

REVIEW ARTICLE

A systematic review of primary outcomes and outcome measure reporting in randomized trials evaluating treatments for pre-eclampsia ☆

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

Abstract

Background: An evaluation of outcome reporting is required to develop a core outcome set.

Objectives: To assess primary outcomes and outcome measure reporting in pre-eclampsia trials.

Search strategy: Five online databases were searched from inception to January 2016 using terms including “pre-eclampsia” and “randomized controlled trial”.

Selection criteria: Randomized controlled trials evaluating treatments for pre-eclampsia published in any language were included.

Data collection and analysis: Primary outcomes and data on outcome measure reporting were systematically extracted and categorized.

Main results: Overall, 79 randomized trials including data from 31 615 women were included. Of those, 38 (48%) reported 35 different primary outcomes; 28 were maternal outcomes and seven were fetal/neonatal outcomes. Three randomized trials reported composite outcomes, incorporating between six and nine outcome components. The method of definition or measurement was infrequently or poorly reported. Even when outcomes were consistent across trials, different methods of definition or measurement were frequently described.

Conclusions: In randomized trials evaluating interventions for pre-eclampsia, critical information related to the primary outcome, including definition and measurement, is regularly omitted. Developing a core outcome set for pre-eclampsia trials would help to inform primary outcome selection and outcome measure reporting.

1 INTRODUCTION

Pre-eclampsia—a pregnancy-specific multisystem syndrome—is a common cause of maternal and neonatal 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 pre-eclampsia 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 could make arbitrary decisions when choosing among several important outcomes [5]. Within the context of pre-eclampsia, the requirement to evaluate efficacy and safety for the mother and her fetus provides additional complexity. Outcome reporting bias might occur if this selection is made retrospectively on the basis of statistical significance of the results [6,7].

Influenced by factors such as sample size requirement, costs, and time, researchers may need to make pragmatic decisions and select a less informative primary outcome when designing trials [8]. Similarly, researchers may be unable to select otherwise appropriate outcomes owing to a lack of objective definitions or validated instruments. The selection of a composite outcome could increase statistical efficiency owing to higher event rates and can avoid the need to make arbitrary choices among several important outcomes, and would reflect the multisystem nature of pre-eclampsia [9].

The first step in developing a core outcome set for pre-eclampsia requires an evaluation of the reporting of primary outcomes and outcome measures [3]. The aim of the present study was therefore to assess the consistency of primary outcome reporting, including the adequacy of information pertaining to definition and measurement, among randomized trials evaluating treatments for pre-eclampsia.

2 MATERIALS AND METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. A protocol including explicitly defined objectives, study selection criteria, approaches for assessment of study quality, and statistical methods was developed.

The review was undertaken by searching the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINHAL), MEDLINE, EMBASE, and PsycINFO, from their inception to January 31, 2016 (Appendix S1). Two researchers (JMD and AK) independently screened each potentially relevant record on the basis of its title and abstract, and then reviewed the full text of each selected study to assess eligibility. Discrepancies between the two researchers were resolved through discussion.

The studies included in the review were randomized controlled trials evaluating the efficacy of any treatment for pre-eclampsia. Trials in mixed populations of prenatal and postnatal women, or in mixed populations of women with pre-eclampsia and

chronic hypertension and/or gestational hypertension were excluded. There were no restrictions on language or publication date; two trial reports were translated.

Via a pilot-tested and standardized data extraction form, two researchers independently extracted study characteristics, including participants, interventions, and outcomes. Again, discrepancies between the researchers were resolved by discussion. None of the authors of the trials was contacted to clarify primary outcomes or outcome measures that were unclearly reported.

A comprehensive inventory of primary outcomes was developed. If a primary outcome was not stated explicitly, the outcome included in the study's power calculation was extracted. Outcomes were initially organized into two broad categories: maternal outcomes, and fetal/neonatal outcomes. These outcomes were then organized into individual domains after consultation with healthcare providers, researchers, and patients.

Descriptive statistics were used to characterize the trials included in the review, mapping primary outcomes and their methods of definition or measurement across included trials. These data were managed in Microsoft Excel (Microsoft Cooperation, United States).

3 RESULTS

In total, 7093 titles and abstracts were screened, and 162 potentially relevant studies were examined in detail (Figure 1). Seventy-nine randomized trials, reporting data

from 31 615 women, met the inclusion criteria. Nearly half of these trials (38/79, 48%) reported a primary outcome (Appendix S2).

In total, 35 different primary outcomes were reported, of which 28 were maternal outcomes and seven were fetal/neonatal outcomes. These outcomes were organized in consultation with healthcare professionals, researchers, and patients into 10 domains, including five maternal domains and five fetal/neonatal domains (Table 1).

Primary maternal outcomes that were more frequently reported included blood pressure (10/79, 13%), eclampsia (7/79, 9%), maternal mortality (3/79, 4%), and pulmonary edema (3/79, 4%). Primary fetal/neonatal outcomes were infrequently reported: for example, neonatal mortality was reported by 2 (3%) trials, neonatal respiratory distress syndrome was reported by 1 (1%) trial, and neurologic development by 1 (1%) trial (Table 2).

Three (4%) trials reported composite outcomes. The number of components ranged from six to nine. Two components—maternal mortality and pulmonary edema—were common to all composite outcomes. A single trial included a fetal/neonatal outcome (neonatal respiratory distress syndrome) within the composite outcomes. In each of the three trial reports, the components of the composite outcome were the same in the abstract, methods, and results.

Six (8%) trials reported more than one primary outcome. Three (3%) reported more than one primary maternal outcome (range 2–3). One (1%) trial reported two primary

fetal/neonatal outcomes. Two (3%) trials reported primary maternal and fetal/neonatal outcomes (range 2–3).

Thirty-four different methods of definition or measurement were reported (Table 2). Even when outcomes were consistently reported across the trials reviewed, different methods of definition or measurement were described. For example, blood pressure was reported in the following three ways: systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure.

4 DISCUSSION

Randomized trials evaluating interventions for pre-eclampsia were found to regularly omit information pertaining to primary outcomes and outcome measures. Nearly half of trials in the review explicitly reported a primary outcome. When primary outcomes were consistent across trials, different methods of definition or measurement were frequently described. This variation means that individual studies cannot be compared, contrasted, and combined; the usefulness of research to inform clinical practice is limited.

The strengths of the present systematic review include its originality, comprehensive search strategy, and methodologic design. To our knowledge, the present systematic review is the first to map primary outcomes and their means of definition and measurement in pre-eclampsia trials. To prevent bias in the review process, study selection and data extraction and assessment were conducted independently by two researchers. An international steering group, including women with experience of

pre-eclampsia, was formed to oversee the study; their input was central to the development of a comprehensive inventory of primary outcomes.

The empirical evaluation has limitations. Outcomes that were included within a sample size calculation were considered as a primary outcome in the present review. The lack of explicit primary outcome in many trials meant that outcomes that were not recorded as primary outcomes within the trial report were occasionally mapped. Study authors were not contacted to clarify primary outcomes or outcome measures that appeared unclear. Primary outcomes, especially in earlier-phase efficacy trials, might be chosen to reflect the aim of the intervention; for example, the primary outcome for trials of antihypertensive drugs would not necessarily be expected to be the same as that for trials of anticonvulsants. Examining primary outcome reporting and its relationship with other factors including year of publication, commercial funding, and journal impact factor might provide additional understanding [11]; at present, however, no validated tools for quality assessment of outcome reporting exist, limiting the ability to undertake such an analysis.

The Global Pregnancy CoLaboratory an international collaboration involving key stakeholders including healthcare providers, researchers, and women with experience of pre-eclampsia—have published a strategy to standardize pre-eclampsia research study design, including data set standards for research studies [12]. 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, which drives 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 [13]. Participating journals aim to reduce research waste by facilitating consistent reporting of core outcomes [14]. Core outcome sets are minimum collections of outcomes that are predefined, measured in a standardized manner, and reported consistently in the final publication [15]. 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 providers, researchers, and patients. Their development typically includes three stages: first, identifying potential core outcomes; second, determining core outcomes via robust consensus methods among key stakeholders; and third, determining how core outcomes should be measured [8,15]. Several consortiums have been established to develop core outcome sets in the obstetrics specialty [16–18].

An international steering group, including healthcare professionals, researchers, and patients, has been formed to develop a core outcome set for pre-eclampsia. The inventory of primary outcomes identified by this systematic review will contribute to the long list of outcomes entered in a modified Delphi method [19]. Consensus “core” outcomes for pre-eclampsia have been identified by 283 healthcare providers, 41 researchers, and 112 patients from 55 countries.

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

Author contributions

JMD, PRW, KSK, SZ, and RJM contributed to study concept and design. JMD, MH, LP, AK, and MS contributed to acquisition of data. JMD, MH, CG, PRW, KSK, SZ, and RJM analyzed and interpreted the data. JMD, CG, KSK, SZ, and RJM drafted the manuscript. MH, CG, LP, AK, MS, and PRW revised the manuscript for intellectual content. JMD, PRW, KSK, SZ, and RJM obtained funding. MS and PRW provided administrative, technical, or material support. PRW, KSK, SZ, and RJM provided educational supervision. A full description of author contributions is given in Appendix S3.

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International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE)

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Conflicts of interest

RJM has received blood pressure monitors for research from Lloyds Pharmacies and Omron, and expenses and honoraria for speaking from the American Society of Nephrology and the Japanese Society of Hypertension. The other authors have no conflicts of interest.

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