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Carbetocin for the Management of Postpartum Hemorrhage

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ABSTRACT

The heat-stable formulation of carbetocin is a new synthetic analogue of oxytocin, with greater biological effect and longer half-life. It has a four-fold longer uterotonic activity, which eliminates the need for continuous intravenous infusion to achieve a sustained uterine contraction. In addition, the heat stable formulation of carbetocin does not require cold-chain transportation and storage so it can be used in settings where cold-chain facilities are not readily available or reliable. The heat stable carbetocin has been recommended for the prevention of primary postpartum hemorrhage by the World Health Organization (WHO), and other professional associations within the Low- and Middle-Income countries (LMICs). Although it is relatively more expensive compared to oxytocin, the manufacturer has agreed to provide the drug at an affordable price in public sector healthcare facilities in low income settings. In this article we explore the evidence for its use for prevention of postpartum haemorrhage (PPH). Carbetocin is also currently undergoing investigation for use as a PPH treatment in WHO's REACH trial.

INTRODUCTION

Postpartum hemorrhage (PPH) is defined by WHO as the loss of 500 ml of blood from the female genital tract after childbirth[1]. Other definitions are used however, including the higher loss of 1000 ml for just CS or for all births, blood loss sufficient to cause hemodynamic instability or a 10% decrease in hematocrit or requiring transfusion of blood products[2]. Primary PPH occurs within the first 24 hours of delivery, whereas secondary PPH occurs between 24 hours and 12 weeks after delivery and is less common.

Each year, about 14 million women experience PPH and it accounts for 27% of maternal deaths worldwide[3,4]. The majority of maternal deaths associated with PPH occur in low- and middle-income countries (L/MICs)[3,5], where cold chain is particularly difficult to achieve. In many of these countries, the decline in maternal mortality rates has stagnated, and they may not achieve the Sustainable Development Goal (SDG) 5 of 70 maternal deaths per 100,000 by 2030[3].

The four major causes of primary PPH (4Ts) include lack of tone, trauma (including lacerations and uterine rupture), retained tissue, and disorders of thrombin (including inherited coagulopathy and disseminated intravascular coagulation[6]. Uterine atony, which is defined as failure of the uterus to contract adequately following child birth is responsible for up to 70% of maternal deaths due to primary postpartum haemorrhage[7]. Active Management of the Third Stage of Labour (AMTSL)[8–10], is an evidence-based practice known to reduce the incidence of primary postpartum haemorrhage by up to 40%[10–12]. This low-cost intervention for prevention of primary PPH due to uterine atony is recommended for every mother after childbirth. It involves three cardinal steps in a sequence, namely: (1) administration of an oxytocic within in 1 minute of child birth; (2) controlled cord traction to deliver the placenta after it has separated from the uterine wall; and (3) ongoing uterine massage to keep the uterus contracted[8].

Oxytocin is the recommended first choice uterotonic drug for use in AMTSL, but it requires constant refrigeration[8,13]. However, in many low- and middle-income countries where a sustained cold-chain is not guaranteed, the efficacy of oxytocin is often reduced because of heat degradation[14–16]. In order to overcome this challenge, a heat-stable formulation of carbetocin, an old medicine that has been known since the 1970's was developed in pursuit of suitable alternatives[17]. This chapter will review the pharmacology of heat stable carbetocin, its clinical effectiveness as compared to other uterotonics, and current guidance for its use. Table 1 for the comparison between Oxytocin and heat stable carbetocin.

PHARMACOLOGY OF CARBETOCIN

Chemical structure

Carbetocin [1-diamino-1-carba-2-tyrosine (o-methyl)-oxytocin] is a synthetic analogue of oxytocin that binds to same oxytocin receptors in the myometrium[23,24]. By removing the amino group (1-deamino), and replacing the sulfur atom at
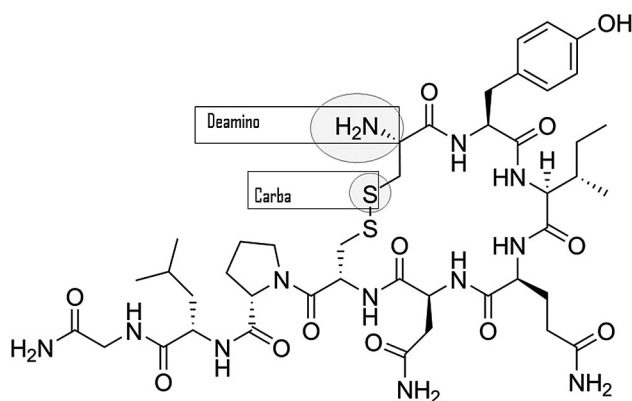
Table 1 Heat stable Carbetocin vs. Oxytocin

	Heat stable carbetocin	Oxytocin
Indication	Prevention of PPH due to uterine atony	Induction of labor Augmentation of labor Prevention of PPH due to uterine atony (AMSTL) Treatment of PPH due to uterine atony
Storage[18,19]	Below 30°C (room temperature)	2–8°C (cold chain)
Posology and methods of administration	One-time dose (100 micrograms) IV or IM	10 IU IM or IV for AMSTL Can be repeated for PPH treatment
Onset of contractions	1–2 minutes	1–2 minutes
Duration of contractions	1 hour after IV injection 2 hours after IM injection	No data for IV injection 30 minutes after IM injection
Half-life[20,21,22]	40 minutes	3–17 minutes

AMTSL, active management of third stage of labor

position 1 with a carba group (–CH₂–), a prolonged myometrial action was obtained[25]. The deamination protects Carbetocin from aminopeptidase cleavage, and replacement of the disulfide bond by CH_2S protects the analogue from disulfidase cleavage (Figure 1).

Pharmacokinetic properties

Carbetocin has a rapid onset of action (within 1–2 min) and a prolonged duration of action (approximately 1 h) because of sustained uterine response with contractions of higher amplitude and frequency[26,27]. It reaches peak plasma concentrations in 30 minutes and its bioavailability is 80%. It has got a half-life of approximately 40 minutes, which is 4–10 times longer than oxytocin[22,26]. The median terminal elimination half-life is 33 minutes after intravenous administration and 55 minutes after intramuscular

Figure 1 Oxytocin molecule. The amino group and the disulfide bond, which were altered in order to create carbetocin, are indicated. The amino group was removed and the sulfur atom was replaced by a carba group[24]

administration. After intramuscular administration, peak concentrations are reached after 30 minutes and the mean bioavailability is 77–80%[28]. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney[26]. A small amount of Carbetocin crosses to the breast milk, with a mean peak concentration that is 50 times lower than in plasma. This is of no clinical concern because it is readily degraded by peptidases in the infant's gastrointestinal tract.
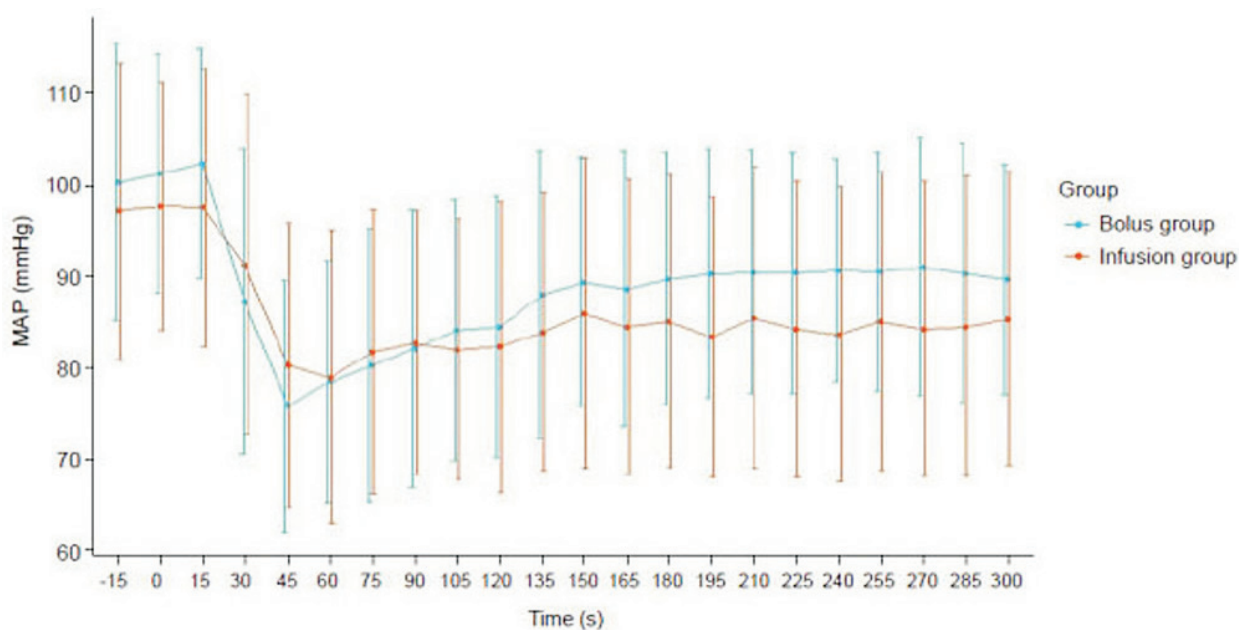
Pharmacodynamics

Following administration, carbetocin binds to same oxytocin receptors within the myometrium with an affinity similar to that of oxytocin. It then causes an increase in the intracellular concentration of calcium that promotes uterine contractility through the generation of inositol phosphate[23]. Uterine contractions last for one hour after intravenous (IV) injection, and two hours after intramuscular (IM) injection[27,29]. This protracted uterotonic activity is attributed to the alterations in the structure of the molecule; and the higher lipophilicity that can alter its intracellular tissue distribution[25,29]. Carbetocin can be administered either by the IV or IM route because the onset of action is not affected by the route of administration[30,31], with a firm contraction being obtained within 2 minutes[26]. Kwon et al.[31] have demonstrated that the hypotensive effect of carbetocin occurs whether it is administered as an intravenous bolus or as an infusion over 5 minutes (Figure 2).

Drug interactions

Specific interaction studies have not been undertaken but, since carbetocin is closely related in structure to oxytocin, the occurrence of interactions known to be associated with oxytocin cannot be excluded. However, during clinical trials, carbetocin has been administered in association with several analgesics, and spasmolytic agents used for epidural or spinal anaesthesia, and no drug interactions have been identified.

INDICATIONS AND CONTRAINDICATIONS FOR CARBETOCIN

In settings where the quality of oxytocin can't be guaranteed, HSC is indicated for prevention of primary PPH due to uterine atony. It should never be used at any stage before childbirth, either for induction or augmentation of labour because, like ergometrine, it induces strong uterotonic activity that is long lasting. For this reason, there haven't been clinical studies investigating its role for induction and augmentation and as such it has not been utilized because this may be dangerous for the unborn baby. For AMTSL, the recommended route for administration of Carbetocin is intramuscular (IM) injection for the vaginal deliveries and at Caesarean section, it can be given either intravenously (IV) or IM. It must be given as a single dose

Figure 2 The changes of mean arterial pressure (MAP) in two groups. Values are presented as mean ± SD

of 100 micrograms (1 ml undiluted), within 1 minute of delivery of the baby. No further doses of carbetocin should be administered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin. Alternatively, carbetocin can be administered intravenously (IV), in this case it should be given slowly over at least 1 minute.

The contraindications for Carbetocin include[32];

(1) During pregnancy and labour before delivery of the infant.

(2) Carbetocin must not be used for the induction of labour.

(3) Hypersensitivity to carbetocin, oxytocin or to any of the excipients listed in Clinical research on carbetocin section below;

(4) Hepatic or renal disease.

(5) Serious cardiovascular disorders.

(6) Epilepsy.

SIDE EFFECTS

It is not surprising that the side effects of carbetocin are similar to those of oxytocin because one is a modified version of the other[33]. A systematic review of 17 RCTs involving 32,702 women identified 24 side-effects associated with Carbetocin compared with oxytocin, and only diarrhoea was found to be statistically different[34]. The CHAMPION trial, the largest single study comparing intramuscular HSC and intramuscular oxytocin for PPH prevention, reported that they had a similar side-effect profile[35]. Furthermore hypotension, an important hemodynamic side-effect described following IV administration, was the same for iv boluses of both carbetocin and oxytocin – about

20% at peak of 40 seconds and lasting 90 seconds (Figure 3)[36]. An equivalent hypotensive effect is also seen when carbetocin is given as an infusion over 5 minutes (Figure 4).

HEAT STABILITY

Prior attempts to develop a heat-stable oxytocin formulation for injection have been unsuccessful[24,38]. Peptides in solution are generally prone to undergo degradation via, e.g. deamidation, dimerization, and oxidation, making refrigeration in some cases necessary[24,39]. The heat-stable formulation of carbetocin differs from the existing non–heat-stable formulation only in its excipients[24,38]. It does not require cold-chain transport and storage because it has been shown to maintain stability over a period of 36 months at 30°C and 75% relative humidity. Therefore, in resource-challenged and warm-climate settings, where cold chain transport and storage is often not available and the quality of oxytocin and other injectable uterotonics is compromised, this product can play a critical role in reducing PPH related morbidity and mortality[40]. Subsequently, in 2019, this product was added by the WHO to the core list of essential medicines for reproductive health[40].

The stability of carbetocin was achieved through 3 structural modifications of oxytocin, highlighted by dash line circles in Figure 5[24,38,39]. Namely: the Nα of oxytocin is removed; Sulphur atom on Cys^1 is replaced by a methylene group, and Tyr^2 is replaced by $Tyr(Me)^{39}$. The degradation of carbetocin by the major pathway of dimerization is blocked by the removal of the disulphide and N^α groups from the oxytocin molecular structure[24,38]. The presence of these two groups increase the susceptibility of oxytocin to degradation by isomerization and hydrolysis at pH values ≥ 4.
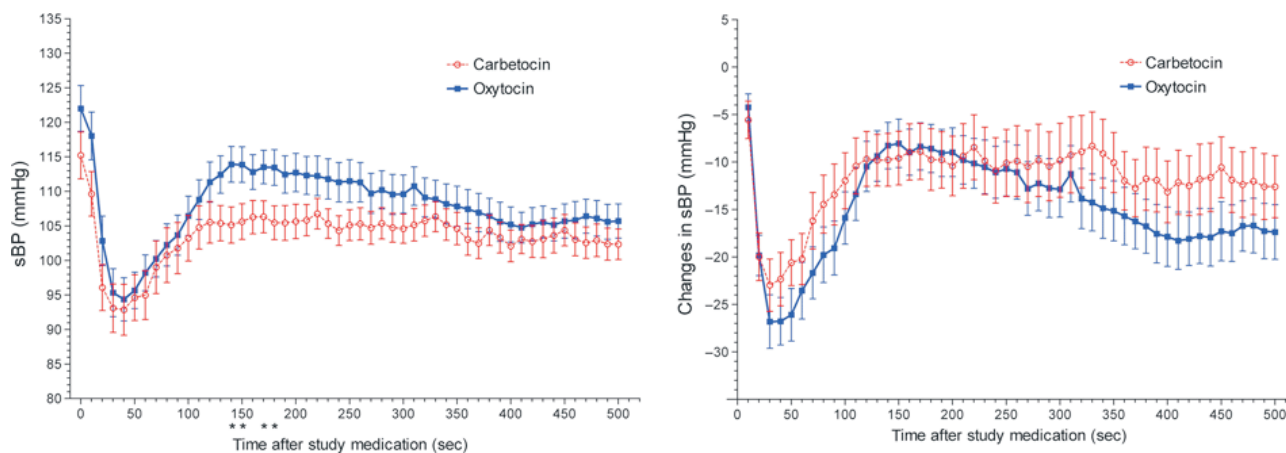
Figure 3   Maternal systolic blood pressure (sBP) after the administration of the study medication[36]

Outcome	No. of Studies	No. of Events	No. of Participants		RR (95%CI)	Heterogeneity			Begger		Egger	
						tau^2	I^2	p	Kendall's tau	p	z	p
Vomiting	15	234	32087		0.63 (0.38-1.06)	0.4204	55.20	0.0085	0.0192	0.9210	0.5073	0.6120
Nausea	15	381	2636		0.86 (0.72-1.03)	0.0001	0.01	0.2854	0.1429	0.4951	-0.0772	0.9384
Headache	15	249	2485		0.92 (0.63-1.35)	0.1393	33.60	0.0700	0.3143	0.1142	1.8455	0.0650
Flushing	11	216	31219		1.19 (0.93-1.52)	0.0001	0.01	0.6194	0.3455	0.1646	0.9637	0.3352
Shivering	10	150	2232		1.10 (0.59-2.06)	0.3922	46.02	0.0855	0.3636	0.1491	1.6768	0.0936
Heart disorders	9	105	1660		0.94 (0.50-1.79)	0.5356	36.33	0.0908	-0.0556	0.9195	-1.4701	0.1415
Dizziness	8	41	1279		0.97 (0.49-1.92)	0.0001	0.01	0.3660	0.4286	0.1789	0.8928	0.3719
Dyspnea	8	34	1005		1.60 (0.76-3.34)	0.0001	0.01	0.7189	0.0001	0.9999	0.3903	0.6963
Pruritus	6	61	849		1.11 (0.23-5.39)	2.4223	69.44	0.0226	0.2000	0.7194	0.3779	0.7055
Metallic taste	6	54	1499		1.10 (0.64-1.89)	0.0001	0.01	0.6593	0.3333	0.4694	1.0923	0.2747
Abdominal pain	5	426	30799		1.06 (0.91-1.24)	0.0001	0.01	0.6362	0.6000	0.2333	1.0667	0.2861
Fever	5	21	540		1.81 (0.62-5.29)	0.0001	0.01	0.4466	0.0001	0.9999	0.3993	0.6897
Chest pain	6	44	29914		1.66 (0.89-3.10)	0.0001	0.01	0.7141	0.3333	0.4694	0.6061	0.5444
Feeling of warmth	4	136	880		1.23 (0.90-1.69)	0.8572	41.25	0.1941	0.0001	0.9999	1.8391	0.0659
Hypotension	3	43	539		1.05 (0.61-1.80)	0.0001	0.01	0.7008	0.9999	0.3333	0.8432	0.3991
Backache	3	34	1144		0.86 (0.43-1.70)	0.0001	0.01	0.4344	-0.3333	0.9999	0.4119	0.6804
Sweating	3	50	1216		0.34 (0.04-3.00)	2.7493	77.17	0.0104	-0.3333	0.9999	-0.1706	0.8646
Chills	2	17	219		1.16 (0.46-2.91)	0.0001	0.01	0.5506	0.9999	0.9999	0.5969	0.5506
Anemia	2	69	306		3.78 (0.18-77.51)	3.9062	78.86	0.0296	0.9999	0.9999	---	---
Xerostomia	2	4	105		3.06 (0.33-28.45)	0.0000	0.00	0.9868	0.9999	0.9999	---	---
Arm pain	1	2	379		0.34 (0.01-8.17)	---	---	---	---	---	---	---
Diarrhea	1	9	200		8.00 (1.02-62.79)	---	---	---	---	---	---	---
Leukocytosis	1	14	160		0.70 (0.25-1.91)	---	---	---	---	---	---	---
Serious adverse event	1	192	29497		1.16 (0.87-1.53)	---	---	---	---	---	---	---

Figure 4   Side effects of carbetocin compared to oxytocin[37]
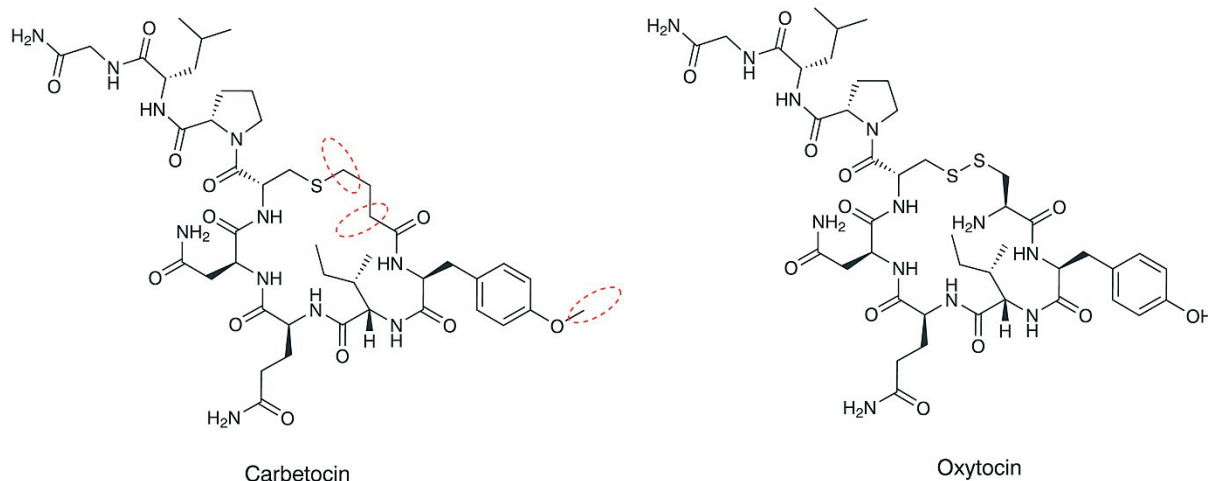

Carbetocin

Oxytocin

Figure 5   Differences in the molecular structures of Carbetocin and Oxytocin[24]

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CLINICAL RESEARCH ON CARBETOCIN

Prevention of postpartum haemorrhage at vaginal birth using intramuscular carbetocin

The WHO CHAMPION trial published in 2018 compared heat stable carbetocin with oxytocin for prevention of haemorrhage and the need for extra uterotonic agents after vaginal birth. This was a large multi-country study that randomised 29,645 women across 23 sites in 10 countries in a double blind, non-inferiority trial comparing IM injection of heat stable Carbetocin (100 micrograms) with IM oxytocin (10 IU) administered immediately after vaginal birth. Heat stable carbetocin was non-inferior to oxytocin for prevention of blood loss and use of additional uterotonic agents after childbirth[35]. There were no significant differences between the groups in any of the primary or secondary outcomes. Details of the primary outcomes are indicated in the Table 2.

The IMox study published in 2020 was a UK multicenter trial conducted to compare the effectiveness, side effects and quality of life associated with three commonly used oxytocic agents. A total of 5,929 women from six sites were randomised into three parallel arms in a double-blind controlled trial; oxytocin (10 IU), syntometrine (5 IU oxytocin + 500 microgram ergometrine), and 100 microgram carbetocin. The three medications were found to have very similar efficacy (pooled prevalence of the need for subsequent additional uterotonic drugs) oxytocin 19.1%, syntometrine 15.2% and carbetocin 11.5%. However, syntometrine was associated with increased maternal adverse effects and reduced ability of the mother to bond with her baby[41]. Details from the other studies are summarized in Table 3.

In summary, two large, randomised trials have shown that intramuscular carbetocin offers no clinical advantage over intramuscular oxytocin for the prevention of PPH after vaginal birth in clinical trial settings. However, the two are equivalent and so in settings where the oxytocin is of poor quality or the cold chain unreliable, there may be 'real-life' superior effectiveness over oxytocin.

Prevention of postpartum haemorrhage at CS using iv carbetocin

In 2018, Voon *et al.*[42] published a systematic review of trials to analyze the effectiveness of carbetocin compared to oxytocin for the prevention of postpartum hemorrhage in caesarean births. The review included 2012 women from seven countries, but only one was a low-income country where the burden of PPH is highest. The review found carbetocin to be more effective than oxytocin when used during caesarean deliveries, with reduced rates of postpartum hemorrhage (RR 0.79; 95% CI 0.66 to 0.94; $p = 0.009$), use of additional uterotonics (RR 0.57; 95% CI 0.49 to 0.65; $p < 0.001$) and transfusion (RR 0.31; 95% CI 0.15 to 0.64; $p = 0.002$). Details from the other studies are summarized in Table 3.

However, the data on PPH prevention is complicated by the mixture of comparisons in the review. Some of the original benefits of carbetocin at CS may have been due to the fact that some studies compared iv carbetocin and intramuscular oxytocin. However, several trials have now shown the benefit of iv oxytocin over IM oxytocin, leading to the 2021 WHO recommendation that in high risk births clinicians should be giving oxytocin as a slow intravenous dose rather than intramuscularly[43]. Thus, the appropriate comparisons should be between iv carbetocin and iv oxytocin, and systematic reviews should not include IM oxytocin at CS.

The Cochrane network metanalysis (comparison no 38)[44], had only four relevant studies comparing IV carbetocin and Oxytocin. Cumulatively, these had a total of 472 patients undergoing CS. They are:

(1) Borruto 2009: Oxytocin 10 IU iv vs. carbetocin 100 mg iv at CS with at least one risk factor for PPH (Italy, $n = 104$)[45].

(2) El Behery 2015: Oxytocin 20 IU inf vs. carbetocin 100 mg iv at emergency CS (Egypt, $n = 180$)[46].

(3) Roseland 2013: Oxytocin 5 IU iv vs. carbetocin 100 mg iv at elective CS (Norway, $n = 76$)[47].

(4) Whigham 2016: Oxytocin 5 IU iv vs. carbetocin 100 mg IV at emergency CS (Australia, $n = 112$)[48].

Since then there have been three other studies of carbetocin vs. oxytocin at CS, with a total of 640 patients. They are:

(1) Ibrahim 2020: Oxytocin 10 IU infusion over 8 h vs. carbetocin 100 mg iv at CS among hypertensive women (Egypt, $n = 160$) – estimated blood loss and fall in Hb was reduced with carbetocin[49].

(2) Al Zubaidi 2021: Oxytocin 10 IU iv vs. carbetocin 100 mg iv at emergency CS (Iraq, $n = 300$) – less additional uterotonics & transfusion with carbetocin[50].

(3) McDonagh 2022: Oxytocin 0.5 IU vs. oxytocin 5 IU vs. carbetocin 20 mg vs. carbetocin 100 mg

Table 2 Summary of the primary outcomes from the CHAMPION trial

Primary outcome	Carbetocin (N = 14,771)	Oxytocin (N = 14,768)	Relative Risk (95% CI)	Risk Difference (95% CI)
Blood loss ≥500 ml or use of additional uterotonic agents	2135 (14.5)	2122 (14.4)	1.01 (0.95 to 1.06)	0.09 (−0.68 to 0.87)
Blood loss ≥1000 ml	223 (1.51)	214 (1.45)	1.04 (0.87 to 1.25)	0.06 (−0.21 to 0.33)

Table 3 A summary of systematic reviews, meta-analysis, and cost-effectiveness studies on Carbetocin for PPH management published since 2020

Systematic reviews and Network meta-analysis

Author	Year	Type of study	Population	Intervention/aim	Outcomes
Huang X et al.[53]	2022	A meta-analysis	Five randomised control studies in English, including a total of 4631 pregnant women, among which, 2323 pregnant women used carbetocin and 2308 used oxytocin	To compare the efficacy of carbetocin and oxytocin in the prevention of PPH among women with vaginal delivery	The incidence of PPH in the carbetocin group was lower than that in the oxytocin group (OR = 0.62, 95% CI (0.46, 0.84), Z = 3.14, p = 0.002) The proportion of women requiring additional uterotonics in the carbetocin group was lower than that in the oxytocin group (OR = 0.41, 95% CI (0.29, 0.56), Z = 5.34, p < 0.00001) There was no significant difference in the proportion of women needing blood transfusion between the carbetocin group and the oxytocin group (OR = 0.92, 95% CI (0.66, 1.29), Z = 0.46, p = 0.64) "Carbetocin is superior to oxytocin in preventing PPH among women with vaginal delivery and can be widely used in clinical practice."
Onwochei DN et al.[54]	2020	A systematic review, meta-analysis, and trial sequential analysis of randomized-controlled trials	Five RCTs were included, with a total of 1214 patients	To determine whether Carbetocin could reduce the requirement for additional uterotonics in women exclusively undergoing elective Cesarean delivery	The need for additional uterotonics was reduced with carbetocin compared with oxytocin (odds ratio, 0.30; 95% CI, 0.11 to 0.86; I2, 90.60%) Trial sequential analysis (TSA) confirmed that the information size needed to show a significant reduction in the need for additional uterotonics had been exceeded No significant differences were shown with respect to any of the secondary outcomes, but there was significant heterogeneity between the studies
Ai W et al.[37]	2021	A systematic review and meta-analysis of randomized controlled trials	Seventeen RCTs involving 32,702 women. Studies that considered pregnant women who received carbetocin before delivery and provided at least one adverse event were included	To investigate the side-effects of carbetocin to prevent PPH	Twenty-four side-effects were reported The use of carbetocin had a lower risk of vomiting when used intravenously (0.53, 0.30 to 0.93) and at caesarean birth (0.51, 0.32 to 0.81) women, and had a slightly higher risk of diarrhoea (8.00, 1.02 to 62.79) compared with oxytocin intervention No significant difference was found among other side-effects
Feduniw S et al.[55]	2020	A systematic review	52 studies were included	To estimate the incidence and predictors of early postpartum hemorrhage, and to assess available prevention and treatment methods	The majority of uterotonics seem to have a similar effect However, in twin pregnancies carbetocin prophylaxis of EPH after CS seems to be more effective than oxytocin in the prevention of EPH The authors found several publications concerning a higher efficacy of carbetocin than oxytocin in the 3rd stage of labor Moreover, in another study carbetocin was a better alternative to traditional oxytocin in the prevention of PPH after vaginal delivery

Author	Year	Study type	Sample	Objective	Results
Sun H et al.[56]	2022	A systematic review and meta-analysis	A total of 24 studies involving 37,383 patients were included for analysis	To compare the effectiveness and safety of carbetocin and oxytocin in preventing postpartum hemorrhage (PPH)	For cesarean section patients, carbetocin was superior to oxytocin in reduction of the need for additional uterine contraction (odds ratio [OR] = 0.48, 95% confidence interval [CI] [0.35, 0.65], $p < 0.00001$), PPH (OR = 0.70, 95% CI [0.51, 0.95], $p = 0.02$), blood loss (mean [MD] = −64.36, 95% CI [−107.78, −20.93], $p = 0.004$), and transfusion (OR = 0.59, 95% CI [0.42, 0.82], $p = 0.002$), but there was no significant difference in severe PPH (OR = 0.84, 95% CI [0.66, 1.090], $p = 0.19$) For vaginal delivery patients, carbetocin was superior to oxytocin in reduction of the need for additional uterine contractions (OR = 0.48, 95% CI [0.25, 0.93], $p = 0.03$), PPH (OR = 0.28, 95% CI [0.09, 0.91], $p = 0.03$), and blood loss (MD = −63.52, 95% CI [−113.43, −13.60], $p = 0.01$), and there were no significant differences in severe PPH (OR = 0.82, 95% CI [0.40, 1.69], $p = 0.59$) or transfusion (OR = 0.60, 95% CI [0.22, 1.61], $p = 0.31$) With regard to safety for cesarean section patients, carbetocin was superior to oxytocin in reduction of the incidence of headache (OR = 0.72, [0.55, 0.95], $p = 0.02$), and there were no significant differences in nausea, vomiting, abdominal pain, flushing, tremors, itching, dizziness, and fever For vaginal delivery patients, there were no significant differences in nausea, vomiting, headache, abdominal pain, flushing, tremors, itching, dizziness, and fever between the two drugs
Patrick HS et al.[57]	2020	a systematic review and meta-analysis of randomized trials	Identified 29 randomized controlled trials that met the inclusion criteria (2682 subjects)	To evaluate the efficacy of pharmacologic interventions for the management of retained placenta	Oxytocin was inferior to carbetocin (risk ratio, 1.61; 95% confidence interval, 1.03–2.52) and prostaglandins (risk ratio, 2.63; 95% confidence interval, 1.18–5.86) of the need for manual extraction of the placenta or dilation and curettage Compared with placebo or control, estimated blood loss was lower if pharmacologic interventions were administered, with a mean difference of 121.5 ml (95% confidence interval, −185.7 to −52.3) There was no difference in postpartum hemorrhage or the need for blood transfusion between pharmacologic interventions and placebo or control
Kalafat E et al.[58]	2021	A systematic review and Bayesian meta-analysis of randomized trials	30 RCTs comparing carbetocin to any other uterotonic agent among women at high risk of PPH Carbetocin vs. Oxytocin ($n = 3216$) Carbetocin vs. any other uterotonic ($n = 2926$)	To evaluate the efficacy of carbetocin for the prevention of postpartum hemorrhage (PPH) and related events after vaginal or cesarean delivery	Compared to oxytocin, carbetocin was associated with a reduced need for additional uterotonic use in women undergoing cesarean delivery (RR 0.43, 95% CI 0.30–0.59, I2 = 71%, 3216 women, PP > 99.9%) Women at high risk of PPH delivering vaginally also had a reduced need for additional uterotonic use with carbetocin compared to oxytocin (RR 0.56, 95% CI 0.34–0.94, I2 = 38%, 789 women, PP = 81.2%) The risk of postpartum blood transfusion (RR 0.57, 95% CI 0.33–0.96, I2 = 0%, 1991 women, PP = 97.9%) was also less with carbetocin compared to oxytocin in high-risk women undergoing cesarean delivery The risk of PPH (defined as per individual study protocols) was similar between carbetocin and other uterotonic agents for both cesarean (RR 0.69, 95% CI 0.45–1.05, I2 = 27%, 2926 women, PP = 96.3%) and vaginal deliveries (RR 0.61, 95% CI 0.32–1.14, I2 = 35%, 1515 women, PP = 88.9%)

Continued

Table 3 *Continued*

	Year	Design	Population	Objective	Findings
Jaffer D et al.[59]	2022	A network meta-analysis	46 studies with 7368 participants. Of those, 21 trials (6 agents and 3665 participants) formed the "estimated blood loss" network. A total of 37 trials (8 agents and 6193 participants) formed the "additional uterotonic" network	To compare the ability of pharmacologic agents (oxytocin, carbetocin, misoprostol, ergometrine, carboprost, or combinations of these) to reduce blood loss and minimize the need for additional uterotonics during cesarean delivery	Carbetocin was assessed to probably be superior to oxytocin, but only in reducing the estimated blood loss by a clinically insignificant volume (54.83 ml; 95% confidence interval, 26.48–143.78). Misoprostol, ergometrine, and the combination of oxytocin and ergometrine were assessed to probably be inferior, whereas the combination of oxytocin and misoprostol was assessed to definitely be inferior to oxytocin carbetocin was assessed to probably be superior to oxytocin, requiring additional uterotonics 185 (95% confidence interval, 130–218) fewer times per 1000 cases. Oxytocin plus misoprostol, oxytocin plus ergometrine, and misoprostol were assessed to probably be inferior, whereas carboprost, ergometrine, and the placebo were definitely inferior to oxytocin

Cost effectiveness studies

	Year	Design	Population	Objective	Findings
Matthijsse S et al.[60]	2022	Cost-effectiveness study, using a decision tree model	A hypothetical cohort of 100 women having a vaginal birth in the UK National Health Service	To analyze the cost per PPH event avoided associated with utilizing carbetocin vs. oxytocin for prophylactic treatment of PPH in women following vaginal birth from a UK perspective	Carbetocin utilization led to 3.42 avoided PPH events compared to oxytocin and 0.0001 additional QALYs per woman. The reduction in PPH events led to total cost savings of £5495
Briones, JR et al.[61]	2020	A cost-utility analysis using a decision tree was conducted to compare the costs and outcomes of carbetocin with oxytocin for PPH prophylaxis among women undergoing either vaginal delivery (VD) or cesarean section	Direct medical cost data were collected from women in the Philippines without complication (n = 31 for VD), with additional treatment dose (n = 38 for CS, n = 31 for CS, n = 37 for VD), blood transfusion (n = 13 for CS, n = 13 for VD), and hysterectomy (n = 12 for CS)	Carbetocin vs. Oxytocin for PPH prophylaxis	Carbetocin is not a cost-effective choice in PPH prevention for either mode of delivery in the Philippines without a price reduction
You JHS, Leung T-y[62]	2022	A decision-analytic model study, with base-case analysis	All women giving birth vaginally or by CS in the public healthcare system in Hong Kong	To examine the cost-effectiveness of PPH prevention with carbetocin from the perspective of Hong Kong public healthcare provider (Oxytocin vs. Carbetocin for AMTSL)	Using summary efficacy data from various studies, the authors found that Carbetocin (vs. oxytocin) reduced PPH-related cost (by USD29 per birth) and saved 0.00059 QALY per birth. Carbetocin was accepted as cost-effective in >99.7% of the 10,000 Monte Carlo simulations at a willingness-to-pay threshold of zero USD/QALY
Barrett J et al.[63]	2022	Decision-analytic model study, with base-case analysis	Women giving birth in a single hospital in Toronto, Canada (n = 3242)	To evaluate the financial implications of replacing oxytocin with carbetocin as a first-line prophylactic agent for PPH prevention	Using efficacy data from the 2018 Gallos network meta-analysis[53] the authors estimated that replacing oxytocin with carbetocin for PPH prophylaxis would save CAD$349,000 annually
Cook, JR et al.[64]	2023	Decision-tree model was developed from the public healthcare system perspective	Among women giving birth in Public healthcare facilities in India	To compare HSC vs. Oxytocin and Misoprostol for PPH prevention	Using efficacy data from the 2018 Gallos network meta-analysis[53] the authors estimated that HSC rather than oxytocin would avert 5 deaths per 100,000 births with a cost to India of US$171,700 per 100,000 births

(all iv) in low risk patients undergoing CS (Canada, $n = 280$) – no differences between the 4 groups[51].

Broadly speaking, Borruto[45], El Behery[46], Ibrahim[49] and Al Zubaidi[50] show benefits in blood loss and morbidity, whilst the higher quality studies of Roseland[47], Whigham[48] and Mc Donagh[51] show no difference. But in total there are only 1,112 patients at CS in the published RCTs, so it is difficult to be sure. In summary, there is some unconfirmed evidence that iv carbetocin may offer advantages over iv oxytocin, but the evidence is far from definitive.

Network meta-analysis on PPH prevention

In December, 2018, the Cochrane Library published an updated network meta-analysis aimed at generating a ranking according to their effectiveness in preventing PPH and side-effects profile. The review included 196 trials of seven uterotonic agents, conducted on 135,559 women across 53 countries. Three quarters of the studies (72%) included in this review included women that had a vaginal birth, so the uterotonic was administered IM. The results were that the three highest ranked uterotonic agents for prevention of PPH ≥ 500 ml were ergometrine plus oxytocin combination, misoprostol plus oxytocin combination and carbetocin. The two combination regimens, however, were associated with significant side effects. The analysis concluded that carbetocin may be more effective than oxytocin for some outcomes, with an equivalent rate of side effects[52].

Treatment of postpartum haemorrhage

There is currently no good evidence on the use of carbetocin for the treatment of PPH, either for what drug to use for treatment after failed prophylaxis.

Given the long half-life of carbetocin, it would be expected that if a woman had a PPH shortly after receiving carbetocin prophylaxis, there would be little benefit in giving further oxytocin or carbetocin. There is however no evidence on this, and guidelines continue to recommend that women receive oxytocin for atonic PPH treatment irrespective of the type of prophylaxis given.

Carbetocin might be an effective drug for the treatment of PPH, even after carbetocin prophylaxis. WHO is currently running a large randomised trial (the REACH Study) to evaluate whether carbetocin is non-inferior to oxytocin for treatment of PPH in women who receive carbetocin for PPH prophylaxis. The trial will include 6,200 women delivering vaginally and diagnosed with PPH.

PRESENCE OF HEAT STABLE CARBETOCIN IN INTERNATIONAL GUIDELINES AND PRICE ISSUES

Available evidence shows that the effectiveness and safety of carbetocin in the prevention of PPH is comparable to that of oxytocin. Details of its presence in international guidelines is summerised in Table 4. However, the disparity between the cost of carbetocin and oxytocin especially in LMIC appears to be the major stumbling block to it adoption in international guidelines. Therefore, Ferring Pharmaceuticals, the World Health Organization, and Merck Sharp & Dohme (MSD) for Mothers have established a collaboration to develop this heat-stable formulation of carbetocin for the prevention of post-partum hemorrhage in women after vaginal childbirth. The organisations are working together with the aim of making the medicine available in the public sector of developing countries that have a high burden of maternal mortality and where consistent refrigeration is burdensome[19]. This low-cost product is referred to as *Heat Stable Carbetocin*.

Table 4 Presence in guidelines internationally (WHO, RCOG, ACOG, SOGC, FIGO)

Organisation	Recommendation	Level of evidence
WHO[13]	WHO also recommends the use of carbetocin (if cost-effective), ergot alkaloids (alone or combined if there are no contraindications), or oral misoprostol in settings where oxytocin is not available, or its quality cannot be guaranteed. Carbetocin has also been added to the 21st edition of the WHO Model List of Essential Medicines	NA
National Institute for Health and Clinical Excellence: Guidance. RCOG[65]	Carbetocin is licensed in the UK specifically for the indication of prevention of PPH in the context of caesarean delivery. Recommends oxytocin 5 IU by slow intravenous injection for prophylaxis in the context of caesarean delivery	NA
ACOG[65]	PPH practice Bulletin No.138, Uterotonic agents should be first-line treatment for postpartum hemorrhage caused by uterine atony. The specific agent selected, outside of recognized contraindications, is at the health care provider's discretion	NA
The Society of Obstetricians and Gynaecologists of Canada (SOCG) https://doi.org/10.1016/j.jogc.2022.10.002	Carbetocin, 100 microg given as an IV bolus over 1 minute, should be used instead of continuous oxytocin infusion in elective Caesarean section for the prevention of PPH and to decrease the need for therapeutic uterotonics. SOGC mentions carbetocin as a uterotonic available for treatment	(I-B) 7
FIGO[40]	In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other uterotonics (carbetocin, ergometrine/methylergometrine, or misoprostol) is recommended	NA

CONCLUSION

Carbetocin combines the quick onset of oxytocin with the long-acting effect of ergometrine. The side effect profile is similar to that of oxytocin. However, carbetocin can only be used for PPH prophylaxis, whereas oxytocin has numerous uses in maternity care including labour induction, PPH prevention and PPH treatment.

The clinical data on carbetocin for PPH prophylaxis is complex given the possible differences in efficacy between IM and IV routes, the differences between vaginal birth and CS, the effect of heat instability on oxytocin effectiveness in clinical practice, and the large variation in price of carbetocin. However, considering all the above the situation can be summarized as follows:

After **vaginal births**, intramuscular carbetocin offers no advantage over intramuscular oxytocin in settings where the quality of oxytocin can be assured.

In high-income settings, carbetocin is significantly more expensive and so is not recommended after vaginal births. In settings where heat stable carbetocin is provided at low cost and where oxytocin is unavailable (or its quality cannot be guaranteed) owing to deficiencies in the cold chain, carbetocin may offer a clinical advantage.

After **CS birth**, there is some evidence that intravenous carbetocin may have some advantages over intravenous oxytocin. However, the study results are far from consistent. In high income settings where the cold chain for oxytocin is assured, there seems little benefit in selecting carbetocin over oxytocin. However, as with vaginal births, in situations where the oxytocin is poor quality and the carbetocin is being offered at low cost it may offer practical advantages. However, given that oxytocin is also needed for PPH treatment and induction of labour, and carbetocin is not used for these indications, the priority in settings offering CS should be to improve the cold chain so that all the oxytocin is of high quality.

References

1. WHO. WHO recommendations for the prevention and treatment of postpartum haemorrhage: World Health Organization, 2012.
2. Kerr R, Weeks A. Postpartum haemorrhage: a single definition is no longer enough. BJOG: An International Journal of Obstetrics & Gynaecology 2017;124(5):723–6.
3. WHO. "Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division". In: World Health Organization, 2023.
4. Sheldon WR, Blum J, Vogel JP, Souza JP, Gülmezoglu AM, Winikoff B. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014;121(1):5–13.
5. Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, Fat DM, Boerma T, Temmerman M, Mathers C, *et al*. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet 2016;387(10017):462–74.
6. Klufio CA, Amoa AB, Kariwiga G. Primary postpartum haemorrhage: causes, aetiological risk factors, prevention and management. P N G Med J 1995;38(2):133–49.
7. Nigussie J, Girma B, Molla A, Tamir T, Tilahun R. Magnitude of postpartum hemorrhage and its associated factors in Ethiopia: a systematic review and meta-analysis. Reproductive Health 2022;19(1):63.
8. Leduc D, Senikas V, Lalonde AB. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can 2009;31(10):980–93.
9. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012(4):Cd005457.
10. Begley CM, Gyte GML, Devane D, McGuire W, Weeks A, Biesty LM. Active versus expectant management for women in the third stage of labour. Cochrane Database of Systematic Reviews 2019(2).
11. Peters NC, Duvekot JJ. Carbetocin for the prevention of postpartum hemorrhage: a systematic review. Obstet Gynecol Surv 2009;64(2):129–35.
12. Vercauteren M, Palit S, Soetens F, Jacquemyn Y, Alahuhta S. Anaesthesiological considerations on tocolytic and uterotonic therapy in obstetrics. Acta Anaesthesiol Scand 2009;53(6):701–9.
13. Vogel JP, Williams M, Gallos I, Althabe F, Oladapo OT. WHO recommendations on uterotonics for postpartum haemorrhage prevention: what works, and which one? BMJ Global Health 2019;4(2):e001466.
14. Mullany LC, Newton S, Afari-Asiedu S, Adiibokah E, Agyemang CT, Cofie P, Brooke S, Owusu-Agyei S, Stanton CK. Cumulative effects of heat exposure and storage conditions of Oxytocin-in-Uniject in rural Ghana: implications for scale up. Glob Health Sci Pract 2014;2(3):285–94.
15. Hogerzeil HV, Walker GJA, Goeje MJd, Drugs WHOAPoE, World Health Organization. Safe Motherhood Research P. Stability of injectable oxytocics in tropical climates: results of field surveys and simulation studies on ergometrine, methylergometrine and oxytocin/HV Hogerzeil, GJA Walker, MJ de Goeje. In. Geneva: World Health Organization, 1993.
16. Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. BJOG 2016;123(13):2076–86.
17. Malm M, Madsen I, Kjellström J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. J Pept Sci 2018;24(6):e3082.
18. Nguyen T-H, Lambert P, Minhas RS, McEvoy C, Deadman K, Wright P, Prankerd RJ, Mogatle S, McIntosh MP. Temperature stability of oxytocin ampoules labelled for storage at 2°C–8°C and below 25°C: an observational assessment under controlled accelerated and temperature cycling conditions. BMJ Open 2019;9(7):e029083.
19. Lambert P, McIntosh MP, Widmer M, Evans L, Rauscher M, Kuwana R, Theunissen F, Yeager B, Petach H. Oxytocin quality: evidence to support updated global recommendations on oxytocin for postpartum hemorrhage. Journal of Pharmaceutical Policy and Practice 2020;13(1):14.
20. Moran C, Ni Bhuinneain M, Geary M, Cunningham S, McKenna P, Gardiner J. Myocardial ischaemia in normal patients undergoing elective Caesarean section: a peripartum assessment. Anaesthesia 2001;56(11):1051–8.
21. Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER, Farine D, Schulz ML, Horbay GL, Griffin P, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol 1999;180(3 Pt 1):670–6.
22. van Dongen PW, Verbruggen MM, de Groot AN, van Roosmalen J, Sporken JM, Schulz M. Ascending dose tolerance study of intramuscular carbetocin administered after

normal vaginal birth. Eur J Obstet Gynecol Reprod Biol 1998;77(2):181–7.

23. Engstrøm T, Barth T, Melin P, Vilhardt H. Oxytocin receptor binding and uterotonic activity of carbetocin and its metabolites following enzymatic degradation. Eur J Pharmacol 1998;355(2–3):203–10.

24. Malm M, Madsen I, Kjellström J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. Journal of Peptide Science 2018;24(6): e3082.

25. Barth T, Krejcí I, Kupková B, Jost K. Pharmacology of cyclic analogues of deamino-oxytocin not containing a disulphide bond (carba analogues). Eur J Pharmacol 1973;24(2):183–8.

26. Sweeney G, Holbrook A, Levine M, Yip M, Alfredsson K, Cappi S, Ohlin M, Schulz P, Wassenaar W. Pharmacokinetics of carbetocin, a long-acting oxytocin analogue, in non-pregnant women. Current Therapeutic Research-Clinical and Experimental 1990;47(3):528–40.

27. Meshykhi L, Nel M, Lucas D. The role of carbetocin in the prevention and management of postpartum haemorrhage. International journal of obstetric anesthesia 2016;28:61–9.

28. van Dongen PWJ, Verbruggen MM, de Groot ANJA, van Roosmalen J, Sporken JMJ, Schulz M. Ascending dose tolerance study of intramuscular carbetocin administered after normal vaginal birth. European Journal of Obstetrics & Gynecology and Reproductive Biology 1998;77(2):181–7.

29. Pharmaceuticals" F. Carbetocin Ferring Summary of Product Characteristics. In: 2020.

30. Hunter DJS, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clinical Pharmacology & Therapeutics 1992;52(1):60–7.

31. Kwon K, Kim D, Jo H, Park JE, Kim KO. Hemodynamic effects of carbetocin administered as an intravenous bolus or infusion during cesarean delivery. Anesth Pain Med (Seoul) 2020;15(2):167–72.

32. Leathersich SJ, Vogel JP, Tran TS, Hofmeyr GJ. Acute tocolysis for uterine tachysystole or suspected fetal distress. Cochrane Database Syst Rev 2018;7(7):Cd009770.

33. Mannaerts D, Van der Veeken L, Coppejans H, Jacquemyn Y. Adverse Effects of Carbetocin versus Oxytocin in the Prevention of Postpartum Haemorrhage after Caesarean Section: A Randomized Controlled Trial. J Pregnancy 2018;2018: 1374150.

34. Zeng Y, Zhang Y, Zhen M, Lao L, Ma Y, Liu L, Fan D, Ai W. Side-effects of oxytocin in postpartum hemorrhage: a systematic review and meta-analysis. Am J Transl Res 2022;14(3):1934–51.

35. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, Coomarasamy A, Abdel-Aleem H, Mallapur AA, Qureshi Z et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med 2018;379(8):743–52.

36. Moertl M, Friedrich S, Kraschl J, Wadsack C, Lang U, Schlembach D. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. BJOG: An International Journal of Obstetrics & Gynaecology 2011;118(11): 1349–56.

37. Ai W, Zeng Y, Ma Y, Liu L, Fan D, Wu S, Zhang Y. Side-effects of carbetocin to prevent postpartum hemorrhage: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res Perspect 2021;9(2):e00745.

38. Hawe A, Poole R, Romeijn S, Kasper P, van der Heijden R, Jiskoot W. Towards heat-stable oxytocin formulations: analysis of degradation kinetics and identification of degradation products. Pharmaceutical research 2009;26:1679–88.

39. Wiśniewski K, Finnman J, Flipo M, Galyean R, Schteingart CD. On the mechanism of degradation of oxytocin and its analogues in aqueous solution. Peptide Science 2013;100(4): 408–21.

40. Guidance on the use of heat-stable carbetocin as an alternative to oxytocin in the prevention of postpartum haemorrhage.

[https://www.figo.org/resources/figo-statements/guidance-use-heat-stable-carbetocin-alternative-oxytocin-prevention-postpartum-haemorrhage]

41. van der Nelson H, O'Brien S, Burnard S, Mayer M, Alvarez M, Knowlden J, Winter C, Dailami N, Marques E, Burden C, et al. Intramuscular oxytocin versus Syntometrine® versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth: a randomised double-blinded clinical trial of effectiveness, side effects and quality of life. BJOG: An International Journal of Obstetrics & Gynaecology 2021; 128(7):1236–46.

42. Voon HY, Suharjono HN, Shafie AA, Bujang MA. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries. Taiwanese Journal of Obstetrics and Gynecology 2018;57(3):332–9.

43. WHO. WHO recommendation on routes of oxytocin administration for the prevention of postpartum haemorrhage after vaginal birth: World Health Organization, 2020.

44. Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev 2018;4(4):Cd011689.

45. Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. Arch Gynecol Obstet 2009;280(5):707–12.

46. El Behery MM, El Sayed GA, El Hameed AA, Soliman BS, Abdelsalam WA, Bahaa A. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. J Matern Fetal Neonatal Med 2016;29(8):1257–60.

47. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesæter E. Changes in blood pressure and cardiac output during cesarean delivery: the effects of oxytocin and carbetocin compared with placebo. Anesthesiology 2013; 119(3):541–51.

48. Whigham CA, Gorelik A, Loughnan TE, Trivedi A. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial. J Matern Fetal Neonatal Med 2016;29(23): 3866–9.

49. Ibrahim ZM, Sayed Ahmed WA, Abd El-Hamid EM, Taha OT, Elbahie AM. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in hypertensive women undergoing elective cesarean section. Hypertens Pregnancy 2020; 39(3):319–25.

50. Al Zubaidi S, Alhaidari T. Heat stable carbetocin vs. oxytocin for the prevention of post-partum hemorrhage in emergency caesarean delivery: a randomized controlled trial. J Perinat Med 2022;50(2):150–6.

51. McDonagh F, Carvalho JCA, Abdulla S, Cordovani D, Downey K, Ye XY, Farine D, Morais M, Balki M. Carbetocin vs. oxytocin at elective caesarean delivery: a double-blind, randomised, controlled, non-inferiority trial of low- and high-dose regimens. Anaesthesia 2022;77(8):892–900.

52. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, Williams MJ, Diaz V, Pasquale J, Chamillard M, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database Syst Rev 2018;12(12):Cd011689.

53. Huang X, Xue W, Zhou J, Zhou C, Yang F. Effect of Carbetocin on Postpartum Hemorrhage after Vaginal Delivery: A Meta-Analysis. Comput Math Methods Med 2022; 2022:6420738.

54. Onwochei DN, Owolabi A, Singh PM, Monks DT. Carbetocin compared with oxytocin in non-elective Cesarean delivery: a systematic review, meta-analysis, and trial sequential analysis of randomized-controlled trials. Can J Anaesth 2020;67(11):1524–34.

55. Feduniw S, Warzecha D, Szymusik I, Wielgos M. Epidemiology, prevention and management of early postpartum

hemorrhage – a systematic review. Ginekol Pol 2020;91(1): 38–44.

56. Sun H, Xu L, Li Y, Zhao S. Effectiveness and safety of carboxytocin versus oxytocin in preventing postpartum hemorrhage: A systematic review and meta-analysis. J Obstet Gynaecol Res 2022;48(4):889–901.

57. Patrick HS, Mitra A, Rosen T, Ananth CV, Schuster M. Pharmacologic intervention for the management of retained placenta: a systematic review and meta-analysis of randomized trials. Am J Obstet Gynecol 2020;223(3):447.e441–19.

58. Kalafat E, Gokce A, O'Brien P, Benlioglu C, Koc A, Karaaslan O, Khalil A. Efficacy of carbetocin in the prevention of postpartum hemorrhage: a systematic review and Bayesian meta-analysis of randomized trials. J Matern Fetal Neonatal Med 2021;34(14):2303–16.

59. Jaffer D, Singh PM, Aslam A, Cahill AG, Palanisamy A, Monks DT. Preventing postpartum hemorrhage after cesarean delivery: a network meta-analysis of available pharmacologic agents. Am J Obstet Gynecol 2022;226(3):347–65.

60. Matthijsse S, Andersson FL, Gargano M, Yip Sonderegger YL. Cost-effectiveness analysis of carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal birth in the United Kingdom. J Med Econ 2022; 25(1):129–37.

61. Briones JR, Talungchit P, Thavorncharoensap M, Chaikledkaew U. Economic evaluation of carbetocin as prophylaxis for postpartum hemorrhage in the Philippines. BMC Health Serv Res 2020;20(1):975.

62. You JHS, Leung T-y. Cost-effectiveness analysis of carbetocin for prevention of postpartum hemorrhage in a low-burden high-resource city of China. PLOS ONE 2022;17(12):e0279130.

63. Barrett J, Ko S, Jeffery W. Cost Implications of Using Carbetocin Injection to Prevent Postpartum Hemorrhage in a Canadian Urban Hospital. J Obstet Gynaecol Can 2022; 44(3):272–8.

64. Cook JR, Saxena K, Taylor C, Jacobs JL. Cost-effectiveness and budget impact of heat-stable carbetocin compared to oxytocin and misoprostol for the prevention of postpartum hemorrhage (PPH) in women giving birth in India. BMC Health Serv Res 2023;23(1):267.

65. Prevention and Management of Postpartum Haemorrhage. BJOG: An International Journal of Obstetrics & Gynaecology 2017, 124(5):e106–49.

66. Practice Bulletin No. 183. Postpartum Hemorrhage. Obstet Gynecol 2017;130(4):e168–86.