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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) includes conditions that are on a continuum of maternal morbidity to maternal death. Rates of SMM are increasing both in high-income countries (HICs) as well as in low/middle-income countries (LMICs). 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 HICs 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 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 are not required. The findings will be published in peer-reviewed journals and disseminated at scientific conferences.

PROSPERO registration number CRD42019130933.

Strengths and limitations of this study

- This systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines.
- The systematic review and meta-analysis aims to provide evidence of the relationship between severe maternal morbidity (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/middle-income countries (LMICs) 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 mostly occur outside of health facilities. As a result, determining the precise aetiology is frequently challenging. However, a plethora of evidence has shown that obstetric haemorrhage, hypertension and sepsis are leading causes of maternal mortality. Although causes of maternal morbidity vary by region; anaemia, medical comorbidities 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 standardised 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, from 13 high-income countries (HIC), have developed agreed definitions for eight SMM conditions.[15] These include eclampsia, amniotic fluid embolism, pregnancy-related hysterectomy, severe primary postpartum haemorrhage, uterine rupture, abnormally invasive placentation, spontaneous haemoperitoneum in pregnancy and cardiac arrest in pregnancy. The WHO's 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] In addition, 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]

While maternal mortality rates have 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 USA.[21 22] In contrast, SMM complicates almost 8% of births in LMICs.[7 23]

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.[24] 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 healthcare. 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.[7]

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 min and low birth weight (BW) correlate with SMM.[25]

Rationale for current systematic review

While there is evidence both from HICs 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 are 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 SMM 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.[26]

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 population/participants, interventions, comparisons, outcomes, and study (PICOS) design) framework.[27]

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 World Bank 2017 classification.[28]

Intervention/exposure

SMM will be the exposure variable. The list of WHO maternal near-miss conditions[29] will be used to develop search terms. Variant terms and synonymous terminologies of SMM 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-ischaemic encaephalopathy, periventricular leukomalacia and interventricular haemorrhage.

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]

NICU, neonatal intensive care unit.

Study design/type

- Only studies which report the association between SMM (using the WHO near-miss criteria[29]) and adverse perinatal outcomes (either as a composite or separate) in singleton pregnancies >20-week gestation in HICs will be included. The association should be presented as OR/relative risk (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-week 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 OR, 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)[30] 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[31] 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.[26] The characteristics and quality assessment of the included studies will be presented in tables. RevMan V.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% CI) risk of adverse perinatal outcomes associated with SMM. Statistical heterogeneity of studies will be assessed using the Cochran's Q and I^2 statistic.[32] The average effect of SMM on perinatal outcomes will be assessed by random effects estimation (if heterogeneity I^2 >50%) or by fixed effects estimation (if I^2 <50%).[32 33]

ETHICS AND DISSEMINATION

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

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. In addition, 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 comorbidities (diabetes mellitus, hypertension), mode of delivery, gestation at birth and BW 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 SMM 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.

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

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