


# How to use heat-stable carbetocin and tranexamic acid for the prevention and treatment of postpartum haemorrhage in low-resource settings

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## BACKGROUND

The least developed countries, which include those affected by fragility and humanitarian crises, account for 44% of all maternal deaths globally.<sup>1</sup> Postpartum haemorrhage (PPH) is a leading cause of maternal mortality in these low-resource settings.<sup>2</sup> Because uterine atony accounts for approximately two-thirds of PPH cases, WHO recommends that every woman receives a prophylactic uterotonic immediately after birth to prevent PPH as part of the active management of the third stage of labour.<sup>3 4</sup>

Some PPH prevention and treatment medicines are well evidenced with a long implementation history, including oxytocin, misoprostol and ergometrine.<sup>5</sup> Heat-stable carbetocin (HSC), a uterotonic recommended for PPH prevention and tranexamic acid (TXA), an antifibrinolytic recommended for PPH treatment, were recently added to the core list of reproductive health medicines in the 2019 Model List of Essential Medicines by the WHO.<sup>4 6 7</sup> Since 2021, both medications have been made available at public sector pricing through the Product Catalogue of the United Nations Population Fund.<sup>8</sup> Unlike heat-sensitive oxytocin or ergometrine, HSC and TXA have the operational advantage of overcoming the logistic costs and challenges inherent to ensuring a cold chain system. Therefore, they could play a critical role in resource-challenged and warm climate settings, where cold chain transport and storage is often not available, which compromises the quality of oxytocin.

The growing number of medications now available in the PPH prevention and treatment toolkit can make it difficult for policymakers, programme managers and clinicians

## Summary box

- ⇒ Heat-stable carbetocin, a uterotonic used for postpartum haemorrhage (PPH) prevention and tranexamic acid, an antifibrinolytic indicated for PPH treatment, are recently recommended medications.
- ⇒ The growing number of medications in the PPH prevention and treatment toolkit can challenge policymakers, programme managers and clinicians operating in resource-constrained settings in deciding where and how to invest limited resources to achieve the best possible maternal health outcomes.
- ⇒ This paper argues that there is no one-size-fits-all approach to implementing international PPH prevention and treatment guidance.
- ⇒ A programmatic strategy tailored to the different levels of maternity care and the availability of skilled providers and cold chain systems is proposed.

operating in resource-constrained settings to decide where and how to invest limited resources to achieve the best possible health outcomes. In this paper, we focus on pharmaceutical products for PPH prevention and treatment. We argue that there is no one-size-fits-all approach to preventing and treating PPH and propose a programmatic approach that distinguishes the different levels of maternity care and accounts for existing human and infrastructural resources.

## WHAT, WHERE, AND HOW

First, the critical features of HSC and TXA should be understood in light of other established PPH medications. Established medications include oxytocin (a first-line and highly effective injectable uterotonic to prevent and treat PPH in all births), misoprostol (a non-injectable uterotonic for PPH prevention and treatment when there are no trained

**Table 1** Summary of clinical indications and health system requirements of uterotonics and tranexamic acid

Use and health system requirements	Uterotonics				Non-uterotonic
	Oxytocin	Misoprostol	Heat-stable carbetocin*	Ergometrine†	Tranexamic acid
PPH prevention	Recommended‡	Recommended	Recommended	Recommended	Not recommended
PPH treatment	Recommended‡	Recommended	Not recommended	Recommended	Recommended
Labour induction	Recommended	Recommended	Not recommended	Contraindicated	Not recommended
Labour augmentation	Recommended	Contraindicated	Contraindicated	Contraindicated	Not recommended
Abortion care	Not recommended	Recommended§	Not recommended	Not recommended	Not recommended
Postabortion care	Not recommended	Recommended	Not recommended	Not recommended	Not recommended
Administration route	Intravenous, IM	Oral, sublingual, vaginal¶	Intravenous, IM	Intravenous, IM	Intravenous
Skilled health provider requirement	Yes	No	Yes	Yes	Yes
Cold chain transport and storage requirement	Yes (2°C–8°C)	No (but ≤25°C) in double aluminium blisters	No (but ≤30°C)	Yes (2°C–8°C) away from light	No
Presentation**	10IU ampoule	200 mcg tablet††	100 mcg in 1 mL ampoule	Ergometrine maleate 0.2 mg/mL in 1 mL ampoule	100 mg/mL in 10 mL ampoule
Price per unit**	US\$0.334 per ampoule	US\$0.054 per oral tablet of 200 mcg	US\$0.413 per ampoule	US\$0.219 per ampoule	US\$1.30 per ampoule

The colour shadings reflecting a traffic light approach (red, orange and green) were used to give the reader an instant recognition of the level of caution that is needed in regards to the use of the uterotonics and non-uterotonics in different clinical situations. The use of lighter orange and grey in rows 10 and below of table 1 were to help the reader easily identify which uterotonics and non uterotonics required a skilled health provider for their administration and which required a cold chain transport and storage requirement.

\*Heat-stable carbetocin: only in contexts where its cost is comparable to that of other effective uterotonics.

†Ergometrine: only in contexts where hypertensive disorders can be safely ruled out before use. Ergometrine refers to ergometrine/methylergometrine.

‡First line.

§Alone or preceded by mifepristone.

¶The vaginal route is not recommended for PPH prevention and treatment.

\*\*Per UNFPA Product Catalogue (2021).

††The 25 mcg oral or vaginal tablet is not in the 2021 UNFPA Product Catalogue. The 200 mcg tablet must not be divided into 25 mcg portions, as this is virtually impossible to be achieved precisely by hand.

IM, intramuscular; IU, international units; PPH, postpartum haemorrhage; UNFPA, Product Catalogue of the United Nations Population Fund.

providers to give injectable uterotonics or oxytocin is not available or of questionable quality) and ergometrine (an injectable uterotonic for PPH prevention and treatment). Table 1 synthesises the main features of these medications. Notably, some uterotonics, for example, oxytocin and misoprostol, have multiple obstetric and gynaecological applications, such as labour induction and augmentation as well as abortion and postabortion care.<sup>9</sup> In contrast, HSC and TXA have currently a single obstetric application.

HSC is an injectable uterotonic recommended only for PPH prevention. WHO recommends HSC in situations when (1) oxytocin is unavailable or of dubious quality, (2) there is no cold transportation and storage capability, (3) its cost is comparable to that of other effective uterotonics and (4) there is skilled health personnel to inject it.<sup>4</sup> TXA is an antifibrinolytic administered intravenously. It is not a uterotonic—therefore, not a uterotonic substitute. TXA is recommended only for PPH treatment in complement with

uterotonics as part of the standard PPH treatment package.<sup>6</sup> TXA decreases mortality from bleeding in women with PPH, irrespective of the aetiology, be it uterine atony, trauma to the genital tract, retained tissue or clotting disorder.<sup>6</sup>

Second, prioritising the different medications should align with WHO guidance. For PPH prevention, the following uterotonic hierarchy is recommended: (1) in settings where multiple uterotonics are available, oxytocin (10 IU, intramuscular/intravenous) is the recommended uterotonic in all births, (2) in settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics (HSC, or, if appropriate, ergometrine/methylergometrine or oxytocin-ergometrine fixed-dose combination) or oral misoprostol is recommended and (3) in settings where skilled health personnel are not present to administer injectable uterotonics, the administration of misoprostol (400 µg or 600 µg orally) by community healthcare workers and lay health workers

		Availability of health providers competent in administering injections				
		Yes	No			
Availability of 2-8 °C cold chain transport and storage	Yes	<b>Prevention</b> <input type="checkbox"/> oxytocin (first line) If quality oxytocin is not available: <input type="checkbox"/> heat-stable carbetocin* <i>or</i> <input type="checkbox"/> misoprostol <i>or</i> <input type="checkbox"/> ergometrine§	E.g.: comprehensive emergency obstetric care facilities or basic emergency obstetric care facilities with reliable cold storage	Situation rarely encountered		
		<b>Treatment¶</b> <input type="checkbox"/> oxytocin (first line) <i>and</i> <input type="checkbox"/> tranexamic acid (first line) If quality oxytocin is not available or in addition to oxytocin: <input type="checkbox"/> misoprostol <i>and/or</i> <input type="checkbox"/> ergometrine§				
	No	<b>Prevention</b> <input type="checkbox"/> heat-stable carbetocin* <i>or</i> <input type="checkbox"/> misoprostol	E.g.: basic emergency obstetric care facilities without reliable cold storage		<b>Prevention</b> <input type="checkbox"/> misoprostol	E.g.: community-based distribution of misoprostol for home births
		<b>Treatment¶</b> <input type="checkbox"/> misoprostol <i>and</i> <input type="checkbox"/> tranexamic acid			<b>Treatment</b> <input type="checkbox"/> misoprostol	
<b>All the medications and related supplies, including heat-stable carbetocin and tranexamic acid, are available in the UNFPA Product Catalogue at public pricing</b>						

**Figure 1** Practical considerations for procuring and using medicines for PPH prevention and treatment with examples of implementation settings. **In blue:** 2°C–8°C cold chain transport and storage required (oxytocin and ergometrine). \*Heat-stable carbetocin: only in contexts where its cost is comparable to that of other effective uterotonics. §Ergometrine: only in contexts where hypertensive disorders can be safely ruled out before use. PPH, postpartum haemorrhage. ¶For PPH treatment in contexts where there are competent health providers, it is imperative to procure other essential supplies according to the level of care, including crystalloid for fluid replacement and oxygen.

is recommended.<sup>4</sup> As for PPH treatment, (1) intravenous oxytocin is the recommended uterotonic; (2) the early use of intravenous TXA within 3 hours of birth in addition to standard care is recommended in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes and (3) if intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin-ergometrine fixed-dose, or a prostaglandin drug (including misoprostol) is recommended (ergometrine and oxytocin-ergometrine are not recommended in case of hypertensive disorder).<sup>6</sup>

Third, these recommendations must, in practice, account for various health system requirements, as summarised in table 1. To help programme managers operationalise the information in table 1, the different health system requirements can be streamlined by focusing on the availability of skilled providers and cold chain transport and storage of 2°C–8°C, two critical constraints often encountered in resource-challenged settings (figure 1).

Additionally, figure 1 offers examples of implementation settings, such as comprehensive obstetric care facilities with skilled providers and reliable cold storage (yellow box). Basic emergency obstetric care facilities with skilled providers are subdivided according to the availability (yellow box) or non-availability (orange box) of a consistent electric power source to ensure cold storage. Community-based programmes with the distribution of

misoprostol for home births are captured in the grey box.<sup>10</sup>

Fourth, the reflection on whether HSC and TXA should be integrated into PPH prevention and treatment strategies offers an opportunity to examine the health system and health service gaps that prevent optimal maternal health outcomes. There is, however, no single solution that matches the resources and needs of all the different settings. Therefore, policymakers and programme managers should consider a stepwise programmatic approach to averting maternal deaths. First, existing emergency obstetric care services should undertake a continuous quality improvement process, notably in terms of staff competencies, facility materials and supplies, functional referral mechanisms and performance and accountability. Health facilities should have a working supply chain to avail uterotonics for PPH prevention round-the-clock in addition to essential equipment, medications and up-to-date protocols and job aids for emergency obstetric treatment if PPH or other complications occur. As a complement to uterotonics for PPH treatment, the introduction of TXA for all PPH cases should be considered at this step. This aligns with the WHO guidance and the recommendations of the International Federation of Gynecologists and Obstetricians and the International Confederation of Midwives.<sup>6 11</sup> Second, the integration of HSC—and TXA if not done in the previous step—into the



If the decision is made to include heat-stable carbetocin and/or tranexamic acid into the national PPH prevention and treatment package, the following actions should be considered:

#### *National policy and planning readiness*

- Update existing national PPH prevention and treatment guidelines, including PPH algorithms integrating heat-stable carbetocin and/or tranexamic acid into the standard PPH prevention and treatment package.
- Define where (levels of care) heat-stable carbetocin and/or tranexamic acid may be positioned and who (health cadres) can administer it.
- Establish a plan for addressing the financial and program needs in accordance with revised national guidelines.
- Assess the status of procurement, distribution, and storage of existing PPH supplies, heat-stable carbetocin, and/or tranexamic acid.
- Review and update national pre-service education curricula for PPH prevention and treatment in accordance with revised national guidelines, focusing on competency-based training.
- Develop updated provider job aids and decision support tools to help providers acquire necessary skills to integrate heat-stable carbetocin and/or tranexamic acid into routine PPH prevention and treatment (e.g., pre- and in-service education/training, onsite job aids, and clinical algorithms).
- Incorporate heat-stable carbetocin and/or tranexamic acid into the national health management information system indicators relevant for PPH surveillance, prevention, and treatment, prioritizing indicators pertinent for quality improvement action (e.g., stock-outs).
- Incorporate heat-stable carbetocin and/or tranexamic acid into patient records for childbirth and postpartum care (e.g., time and dose of PPH prevention measures, diagnostic time and cause of PPH, time and dose of PPH treatments, PPH outcome).

#### *Health facility readiness*

- Ensure provider competencies and positive behavior change by enlisting respected clinical champions and leaders to:
  - (1) Offer competency-based in-service refresher training and follow-up supportive supervision on PPH prevention and treatment, inclusive of heat-stable carbetocin and/or tranexamic acid.
  - (2) Address barriers and enablers to provider behavior change, including potential concerns and areas of resistance.
- Make copies of the updated PPH prevention and treatment protocols, job aids, decision support tools, and standardized patient charts immediately accessible in labor, delivery, and postpartum areas.
- Support a functioning supply chain to ensure 24/7 availability of heat-stable carbetocin and/or tranexamic acid and other essential emergency obstetric care supplies in labor, delivery, and postpartum areas.

**Figure 2** Policy and programme considerations for establishing an enabling environment to introduce heat-stable carbetocin or tranexamic acid, or both. PPH, postpartum haemorrhage.

health system should be carefully considered at the appropriate level of care. [Figure 2](#) outlines key actions to establishing an enabling policy and programme environment for the introduction of HSC or TXA, or both. Finally, it is important to recognise that contraception remains the most cost-effective intervention to avert maternal deaths globally by preventing unintended pregnancies and allowing healthy timing and

spacing of pregnancies.<sup>12</sup> Therefore, in conjunction with the previous two steps, health systems should invest in generating demand for family planning and optimising the quality of contraceptive programmes and services (eg, commodities, providers' clinical skills, provider-client decision-making tools). This includes the first year postpartum when the unmet need for family planning is particularly high.<sup>13</sup>

## CONCLUSIONS

HSC and TXA are recently recommended medications for inclusion in the PPH prevention and treatment toolbox and could potentially play a critical role in decreasing maternal deaths in low-resource settings. Securing their availability in-country should be embedded in a thorough understanding of their clinical indications and the enabling health system environment. Considering whether HSC and TXA should be included in maternal health services provides a new opportunity to engage key national and local stakeholders, including health professionals, to look at the overall health system challenges and opportunities that hinder or support the reduction of maternal mortality and morbidity in general, and that due to PPH specifically.

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## REFERENCES

- 1 World Health Organization. Maternal mortality: levels and trends 2000-2017; estimates from who, UNICEF, UNFPA, world bank group and the United nations population division. Geneva: World Health organization, 2017. Available: <https://www.who.int/reproductivehealth/publications/maternal-mortality-2000-2017/en/> [Accessed 8 Oct 2021].

- 2 World Health Organization. *Maternal mortality: evidence brief*. Geneva: World Health Organization, 2019. <https://apps.who.int/iris/bitstream/handle/10665/329886/WHO-RHR-19.20-eng.pdf?sequence=1&isAllowed=y>
- 3 Begley CM, Gyte GML, Devane D, *et al*. Active versus expectant management for women in the third stage of labour. *Cochrane Database Syst Rev* 2019;2019.
- 4 World Health Organization. *WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage*. Geneva: World Health Organization, 2018. <https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf>
- 5 Jonathan H, Stoltenberg RHJ. *UN Commission on life-saving commodities for women and children*. New York: United Nations, 2012.
- 6 World Health Organization. *WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage*. Geneva: World Health Organization, 2017. <https://www.who.int/reproductivehealth/publications/tranexamic-acid-pph-treatment/en/>
- 7 World Health Organization. *WHO model Lists of essential medicines, 21st list 2019*. Geneva: World Health Organization, 2019. <https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists>
- 8 United Nations Population Fund. UNFPA procurement services: product catalogue, 2021. Available: [www.unfpaprocurement.org/products](http://www.unfpaprocurement.org/products) [Accessed 10 Oct 2021].
- 9 World Health Organization. *Medical management of abortion*. Geneva: World Health Organization, 2019. <https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/>
- 10 Smith JM, Gubin R, Holston MM, *et al*. Misoprostol for postpartum hemorrhage prevention at home birth: an integrative review of global implementation experience to date. *BMC Pregnancy Childbirth* 2013;13:1–11.
- 11 International Federation of Gynecology and Obstetrics (FIGO) & International Confederation of Midwives (ICM). Joint statement of recommendation for the use of tranexamic acid for the treatment of postpartum haemorrhage, 2021. Available: <https://www.figo.org/joint-statement-recommendation-tranexamic-acid-treatment-pph> [Accessed 24 Feb 2022].
- 12 Darroch JE, Sully E, Biddlecom A. *Adding it up: investing in contraception and maternal and newborn health, 2017—Supplementary tables*. New York, NY: The Guttmacher Institute, 2017.
- 13 Rossier C, Bradley SEK, Ross J, *et al*. Reassessing unmet need for family planning in the postpartum period. *Stud Fam Plann* 2015;46:355–67.