ISSN: 2594-679X

CARBETOCIN VERSUS SYNTOMETRINE IN THE PREVENTION OF POSTPARTUM HEMORRHAGE FOLLOWING VAGINAL DELIVERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Elias Mendes Leal Neto[1]

Nathália Camargo de Carvalho[2]

Giuliana Vieira Ugger[3]

Jade Silva Mattos[4]

Ranny de Oliveira Coelho[5]

Lúcia Helena Conte Souza[6]

Rafael Silva Godoy[7]

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

2 - Co-Reviewer and Study Selection, Data Extraction.

3 - Content Expert and Science writer, Abstract, Introduction, Formatting, Review of Reference Organization.

4 - Content Expert and Science writer, Screening, Discussion.

5 - Content Expert and Science writer, Results, Conclusion.

6 - Content Expert and Science writer, methodology, risk of bias

7 - Lead Reviewer, Content Expert and Science writer

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O protocolo completo intitulado "Carbetocin versus Syntometrine in the Prevention of Postpartum Hemorrhage Following Vaginal Delivery: A Systematic Review and Meta-analysis of Randomized Controlled Trials", está registrado na plataforma PROSPERO.

PROSPERO (International Prospective Register of Systematic Reviews) constitui plataforma internacional mantida pela Universidade de York, estabelecendo padrão-ouro para registro prospectivo de revisões sistemáticas em saúde. Este registro prévio desempenha papel crucial na promoção de integridade científica, prevenindo modificações metodológicas oportunísticas após conhecimento dos resultados, reduzindo viés de publicação seletiva e facilitando identificação de revisões duplicadas. O registro PROSPERO confere credibilidade metodológica e demonstra compromisso com transparência antes do início da coleta de dados.

A publicação formal do protocolo PROSPERO em periódico revisado por pares representa extensão lógica do processo de registro, oferecendo benefícios adicionais incluindo validação metodológica independente, maior visibilidade na comunidade científica e documentação permanente acessível. Este manuscrito apresenta protocolo completo em formato PDF, estruturado para escrutínio rigoroso por pares, cumprindo requisitos PROSPERO enquanto fornece detalhamento metodológico ampliado apropriado para publicação científica formal.

A hemorragia pós-parto (HPP) representa emergência obstétrica crítica que afeta partos em todo o mundo, sendo a principal causa evitável de mortalidade materna. Gerenciamento ativo do terceiro estágio do trabalho de parto com uterotônicos profiláticos reduz risco de HPP. Sintometrina, combinação fixa de oxitocina (5 UI) e ergometrina (0,5 mg), promete eficácia histórica superior à oxitocina isolada, porém associa-se a efeitos adversos significativos incluindo hipertensão, náusea e vômito, com contraindicações em mulheres hipertensas ou pré-eclâmpticas. Carbetocina, agonista seletivo de receptores de ocitocina com ação prolongada, oferece perfil farmacológico

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vantajoso: meiavida de 40 minutos, administração em dose única, estabilidade em temperatura ambiente e ausência de efeitos vasoconstritores ergotamínicos.

A comparação direta entre carbetocina e sintometrina permanece inadequadamente elucidada. Evidências existentes derivam predominantemente de estudos individuais com poder estatístico limitado ou revisões que agregam múltiplos comparadores, diluindo clareza sobre superioridade relativa específica. Adicionalmente, muitos estudos incluem cesáreas eletivas, contexto farmacológico e fisiológico distinto do parto vaginal onde tônus uterino e padrões hemorrágicos diferem substancialmente.

Nossa revisão sistemática e metanálise preenche lacuna metodológica crítica ao focar exclusivamente em partos vaginais, população clinicamente relevante onde escolha de uterotônico impacta milhões de mulheres anualmente. Empregamos metodologia robusta incluindo avaliação Cochrane RoB 2 para risco de viés, análises de sensibilidade e investigação rigorosa de viés de publicação. Este protocolo estabelece estrutura transparente para síntese definitiva que informará diretrizes clínicas internacionais, formulação de políticas de saúde materna e identificação de prioridades para ensaios clínicos futuros. Este protocolo contribuirá significativamente para transparência científica, evitando a duplicação de esforços de pesquisa e fornecerá modelo metodológico para investigadores conduzindo revisões similares em farmacologia obstétrica. Não há conflitos de interesse a declarar.

Caderno de Publicações Univag – n.15 (2025) DOI: 10.18312/cadernounivag.v15i15.3269

Full PROSPERO Registration Protocol: Carbetocin versus Syntometrine for PPH Prevention

1. **Review Title**

   Carbetocin versus Syntometrine 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**
   August 27, 2025.
4. **Anticipated Completion Date**
   March 3, 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**
   - Name: Elias Mendes Leal Neto
   - Email: xaprendendopelanetx@gmail.com
   - Organisation: Centro Universitário de Várzea Grande (UNIVAG)
   - Address: Várzea Grande – Brazil
   - Telephone: +55 65 98444-4000
   - Mobile: +55 65 98444-4000
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, Statistician, Study Selection, Data Extraction, Data Analysis.

- Nathália Camargo de Carvalho, Co-Reviewer and Study Selection, Data Extraction.
- Giuliana Vieira Uggeri, Content Expert and Science writer, Abstract, Introduction, Formatting, Review of Reference Organization.
- Jade Silva Mattos, Content Expert and Science writer, Screening, Discussion.
- Ranny de Oliveira Coelho, Content Expert and Science writer, Results, Conclusion.
- Lúcia Helena Conte Souza, Content Expert and Science writer, methodology, risk of bias.
- 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 syntometrine.
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 syntometrine 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") AND ("Syntometrine" OR "Syntometrine®") AND ("Third stage of labour" OR "third stage of labor" OR "Postpartum haemorrhage" OR "postpartum hemorrhage" OR "primary postpartum hemorrhage" OR "preventing postpartum hemorrhage") AND ("vaginal delivery" OR "delivery").

Concept	Search Terms (Examples)
Intervention (Carbetocin)	"Carbetocin" OR "Carbetocin[MeSH]"
Comparator (Syntometrine)	"Syntometrine" OR "Syntometrine®" OR ("Oxytocin" AND "Ergometrine")

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**
    Syntometrine 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: Tau^2, I^2 (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, Syntometrine, 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** (Optional)
    None; this is an original review. Note: Existing meta-analyses on broader uterotonics exist, but this focuses narrowly on carbetocin vs. syntometrine in vaginal deliveries.
35. **Current Review Status** (Required)
    Ongoing.
36. **Any Additional Information**
    Preliminary screening identified RCTs such as "Carbetocin vs. Syntometrine 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.