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Impact of severe maternal morbidity on adverse perinatal outcomes in high income countries: Systematic review and meta-analysis protocol

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Abstract

Introduction: Serious maternal morbidity (SMM) rates are increasing worldwide both in high-income countries (HIC) as well as in low and middle-income countries (LMIC). SMM is considered a continuum of severity with normal maternal health outcomes at one end and death at the other end of the spectrum. There is evidence that analysis of SMM trends and detailed investigation of factors implicated in these cases provides a good picture of maternal healthcare both in HIC and LMICs. SMM is also associated with poorer perinatal outcomes. Therefore, the aim of this protocol is to describe the proposed methodology for the synthesis and analyses of the data describing the relationship between SMM and adverse perinatal outcomes in a systematic review and meta-analysis.

Methods: This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). English language, peer-reviewed randomized controlled trials, non-randomized controlled trials, prospective and retrospective cohort, case-control and cross-sectional studies conducted in high-income countries where SMM and perinatal outcomes either as a composite or as separate outcomes are reported, will be included. An electronic search of the PubMed, Embase, CINAHL, and Scopus databases will be performed, and two authors will independently review the titles and abstracts and perform data extraction. Where possible, meta-analyses will be done to calculate pooled estimates.

Ethics and dissemination: As this is a protocol for analyses of published data, ethics review and approval is not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

Strengths and limitations of this study

- This systematic review and meta-analysis will adhere to the PRISMA guidelines.
- The systematic review and meta-analysis aims to provide evidence of the relationship between SMM and its impact on perinatal outcomes.
- Two reviewers will screen for eligibility and perform the data extraction with a third reviewer involved when disagreement arises thus ensuring that reviewer bias is minimised.
- It is limited by the inclusion of only English language articles and the lack of a uniform global definition of SMM and adverse perinatal outcomes.

Introduction

Maternal mortality and serious morbidity remain major public health challenges to global healthcare systems.[1] Although the global maternal mortality ratio has declined by 44% between 1990 and 2015,[2-4] low and middle-income countries (LMIC) still account for 99% of maternal deaths with the highest rates seen in South Asia and Sub-Saharan Africa.[2] Overall the leading causes of maternal death are obstetric hemorrhage, hypertension and sepsis. However, as most maternal deaths often have a combination of causes and given that many occur outside of health facilities, determining the precise etiology is frequently challenging. Causes of maternal morbidity vary by region but anaemia, medical co-morbidities particularly hypertension and diabetes mellitus, sepsis and mental health conditions are often implicated. Nevertheless, the true extent of maternal morbidity is not known because of difficulties in definition and ascertainment.[5-8]

Severe maternal morbidity (SMM) is generally defined as an unintended outcome following labour and delivery that results in significant short or long-term consequences to a woman's health. However, there is currently no single widely accepted definition although various organisations have proposed classifications systems of severe morbidity and the components of conditions and complications that constitute these definitions.[9-14] More recently, representatives from the International Network of Obstetric Surveillance Systems (INOSS) from 13 high-income countries (HIC), using a Delphi technique, developed agreed definitions for eight severe maternal morbidity conditions.[15] These include eclampsia, amniotic fluid embolism, pregnancy-related hysterectomy, severe primary postpartum hemorrhage, uterine rupture, abnormally invasive placentation, spontaneous hemoperitoneum in pregnancy, and cardiac arrest in pregnancy. The World Health Organisation's (WHO) Maternal Morbidity Working Group defines maternal morbidity as "any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing".[6] Additionally, the WHO prefers the term "maternal near miss" as a surrogate for SMM. Maternal near miss occurs when a woman develops one or more signs of organ dysfunction based on various clinical, laboratory, or management criteria.[16-18]

Whilst maternal mortality rates has traditionally been used as a benchmark of maternal health there is evidence that it represents only the "tip of the iceberg" [6 19 20] of adverse maternal outcomes with 50-100 women experiencing SMM for every maternal mortality even in a HIC like the United States.[21 22] In contrast, SMM complicates almost 8% of births in LMICs.[23 24] Maternal mortality and SMM are intricately linked as SMM can be considered a near miss for maternal mortality because without identification and treatment, maternal death would ensue.[25] Indeed, in addition to maternal mortality, prevention of SMM is now a major focus in HICs as a means to monitor the quality of maternal health care. The WHO too has recommended that HICs with low maternal mortality rates closely monitor SMM trends to identify preventable causes as well as systems and provider-related failures.[24]

Alongside the consequences to the woman itself, SMM also significantly impacts perinatal outcomes. There is now some evidence that rates of perinatal death, neonatal intensive care unit (NICU) admission, preterm birth, low Apgar scores at 5 minutes and low birth weight correlate with the occurrence of SMM.[26]

Rationale for current systematic review

Whilst there is clear evidence both from HIC and LMICs that SMM significantly contributes to poor maternal health outcomes, the impact on perinatal outcomes is less clear. Therefore, the aim of this systematic review and meta-analysis is to summarise available evidence pertaining to SMM and perinatal outcomes in HICs, and if possible, ascertain pooled estimates of any association. The following criteria will apply:

Population

Pregnant women and their neonates in HICs. HICs is defined by the Word Bank-2017 classification.[27]

Intervention/exposure

Serious maternal morbidity as defined by the WHO potential life threatening/near-miss criteria[18] (Table 1).

Outcomes

Any of the following either in isolation or as a composite measure: preterm birth (<37 weeks gestation), small for gestational age (BW <10th centile for gestation), 5 min-Apgar score < 7, neonatal acidosis, NICU admission, stillbirth, neonatal death (death ≤28 days from birth), perinatal death (stillbirths plus neonatal deaths), hypoxic-ischemic encephalopathy (HIE), periventricular leukomalacia and interventricular haemorrhage. (Table 1)

Methods and design

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[28] and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Objectives

The aim of this systematic review is to ascertain the association between SMM and adverse perinatal outcomes.

Review question

What are the pooled estimates from the published English language literature for the association between SMM and adverse perinatal outcomes?

Inclusion and Exclusion criteria for studies for this review

The eligibility of studies will be determined using the PICOS (Population/participants, Interventions, Comparisons, Outcomes, and Study design) framework.[29] Studies will only be included if they fulfil the following criteria:

Inclusion criteria

- Only studies which report SMM using the WHO near-miss criteria [30] in singleton pregnancies >20 weeks gestation in HICs.

- Peer-reviewed randomized and non-randomized controlled trials, prospective and retrospective cohort, case-control and cross-sectional studies where SMM and perinatal outcomes (either as a composite or as separate outcomes) are reported.
- Studies published in English with no publication year restriction until July 2018 will be included

Exclusion criteria

- Studies that are not in English
- Publications involving women with multiple pregnancy or <20 weeks gestation.
- Systematic reviews, case series/reports, conference papers, proceedings, articles available only in abstract form, editorial reviews, letter of communications, commentaries, studies with small sample size (n <10), qualitative studies and studies done in LMICs.

Search strategy for identifying relevant studies

Bibliographic database search and selection of studies

A systematic search of the following electronic databases will be performed: PubMed, Embase, CINAHL, and Scopus. Key search teams and combinations as detailed in Table 1 will be employed. Searches of the electronic databases will be supplemented by hand-searching the reference lists of included studies to identify further potentially eligible studies. The search will be limited to full-text publications. All citations will be pooled in an EndNote reference library and duplicates will be removed. Studies that assess the impact of SMM on either a single or multiple or a composite of perinatal outcomes will be selected and included. However, studies conducted to assess the effect of management/treatment of SMM on perinatal outcomes will be excluded. Two authors will independently review the titles, abstracts or full text of the screened publications for eligibility for inclusion using the predefined inclusion and exclusion criteria. Where the first two reviewers do not have consensus on eligibility, a third reviewer will be involved. As the objective of this study is to quantify the effect/risk of SMM on perinatal outcomes, only studies which report odds ratio (OR) /relative risk (RR) will be considered.

Data extraction

Two reviewers will independently extract data from the final list of eligible studies. This will include the year and author of the publication, definition of SMM and perinatal outcome, study design, sample size as well crude or adjusted effect estimates.

Assessment of quality and bias

The methodological quality of studies will be assessed using the Newcastle–Ottawa Scale (NOS)[31] independently by two reviewers. This tool consists of three domains; selection, comparability and outcome domains with a maximum of four, two and three-star points respectively. Assessments will be made in three categories: selection of study participants, comparability of study groups and reporting and determination of outcomes. Each study will be graded as per the NOS coding manual and assigned a star rating based on the study fulfilling the specified criteria.[32] Publication bias will be assessed using funnel plots. Where the data permit, meta-analyses will be performed to calculate pooled estimates (with 95% confidence intervals) of the relationship between SMM and perinatal outcomes.

Statistical heterogeneity of studies will be assessed using the Cochran's Q and I^2 statistic.[33] The average effect of SMM on perinatal outcomes will be assessed by random-effects estimation (if heterogeneity $I^2 > 50\%$) or by fixed-effect estimation (if $I^2 < 50\%$).[33 34]

Presenting of results

The study selection process and rationale for inclusion/exclusion will be presented in a PRISMA flow diagram.[28] The characteristics and quality assessment of the included studies will be presented in tables. Pooled estimates will be presented using forest plots with 95% confidence intervals.

Ethics and dissemination

As this is a protocol for analyses of published data, ethics review and approval is not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

Potential limitations

Publication bias is a likely limitation of this review, given that there is inconsistency in the definitions of SMM and adverse perinatal outcome. However, the use of a recent widely accepted definition (WHO near-miss classification) and the use of individual as well as composite perinatal outcomes should somewhat mitigate this limitation. Additionally, confounding is always a major methodological concern in observational studies as numerous confounders such as maternal age, body mass index, mode of conception, smoking, alcohol consumption, medical co-morbidities (diabetes mellitus, hypertension etc.) influence the development of SMM. Furthermore, these variables and others such as mode and gestation at birth and birthweight also adversely influence perinatal outcomes.

Conclusions

This systematic review and meta-analysis will critically evaluate the relationship between SMM and adverse perinatal outcomes in HICs based on this detailed protocol. In HIC, as maternal mortality rates are fortunately low, there is increasing emphasis on interventions and management strategies to reduce not just the maternal burden of serious morbidity but also the concomitant perinatal consequences. We hope that by identifying the associations and quantifying the risks, mitigating strategies can be developed.

Authors' contribution

TSM and SK: conceived and designed the study and drafted the protocol. TSM, JT and SK: developed the search terms and strategy. CF: critically reviewed the protocol. All authors read and approved the final version.

Competing interests

None

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Table 1. Lists of life-threatening maternal conditions (severe maternal morbidity) based on the WHO near-miss criteria and search terms/query

Search terms [to be combined with "OR"]	Perinatal outcome search terms and query
WHO potentially life-threatening/near-miss criteria	"perinatal morbidity"[tiab]
shock, cardiac arrest, use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion, severe acidosis, acute cyanosis, gasping, severe tachypnea, severe bradypnea, intubation and ventilation (non-anaesthetic), severe hypoxemia, oliguria, acute renal failure, acute kidney injury, dialysis, amniotic fluid embolism, pulmonary embolism, deep vein thrombosis, coagulopathy, severe acute thrombocytopenia, acute fatty liver, cholecystitis, intrahepatic cholestasis of pregnancy, liver failure, severe acute hyperbilirubinemia, coma, seizure, stroke, transient ischemic attack, status epilepticus, acute epileptic seizure, cerebrovascular accident, paralysis	OR "adverse outcome"[tiab] OR "neonatal mortality"[tiab] OR "neonatal death" [tiab] OR stillbirth[tiab] OR "fetal death" [tiab] OR "perinatal death" [tiab] OR "perinatal mortality"[tiab] OR "growth restrict*"[tiab] OR "small for gestational age"[tiab] OR "low birthweight"[tiab] OR "preterm birth"[tiab] OR "Apgar score"[tiab] OR "neonatal acidosis"[tiab] OR "NICU admission"[tiab] OR "neonatal intensive care admission"[tiab] OR "hypoxic-ischemic encephalopathy"[tiab] OR "periventricular leukomalacia"[tiab] OR "interventricular haemorrhage"[tiab]
maternal near miss, obstetric near miss, near miss morbidity, obstetric near miss, severe maternal complications, severe maternal morbidity, severe acute maternal morbidity, severe pregnancy complications, intensive care unit admission, blood transfusion	

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Impact of severe maternal morbidity on adverse perinatal outcomes in high income countries: Systematic review and meta-analysis protocol

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Abstract

Introduction: Severe maternal morbidity (SMM) include conditions that are on a continuum of maternal morbidity to maternal death. Rates of SMM are increasing both in high-income countries (HIC) as well as in low and middle-income countries (LMIC). There is evidence that analysis of SMM trends and detailed investigation of factors implicated in these cases, may reflect the standard of maternal healthcare both in HIC and LMICs. SMM is also associated with poorer perinatal outcomes. The aim of this protocol is to describe the proposed methodology for the synthesis and analyses of the data describing the relationship between SMM and adverse perinatal outcomes in a systematic review and meta-analysis.

Methods: This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). Original peer-reviewed epidemiologic/clinical studies of observational (cross-sectional, cohort, case–control) and randomised controlled trial studies conducted in high-income countries will be included. An electronic search of PubMed, Embase, CINAHL, and Scopus databases will be performed without restricting publication date/year. Two authors will independently screen the titles, review abstracts and perform data extraction. Where possible, meta-analyses will be done to calculate pooled estimates.

Ethics and dissemination: As this is a protocol for analyses of published data, ethics review and approval is not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

Strengths and limitations of this study

- This systematic review and meta-analysis will adhere to the PRISMA guidelines.
- The systematic review and meta-analysis aims to provide evidence of the relationship between SMM and its impact on perinatal outcomes.
- Two reviewers will screen for eligibility and perform the data extraction with a third reviewer involved when disagreement arises, thus ensuring that reviewer bias is minimised.
- Ascertaining temporal association between some SMM conditions and adverse perinatal outcomes may be difficult as some of the SMM conditions occur following childbirth.
- The review may be limited by the inclusion of only English language articles and the lack of a uniform global definition of SMM and adverse perinatal outcomes.

Introduction

Severe maternal morbidity (SMM) is generally defined as an unintended outcome following labour and delivery resulting in significant short or long-term consequences to a woman's health. However, despite significant progress, maternal mortality and SMM remain major public health challenges to global healthcare systems.[1] Although the global maternal mortality ratio has declined by 44% between 1990 and 2015,[2-4] low and middle-income countries (LMIC) still account for 99% of maternal deaths with the highest rates seen in South Asia and Sub-Saharan Africa.[2] Maternal death often has multiple causes and most occur outside of health facilities. As a result, determining the precise etiology is frequently challenging. However, a plethora of evidence has shown that obstetric hemorrhage, hypertension and sepsis are leading causes of maternal mortality. Although causes of maternal morbidity vary by region; anaemia, medical co-morbidities particularly hypertension and diabetes mellitus, sepsis and mental health conditions are often implicated.[5-8]

The true burden of SMM is less recognised because of the absence of standardized measurement tools, definition of SMM and ascertainment criteria.[5-8] However, various organisations have proposed classification systems of SMM and corresponding lists of obstetric conditions and complications that constitute these definitions.[9-14] More recently, representatives from the International Network of Obstetric Surveillance Systems (INOSS), from 13 high-income countries (HIC), have developed agreed definitions for eight severe maternal morbidity conditions.[15] These include eclampsia, amniotic fluid embolism, pregnancy-related hysterectomy, severe primary postpartum hemorrhage, uterine rupture, abnormally invasive placentation, spontaneous hemoperitoneum in pregnancy and cardiac arrest in pregnancy. The World Health Organisation's (WHO) Maternal Morbidity Working Group defines maternal morbidity as "any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing".[6] Additionally, the WHO prefers the term "maternal near-miss" as a surrogate for SMM to include women who develop one or more signs of organ dysfunction based on various clinical, laboratory, or management criteria.[16-18]

Whilst maternal mortality rates has traditionally been used as a benchmark of maternal health status, there is evidence that it represents only the "tip of the iceberg" [6 19 20] of adverse maternal outcomes with 50-100 women experiencing SMM for every maternal mortality even in HICs such as the United States.[21 22] In contrast, SMM complicates almost 8% of births in LMICs.[23 24]

SMM is intricately linked with maternal mortality as it can include multiple near-miss conditions leading to maternal death if not properly identified and managed. [25] Indeed, in addition to maternal mortality, prevention of SMM is now a major focus in HICs as a means to monitor the quality of maternal health care. The WHO has recommended that HICs with low maternal mortality rates closely monitor SMM trends to identify preventable causes as well as systems and provider-related failures.[24]

Alongside the consequences to the women's health, SMM also significantly impacts perinatal outcomes. There is emerging evidence suggesting that rates of perinatal death, neonatal intensive care unit (NICU) admission, preterm birth, low Apgar scores at 5 minutes and low birth weight correlate with SMM.[26]

Rationale for current systematic review

Whilst there is evidence both from HIC and LMICs that SMM significantly contributes to poor maternal health outcomes, there has been limited exploration of its impact on perinatal outcomes. Global efforts to improve maternal health mainly focused on reducing maternal death. However, just simply surviving pregnancy and childbirth should not be regarded as the standard benchmark for adequate maternal health outcomes. Hence, planning beyond maternal mortality and directing focused investigation towards the impact of SMM on adverse perinatal outcomes is needed to inform clinical policy and improve healthcare practice.

Objectives

The objective of this systematic review is to ascertain the association between SMM and adverse perinatal outcomes in HICs and summarise available evidence through presenting SMM risk factors of adverse perinatal outcomes, effect estimates/strength and directions of statistical associations to pinpoint the temporal association between SMM and adverse perinatal outcome.

Review question

What is the impact of severe maternal morbidity on adverse perinatal outcomes in HICs?

Methods

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[27] and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Bibliographic database sources and search strategies

A systematic search of PubMed, Embase, CINAHL, and Scopus databases will be performed. Key search terms and combinations as detailed in Table 1 will be employed. Search terms will be flexible and adapted to different electronic databases. The search will be limited to human subject, full-text articles and English language. Reference lists of included citations will be cross-checked to identify further potentially eligible studies. Detailed search strategies for electronic databases will be annexed in the systematic review.

Criteria for considering studies for this review

The eligibility of studies will be determined using the PICOS (Population/participants, Interventions, Comparisons, Outcomes, and Study design) framework.[28]

Inclusion criteria

Studies will only be included if they fulfil the following PICOS criteria:

Population

Pregnant women and their neonates in HICs as defined by the Word Bank-2017 classification.[29]

Intervention/exposure

Severe maternal morbidity (SMM) will be the exposure variable. The list of WHO maternal near-miss conditions [30] will be used to develop search terms. Variant terms and synonymous terminologies of severe maternal morbidity and maternal near-miss will also be used as generic free-text search terms (Table 1).

Outcomes

Any of the following either in isolation or as a composite measure: preterm birth (<37 weeks' gestation), small for gestational age (BW <10th centile for gestation), 5 min-Apgar score < 7, neonatal acidosis, NICU admission, stillbirth, neonatal death (death ≤28 days from birth), perinatal death (stillbirths plus neonatal deaths), hypoxic-ischemic encephalopathy (HIE), periventricular leukomalacia and interventricular haemorrhage.

Study design/type

- Only studies which report the association between SMM (using the WHO near-miss criteria[30]) and adverse perinatal outcomes (either as a composite or separate) in singleton pregnancies >20 weeks' gestation in HICs will be included. The association should be presented as OR/RR estimates or provide sufficient information to calculate risk estimates.
- Studies will include original peer-reviewed epidemiologic/clinical studies of observational (cross-sectional, cohort, case–control) and randomised controlled trial studies.

  Studies published in English with no publication year restriction until July 2018 will be included.

Exclusion criteria

- Studies that are not published in English.
- Publications involving women with multiple pregnancy or births <20 weeks' gestation.
- Studies conducted to assess the effect of management/treatment of SMM on perinatal outcomes.
- Systematic reviews, case series/reports, conference papers, proceedings, articles available only in abstract form, editorial reviews, letter of communications, commentaries, studies with small sample size (n <10), qualitative studies and studies done in LMICs.

Study selection and data extraction

All citations will be pooled to Endnote X7 reference library and duplicates will be removed. Studies that assess the impact of SMM on either a single or multiple or a composite of perinatal outcomes will be screened. Two authors will independently review the titles, abstracts or full text of the screened publications for eligibility using the predefined inclusion and exclusion criteria. Where the first two reviewers do not have consensus on eligibility, a third reviewer will be involved.

Two reviewers will independently extract data from the final list of eligible studies. This will include first author, year of publication, study location, study type/design, data source/setting, study population, sample size, SMM definition, adverse perinatal outcomes, confounders accounted/ adjusted in the

analysis and key findings (effect estimates). Since the objective of this study is to ascertain the effect/risk of SMM on adverse perinatal outcomes, studies which report odds ratio (OR), relative risk (RR) and studies which provide sufficient data to calculate risk estimates will be considered. Only the effect estimates of the main exposure variable (SMM) will be extracted and confounder variables used in selected studies will be presented separately.

Assessment of quality and bias

The methodological quality of studies will be assessed using the Newcastle–Ottawa Scale (NOS)[31] independently by two reviewers. This tool consists of three domains; selection, comparability and outcome domains with a maximum of four, two and three-star points respectively. Each study will be graded out of nine points (separately for case-control and cohort studies) as per the NOS coding manual. Star rating will be performed based on the specified criteria[32] and the overall result will be summarised in three categories as good, fair or poor quality. Publication bias will be assessed using funnel plots.

Data analysis and presenting of results

The study selection process and rationale for inclusion/exclusion will be presented in a PRISMA flow diagram.[27] The characteristics and quality assessment of the included studies will be presented in tables. RevMan Version 5.3 software will be used for data entry and analysis. Where the data permit, meta-analyses will be performed to calculate estimated (with 95% confidence intervals) risk of adverse perinatal outcomes associated with SMM. Statistical heterogeneity of studies will be assessed using the Cochran's Q and I^2 statistic.[33] The average effect of SMM on perinatal outcomes will be assessed by random-effects estimation (if heterogeneity $I^2 > 50\%$) or by fixed-effect estimation (if $I^2 < 50\%$).[33 34]

Ethics and dissemination

As this is a protocol for analyses of published data, ethics review and approval is not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

Patient and public involvement

None

Potential limitations

Publication bias is a likely limitation of this review, given that there are inconsistencies in the definitions of SMM and adverse perinatal outcomes. However, the use of a recent widely accepted definition (WHO near-miss classification) and the use of individual as well as composite perinatal outcomes should somewhat mitigate this limitation. Ascertaining the temporal association between SMM conditions and adverse perinatal outcomes may be difficult as some SMM events occur following childbirth. Additionally, confounding is a major methodological concern in observational studies as numerous confounders for example: maternal age, body mass index, mode of conception, smoking, alcohol consumption, medical co-morbidities (diabetes mellitus, hypertension), mode of delivery, gestation at birth and birthweight may influence SMM and perinatal outcomes.

Conclusions

This systematic review and meta-analysis will critically evaluate the relationship between SMM and adverse perinatal outcomes in HICs based on this detailed protocol. In HIC, as maternal mortality rates are fortunately low, there is increasing emphasis on interventions and management strategies to reduce not just the maternal burden of severe maternal morbidity but also the concomitant perinatal consequences. We hope that by identifying the associations and quantifying the risks, mitigating strategies can be developed.

Protocol amendment

If we need to amend this protocol, we will give the date of each amendment, indicate the amended section, describe the change and give the rationale for amendments in each section.

Funding statement

There are no funders to report for this submission

Authors Contribution

TSM and SK: conceived and designed the study and drafted the protocol. TSM, JT and SK: developed the search terms and strategy. JF and CF: critically reviewed the protocol. All authors read and approved the final version.

Competing interests

None

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Table 1. Lists of life-threatening maternal conditions (severe maternal morbidity) based on the WHO near-miss criteria, search terms/query

Search terms [to be combined with "OR"	Perinatal outcome search terms and query
WHO potentially life-threatening/near-miss criteria shock, cardiac arrest, use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion, severe acidosis, acute cyanosis, gasping, severe tachypnea, severe bradypnea, intubation and ventilation (non-anaesthetic), severe hypoxemia, oliguria, acute renal failure, acute kidney injury, dialysis, amniotic fluid embolism, pulmonary embolism, deep vein thrombosis, coagulopathy, severe acute thrombocytopenia, acute fatty liver, cholecystitis, intrahepatic cholestasis of pregnancy, liver failure, severe acute hyperbilirubinemia, coma, seizure, stroke, transient ischemic attack, status epilepticus, acute epileptic seizure, cerebrovascular accident, paralysis **Generic free-text search terms-Synonymous with 'Severe maternal morbidity'** maternal near miss, obstetric near miss, near miss morbidity, obstetric near-miss, emergency hysterectomy, emergency obstetric hysterectomy, maternal complications, severe maternal morbidity, severe acute maternal morbidity, pregnancy complications, intensive care unit admission, blood transfusion	"perinatal morbidity"[tiab] OR "adverse outcome"[tiab] OR "neonatal mortality"[tiab] OR "neonatal death" [tiab] OR stillbirth[tiab] OR "fetal death" [tiab] OR "perinatal death" [tiab] OR "perinatal mortality"[tiab] OR "growth restrict*"[tiab] OR "small for gestational age"[tiab] OR "low birthweight"[tiab] OR "preterm birth"[tiab] OR "Apgar score"[tiab] OR "neonatal acidosis"[tiab] OR "NICU admission"[tiab] OR "neonatal intensive care admission"[tiab] OR "hypoxic-ischemic encephalopathy"[tiab] OR "periventricular leukomalacia"[tiab] OR "interventricular haemorrhage"[tiab]

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8, 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support:			11
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8,9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8,9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7, 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	---
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	---
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	---
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	---

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Impact of severe maternal morbidity on adverse perinatal outcomes in high income countries: Systematic review and meta-analysis protocol

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Impact of severe maternal morbidity on adverse perinatal outcomes in high income countries: Systematic review and meta-analysis protocol

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Abstract

Introduction: Severe maternal morbidity (SMM) include conditions that are on a continuum of maternal morbidity to maternal death. Rates of SMM are increasing both in high-income countries (HIC) as well as in low and middle-income countries (LMIC). There is evidence that analysis of SMM trends and detailed investigation of factors implicated in these cases, may reflect the standard of maternal healthcare both in HIC and LMICs. SMM is also associated with poorer perinatal outcomes. The aim of this protocol is to describe the proposed methodology for the synthesis and analyses of the data describing the relationship between SMM and adverse perinatal outcomes in a systematic review and meta-analysis.

Methods: This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). Original peer-reviewed epidemiologic/clinical studies of observational (cross-sectional, cohort, case–control) and randomised controlled trial studies conducted in high-income countries will be included. An electronic search of PubMed, Embase, CINAHL, and Scopus databases will be performed without restricting publication date/year. Two authors will independently screen the titles, review abstracts and perform data extraction. Where possible, meta-analyses will be done to calculate pooled estimates.

Ethics and dissemination: As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval is not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

PROSPERO identification number: 130933.

Strengths and limitations of this study

- This systematic review and meta-analysis will adhere to the PRISMA guidelines.
- The systematic review and meta-analysis aims to provide evidence of the relationship between SMM and its impact on perinatal outcomes.
- Two reviewers will screen for eligibility and perform the data extraction with a third reviewer involved when disagreement arises, thus ensuring that reviewer bias is minimised.
- Ascertaining temporal association between some SMM conditions and adverse perinatal outcomes may be difficult as some of the SMM conditions occur following childbirth.
- The review may be limited by the inclusion of only English language articles and the lack of a uniform global definition of SMM and adverse perinatal outcomes.

Introduction

Severe maternal morbidity (SMM) is generally defined as an unintended outcome following labour and delivery resulting in significant short or long-term consequences to a woman's health. However, despite significant progress, maternal mortality and SMM remain major public health challenges to global healthcare systems.[1] Although the global maternal mortality ratio has declined by 44% between 1990 and 2015,[2-4] low and middle-income countries (LMIC) still account for 99% of maternal deaths with the highest rates seen in South Asia and Sub-Saharan Africa.[2] Maternal death often has multiple causes and most occur outside of health facilities. As a result, determining the precise etiology is frequently challenging. However, a plethora of evidence has shown that obstetric hemorrhage, hypertension and sepsis are leading causes of maternal mortality. Although causes of maternal morbidity vary by region; anaemia, medical co-morbidities particularly hypertension and diabetes mellitus, sepsis and mental health conditions are often implicated.[5-8]

The true burden of SMM is less recognised because of the absence of standardized measurement tools, definition of SMM and ascertainment criteria.[5-8] However, various organisations have proposed classification systems of SMM and corresponding lists of obstetric conditions and complications that constitute these definitions.[9-14] More recently, representatives from the International Network of Obstetric Surveillance Systems (INOSS), from 13 high-income countries (HIC), have developed agreed definitions for eight severe maternal morbidity conditions.[15] These include eclampsia, amniotic fluid embolism, pregnancy-related hysterectomy, severe primary postpartum hemorrhage, uterine rupture, abnormally invasive placentation, spontaneous hemoperitoneum in pregnancy and cardiac arrest in pregnancy. The World Health Organisation's (WHO) Maternal Morbidity Working Group defines maternal morbidity as "any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing".[6] Additionally, the WHO prefers the term "maternal near-

miss" as a surrogate for SMM to include women who develop one or more signs of organ dysfunction based on various clinical, laboratory, or management criteria.[16-18]

Whilst maternal mortality rates has traditionally been used as a benchmark of maternal health status, there is evidence that it represents only the "tip of the iceberg" [6 19 20] of adverse maternal outcomes with 50-100 women experiencing SMM for every maternal mortality even in HICs such as the United States.[21 22] In contrast, SMM complicates almost 8% of births in LMICs.[23 24]

SMM is intricately linked with maternal mortality as it can include multiple near-miss conditions leading to maternal death if not properly identified and managed. [25] Indeed, in addition to maternal mortality, prevention of SMM is now a major focus in HICs as a means to monitor the quality of maternal health care. The WHO has recommended that HICs with low maternal mortality rates closely monitor SMM trends to identify preventable causes as well as systems and provider-related failures.[24]

Alongside the consequences to the women's health, SMM also significantly impacts perinatal outcomes. There is emerging evidence suggesting that rates of perinatal death, neonatal intensive care unit (NICU) admission, preterm birth, low Apgar scores at 5 minutes and low birth weight correlate with SMM.[26]

Rationale for current systematic review

Whilst there is evidence both from HIC and LMICs that SMM significantly contributes to poor maternal health outcomes, there has been limited exploration of its impact on perinatal outcomes. Global efforts to improve maternal health mainly focused on reducing maternal death. However, just simply surviving pregnancy and childbirth should not be regarded as the standard benchmark for adequate maternal health outcomes. Hence, planning beyond maternal mortality and directing focused investigation towards the impact of SMM on adverse perinatal outcomes is needed to inform clinical policy and improve healthcare practice.

Objectives

The objective of this systematic review is to ascertain the association between SMM and adverse perinatal outcomes in HICs and summarise available evidence through presenting SMM risk factors of adverse perinatal outcomes, effect estimates/strength and directions of statistical associations to pinpoint the temporal association between SMM and adverse perinatal outcome.

Review question

What is the impact of severe maternal morbidity on adverse perinatal outcomes in HICs?

Methods

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[27]. This protocol was submitted for registration in the International Prospective Register of Systematic Reviews (PROSPERO) (ID: 130933).

Bibliographic database sources and search strategies

A systematic search of PubMed, Embase, CINAHL, and Scopus databases will be performed. Key search terms and combinations as detailed in Table 1 will be employed. Search terms will be flexible and adapted to different electronic databases. The search will be limited to human subject, full-text articles and English language. Reference lists of included citations will be cross-checked to identify further potentially eligible studies. Detailed search strategies for electronic databases will be annexed in the systematic review.

Criteria for considering studies for this review

The eligibility of studies will be determined using the PICOS (Population/participants, Interventions, Comparisons, Outcomes, and Study design) framework.[28]

Inclusion criteria

Studies will only be included if they fulfil the following PICOS criteria:

Population

Pregnant women and their neonates in HICs as defined by the Word Bank-2017 classification.[29]

Intervention/exposure

Severe maternal morbidity (SMM) will be the exposure variable. The list of WHO maternal near-miss conditions [30] will be used to develop search terms. Variant terms and synonymous terminologies of severe maternal morbidity and maternal near-miss will also be used as generic free-text search terms (Table 1).

Outcomes

Any of the following either in isolation or as a composite measure: preterm birth (<37 weeks' gestation), small for gestational age (BW <10th centile for gestation), 5 min-Apgar score < 7, neonatal acidosis, NICU admission, stillbirth, neonatal death (death ≤28 days from birth), perinatal death (stillbirths plus neonatal deaths), hypoxic-ischemic encephalopathy (HIE), periventricular leukomalacia and interventricular haemorrhage.

Study design/type

- Only studies which report the association between SMM (using the WHO near-miss criteria[30]) and adverse perinatal outcomes (either as a composite or separate) in singleton pregnancies >20 weeks' gestation in HICs will be included. The association should be presented as OR/RR estimates or provide sufficient information to calculate risk estimates.

- Studies will include original peer-reviewed epidemiologic/clinical studies of observational (cross-sectional, cohort, case–control) and randomised controlled trial studies.

  Studies published in English with no publication year restriction until July 2018 will be included.

Exclusion criteria

- Studies that are not published in English.
- Publications involving women with multiple pregnancy or births <20 weeks' gestation.
- Studies conducted to assess the effect of management/treatment of SMM on perinatal outcomes.
- Systematic reviews, case series/reports, conference papers, proceedings, articles available only in abstract form, editorial reviews, letter of communications, commentaries, studies with small sample size (n <10), qualitative studies and studies done in LMICs.

Study selection and data extraction

All citations will be pooled to Endnote X7 reference library and duplicates will be removed. Studies that assess the impact of SMM on either a single or multiple or a composite of perinatal outcomes will be screened. Two authors will independently review the titles, abstracts or full text of the screened publications for eligibility using the predefined inclusion and exclusion criteria. Where the first two reviewers do not have consensus on eligibility, a third reviewer will be involved.

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Ethics and dissemination

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Patient and public involvement

Patients nor the public were involved in either the design or planning of this study.

Potential limitations

Publication bias is a likely limitation of this review, given that there are inconsistencies in the definitions of SMM and adverse perinatal outcomes. However, the use of a recent widely accepted definition (WHO near-miss classification) and the use of individual as well as composite perinatal outcomes should somewhat mitigate this limitation. Ascertaining the temporal association between SMM conditions and adverse perinatal outcomes may be difficult as some SMM events occur following childbirth. Additionally, confounding is a major methodological concern in observational studies as numerous confounders for example: maternal age, body mass index, mode of conception, smoking, alcohol consumption, medical co-morbidities (diabetes mellitus, hypertension), mode of delivery, gestation at birth and birthweight may influence SMM and perinatal outcomes.

Conclusions

This systematic review and meta-analysis will critically evaluate the relationship between SMM and adverse perinatal outcomes in HICs based on this detailed protocol. In HIC, as maternal mortality rates are fortunately low, there is increasing emphasis on interventions and management strategies to reduce not just the maternal burden of severe maternal morbidity but also the concomitant perinatal consequences. We hope that by identifying the associations and quantifying the risks, mitigating strategies can be developed.

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Funding statement

No funding has been received for this study from any funding agencies in the public, commercial, or not-for-profit sectors.

Authors Contribution

TSM and SK: conceived and designed the study and drafted the protocol. TSM, JT and SK: developed the search terms and strategy. CF and JF: critically reviewed the protocol. All authors read and approved the final version.

Competing interests

None

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Table 1. Lists of life-threatening maternal conditions (severe maternal morbidity) based on the WHO near-miss criteria, search terms/query

Search terms [to be combined with "OR"	Perinatal outcome search terms and query
WHO potentially life-threatening/near-miss criteria shock, cardiac arrest, use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion, severe acidosis, acute cyanosis, gasping, severe tachypnea, severe bradypnea, intubation and ventilation (non-anaesthetic), severe hypoxemia, oliguria, acute renal failure, acute kidney injury, dialysis, amniotic fluid embolism, pulmonary embolism, deep vein thrombosis, coagulopathy, severe acute thrombocytopenia, acute fatty liver, cholecystitis, intrahepatic cholestasis of pregnancy, liver failure, severe acute hyperbilirubinemia, coma, seizure, stroke, transient ischemic attack, status epilepticus, acute epileptic seizure, cerebrovascular accident, paralysis **Generic free-text search terms-Synonymous with 'Severe maternal morbidity'** maternal near miss, obstetric near miss, near miss morbidity, obstetric near-miss, emergency hysterectomy, emergency obstetric hysterectomy, maternal complications, severe maternal morbidity, severe acute maternal morbidity, pregnancy complications, intensive care unit admission, blood transfusion	"perinatal morbidity"[tiab] OR "adverse outcome"[tiab] OR "neonatal mortality"[tiab] OR "neonatal death" [tiab] OR stillbirth[tiab] OR "fetal death" [tiab] OR "perinatal death" [tiab] OR "perinatal mortality"[tiab] OR "growth restrict*"[tiab] OR "small for gestational age"[tiab] OR "low birthweight"[tiab] OR "preterm birth"[tiab] OR "Apgar score"[tiab] OR "neonatal acidosis"[tiab] OR "NICU admission"[tiab] OR "neonatal intensive care admission"[tiab] OR "hypoxic-ischemic encephalopathy"[tiab] OR "periventricular leukomalacia"[tiab] OR "interventricular haemorrhage"[tiab]

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8, 11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support:			11
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8,9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8,9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7, 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	---
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	---
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	---
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	---

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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