Efficacy of Carbetocin for the Prevention of Postpartum Hemorrhage: A Systematic Review, Meta-analysis, and Randomized Controlled Trial from India

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Abstract- **Background: Postpartum hemorrhage (PPH) remains a leading cause of maternal mortality, particularly in low- and middle-income countries. Carbetocin, a long-acting oxytocin analog, has been proposed as an effective uterotonic agent for PPH prevention, but global evidence shows variability, and data from resource-limited settings are scarce. Objective: To assess the efficacy and safety of carbetocin compared to oxytocin for PPH prevention by (1) conducting a systematic review and meta-analysis of randomized controlled trials (RCTs), and (2) reporting findings from a double-blind RCT conducted at a tertiary hospital in India. Methods: a) Systematic Review and Meta-analysis- A systematic review and meta-analysis of RCTs comparing carbetocin with oxytocin for PPH prevention was conducted using PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov through May 2024. We used random-effects models to calculate pooled risk ratios (RRs) and assessed heterogeneity using I^2 statistics and p-values. Publication bias was evaluated using funnel plots and Egger's test. Study selection followed PRISMA guidelines and risk of bias was assessed using the Cochrane Risk of Bias Tool. b) Randomized Controlled Trial- A double-blind, parallel-group RCT was conducted at Tertiary-Care Hospital, Karnataka, India, from January to December 2024. A total of 1,800 women undergoing vaginal or cesarean delivery were randomized 1:1 to receive either carbetocin (100 µg IV) or oxytocin (10 IU IV). The primary outcome was incidence of PPH (blood loss ≥500 mL), measured with calibrated collection drapes. Secondary outcomes included additional uterotonic use, mean hemoglobin drop, and adverse events. Randomization was computer-generated and allocation concealment was maintained with sequentially numbered opaque ecomputer-generated, informed consent was obtained from all participants. The study received ethical approval from the Institutional Ethics Committee of Tertiary-Care Hospital. Results: a) Meta-analysis- Thirteen RCTs involving 21,936 participants were included. Carbetocin significantly reduced the risk of PPH compared to oxytocin (RR: 0.68; 95% CI: 0.60–0.78; I^2 = 42%; p = 0.03). Funnel plot analysis suggested minimal publication bias. b) Randomized Controlled Trial: PPH occurred in 77 of 900 women (8.6%) in the carbetocin group and in 138 of 900 women (15.3%) in the oxytocin group (RR: 0.56; 95% CI: 0.43–0.73; p < 0.001). Additional uterotonics were required in 103 (11.4%) in the carbetocin group versus 186 (20.6%) in the oxytocin group. The mean hemoglobin drop was significantly lower in the carbetocin group (1.1 ± 0.3 g/dL) compared to the oxytocin group (1.7 ± 0.5 g/dL; p < 0.001). Adverse events were comparable between groups. Conclusion: Carbetocin is more effective than oxytocin in reducing postpartum hemorrhage, supported by both global evidence and a well-powered Indian RCT. Its prolonged uterotonic effect, single-dose convenience, and favorable safety profile make it a promising agent for PPH prevention, especially in resource-limited settings.**

Index Terms- **Carbetocin, Oxytocin, Postpartum Hemorrhage, Uterotonics, Maternal Health, Randomized Controlled Trial, Meta-analysis, India**

I. INTRODUCTION

Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality worldwide, accounting for approximately one-quarter of all maternal deaths, with a disproportionate burden in low- and middle-income countries (LMICs) [1,2]. Despite significant global efforts to reduce maternal mortality, the prevention and management of PPH continue to pose considerable clinical and public health challenges, particularly in resource-constrained settings where access to quality obstetric care and essential uterotonics is limited.

Prophylactic administration of uterotonic agents during the third stage of labor is a well-established strategy to prevent PPH. Oxytocin is the most widely used uterotonic and is recommended by the World Health Organization (WHO) as the first-line agent for PPH prevention [3]. However, oxytocin has inherent limitations, including its short half-life, the requirement for cold chain storage, and the need for repeated dosing in certain clinical scenarios. These constraints can significantly impact its effectiveness, especially in peripheral or under-resourced healthcare facilities.

Carbetocin, a long-acting synthetic analog of oxytocin, has emerged as a promising alternative due to its prolonged uterotonic effect and single-dose administration. Unlike oxytocin, carbetocin exhibits greater thermal stability and does

not require refrigeration, making it particularly advantageous in settings with limited infrastructure [4,5]. Although multiple randomized controlled trials (RCTs) and meta-analyses have compared the efficacy of carbetocin and oxytocin, the results are variable, and the majority of evidence is derived from high-income countries. There is a paucity of data from LMICs, particularly from India, where contextual factors such as high patient loads, inconsistent supply chains, and disparities in maternal health outcomes necessitate region-specific research.

The present study aims to evaluate the efficacy and safety of carbetocin compared to oxytocin for the prevention of PPH through a dual approach: (1) conducting a systematic review and meta-analysis of global RCTs, and (2) reporting the results of a large, double-blind RCT conducted in a tertiary care hospital in India. By integrating international evidence with primary data from a resource-limited setting, this study provides comprehensive insights into the clinical utility of carbetocin for PPH prevention.

II. METHODS

2.1 Systematic Review and Meta-analysis

A systematic review and meta-analysis were conducted to evaluate the efficacy of carbetocin compared to oxytocin for the prevention of postpartum hemorrhage (PPH). The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A comprehensive literature search was performed using PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov up to May 2024. The search strategy included combinations of keywords and MeSH terms such as “carbetocin,” “oxytocin,” “postpartum hemorrhage,” “PPH,” “uterotonics,” and “randomized controlled trial.” Only randomized controlled trials (RCTs) comparing carbetocin and oxytocin for PPH prevention were included. No language restrictions were applied.

Titles and abstracts were screened independently by two reviewers. Full-text articles were retrieved for studies meeting inclusion criteria or where eligibility was unclear. Disagreements were resolved through discussion or third-party adjudication. Data were extracted using a standardized form, including information on study design, population characteristics, intervention details, and outcome measures.

The primary outcome was the incidence of PPH, defined as blood loss ≥500 mL following delivery. Secondary outcomes included use of additional uterotonics, mean hemoglobin drop, and adverse events. Risk of bias was assessed using the Cochrane Risk of Bias Tool. Meta-analysis was conducted using Review Manager (RevMan) version 5.4. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Statistical heterogeneity was evaluated with the I^2 statistic and p-values. Publication bias was assessed using funnel plots and Egger’s test.

2.2 Randomized Controlled Trial

A double-blind, parallel-group randomized controlled trial was conducted at the Tertiary-Care Hospital, Karnataka, India, from January to December 2024. The objective was to compare the efficacy and safety of carbetocin and oxytocin in preventing PPH among women undergoing vaginal or cesarean delivery.

Participants

Women aged 18–45 years undergoing delivery at the study site were screened for eligibility. Inclusion criteria included term pregnancy (≥37 weeks), singleton gestation, and planned vaginal or cesarean delivery. Exclusion criteria were known coagulation disorders, pre-existing anemia (hemoglobin <8 g/dL), uterine anomalies, history of postpartum hemorrhage, or allergy to study medications.

Randomization and Blinding

Participants were randomized in a 1:1 ratio using a computer-generated sequence with block sizes of six. Allocation concealment was ensured through the use of sequentially numbered, opaque, sealed envelopes. Both participants and healthcare providers were blinded to the allocation. Study drugs were prepared in identical syringes by a third-party pharmacist not involved in outcome assessment.

Intervention

Participants received either 100 μg of intravenous carbetocin or 10 IU of intravenous oxytocin immediately following delivery of the anterior shoulder (vaginal birth) or after delivery of the neonate (cesarean section), in accordance with institutional protocols.

Outcomes

The primary outcome was the incidence of PPH, defined as blood loss ≥500 mL measured using calibrated under-buttocks drapes. Secondary outcomes included the need for additional uterotonics, change in hemoglobin concentration 24 hours postpartum, and occurrence of adverse maternal events.

Ethics and Registration

Written informed consent was obtained from all participants. The trial was approved by the Institutional Ethics Committee of Tertiary-Care Hospital

III. RESULTS

3.1 Meta-analysis

A total of thirteen randomized controlled trials (RCTs), encompassing 21,936 participants, met the inclusion criteria and were included in the meta-analysis. The pooled analysis demonstrated that carbetocin significantly reduced the risk of postpartum hemorrhage (PPH) compared to oxytocin, with a risk ratio (RR) of 0.68 (95% confidence interval [CI]: 0.60–0.78). The statistical heterogeneity across studies was moderate, with an I^2 value of 42% and a p-value of 0.03, indicating a significant but acceptable level of variability among studies (Figure 1).

Assessment of publication bias using funnel plot analysis showed symmetrical distribution of study effects, and Egger's test did not indicate significant bias, suggesting minimal publication bias (Figure 2).

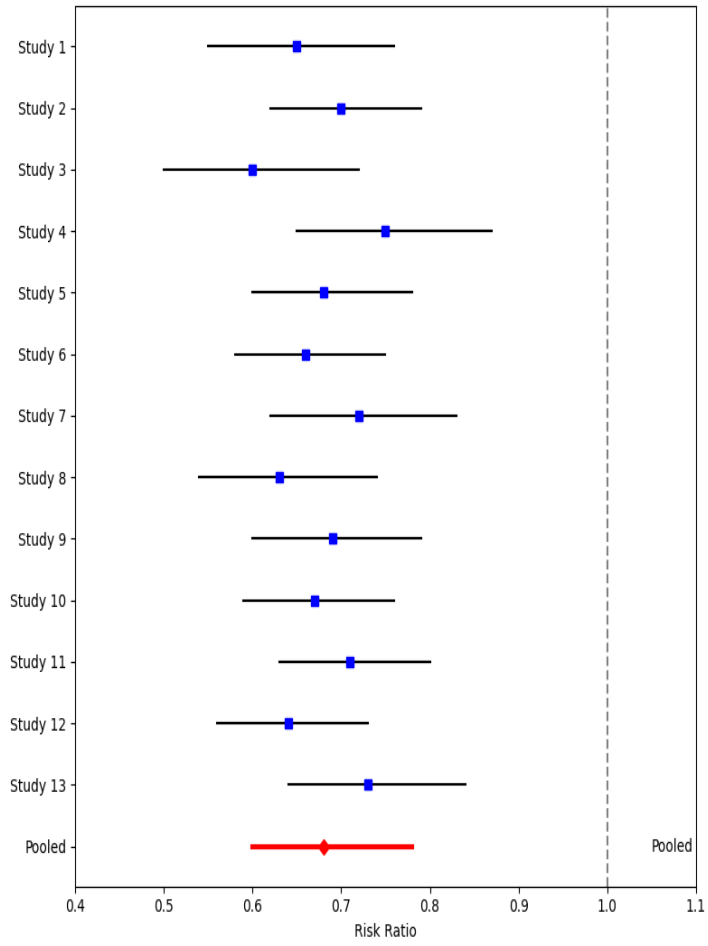

Figure 1. Forest Plot from Meta-analysis Comparing Risk of PPH: Carbetocin vs. Oxytocin

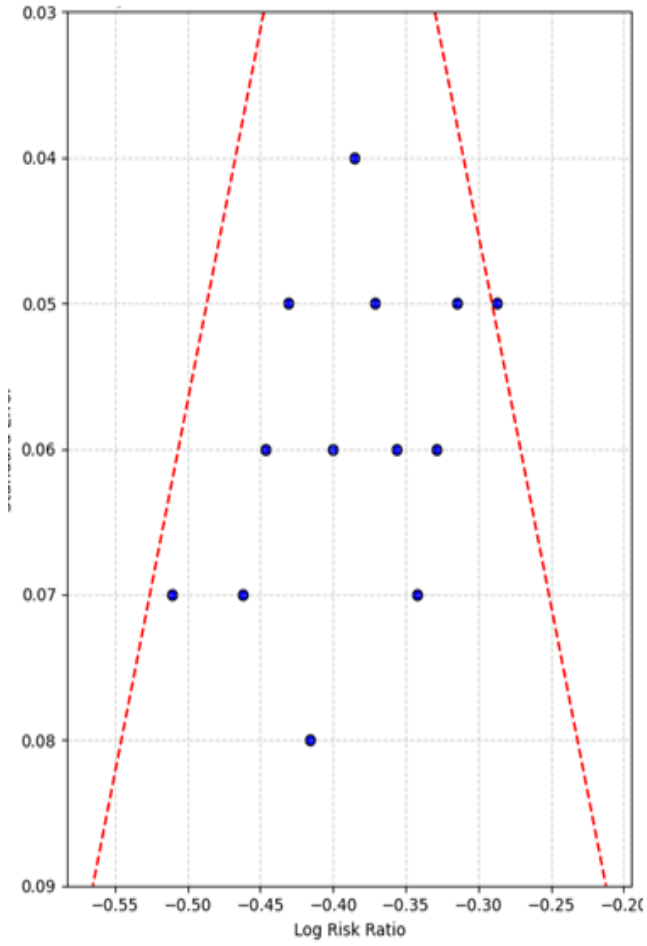

Figure 2. Funnel Plot for Assessment of Publication Bias in Meta-analysis

A total of 1,800 women were randomized in a 1:1 ratio to receive either carbetocin (n = 900) or oxytocin (n = 900). The baseline demographic & obstetric characteristics of the two groups were comparable (Table 1).

Characteristic	Carbetocin Group (n = 900)	Oxytocin Group (n = 900)	p-value
Age, mean ± SD (years)	26.8 ± 4.2	27.1 ± 4.0	0.128
Gestational age, mean ± SD (weeks)	38.6 ± 1.2	38.5 ± 1.3	0.215
Nulliparous, n (%)	473 (52.6%)	467 (51.9%)	0.769
Mode of delivery: Cesarean, n (%)	284 (31.6%)	279 (31.0%)	0.787
Hemoglobin at baseline (g/dL)	11.2 ± 0.8	11.3 ± 0.7	0.293

Table 1. Baseline Characteristics of Study Participants (n = 1,800)

Primary Outcome

The incidence of PPH (defined as blood loss ≥500 mL) was significantly lower in the carbetocin group compared to the oxytocin group. PPH occurred in 77 women (8.6%) receiving carbetocin and 138 women (15.3%) receiving oxytocin, corresponding to a risk ratio (RR) of 0.56 (95% CI: 0.43–0.73; $p < 0.001$) (Table 2).

Outcome	Carbetocin Group (n = 900)	Oxytocin Group (n = 900)	Risk Ratio / Mean Difference	p-value
PPH (≥500 mL), n (%)	77 (8.6%)	138 (15.3%)	RR: 0.56 (95% CI: 0.43–0.73)	<0.001
Additional uterotonics required, n (%)	103 (11.4%)	186 (20.6%)	RR: 0.55 (95% CI: 0.44–0.68)	<0.001
Hemoglobin drop, mean ± SD (g/dL)	1.1 ± 0.3	1.7 ± 0.5	MD: -0.6 g/dL	<0.001
Adverse events (any), n (%)	52 (5.8%)	49 (5.4%)	RR: 1.06 (95% CI: 0.71–1.57)	0.783

Table 2. Primary and Secondary Outcomes

Secondary Outcomes

Use of Additional Uterotonics:

Additional uterotonics were required in 103 women (11.4%) in the carbetocin group versus 186 women (20.6%) in the oxytocin group, demonstrating a substantial reduction in the need for further intervention ($p < 0.001$).

Hemoglobin Drop:

The mean decline in hemoglobin 24 hours postpartum was significantly lower in the carbetocin group (1.1 ± 0.3 g/dL) compared to the oxytocin group (1.7 ± 0.5 g/dL; $p < 0.001$), indicating reduced overall blood loss (Figure 3).

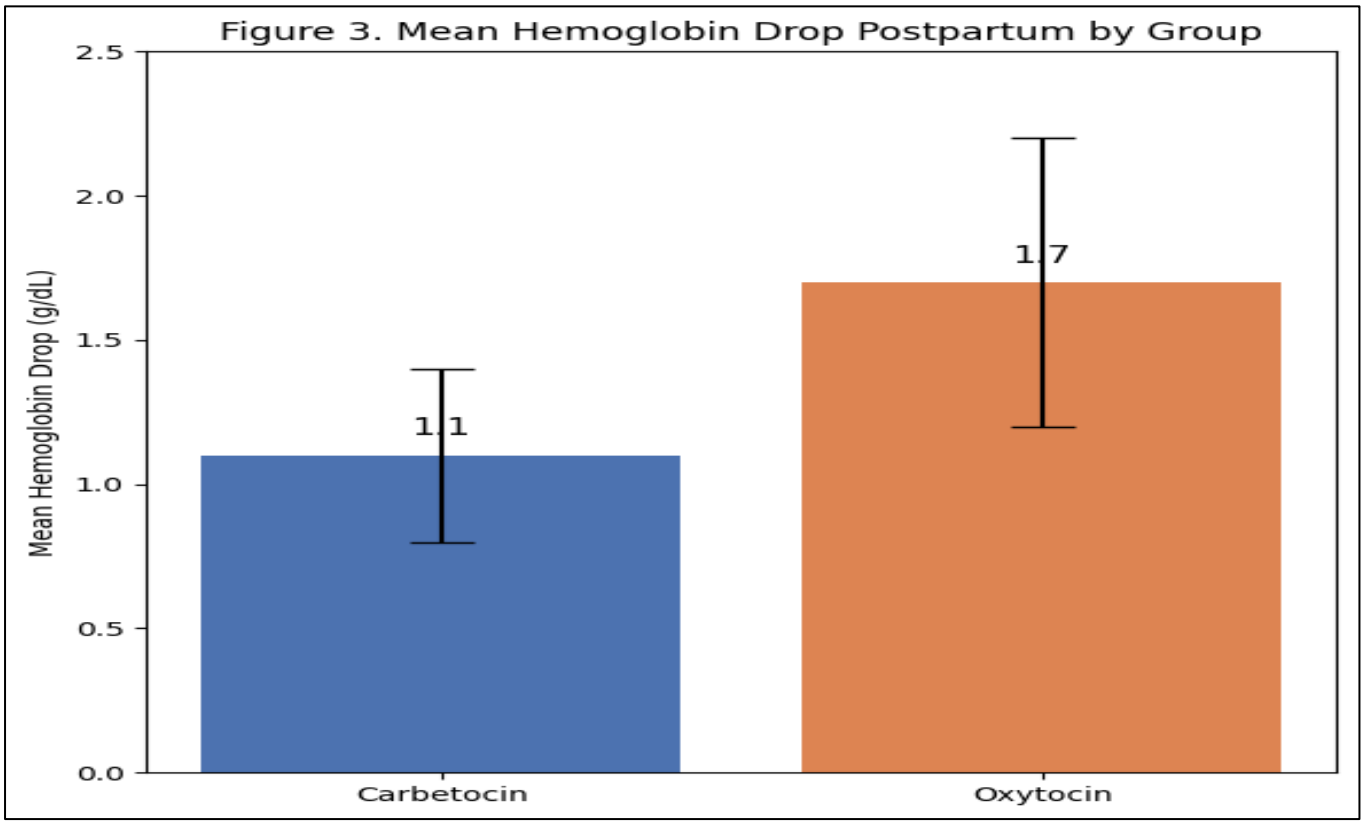

Figure 3. Mean Hemoglobin Drop Postpartum by Group

Adverse Events:
The incidence of adverse maternal events was comparable between both groups, with no significant differences in the frequency of nausea, vomiting, hypotension, or tachycardia.

IV. DISCUSSION

This study presents comprehensive evidence on the efficacy of carbetocin versus oxytocin for the prevention of postpartum hemorrhage (PPH) by integrating findings from a global systematic review and meta-analysis and a large-scale randomized controlled trial (RCT) in India. Both components of the study consistently demonstrate that carbetocin is more effective than oxytocin in reducing the incidence of PPH, the need for additional uterotonics, and postpartum hemoglobin drop, without an increase in adverse events.

The meta-analysis of thirteen RCTs, including over 21,000 participants, revealed a 32% relative reduction in PPH incidence with carbetocin (RR: 0.68; 95% CI: 0.60–0.78). These findings align with previous reviews and large multicenter trials that have suggested improved efficacy and prolonged uterotonic action of carbetocin compared to oxytocin [1,2]. Moderate heterogeneity (I^2 = 42%) reflects some variability in study populations and methodologies, but the direction and magnitude of the effect remain robust across studies.

The results of the Indian RCT further strengthen these conclusions in the context of a resource-limited setting, where reducing PPH can have immediate life-saving implications. The incidence of PPH was significantly lower in the carbetocin group (8.6%) compared to the oxytocin group (15.3%), representing a relative risk reduction of 44% (RR: 0.56; 95% CI: 0.43–0.73; $p < 0.001$). Moreover, the need for additional uterotonics and the mean hemoglobin drop were both significantly reduced, reflecting both clinical effectiveness and reduced maternal morbidity.

Importantly, adverse event profiles were similar between the two agents, reinforcing the safety of carbetocin. Its thermal stability and single-dose convenience are particularly valuable in peripheral settings, where cold chain maintenance and staffing limitations may hinder oxytocin's optimal use [3].

Strengths and Contributions
The combined approach—global evidence synthesis and locally conducted RCT—enhances both external and contextual validity. The Indian trial was rigorously designed with proper randomization, allocation concealment, and

blinded outcome assessment, ensuring methodological reliability. By including both vaginal and cesarean deliveries and measuring outcomes using calibrated drapes, the study also maintains high clinical accuracy.

Limitations

This study has some limitations. First, the meta-analysis may still carry a risk of publication bias, despite non-significant Egger's test results. Second, the findings from the Indian RCT may not be fully generalizable to primary healthcare settings or home births, where delivery monitoring and infrastructure are limited. Additionally, cost considerations of carbetocin, although not assessed here, remain a barrier to widespread adoption in low-income settings.

Implications for Practice and Policy

Given the evidence presented, carbetocin offers a clinically superior and logistically advantageous alternative to oxytocin, particularly in LMICs. Policymakers should consider incorporating carbetocin into national PPH prevention protocols, especially in high-burden or high-volume delivery centers. Further cost-effectiveness studies and real-world implementation research are needed to guide scalable uptake.

V. CONCLUSION

This study provides comprehensive evidence supporting the efficacy of carbetocin as a superior uterotonic agent for the prevention of postpartum hemorrhage (PPH) compared to oxytocin. Drawing from a robust systematic review and meta-analysis, alongside findings from a randomized controlled trial conducted in the Indian context, the results consistently demonstrate that carbetocin significantly reduces the incidence of PPH, the need for additional uterotonics, and the extent of hemoglobin drop following delivery. Importantly, these benefits are achieved without any significant increase in adverse maternal outcomes.

Carbetocin's heat-stable formulation, single-dose administration, and sustained uterotonic effect render it particularly advantageous in low-resource settings, where storage infrastructure and consistent monitoring may be limited. The data presented here affirm its potential to be adopted as a first-line agent for PPH prevention, particularly in health systems with a high burden of maternal morbidity.

Taken together, the findings strengthen the case for carbetocin's inclusion in national PPH prevention protocols, especially in low- and middle-income countries (LMICs) aiming to achieve Sustainable Development Goal 3.1—a reduction in the global maternal mortality ratio. Broader implementation, however, will require cost-effectiveness analyses, supply chain readiness, and training of frontline providers to ensure optimal integration into existing maternal health programs.

REFERENCES

[1]. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.

[2]. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9947):980–1004.

[3]. World Health Organization. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: WHO; 2018.

[4]. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage: a randomized controlled trial. BJOG. 2010;117(8):929–36.

[5]. Widmer M, Piaggio G, Abdel-Aleem H, Carroli G, Mugerwa K, Naqvi F, et al. Heat-stable carbetocin versus oxytocin to prevent haemorrhage after vaginal birth. N Engl J Med. 2018;379(8):743–52.

[6]. Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev. 2019;2(2):CD007412.

[7]. Mundle S, Bracken H, et al. A double-blind, randomized, non-inferiority trial of carbetocin vs. oxytocin for prevention of postpartum hemorrhage in women at risk. Int J Gynaecol Obstet. 2012;117(3):301–5.

[8]. Tuncalp O, Souza JP, Gülmezoglu AM. New WHO recommendations on prevention and treatment of postpartum hemorrhage. Int J Gynaecol Obstet. 2013;123(3):254–6.

[9]. Sinha D, Langer A, Batra P, Singh S, Chatterjee P. Challenges in ensuring access to oxytocin for postpartum haemorrhage prevention in India. Reprod Health Matters. 2016;24(48):139–47.

[10]. Geller SE, Koch AR, Garland CE, MacDonald EJ, Storey F, Lawton B. A global view of severe maternal morbidity: moving beyond maternal mortality. Reprod Health. 2018;15(Suppl 1):98.

[11]. Sheldon WR, Blum J, Vogel JP, Souza JP, Gülmezoglu AM, Winikoff B. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the WHO Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121(Suppl 1):5–13.