Risk Factors for Hemorrhage in The Third Stage of Labor: A Systematic Review Protocol

Maria de Lourdes de Souza (✉ repensul@uol.com.br)

Universidade Federal de Santa Catarina <https://orcid.org/0000-0002-4327-1279>

Adalia Edna Fernando Chipindo

Instituto Superior Politécnico da Caála

Eneida Patrícia Teixeira

Federal University of Santa Catarina: Universidade Federal de Santa Catarina

Anna Carolina Raduenz Huf Souza

Federal University of Santa Catarina: Universidade Federal de Santa Catarina

Rita de Cássia Teixeira Rangel

University of the Vale do Itajaí: Universidade do Vale do Itajaí

Débora Batista Rodrigues

Federal University of Santa Catarina: Universidade Federal de Santa Catarina

Zannis Benevides de Andrade

Federal University of Santa Catarina: Universidade Federal de Santa Catarina

Juliana Fernandes da Nóbrega

Federal University of Santa Catarina: Universidade Federal de Santa Catarina

Inácio Alberto Pereira Costa

Instituto Federal de Santa Catarina: Instituto Federal de Educacao Ciencia e Tecnologia de Santa Catarina

Cheila Maria Lins Bentes

University of Amazonas State: Universidade do Estado do Amazonas

Helder Lucas Chipindo

ISP-CAALA

Protocol

Keywords: Female, Hemorrhage, Humans, Labor, Obstetric, Pregnancy, Risk Factors.

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-638961/v1>

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Abstract

Background

Postpartum hemorrhage (PPH) is the most common form of obstetric hemorrhage. This is the main cause of maternal death around the world: the incidence varies among countries and accounts for 27% (in some countries, more than 50%) of direct obstetric maternal deaths, mainly in the postpartum period. Recognizing risk factors for PPH in prenatal care and during childbirth care is the first stage to prevent maternal death from PPH. The objective this review is: To identify the risk factors for hemorrhage in the third stage of labor described in the literature from 2000 to 2020.

Methods

A protocol for a Systematic Review and Meta-analysis study was developed, supported by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and, registered in the International Prospective Register of Systematic Reviews (PROSPERO). The research question for conducting the review was structured according to the PEOs strategy (P – Populations/People/Patient/Problem, E – Exposure (s), O – Outcome, S – Study design): **P** – women aged from 10 to 49 years, in labor; **E** – risk factors for hemorrhage in the third stage of labor; **O** – women with hemorrhage during birth and postpartum; **S** – observational studies (case control and cohort). Thus, the defined question was: what are the risk factors for hemorrhage in the third stage of labor described in the literature from 2000 to 2020? As for the planning of electronic searches, databases were consulted by using the platform of the Coordination for the Improvement of Higher Education Personnel in Brazil (CAPES, as per its Portuguese acronym). Due to the characteristics of each database, specific search strategies were chosen for each database. After applying the eligibility criteria, the articles that are selected will have the quality of the evidence evaluated by applying the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), with the online tool GRADEpro GDT.

Discussion

Prevention and control of hemorrhage must be initiated in the prenatal period, requiring competent professionals to carry out the appropriate clinical evaluation to classify the degree of risk to which the woman is exposed. This systematic review will support the studies of professionals who working in Angola and Brazil.

Systematic review registration

PROSPERO available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021219303

Background

The reason for maternal mortality and its causes is an indicator of the living conditions and health care of a population; since almost all deaths are preventable and mostly take place in developing countries [1]. Postpartum hemorrhage (PPH) is one of the main causes of maternal morbidity and mortality worldwide. PPH is defined as blood loss above 500 ml, measured up to 24 hours postpartum, while this amount of blood loss after 24 hours is defined as secondary PPH. Blood loss up to 500ml among healthy women does not lead to negative consequences; however, uncontrolled blood loss over 500ml can be fatal [2, 3].

Hemorrhage is the greatest preventable cause of maternal death around the world. In Brazil, in the period from 1997 to 2009, maternal mortality due to hemorrhage was associated with the following causes: ectopic pregnancy; early pregnancy bleeding; malformations of the placenta; placenta previa; abruptio placentae; antepartum hemorrhage; intrapartum hemorrhage; postpartum hemorrhage. It was considered important to explore the causes of hemorrhage, because hemorrhage is merely a symptom of a disease. Therefore, it is the underlying cause, such as uterine atony or abruptio placentae, which will present with hemorrhage, but each of these conditions has a unique etiology. The risk of hemorrhage increases in cases of multiple pregnancies, polyhydramnios, macrosomia, precipitous labor or prolonged labor, chorioamnionitis, or simply the inability to contract the uterine muscle, due to the use of tocolytics or general anesthesia. This is also important because, in order to prevent, control, or intervene effectively in an obstetrical hemorrhage, it is necessary to know the underlying cause [4, 5].

Although it is a physiological process, pregnancy, depending on the woman's life history, can reach varying degrees of risk, especially when there is a juxtaposition of several factors such as age, adverse events in previous pregnancies, multiple gestation, polyhydramnios, fetal macrosomia, great-grand multiparity, obesity and hypertension. The severity can also be expanded by the assistance that is provided to women, whether in the prenatal, birth and postpartum periods, associated with the infrastructure of the services, the qualification of professionals, the distances and the access to intensive care units [5, 6].

Maternal deaths are mostly preventable, constituting markers of a Nation's socioeconomic development level. Most of these deaths could be prevented by improving access, in a timely manner, to qualified health services. Although the Maternal Mortality Ratio varies from country to country, the causes, in general, are mainly: hemorrhage (25% of maternal deaths), sepsis (15%), abortion complications (13%), eclampsia (12%) and obstructed labor (8.0%); and can be associated with each other [7, 8].

Other research reported that it is difficult to understand why maternal mortality, most of the causes of which are preventable, does not receive adequate attention from health professionals, politicians and policy makers. Among the professionals, it is worth mentioning the obstetricians, who have been particularly negligent in relation to the reduction of maternal mortality. It is even observed that most obstetricians are concentrated in subspecialties that place emphasis on high technology [9].

Therefore, the theme of this Systematic Review (SR) is current, since identifying the risks will be contribute to actions that result in the reduction of maternal deaths. The reduction of maternal deaths

was assumed as a global commitment, guided by the 2030 Agenda, in the context of the Sustainable Development Goals [10].

Carrying out a SR of primary studies on the risk for hemorrhage in the third stage of labor, described in the literature from 2000 to 2020, provides the analysis of risk factors that achieve greater relevance and the application of prevention and control measures that are feasible to put into practice. The obtained results will serve as subsidies for the education of professionals, as a support for the planning of clinical guidelines, as well as for the redefinition of public policies, so that care actions are offered equitably and safely to women.

The risk factors make it possible to determine which women are at risk of postpartum hemorrhage also to propose guidelines for health services to qualify assistance.

The risk factors that obtain more frequency will be applied for validation to the reality of Huambo/Angola of the Instrument “Nursing Care Technology in the Prevention and Management of Hemorrhage in the Third Stage of Labor”

This systematic review is part of a larger project on Maternal Mortality with the production of technologies focused on reducing it. The objective defined for this systematic review is: To identify the risk factors for hemorrhage in the third stage of labor described in the literature from 2000 to 2020.

Methods

Review question

This protocol for a Systematic Review and Meta-Analysis was developed with support from the PRISMA-P. The report of the review will be held in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11,12, 13].

The research question for conducting the review was structured according to the mnemonic PEOS (**P** – Populations: Women aged between 10 and 49 years, in labor; **E** – Exposure (s): risk factors for hemorrhage in the third stage of labor; **O** – Outcome: women with hemorrhage during birth and postpartum; **S** – Study design: observational studies (case-control; cohort). Therefore, studies classified as follows will be included in this review: a) regarding the type of participants, those that address women in labor and birth; b) regarding the exposure, those that address risk factors for postpartum hemorrhage/third period of labor; c) regarding the outcome of interest, women who had hemorrhage during labor; postpartum/third period of labor, survivors or who died from this cause; d) regarding the type of studies, observational studies will be selected, including prospective and retrospective cohort studies, as well as case control [14,15, 16]. Accordingly, the question was defined: What are the risk factors for hemorrhage in the third stage of labor described in the literature from 2000 to 2020?

Search strategy

Databases

As for the planning of electronic searches, the following databases were consulted: Searches Embase, BIREME (Latin American and Caribbean Center for Health Sciences Information), SciELO Brazil (Scientific Electronic Library Online Brazil), PubMed (National Library of Medicine) / MEDLINE (Medical Literature Analysis and Retrieval System Online), Scopus, Web of Science and CINAHL (Cumulative Index of Nursing and Allied Health Literature) will be searched for relevant literature. Due to the characteristics of each database, search strategies were chosen by respecting the specificity of each database.

Controlled descriptors in English, Portuguese and Spanish were used, in the plural and singular possibilities for each descriptor, in addition to recovering their synonyms. To this end, terms indexed in the Medical Subject Headings (MeSH) were retrieved as “MeSH terms” and “All Fields”, also in the *Descritores em Ciências da Saúde* (DeCS) as descriptors and synonyms. Therefore, the following Search Strategy Medline (Table 01) was established. In addition, the Boolean operators AND and OR were adopted in the search strategies.

Table 1 Search strategy - Medline

Domain	Terms
(P) Population	1. postpartum period 2. puerperal 3. labor stage, third 4. third labor stage 5. third labor stages 6. 1 OR 2 OR 3 OR 4 OR 5
(E) Exposure	1. risk factor.mp. or exp risk factors/ 2. population at risk.mp. or exp risk factors/ 3. 7 OR 8
O (Outcome)	1. postpartum hemorrhage 2. hemorrhage 3. hemorrhages 4. hemorrhagic 5. bleeding 6. 10 OR 11 OR 12 OR 13 OR 14
6 AND 9 AND 15	

Eligibility criteria

Full texts of primary studies, written in Portuguese, English or Spanish will be identified and retrieved by screening titles and abstracts.

In addition, two independent researchers will select the articles, reading each of these articles by title, by summary and by the full text, according to the following inclusion criteria: primary scientific articles, published between 2000 and 2020, in English, Portuguese or Spanish that address the Risk Factors for Hemorrhage in the Third Period of Labor in observational analytical studies: cohort studies, case control, available in the selected databases. The following exclusion criteria will be considered: theses, dissertations, editorials, integrative and systematic reviews and qualitative studies.

Process and tool for obtaining data

The collected data will be exported to a reference manager, EndNote. The search results in the databases will be exported to Rayyan®, an electronic tool that allows independent evaluation of studies by reviewers. Through it, studies indexed in more than one database will also be identified, and then duplicate publications will be removed [17]. The titles and abstracts of articles will be analyzed by two reviewers, independently, according to the eligibility criteria.

In order to assess the level of agreement between the reviewers, the Kappa coefficient will be calculated to obtain the proportion of agreement between the researchers, removing those given by chance [18]. The following classification will be adopted: <0.00, poor agreement; 0.00-0.20, slight agreement; 0.21-0.40, reasonable agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect [19].

Articles that do not reach consensus between the two reviewers will be assessed by a third reviewer for inclusion or disposal. The selected articles will be integrated into this SR for full reading and extracting data.

Grading of evidence

The level of evidence identified in the analyzed articles will be classified according to the GRADE [20, 21], a system considered sensitive for grading the quality of evidence. In this system, the quality of evidence is describe in four levels: high, moderate, low and very low. Evidence from randomized clinical trials starts with a high level and evidence from observational studies with a low level.

Data extraction

Only published data will be extracted: article characterization, method design, intervention, outcome, results, statistic test and conclusions. Moreover, a peer-analysis of the extracted data will then be performed. The extracted data will be systematized by creating tables.

Risk of bias assessment

The GRADE criteria will be applied for the risk of bias assessments and will be carried out individually by two independent researchers by using the online tool GRADEpro GDT. The evidence will be classified as high, moderate, low and very low. The main conclusions drawn from the synthesis of the included studies will be given based on the criteria that lower the level of evidence, those being: risk of bias, inconsistency, indirect evidence, inaccuracy and publication bias, a large magnitude of effect, the dose-response gradient and residual confounders. In addition, it will be used, independently, assessed risk of bias by using the Newcastle–Ottawa Scale for evaluating the quality of nonrandomized studies [21,22]. Three factors will be considered to score the quality of included studies: (1) selection, including representativeness of the exposed, selection of the non-exposed, ascertainment of exposure and demonstration that at the start of the study the outcome of interest was not present; (2) comparability, assessed on the basis of study design and analysis, and whether any confounding variables were adjusted for; and (3) outcomes. We will rate the quality of the studies in three levels (good, fair and poor) by awarding stars in each domain following the guidelines.

In this review, based on the adopted classification to assess the quality of the evidence, the risk of bias in observational studies - cohort studies and case control studies will be considered in relation to the limitations identified in the description of the method referring to the design or execution of individual studies. Evidence from observational studies can be elevated by allocation confidentiality, blinding, complete segment, outcome reporting and sufficient information to assess whether there is a risk of bias. For each of these domains, the risk of bias will be assessed and classified as high risk, uncertain and low risk.

In the third stage, after reading the full texts, the data will be systematized for all studies included in the analysis by reconciling the results between the independent researchers.

In order to compile and synthesize the results of the different studies included in the review, tables, charts and figures will be designed to compose the presentation of the results.

Strategy for data synthesis

Narrative synthesis will be made with meta-analysis and will be carried out by using a framework that consists of: 1. Developing a preliminary synthesis of findings of included studies 2. Exploring relationships within and between studies 3. Assessing the robustness of the synthesis. If possible, a statistical meta-analysis will be carried out by using Review Manager software (Revman The Cochrane Collaboration, Oxford, UK). In addition, a random-effect meta-analysis will be used for combining data where appropriate, at certain time points and by the outcome[23].

Discussion

Despite initiatives to reduce the maternal mortality risk in many places around the world, this problem is very important. The hemorrhage is the principal cause of maternal mortality when the health service is not good and the women don't receive the proper care [4, 8, 9].

The strengths of this review will be the use of guidelines such as PRISMA to support a standardized approach to review methods, well-defined inclusion and exclusion criteria. The quality of the evidence of all studies registered in the consulted databases will be evaluated with the support of the GRADE, with the online tool – GRADEpro GDT. In addition, you will be using other computerized supports: EndNote, Rayyan®, Review Manager and Newcastle–Ottawa Scale.

Also as of 01/14/2021, there were no other SR registered in PROSPERO (<https://www.crd.york.ac.uk/prospero>), with similar theme, research question and objective.

This systematic review will support the studies of nursing professionals who are pursuing their doctoral studies in the Graduate Nursing Program from the Federal University of Santa Catarina, Brazil.

The obtained evidence in this systematic review will subsidize the training of physicians and nurses who work in birth and postpartum care in Angola with the *Instituto Superior Politécnico da Caála*, Huambo/Angola and, thus, will contribute to preventing obstetric hemorrhage, especially postpartum.

Abbreviations

BIREME

Latin American and Caribbean Center for Health Sciences Information

CAPES

Coordination for the Improvement of Higher Education Personnel

CINAHL

Cumulative Index of Nursing and Allied Health Literature

DeCS

Descriptors in Health Sciences

GRADE

Grading of Recommendations, Assessment, Development and Evaluation

MEDLINE

Medical Literature Analysis and Retrieval System Online

MeSH

Medical Subject Headings

PPH

Postpartum hemorrhage

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-P

Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols PROSPERO:International

Prospective Register of Systematic Reviews

PubMed

National Library of Medicine

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

There are no competing interests to report.

Funding

Not applicable

Authors' contributions

All authors participated in the study meetings for the planning of this protocol and the formulation of this manuscript.

MLS, AEFC, and EPT conceived the study, developed the criteria and searched the literature, and wrote and register the protocol in PROSPERO. ACRHS, RCTR, IAPC, CMLB, HLC assisted in protocol design, study the support of the literature for suggest tools and performed data analysis. DRB, JFN study references to write the introduction of this protocol. MLS, ZBS reviewed all the authors' suggestions and the journal's norms to compose the manuscript on the protocol. Reading and final review of the manuscript and submission to BMC. All authors read and approved the final manuscript.

Acknowledgements

The authors received no funding for this study.

The authors would like to thank the CAPES/Brazil, for granting the PROEX CAPES Scholarship to Adália Edna Chipindo, Process. 88887.505533 / 2020-00, she is PhD student in the Federal University of Santa Catarina, Graduate Nursing Program (PEN-UFSC), Florianopolis, Santa Catarina, Brazil.

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