprostol 800 µg for AMTSL. Findings showed 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 ($p=0.007$) in the carbetocin group compared to the misoprostol. Both drugs were hemodynamically safe, but adverse effects were commonly observed in the misoprostol group ($p<0.001$).[18]

Another study found that, in the prevention of PPH, a single injection of carbetocin was more effective than a continuous infusion of oxytocin. Women in the carbetocin group were administered a bolus of 100 µg IV; while those in the control group were given 20 IU of oxytocin in 1000 mL of 0.9% Na-Cl solution IV (150 mL/hour). Both drugs were found to have a hypotensive effect, but a greater reduction in blood pressure was observed in the oxytocin group. Additiionally, significantly more women in the oxytocin group required an additional uterotonic agent (23.5% vs. 0%, $p<0.01$), although no significant difference was observed in estimated blood loss and in the drop hemoglobin level ($p>0.05$). Patients treated with carbetocin showed higher diuresis than those treated with oxytocin, especially 12 hours after a cesarean section. The carbetocin group was observed to have an acceptable and safe hemodynamic profile with unmodified systolic and diastolic blood pressure when compared to the beginning of the procedure, whereas lower BP levels observed in the oxytocin group at all the study times after drug administration. Additionally, the absence of antidiuretic effect is another advantage of carbetocin over oxytocin, indicating a favorable carbetocin profile.[19]

When the effect of a single dose of carbetocin was compared with oxytocin infusion in a

woman undergoing elective cesarean section and having at least one risk factor for PPH, carbetocin was observed to be efficacious and safe on the maintenance of uterine tone and on the limitation of blood losses, in peri- and in the postoperative period. Further, even the mean ± SD of postoperative pain on the day of surgery was significantly lower in the carbetocin group than in the oxytocin group and remained significant till the third day after cesarean section. Women requiring analgesic drugs were also significantly lower in the carbetocin vs. oxytocin group.[20]

## FIGO 2022 recommendations for prevention of PPH[21]

1. The use of uterotonics for prevention of PPH during the third stage of labor is recommended for all births. Oxytocin (10 IU intravenously/intramuscularly [IV/IM]) is recommended for the prevention of PPH for vaginal delivery and cesarean section. In settings where oxytocin is used, attention should be paid to maintaining oxytocin cold chain.
2. In settings where oxytocin is unavailable or its quality cannot be guaranteed, the use of other injectable uterotonics (if appropriate ergometrine/methylergometrine 200 µg IM/IV; provided hypertensive disorders can be safely excluded prior to its use) or oral misoprostol (400–600 µg orally) or carbetocin 100 µg IM/IV is recommended for the prevention of PPH.
3. The combinations of ergometrine plus oxytocin or misoprostol plus oxytocin may be more effective uterotonic drug strategies for the prevention of PPH ≥500 ml compared with the current standard, oxytocin. This comes at the expense of a higher risk of adverse effects (vomiting and hypertension with ergometrine and fever with misoprostol).
4. In settings where skilled birth attendants are not present to administer injectable uterotonics and oxytocin is unavailable, the administration of misoprostol (400–600 µg orally) by community healthcare workers and lay health workers is recommended for the prevention of PPH.
5. In settings where skilled birth attendants are unavailable, controlled cord traction (CCT) is not recommended.
6. Sustained uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin.
7. Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women.
8. Oxytocin (IV or IM) and CCT is the recommended method for the removal of the placenta to prevent PPH in cesarean delivery.

# Clinical and pharmacological management of PPH[22]

If despite active management, there is estimated blood loss (greater than or equal to) 500ml, *brisk bleeding, pulse rising, blood pressure falling, or maternal symptoms of hypotension, then initiate resuscitation, investigation of and treatment for postpartum hemorrhage, and quantitative measurement of ongoing blood loss

**Resuscitation**

- Call for help
- Perform bimanual uterine massage
- Institute labor unit hemorrhage protocol
- Use two large-bore intravenous needles
- Provide oxygen by mask
- Monitor blood pressure, pulse, and urine output
- Consider laboratory testing such as type and crossmatch, complete blood count

**Aftercare**

- Monitor for ongoing blood loss (preferably quantitative measurement) and vital signs
- Assess for signs of anemia (fatigue, shortness of breath, chest pain, lactation problems)
- Debrief with and listen to patients and staff regarding their experience with the emergency

Determine cause and treat using the Four T's mnemonic

| 1) Soft, boggy uterus **TONE** | 2) Laceration or uterine inversion **TRAUMA** | 3) Retained placenta or clot **TISSUE** | 4) Blood not clotting **THROMBIN** |
|---|---|---|---|
| Oxytocin†: 20 to 40 IU in 1 L normal saline, infuse 500 mL over 10 minutes then 250 mL per hour<br>Prostaglanding F2α 250 mcg IM<br>Methylergometrine (0.2 mg IM/IV) every two to four hours<br>Misoprostol: 800 to 1,000 mcg rectally or 600 to 800 mcg sublingually or orally<br>Carbetocin (100 mcg IM/IV) | Suture lacerations<br>Drain expanding hematoma<br>Replace inverted uterus<br>Repair of uterine rupture/ hysterctomy | Inspect placenta<br>Explore uterus<br>Manual removal of placenta<br>Curettage | Observe clotting<br>Check coagulation studies<br>Replace clotting factors, platelets<br>Supply fresh frozen plasma |

Tranexemic acid: IV of 1 g, after giving birth, followed by a second dose if bleeding continues after 30 min or restarts within 24 h after the first dose

Severe postpartum hemorrhage

Transfuse red blood cells, platelets, and clotting factors using massive transfusion or emergency release protocol

Consult anesthesia, surgery, and an intensivist

Support blood pressure with vasopressors

Balloon tamponade, vessel embolization or ligation, compression sutures, and hysterectomy

The Recent advances are there on using vacuum suction cannula (Panicker) and trans-vaginal Uterine Artery Clamps (V. P. Paily technique) can be used.

*–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.

## Conclusion

- PPH is defined as blood loss of >500 mL for vaginal births, with severe PPH is defined as loss of >1000 mL
- PPH accounts for about 35% of maternal deaths worldwide
- Risk factors for PPH are dependent on the etiology of the hemorrhage
- Examining the patient during the hemorrhage can help determine the likely source of the bleeding by focusing on the patient's risk factors
- The risk of PPH can be reduced with both active management and the use of prophylactic uterotonics in the third stage of labor.
- FOGSI recommends administering a uterotonic agent within one minute of the delivery of the baby, after ruling out the presence of second fetus.
- Since Oxytocin, Tranexamic acid, and other uterotonics are associated with several shortcomings, highlighting the need for varied choices and newer molecules to reduce the risk of PPH.
- Carbetocin is a preferred alternative to other uterotonics due to its several advantages; rapid onset of action, available as a room-temperature formulation and thus eliminating the need for cold-chain transport.
- Carbetocin also has an acceptable and safe hemodynamic profile with unmodified systolic and diastolic blood pressure compared to lower BP levels with oxytocin. Additionally, the absence of an antidiuretic effect further contributes to the favorable profile of carbetocin as compared to oxytocin.

## References


1. Gonzalez-Brown V, Schneider P. Prevention of postpartum hemorrhage. Semin Fetal Neonatal Med. 2020;25(5):101129.
2. Prevention and Management of Postpartum Hemorrhage (PPH) – Updated Guidelines. Federation of Obstetric and Gynaecological Societies of India (FOGSI); 2022 Sep. Available from: https://www.fogsi.org/wp-content/uploads/tog/pph-prevention-and-management-updated-sept-2022.pdf. Accessed on: August 16, 2024.
3. Meh C, Sharma A, Ram U, et al. Trends in maternal mortality in India over two decades in nationally representative surveys. BJOG. 2022 Mar;129(4):550-561.
4. 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.
5. Hoveyda F, MacKenzie IZ. Secondary postpartum haemorrhage: Incidence, morbidity and current management. 2001;108(9): 927–30.
6. Wormer KC, Jamil RT, Bryant SB. Acute Postpartum Hemorrhage. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499988/
7. Evensen A, Anderson JM, Fontaine P. Postpartum Hemorrhage: Prevention and Treatment. Am Fam Physician. 2017 Apr 1;95(7):442-449. PMID: 28409600.
8. Postpartum Hemorrhage. Available at: https://www.medindia.net/patients/patientinfo/postpartum-hemorrhage.htm. Accessed on: October 18, 2022.
9. Smith JR. Postpartum Hemorrhage. Available at: https://emedicine.medscape.com/article/275038-overview#a10. Accessed on: October 18, 2022.

10. Mostafa HE, Mostafa MK, Abdrabou HA et al. Prevention of postpartum haemorrhage in patients with severe preeclampsia using Carbetocin versus Misoprostol. AIMJ. 2020; 1 (12): 239–43 Available on: https://aimj.journals.ekb.eg/article_141798.html.

11. Prevention of Post-Partum Hemorrhage (PPH). Available at: https://www.fogsi.org/wp-content/uploads/2015/11/pph.pdf. Accessed on: October 18, 2022

12. Chauncey JM, Wieters JS. Tranexamic Acid. Treasure Island (FL): StatPearls Publishing; 2022

13. Mielke RT, Obermeyer S. The use of tranexamic acid to prevent postpartum hemorrhage. J Midwifery Womens Health. 2020; 65(3):410–416.

14. Chao YS, McCormack S. Carbetocin for the Prevention of Post-Partum Hemorrhage: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Jul 29. PMID: 31532600.

15. Reyes OA, Gonzalez GM. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double-blind randomized controlled trial. J Obstet Gynaecol Can. 2011; 33(11):1099–104

16. Widmer M, Piaggio G, Nguyen TMH et al. Heat-Stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. N Engl J Med. 2018; 379(8):743–52.

17. Chikkamath SB, Katageri GM, Mallapur AA et al. Duration of third stage labour and postpartum blood loss: A secondary analysis of the WHO CHAMPION trial data. Reprod Health. 2021; 18(1):230.

18. Maged AM, Waly M, Fahmy RM, et al. Carbetocin versus rectal misoprostol for management of third stage of labor among women with low risk of postpartum haemorrhage. Int J Gynaecol Obstet. 2020; 148(2):238–42.

19. Larciprete G, Montagnoli C, Frigo M et al. Carbetocin versus oxytocin in caesarean section with high risk of post-partum haemorrhage. J Prenat Med. 2013; 7(1): 12–18.

20. De Bonis M, Torricelli M, Leoni L, et al. Carbetocin versus oxytocin after caesarean section: Similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage. J Matern Fetal Neonatal Med. 2012; 25(6):732–5.

21. Escobar MF, Nassar AH, Theron G et al. FIGO recommendations on the management of postpartum hemorrhage 2022. Int J Gynecol Obstet. 2022; 157 (Suppl. 1):3–50

22. Leduc D, Senikas V, Lalonde AB. No. 235-Active Management of the third stage of labour: Prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can. 2018;40(12):e841−55.

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