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# CARBETOCIN VERSUS OXYTOCIN IN THE PREVENTION OF POSTPARTUM HEMORRHAGE FOLLOWING VAGINAL DELIVERY: A SYSTEMATIC REVIEW AND METAANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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1 - Principal Investigator, Lead Reviewer and Statistician, Study Selection, Screening, Data Extraction, Data Analysis, risk of bias.

2 - Co-Reviewer, Content Expert and Science writer, Screening, Discussion, risk of bias.

3 - Content Expert and Science writer, Data Extraction, Results.

4 - Content Expert and Science writer, Data Extraction, Conclusion.

5 - Content Expert and Science writer, Study Selection, Methodology, Formatting, Review of Reference Organization.

6 - Content Expert and Science writer, Abstract, Introduction.

7 - Lead Reviewer, Conten



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O protocolo intitulado "Carbetocin versus Oxytocin in the Prevention of Postpartum Hemorrhage Following Vaginal Delivery: A Systematic Review and Metaanalysis of Randomized Controlled Trials" visa investigar a eficácia comparativa da carbetocina e da ocitocina na prevenção da hemorragia pós-parto em partos vaginais, um tema de grande relevância na prática obstétrica.

PROSPERO (International Prospective Register of Systematic Reviews) é uma plataforma internacional desenvolvida pela Universidade de York e financiada pelo National Institute for Health Research do Reino Unido, dedicada ao registro prospectivo de protocolos de revisões sistemáticas. Este registro representa um marco fundamental na metodologia de pesquisa baseada em evidências, promovendo transparência, reduzindo viés de publicação e minimizando duplicação desnecessária de esforços científicos. O registro prévio do protocolo em PROSPERO estabelece compromisso público com métodos predefinidos, protegendo contra modificações post-hoc que possam comprometer a integridade dos resultados.

O protocolo PROSPERO exige documentação abrangente incluindo estratégia de busca detalhada, critérios de elegibilidade, métodos de extração de dados e planos analíticos. A publicação adicional deste protocolo em periódico revisado por pares confere legitimidade científica adicional, facilita o escrutínio metodológico pela comunidade acadêmica e proporciona acesso ampliado aos detalhes da revisão planejada. Este documento em PDF atende rigorosamente aos padrões PROSPERO e está formatado para revisão por pares, representando compromisso com rigor metodológico e transparência científica.

A hemorragia pós-parto (HPP) constitui causa líder de mortalidade materna globalmente, responsável por aproximadamente 27% das mortes maternas, com incidência desproporcional em países de baixa e média renda. A prevenção farmacológica durante o terceiro estágio do trabalho de parto mediante uterotônicos profiláticos representa intervenção essencial. Apesar da relevância clínica, evidências comparativas diretas permanecem heterogêneas e inconclusivas. Estudos individuais apresentam limitações amostrais e metodológicas, enquanto revisões sistemáticas prévias

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frequentemente incluem cesáreas, confundindo interpretação específica para partos vaginais. Este protocolo oferece contribuição metodológica significativa ao campo da saúde materna, estabelecendo estrutura transparente para síntese de evidências que informará prática clínica, diretrizes políticas e identificação de gaps para pesquisas futuras. Não há conflitos de interesse a declarar



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# Full Prospero Protocol

1. **Review Title**

*Carbetocin versus* Oxytocin *in the Prevention of Postpartum Hemorrhage Following Vaginal Delivery: A Systematic Review and Meta-analysis of Randomized Controlled Trials*

2. **Original Language Title**

*Carbetocina versus Sintometrina na Prevenção de Hemorragia Pós-Parto Após Parto Vaginal: Uma Revisão Sistemática e Metanálise de Ensaios Controlados Randomizados*

3. **Anticipated or Actual Start Date**

*July 26, 2025*.

4. **Anticipated Completion Date**

*February 20, 2026*.

5. **Stage of Review at Time of Submission**

- Started: Yes
- Completed: No
- Preliminary searches: Yes
- Piloting of the study selection process: Yes
- Formal screening of search results against eligibility criteria: No
- Data extraction: No
- Risk of bias (quality) assessment: No
- Data analysis: No

**Review Team Details**

6. **Named Contact**


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7. **Organisational Affiliation of the Review**


Centro Universitário de Várzea Grande - UNIVAG

Website:https://www.univag.com.br/


8. **Review Team Members and Their Organisational Affiliations**

- Elias Mendes Leal Neto, Principal Investigator, Lead Reviewer and Statistician, Study Selection, Screening, Data Extraction, Data Analysis, risk of bias.
- Vinicius Mateus Camarão Ortiz, Co-Reviewer, Content Expert and Science writer, Screening, Discussion, risk of bias.
- Thiago Bonafé, Content Expert and Science writer, Data Extraction, Results.
- Thaiz Nadine Lavezzo Carfi, Content Expert and Science writer, Data Extraction, Conclusion.
- Letícia Moreira Serigiolli, Content Expert and Science writer, Study Selection, Methodology, Formatting, Review of Reference Organization.
- Amanda Amorim Brescancim, Content Expert and Science writer, Abstract, Introduction.
- Rafael Silva Godoy, Lead Reviewer, Content Expert and Science writer.

9. **Funding Sources/Sponsors**


*No external funding; self-funded. No grant ID.*


10. **Conflicts of Interest**

*None declared. Review team members have no financial, professional, or personal ties to pharmaceutical companies producing carbetocin or* Oxytocin.

11. **Collaborators**

Statistician: Hugo Hoffmann

**Review Methods**

12. **Review Question(s)**

Primary: In pregnant women undergoing vaginal delivery, does carbetocin provide superior, comparable, or inferior efficacy and safety compared to Oxytocin for preventing postpartum hemorrhage during the third stage of labor?

Secondary:

- Which agent results in lower mean blood loss? - Which requires fewer additional uterotonics?
- Which has fewer adverse effects?

13. **Searches**

Comprehensive searches will be conducted in PubMed/MEDLINE, Embase. Grey literature via Google Scholar, clinical trial registries (ClinicalTrials.gov, WHO ICTRP), and hand-searching references/conference abstracts. No date or language restrictions; translations obtained as needed. Searches from database inception to novembro 2025.

Full strategy example (PubMed): (("Carbetocin" OR "Carbetocin[MeSH]") AND ("Oxytocin" OR "Oxytocin[MeSH]")) AND ("Postpartum Hemorrhage" OR "Postpartum Bleeding" OR "PPH" OR "hemorragia pós-parto") AND ("Third Stage of Labor" OR "Third Stage" OR "Delivery, Obstetric") AND ("Vaginal Delivery" OR "Spontaneous Vaginal Delivery" OR "Vaginal Birth")

| **Concept** | **Search Terms (Examples)** |
|---|---|
| Intervention (Carbetocin) | "Carbetocin" OR "Carbetocin[MeSH]" |
| Comparator (Oxytocin) | " Oxytocin " OR " Oxytocin [MeSH]" |
| Condition (PPH) | "Postpartum Hemorrhage" OR "Postpartum Bleeding" OR "PPH" OR "hemorragia pós-parto" |
| Labor Stage | "Third Stage of Labor" OR "Third Stage" OR "Delivery, Obstetric" |
| Delivery Type | "Vaginal Delivery" OR "Vaginal Birth" OR "Spontaneous Vaginal Delivery" |

14. **URL to Search Strategy**

*Available via supplemental file. Permission to make public: Yes.*

15. **Condition or Domain Being Studied**

*Prevention of postpartum hemorrhage (PPH), in the third stage of labor after vaginal birth. Domain: Maternal health in obstetrics and gynecology.*

16. **Participants/Population**

Inclusion: Pregnant women (any age, parity, risk level) in the third stage of labor following vaginal delivery, in any setting (hospital).

Exclusion: Cesarean deliveries, pre-existing coagulopathies, or non-obstetric populations.

17. **Intervention(s), Exposure(s)**

*Carbetocin intramuscular or intravenous administered prophylactically in the third stage.*

18. **Comparator(s)/Control**

Oxytocin *intramuscular or intravenous as standard prophylactic uterotonic.*

19. **Types of Study to be Included**

*Randomized controlled trials (RCTs), including parallel, cluster, and multi-arm designs where relevant arms can be extracted. Exclusion: Non-randomized studies, reviews, editorials, letters, animal studies, or those without full methods/outcomes.*

20. **Context**

*Global contexts, emphasizing low- and middle-income countries where PPH burden is high and heat-stable agents like carbetocin may offer logistical benefits.*

21. **Primary Outcome(s)**

*Incidence of PPH (blood loss ≥500 mL or ≥1000 mL for severe). Measure: Risk ratio (RR) with 95% CI. Timing: Within 24 hours post-delivery.*

| Primary Outcome | Measure | Timing/Method |
|---|---|---|
| PPH Incidence (≥500 mL) | RR, 95% CI | 24 hours; objective (gravimetric/volumetric) or clinical assessment |
| Severe PPH (≥1000 mL) | RR, 95% CI | 24 hours |

22. **Secondary Outcomes**

*Mean blood loss (mL), hemoglobin change (g/dL), need for additional uterotonics (RR), adverse effects (e.g., nausea, vomiting, hypertension; RR or odds ratio), maternal mortality/morbidity, quality of life.*

| Secondary Outcome | Measure | Timing |
|---|---|---|
| Mean Blood Loss | Mean Difference (MD), 95% CI | Immediate post- delivery |
| Hemoglobin Change | MD, 95% CI | 24-48 hours |
| Additional Uterotonics | RR, 95% CI | Immediate |
| Adverse Effects (Composite) | RR, 95% CI | Within 48 hours |
| Quality of Life | Standardized MD | Post-discharge follow- up |

23. **Data Extraction (Selection and Coding)**

Two reviewers will independently screen titles/abstracts and full texts using Rayyan software. Disagreements resolved via consensus or third reviewer. Extracted data: Study details (author, year, location, design, sample size), participant characteristics (age, parity, risk factors), intervention/comparator details (dose, timing), outcomes (as defined).

24. **Risk of Bias (Quality) Assessment**

Cochrane RoB 2 tool for each outcome, covering randomization, deviations, missing data, measurement, and reporting. Overall judgment: Low, some concerns, high risk. Inter-rater agreement via kappa; sensitivity analysis excluding high-risk studies. Certainty of evidence graded using GRADE (high, moderate, low, very low) considering inconsistency, imprecision, etc.

25. **Strategy for Data Synthesis**

Meta-analysis using R software with random-effects model (anticipating

heterogeneity). Dichotomous: RR/Mantel-Haenszel; continuous: Inverse variance MD. Heterogeneity: Tau², I² (interpret <40% low, 40-60% moderate, >60% high); funnel plots/Egger's test for publication bias (if ≥10 studies). Narrative synthesis if quantitative pooling inappropriate. Forest plots for visualization.

26. **Analysis of Subgroups or Subsets**

Planned: Risk level (high vs. low), setting (high- vs. low-resource), dose variations, parity (nulliparous vs. multiparous), route of administration. Meta-regression if sufficient studies (>10) to explore moderators like maternal age or comorbidities.

27. **Type and Method of Review**

*Systematic review and Meta-analysis*

**Review General Information**

28. **Language**

*English, Portuguese (for regional studies). Include non-English if relevant: Yes. Summary/abstract in English: Yes.*

29. **Country**

*Brazil* (primary; collaborative input from international experts if needed).

30. **Other Registration Details**

*Protocol also to be registered on Open Science Framework for transparency.*

31. **Reference and/or URL for Published Protocol**

*N/A at submission. Permission to make public: Yes.*

32. **Dissemination Plans**

*Peer-reviewed publication*

33. **Keywords**

*Carbetocin, Oxytocin, Postpartum Hemorrhage, Third Stage of Labor, Vaginal Delivery, Uterotonics, Randomized Controlled Trials, Meta-analysis.*

34. **Details of Any Existing Review of the Same Topic by the Same Authors**

*We identified other systematic review projects on the same or similar topics. We understand that these previous reviews appear to have been interrupted, abandoned or not updated. Our review will therefore provide an updated and comprehensive synthesis of the available evidence, focusing specifically on the comparison between carbetocin and oxytocin in vaginal deliveries.*

35. **Current Review Status**

*Ongoing.*

36. **Any Additional Information**

*Preliminary screening identified RCTs such as "Carbetocin vs. oxytocin in Prevention of Postpartum Hemorrhage: a Double Blind Randomized Control Trial" (PubMed) and others listed below.*

37. **Details of Final Report/Publication(s)**

*To be updated post-completion with DOI and URL.*

This protocol adheres to PROSPERO's requirements, promoting reproducibility and ethical research. It builds on the document's foundation while enhancing with advanced analytical plans for robustness.