Primary outcome and outcome measure reporting in randomized trials evaluating treatments for preeclampsia: a systematic review.

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Synopsis:
Randomized trials evaluating treatments for preeclampsia often omit critical information related to their primary outcome, including definition and measurement. A core outcome set is required.

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Abstract

Background: To develop a core outcome set an evaluation of primary outcome and outcome measure reporting is required.

Objectives: To assess primary outcome and outcome measure reporting across randomized trials evaluating treatments for preeclampsia.

Search strategy: We searched Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, EMBASE, MEDLINE, and PsycINFO from inception to January 2016.

Selection criteria: Randomized trials evaluating treatments for preeclampsia.

Data collection and analysis: We systematically extracted and categorized primary outcome and outcome measure reporting.

Main results: Seventy-nine randomized trials, including data from 31,615 maternal participants were included. Thirty-eight trials (48%) reported 35 different primary outcomes, of which 28 were maternal outcomes and seven were offspring outcomes. Three randomized trials reported composite outcomes including between seven and nine outcome components. The method of definition or measurement was infrequently or poorly reported within trial reports. When outcomes were consistently reported across trials, different methods of definition or measurement were frequently described.

Conclusions: Randomized trials evaluating interventions for preeclampsia regularly omit critical information related to their primary outcome, including definition and measurement. Developing a core outcome set for preeclampsia trials should help inform primary outcome and outcome measure selection.

Introduction

Preeclampsia, a pregnancy specific multisystem syndrome, is a common cause of maternal and offspring mortality and morbidity.(1) Interventions capable of reducing this substantial health burden are urgently required. Randomized trials are the best way of establishing the efficacy and safety of new treatments; but are only as credible as their primary outcomes.(2) There is currently no consensus regarding the selection of primary outcomes and methods of definition or measurement for preeclampsia trials.(3) The primary outcome should be the outcome of greatest therapeutic importance to the study's prospective hypothesis.(4) In the absence of a standardized approach, researchers may make arbitrary decisions when selecting between several important outcomes.(5) Within the context of preeclampsia, the requirement to evaluate efficacy and safety within maternal participants and their offspring provides additional complexity. Outcome reporting bias may occur should this selection occur retrospectively based upon statistical significance of the results. (6, 7)

Researchers may need to make pragmatic decisions and select a less informative primary outcome when designing trials, influenced by factors such as sample size requirement, costs, and time.(8) The selection of a composite outcome could increase statistical efficiency because of higher event rates and avoids arbitrary choices between several important outcomes, reflecting the multisystem preeclampsia syndrome.(9) Researchers may be unable to select otherwise appropriate outcomes because of the lack of objective definitions or validated instruments.

The first step in developing a core outcome set for preeclampsia requires an evaluation of primary outcome and outcome measure reporting.(3) Therefore, we assessed the consistency of primary outcome reporting, including the adequacy of information pertaining to definition and measurement, across randomized trials evaluating treatments for preeclampsia.

Materials and methods

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessing study quality, and statistical methods was developed. We have reported the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(10)

A systematic literature review was undertaken searching the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINHAL), MEDLINE, EMBASE, and PsycINFO, from the inception to January 2016 (Appendix S1). Two authors independently screened each potentially relevant record based on title and abstract then reviewed the full text of each selected study to assess eligibility. Discrepancies between the authors were resolved through discussion.

We included randomized controlled trials evaluating the efficacy of any treatment for preeclampsia. We did not exclude trials in mixed populations of antenatal or postnatal participants. We did not exclude trials in mixed populations of participants with preeclampsia and chronic hypertension and / or gestational hypertension. We

applied no restrictions for languages or publication date and translated two trial reports.

Using a pilot-tested and standardized data extraction form, two authors independently extracted study characteristics including participants, interventions, and outcomes. Discrepancies between authors were resolved through discussion. We did not contact authors to clarify primary outcomes or outcome measures which were unclearly reported.

We developed a comprehensive inventory of primary outcomes. If a primary outcome was not explicitly stated, we extracted the outcome included in the study's power calculation. We initially organized outcomes into two broad categories: maternal and offspring outcomes. We subsequently organized these outcomes into individual domains, in consultation with healthcare professionals, researchers, and patients. We used descriptive statistics to characterize our included trials, mapping primary outcomes and their methods of definition or measurement across included trials.

Results

We discovered 10,720 records, after excluding 3,627 duplicate records, 7,093 titles and abstracts were screened, and 162 potentially relevant studies were examined (Figure 1). Seventy-nine randomized trials, reporting data from 31,615 maternal participants, met our inclusion criteria. Nearly half of included trials (38 trials; 48%) reported a primary outcome.(11-48)

Thirty-five different primary outcomes were reported, of which 28 were maternal outcomes and seven offspring outcomes. These outcomes were organized in consultation with health care professionals, researchers, and patients into 16 domains, including five maternal domains and five offspring domains (Table 1).

Primary maternal outcomes more frequently reported included blood pressure (10 trials; 13%), eclampsia (7 trials; 9%), maternal mortality (3 trials; 4%), and pulmonary edema (3 trials; 4%). Primary offspring outcomes were infrequently reported, for example, Offspring mortality was reported by two trials (3%), neonatal respiratory distress syndrome was reported by a single trial (1%), and a single trial (1%) reported neurological development (Table 1).

Three trials (4%) reported composite outcomes (Table 1). The number of components ranged from seven to nine. Two components, maternal mortality and pulmonary edema, was common to all composite outcomes. Only one trial (1%) included an offspring outcome, neonatal repository distress syndrome, within the composite outcomes. The components of the composite outcome did not change in the three trial reports between the abstract, methods, and results. Six trials (8%) reported more than one primary outcome. Three trials (3%) reported more than one primary maternal outcome (range 2-3 outcomes). A single trial (1%) reported two primary offspring outcomes. Two trials (3%) reported primary maternal and offspring outcomes (range 2-3 outcomes).

Thirty-four different methods of definition or measurement were reported (Table 2). Even when outcomes were consistently reported across included trials, different

methods of definition or measurement were described. For example, blood pressure was reported in three different ways: (1) systolic blood pressure; (2) diastolic blood pressure; (3) mean arterial blood pressure.

Discussion

Randomized trials evaluating interventions for preeclampsia regularly omit information pertaining to primary outcomes and outcome measures. Nearly half of included trials explicitly reported a primary outcome. When primary outcomes were consistently reported across trials, different methods of definition or measurement were frequently described. Such variation contributes to an inability to compare, contrast, and combine individual studies and limits the usefulness of research to inform clinical practice.

The strengths of this systematic review include its originality, comprehensive search strategy, methodological design, and statistical analysis. To our knowledge, this is the first systematic review to map primary outcomes and their means of definition and measurement in preeclampsia trials. To prevent bias in the review process, study selection, and data extraction and assessment were conducted independently by two authors. An international steering group, including women with lived experience of preeclampsia, was formed to oversee the study, their input was central to the development of a comprehensive inventory of primary outcomes.

Our empirical evaluation has limitations. We considered those outcomes which were included within a sample size calculation as a primary outcome. The lack of explicit primary outcome in many trials meant that we occasionally mapped outcomes which

were not recorded as primary outcomes within the trial report. We did not contact authors to clarify primary outcomes or outcome measures which appeared unclear. Primary outcomes, especially in earlier phase efficacy trials, may be chosen to reflect the aim of the intervention. We would not necessarily expect the primary outcome for trials of antihypertensives to be the same as anticonvulsants. Examining primary outcome reporting and its relationship with other factors including year of publication, commercial funding, and journal impact factor could provide additional understanding.(49, 50) However, no validated outcome reporting quality assessment tools currently exist, limiting our ability to undertake this analysis.

The Global Pregnancy CoLaboratory, an international collaboration involving key stakeholders including healthcare professionals, researchers, and women with lived experience of preeclampsia, have published a strategy to standardize preeclampsia research study design including data set standards for research studies.(51) Their work reflects the enthusiasm of the pre-eclampsia research community to work together to improve research design and clinical care. The next challenge is to address poor outcome reporting driving outcome reporting bias by developing and implementing core outcome sets.

The Core Outcomes in Women's and Newborn Health (CROWN) initiative has been formed to tackle the challenge of addressing the unwarranted variation in outcome collection and reporting.(52) Participating journals aim to reduce research waste by facilitating consistent reporting of core outcomes.(53) Core outcome sets are minimum collections of outcomes that are predefined, measured in a standardized manner, and reported consistently in the final publication.(54) The outcomes do not

need to be extensive and researchers remain free to measure and report other outcomes. Ideally the primary outcome and outcome measure should be selected from the core outcome set. The Core Outcome Measures for Efficacy Trials (COMET) initiative advocates the development of core outcome sets by groups including healthcare professionals, researchers, and patients. Their development typical includes three broad stages: (1) identifying potential core outcomes; (2) determining core outcomes using robust consensus methods engaging key stakeholders, and (3) determining how core outcomes should be measured.(8, 54) Several consortiums have been established developing core outcome sets across our specialty.(55-57)

An international steering group, including healthcare professionals, researchers, and patients, has been formed to develop a core outcome set for preeclampsia. The inventory of primary outcomes identified by this systematic review has contributed to the long list of outcomes entered into a modified Delphi method. Consensus ‘core’ outcomes for pre-eclampsia have been identified by 283 healthcare professionals, 41 researchers, and 112 patients from 55 countries.(58)

In conclusion, randomized trials evaluating interventions for preeclampsia regularly omit information related to the primary outcome and its definition or measurement. Implementing a core outcome set in future preeclampsia trials should help inform primary outcome and outcome measure selection and facilitate consistent reporting.

Author contributions

Study concept and design: JMD, PRW, KSK, SZ, and RMcM. Acquisition of data: JMD, MH, AK, LP, and MS. Analysis and interpretation of data: JMD, MH, CG, PRW, KSK, SZ, and RMcM. Drafting of the manuscript: JMD, CG, KSK, SZ, and RMcM. Critical revision of the manuscript for important intellectual content: MH, AK, CG, LP, MS, and PRW. Obtained funding: JMD, PRW, KSK, SZ, and RMcM. Administrative, technical, or material support: PRW and MS. Educational supervision: PRW KSK, SZ, and RMcM.

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Conflict of Interest

RM has received blood pressure monitors for research from Omron and Lloyds Pharmacies and expenses and honoraria for speaking from the Japanese Society of Hypertension and the American Society of Nephrology. The remaining authors declare no competing interests.

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