Outcome reporting across randomised controlled trials evaluating therapeutic interventions for pre-eclampsia: a systematic review.

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**Running title:** Outcome reporting in pre-eclampsia trials.

Abstract

**Background:** Standardising outcome collection and reporting in pre-eclampsia trials requires an appraisal of current outcome reporting.

**Objectives:** To map maternal and offspring outcome reporting across randomised trials evaluating therapeutic interventions for pre-eclampsia.

**Search strategy:** Randomised trials were identified by searching bibliographical databases from inception to January 2016.

**Selection criteria:** Randomised controlled trials.

**Data collection and analysis:** We systematically extracted and categorised outcomes reporting.

**Main results:** Seventy-nine randomised trials, reporting data from 31,615 maternal participants and 28,172 of their offspring, were included. Fifty-five different interventions were evaluated. Included trials reported 119 different outcomes, including 72 maternal outcomes and 47 offspring outcomes. Maternal outcomes were inconsistently reported across included trials, for example, 11 (14%) trials reported maternal mortality, reporting data from 12,422 participants (39%), and 16 (20%) trials reported cardiovascular morbidity, reporting data from 14,963 maternal participants (43%). Forty-three (54%) trials reported fetal outcomes and 23 (29%) trials reported neonatal outcomes. Twenty-eight trials (35%) reported offspring mortality. There was poor reporting of childhood outcomes: six trials (8%) reported neurodevelopmental outcomes. Less than half of included trials reported any relevant information regarding harms for maternal participants and their offspring.

**Conclusions:** Most randomised trials evaluating interventions for pre-eclampsia are missing information on clinically important outcomes and in particular have neglected to evaluate efficacy and safety in the offspring of participants. Developing and implementing a minimum core data set, known as a core outcome set, in future pre-eclampsia trials could help to address these issues.

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**Key words:** (1) Core outcome set; (2) Outcome reporting bias; (3) Pre-eclampsia; and (4) Systematic review.

**Tweetable abstract:** Future #preeclampsia research requires a core outcome set to reduce #research waste. @coreoutcomes

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Introduction

Pre-eclampsia is associated with significant maternal and offspring mortality and morbidity, especially in cases where severe features are present.1 Therapeutic interventions which reduce this health burden require robust evaluation.

While much attention has been paid to standardising randomised controlled trial methods, the selection, collection, and reporting of outcomes has been largely overlooked.2 Selecting appropriate outcomes to reflect both beneficial and harmful effects is a critical step in designing randomised trials. Such outcomes need to be relevant to clinical practice and key stakeholders, including patients, healthcare professionals, and researchers. For example, significant maternal morbidity is likely to be important outcomes for all but may not be collected. Evidence synthesis can be limited by different methods of measurement or definition, even when outcomes have been consistently collected across trials. For example, severe pre-eclampsia has been defined using different combinations of blood pressure thresholds, proteinuria thresholds, clinical symptoms, placental parameters, and fetal parameters.1

No consensus regarding a minimum data set currently exists in pre-eclampsia, therefore, we mapped maternal and offspring outcome reporting across randomised trials evaluating therapeutic interventions for pre-eclampsia.

Methods

We developed a protocol with explicitly defined objectives, including criteria for study selection, approaches to assessing study quality, as well as primary and secondary outcomes, and statistical methods. We registered the protocol with PROSPERO: International Prospective Register of Systematic Reviews, registration number CRD42014010641. We followed the reporting guidelines for meta-analyses and systematic reviews of randomised controlled trials, as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.3

Randomised controlled trials were identified by searching: (1) Cochrane Central Register of Controlled Trials, (2) MEDLINE, (3) EMBASE, (4) PsycINFO, and (5) Cumulative Index to Nursing and Allied Health Literature from the inception of the database to January 2016 (Appendix S1 and S2). Two authors independently performed the screening of each potentially relevant record based on title and abstract and independently reviewed the full text of each selected study to assess eligibility. Discrepancies between the authors were resolved through discussion.

We included randomised controlled trials that evaluated the efficacy of therapeutic intervention for pre-eclampsia. We did not exclude trials in mixed populations of antenatal or postnatal patients with chronic hypertension, gestational hypertension or pre-eclampsia. We applied no restrictions for languages or publication date and translated two trial reports.4, 5

Using a standardised data extraction form, two authors independently extracted study characteristics including participants, interventions, and outcomes. Discrepancies between authors were resolved through discussion. A comprehensive inventory of outcomes was developed. We initially organised outcomes into five broad categories: maternal, fetal, neonatal, childhood and other outcomes. We subsequently organised these data into individual domains, in consultation with healthcare professionals, researchers, and patients. The harm domain included adverse events as defined within the British National Formulary. 6 We used descriptive statistics to characterise our included trials, mapping the availability of maternal and offspring outcomes across included trials.

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Results

We discovered 10,720 records. After excluding 3,627 duplicate records, 7,093 titles and abstracts were screened. Two independent reviewers evaluated 162 potentially relevant studies. Seventy-nine randomised trials reporting data from 31,615 maternal and 28,172 of their offspring met our inclusion criteria (Figure 1). 4, 5, 7-90 Included trials evaluated 55 different interventions of which 29 (37%) evaluated antihypertensive medication and 21 (27%) anticonvulsant medication (Table S1). The remaining 29 (37%) trials, evaluated a range of interventions including immediate delivery (six trials), anti-oxidants (six trials), and curettage (two trials). Eleven trials (14%) evaluated post-natal interventions.

Included trials reported 119 different outcomes, of which 72 were maternal outcomes and 47 offspring outcomes. These outcomes were organised in consultation with health care professionals, researchers, and patients into 28 outcome domains, including 15 maternal domains and 13 offspring domains (Figure 2). Included trials inconsistently reported morbidity and mortality outcomes (Table 1). Of the 79 included trials, reporting data from 31,615 maternal participants, 11 trials reported maternal mortality (reporting data from 12,422 (39%) participants); 16 trials reported cardiovascular morbidity (reporting data from 14,963 (43%) participants); and nine trials reported infectious morbidity (reporting data from 11,749 (37%) participants). When considering the largest 25 included trials, rates of eclampsia were reported by 20 trials (80%), renal failure by eight trials (32%), and disseminated intravascular coagulopathy by eight trials (32%) (Table 2).

Twenty-eight trials (35%) reported offspring mortality, reporting data from 25,839 offspring of participants (92%). Forty-three trials (54%), reporting data from 23,848 offspring of participants, reported fetal outcomes, and 23 trials (29%), reporting data from 24,227 of offspring participants (86%), reported neonatal outcomes (Table 1). When considering the largest 25 included trials, intraventricular haemorrhage by six trials (24%), bronchopulmonary dysplasia was reported by two trials (8%), and necrotising enterocolitis by five trials (6%) (Table 2). There was poor reporting of childhood outcomes: six trials, reported neurodevelopmental outcomes reporting data from 18,783 offspring of participants. The longest duration of follow-up was two years.

Twenty-eight trials included no data related to harms from 15,838 maternal participants and 13,438 of their offspring. Three trials performed an economic evaluation.

Discussion

**Main findings**

This systematic evaluation of the literature in pre-eclampsia illustrates widespread variation in the reporting of maternal, fetal, neonatal, and childhood outcomes in randomised trials. Of 79 randomised trials reporting data from 31,615 maternal and 28,172 of their offspring, fewer than 20% reported information on maternal mortality and less than a third reported information on offspring mortality. For childhood outcomes, including long term neurodevelopmental outcomes, less than a tenth of included trials reported any relevant information. Less than half of included trials reported any relevant information related to harms.

**Strengths and limitations**

The strengths of this prospectively registered systematic review include its comprehensive search strategy, methodological design, and statistical analysis. To our knowledge, this is the first systematic review to describe outcome reporting in obstetric trials. In order to prevent bias in the review process, the search was guided and developed by an experienced Cochrane Collaboration information specialist with no limitations (such as language or date restrictions) applied. We translated two trial reports. Study selection, data extraction, and methodological and outcome quality assessment were conducted independently by two authors.

Our empirical evaluation has some limitations. We included only randomised trials and so may have missed infrequent outcomes often reported in observational studies. By undertaking a systematic review of randomised trials, it is challenging to draw any firm conclusions regarding patient preferred outcomes. Further research utilising qualitative research methods, including semi-structured patient interviews, is required. The majority of trials were performed within high-resource settings, if the outcomes were entered into a modified Delphi method to determine a core outcome set, it may be less applicable to middle and low resource settings.

**Interpretation**

Randomised trials can be difficult and expensive to conduct and so there is an ethical imperative to make the best use of them.91 These results suggest a lost opportunity in trials of pre-eclampsia, with only a minority reporting outcomes concerning morbidity and mortality and even fewer considering long term effects for offspring. Such deficits may lead to misleading results if these outcomes differ systematically between trials that do or do not report them.92-94

Over the past three decades, the outlook of pre-eclampsia research has widened, with long term childhood follow up becoming increasingly prioritised by patients, healthcare professionals, and researchers. Few pre-eclampsia trials have followed up offspring participants for sufficiently long to understand the beneficial and harmful effects of experimental interventions. As the importance of assessing long-term outcomes gains increasing momentum, challenging decisions with regards to the selection of long term outcomes, follow-up durations, and methods need to be made. Conducting long term follow up is costly and time consuming for researchers and impacts patients and their families.95 We must be confident that long term follow-up is useful and justified. There is currently no consensus as to which outcomes are most important to measure, which definition or instrument should be used, and whether outcome measures remain valid regardless of the time point of measurement.

Several systematic reviews have highlighted the inconsistency in outcome reporting across obstetrics and gynaecology.96-98 The Core Outcomes in Women’s and Newborn Health (CROWN) initiative (www.crown-intative.org), aims to facilitate consistent recording and reporting of outcomes across 84 journals, working closely with funders, healthcare professionals, researchers, and patients.99 This requires robust methods to identify appropriate outcomes.100 The Core Outcome Measures for Efficacy Trials (COMET) initiative has performed a systematic review of methods for the derivation of core outcome sets across diverse disciplines and suggests 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.101 Several consortiums have been established developing core outcome sets across a broad range of healthcare conditions relevant to women’s health.102, 103

An international steering group, including healthcare professionals, researchers, and patient representatives, has been formed to guide the development of a core outcome set for pre-eclampsia including maternal, offspring, and long term outcomes.104 The inventory of outcomes identified by this systematic review and outcomes identified by analysing in-depth qualitative patient interviews have been entered into a modified Delphi method. Key stakeholders, including healthcare professionals, researchers, and patients have participated in a multi-perspective online Delphi survey.105 The modified Delphi method has encouraged convergence towards consensus ‘core’ outcomes.105, 106 107

Conclusion

Randomised trials evaluating interventions for pre-eclampsia have reported many different outcomes. Most randomised trials evaluating interventions for pre-eclampsia miss information on clinically important outcomes and neglect to evaluate their efficacy and safety in the participants’ offspring, particularly over the long term. Such variations contribute to an inability to compare, contrast, and combine individual studies and limit the usefulness of secondary research to inform shared decision making. Developing and implementing a clinically relevant core data set, in future pre-eclampsia trials could help to address these issues.

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**Conflicts of interest**

R.J.M 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. The ICMJE disclosure forms are available as online supporting information.

**Author contributions**

JMD and MNP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: JMD, PRW, KSK, SZ, RMcM. Acquisition of data: JMD, MH, AK, LP, MS. Analysis and interpretation of data: JMD, MH, CG, MNP, PRW, KSK, SZ, RMcM. Drafting of the manuscript: JMD, CG, KSK, SZ, RMcM. Critical revision of the manuscript for important intellectual content: MH, AK, CG, LP, MNP, MS, PRW. Statistical analysis: MNP. Obtained funding: JMD, PRW, KSK, SZ, RMcM. Administrative, technical, or material support: PRW, MS. Study supervision: JMD, PRW, KSK, SZ, RMcM.

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**References**

1. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014 Apr;4(2):97-104.

2. Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet. 2014;383(9912):166-75.

3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009 Oct;62(10):e1-34.

4. Walss Rodriguez RJ, Flores Padilla LM. Manejo de la preeclampsia severa/eclampsia. Comparacion entre Nifedipina e Hidralazina como medicamentos antihipertensivos. Ginecol Obstet Mex. 1993;61:76-9.

5. Walss Rodriguez RJ, Reyes Levario A. Tratamiento anticonvulsivante de la preeclampsia severa. Comparacion entre diazepam y sulfato de magnesio. Ginecol Obstet Mex. 1992;60:331-5.

6. JointFormularyCommittee. British National Formulary. London, United Kingdom: BMJ Group and Pharmaceutical Press; 2016.

7. Aali BS, Nejad SS. Nifedipine or hydralazine as a first-line agent to control hypertension in severe preeclampsia. Acta Obstet Gynecol Scand. 2002 Jan;81(1):25-30.

8. Adair CD, Luper A, Rose JC, Russell G, Veille JC, Buckalew VM. The hemodynamic effects of intravenous digoxin-binding fab immunoglobulin in severe preeclampsia: a double-blind, randomized, clinical trial. J Perinatol. 2009 Apr;29(4):284-9.

9. Adair CD, Buckalew VM, Graves SW, Lam GK, Johnson DD, Saade G, et al. Digoxin immune fab treatment for severe preeclampsia. Am J Perinatol. 2010 Sep;27(8):655-62.

10. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002 Jun 1;359(9321):1877-90.

11. Yu L, Hey E, Doyle L, Farrell B, Spark P, Altman D, et al. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. BJOG. 2007;114(3):289-99.

12. Amorim MM, Santos LC, Faundes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol. 1999 May;180(5):1283-8.

13. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN, Jr. Postpartum preeclampsia management with furosemide: a randomized clinical trial. Obstet Gynecol. 2005 Jan;105(1):29-33.

14. Atkinson MW, Guinn D, Owen J, Hauth JC. Does magnesium sulfate affect the length of labor induction in women with pregnancy-associated hypertension? Am J Obstet Gynecol. 1995 Oct;173(4):1219-22.

15. Barton JR, Hiett AK, Conover WB. The use of nifedipine during the postpartum period in patients with severe preeclampsia. Am J Obstet Gynecol. 1990 Mar;162(3):788-92.

16. Belfort MA, Moise KJ, Jr. Effect of magnesium sulfate on maternal brain blood flow in preeclampsia: a randomized, placebo-controlled study. Am J Obstet Gynecol. 1992 Sep;167(3):661-6.

17. Belfort MA, Anthony J, Saade GR, Allen JC, Jr. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med. 2003 Jan 23;348(4):304-11.

18. Bolte AC, van Eyck J, Kanhai HH, Bruinse HW, van Geijn HP, Dekker GA. Ketanserin versus dihydralazine in the management of severe early-onset preeclampsia: maternal outcome. Am J Obstet Gynecol. 1999 Feb;180(2):371-7.

19. Broekhuijsen K, van Baaren GJ, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. Lancet. 2015 Jun 20;385(9986):2492-501.

20. Charoenvidhya D, Manotaya S. Magnesium sulfate maintenance infusion in women with preeclampsia: a randomized comparison between 2 gram per hour and 1 gram per hour. J Med Assoc Thai. 2013 Apr;96(4):395-8.

21. Chen FP, Chang SD, Chu KK. Expectant management in severe preeclampsia: does magnesium sulfate prevent the development of eclampsia? Acta Obstet Gynecol Scand. 1995 Mar;74(3):181-5.

22. Chissell S, Botha JH, Moodley J, McFadyen L. Intravenous and intramuscular magnesium sulphate regimens in severe pre-eclampsia. S Afr Med J. 1994 Sep;84(9):607-10.

23. Collaborative Low-dose Aspirin Study in Pregnancy Collaborative (CLASP) Group. A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet. 1994 Mar 12;343(8898):619-29.

24. Collaborative Low-dose Aspirin Study in Pregnancy Collaborative (CLASP) Group. Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. BJOG. 1995;102(11):861-8.

25. Darngawn L, Jose R, Regi A, Bansal R, Jeyaseelan L. A shortened postpartum magnesium sulfate prophylaxis regime in pre-eclamptic women at low risk of eclampsia. Int J Gynaecol Obstet. 2012 Mar;116(3):237-9.

26. Dasgupta S, Ghosh D, Seal SL, Kamilya G, Karmakar M, Saha D. Randomized controlled study comparing effect of magnesium sulfate with placebo on fetal umbilical artery and middle cerebral artery blood flow in mild preeclampsia at >/= 34 weeks gestational age. J Obstet Gynaecol Res. 2012 May;38(5):763-71.

27. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet. 1995;345(8963):1455-63.

28. Ehrenberg HM, Mercer BM. Abbreviated postpartum magnesium sulfate therapy for women with mild preeclampsia: a randomized controlled trial. Obstet Gynecol. 2006 Oct;108(4):833-8.

29. Elatrous S, Nouira S, Ouanes Besbes L, Marghli S, Boussarssar M, Sakkouhi M, et al. Short-term treatment of severe hypertension of pregnancy: prospective comparison of nicardipine and labetalol. Intensive Care Med. 2002 Sep;28(9):1281-6.

30. Elhassan EM, Mirghani OA, Habour AB, Adam I. Methyldopa versus no drug treatment in the management of mild pre-eclampsia. East Afr Med J. 2002 Apr;79(4):172-5.

31. el-Qarmalawi AM, Morsy AH, al-Fadly A, Obeid A, Hashem M. Labetalol vs. methyldopa in the treatment of pregnancy-induced hypertension. Int J Gynaecol Obstet. 1995 May;49(2):125-30.

32. Facchinetti F, Saade GR, Neri I, Pizzi C, Longo M, Volpe A. L-arginine supplementation in patients with gestational hypertension: a pilot study. Hypertens Pregnancy. 2007;26(1):121-30.

33. Fontenot MT, Lewis DF, Frederick JB, Wang Y, DeFranco EA, Groome LJ, et al. A prospective randomized trial of magnesium sulfate in severe preeclampsia: use of diuresis as a clinical parameter to determine the duration of postpartum therapy. Am J Obstet Gynecol. 2005 Jun;192(6):1788-93; discussion 93-4.

34. Friedman SA, Lim KH, Baker CA, Repke JT. Phenytoin versus magnesium sulfate in preeclampsia: a pilot study. Am J Perinatol. 1993 May;10(3):233-8.

35. Ganzevoort W, Rep A, Bonsel GJ, Fetter WP, van Sonderen L, De Vries JI, et al. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia. BJOG. 2005 Oct;112(10):1358-68.

36. Ginosar Y, Nadjari M, Hoffman A, Firman N, Davidson EM, Weiniger CF, et al. Antepartum continuous epidural ropivacaine therapy reduces uterine artery vascular resistance in pre-eclampsia: a randomized, dose-ranging, placebo-controlled study. Br J Anaesth. 2009 Mar;102(3):369-78.

37. Gulmezoglu AM, Hofmeyr GJ, Oosthuisen MM. Antioxidants in the treatment of severe pre-eclampsia: an explanatory randomised controlled trial. BJOG. 1997 Jun;104(6):689-96.

38. Hall DR, Odendaal HJ, Steyn DW, Smith M. Nifedipine or prazosin as a second agent to control early severe hypertension in pregnancy: a randomised controlled trial. BJOG. 2000 Jun;107(6):759-65.

39. Hennessey MH, Rayburn WF, Stewart JD, Liles EC. Pre-eclampsia and induction of labor: a randomized comparison of prostaglandin E2 as an intracervical gel, with oxytocin immediately, or as a sustained-release vaginal insert. Am J Obstet Gynecol. 1998 Nov;179(5):1204-9.

40. Hjertberg R, Faxelius G, Belfrage P. Comparison of outcome of labetalol or hydralazine therapy during hypertension in pregnancy in very low birth weight infants. Acta Obstet Gynecol Scand. 1993 Nov;72(8):611-5.

41. Hladunewich MA, Derby GC, Lafayette RA, Blouch KL, Druzin ML, Myers BD. Effect of L-arginine therapy on the glomerular injury of preeclampsia: a randomized controlled trial. Obstet Gynecol. 2006 Apr;107(4):886-95.

42. Ismail AA, Medhat I, Tawfic TA, Kholeif A. Evaluation of calcium-antagonist (Nifedipine) in the treatment of pre-eclampsia. Int J Gynaecol Obstet. 1993 Jan;40(1):39-43.

43. Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol. 1994 Sep;84(3):354-9.

44. Keiseb J, Moodley J, Connolly CA. Comparison of the efficacy of continuous furosemide and low-dose dopamine infusion in preeclampsia/eclampsia-related oliguria in the immediate postpartum period. Hypertens Pregnancy. 2002;21(3):225-34.

45. Kobayashi T, Terao T, Ikenoue T, Sameshima H, Nakabayashi M, Kajiwara Y, et al. Treatment of severe preeclampsia with antithrombin concentrate: results of a prospective feasibility study. Semin Thromb Hemost. 2003 Dec;29(6):645-52.

46. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009 Sep 19;374(9694):979-88.

47. Laivuori H, Hovatta O, Viinikka L, Ylikorkala O. Dietary supplementation with primrose oil or fish oil does not change urinary excretion of prostacyclin and thromboxane metabolites in pre-eclamptic women. Prostaglandins Leukot Essent Fatty Acids. 1993 Sep;49(3):691-4.

48. Livingston JC, Livingston LW, Ramsey R, Mabie BC, Sibai BM. Magnesium sulfate in women with mild preeclampsia: a randomized controlled trial. Obstet Gynecol. 2003 Feb;101(2):217-20.

49. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med. 1995 Jul 27;333(4):201-5.

50. Mabie WC, Gonzalez AR, Sibai BM, Amon E. A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. Obstet Gynecol. 1987 Sep;70(3 Pt 1):328-33.

51. Magann EF, Martin JN, Jr., Isaacs JD, Perry KG, Jr., Martin RW, Meydrech EF. Immediate postpartum curettage: accelerated recovery from severe preeclampsia. Obstet Gynecol. 1993 Apr;81(4):502-6.

52. Magann EF, Bass JD, Chauhan SP, Perry KG, Jr., Morrison JC, Martin JN, Jr. Accelerated recovery from severe preeclampsia: uterine curettage versus nifedipine. J Soc Gynecol Investig. 1994 Jul-Sep;1(3):210-4.

53. Maia SB, Katz L, Neto CN, Caiado BV, Azevedo AP, Amorim MM. Abbreviated (12-hour) versus traditional (24-hour) postpartum magnesium sulfate therapy in severe pre-eclampsia. Int J Gynaecol Obstet. 2014 Sep;126(3):260-4.

54. Maki M, Kobayashi T, Terao T, Ikenoue T, Satoh K, Nakabayashi M, et al. Antithrombin therapy for severe preeclampsia: results of a double-blind, randomized, placebo-controlled trial. BI51.017 Study Group. Thromb Haemost. 2000 Oct;84(4):583-90.

55. Manorot M, Tongsong T, Khettglang T. A comparison of serum magnesium sulfate levels in pregnant women with severe preeclampsia between intravenous and intramuscular magnesium sulfate regimens: a randomized controlled trial. J Med Assoc Thai. 1996 Feb;79(2):76-82.

56. Mantel GD, Makin JD. Low dose dopamine in postpartum pre-eclamptic women with oliguria: a double-blind, placebo controlled, randomised trial. BJOG. 1997 Oct;104(10):1180-3.

57. Manzur-Verastegui S, Mandeville PB, Gordillo-Moscoso A, Hernandez-Sierra JF, Rodriguez-Martinez M. Efficacy of nitroglycerine infusion versus sublingual nifedipine in severe pre-eclampsia: a randomized, triple-blind, controlled trial. Clin Exp Pharmacol Physiol. 2008 May;35(5-6):580-5.

58. Martinez-Abundis E, Gonzalez-Ortiz M, Hernandez-Salazar F, Huerta-J-Lucas MT. Sublingual isosorbide dinitrate in the acute control of hypertension in patients with severe preeclampsia. Gynecol Obstet Invest. 2000;50(1):39-42.

59. Matthews G, Gornall R, Saunders NJ. A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery. J Obstet Gynaecol. 1997 Jan;17(1):30-2.

60. Meizner I, Paran E, Katz M, Holcberg G, Insler V. Flow velocity analysis of umbilical and uterine artery flow in pre-eclampsia treated with propranolol or pindolol. J Clin Ultrasound. 1992 Feb;20(2):115-9.

61. Moodley J, Norman RJ. Attempts at dietary alteration of prostaglandin pathways in the management of pre-eclampsia. Prostaglandins Leukot Essent Fatty Acids. 1989 Sep;37(3):145-7.

62. Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. Aggressive or expectant management for patients with severe preeclampsia between 28-34 weeks' gestation: a randomized controlled trial. Obstet Gynecol. 1990;76(6):1070-5.

63. Owens MY, Thigpen B, Parrish MR, Keiser SD, Sawardecker S, Wallace K, et al. Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks? J Miss State Med Assoc. 2014 Jul;55(7):208-11.

64. Ragab A, Goda H, Raghib M, Barakat R, El-Samanoudy A, Badawy A. Does immediate postpartum curettage of the endometrium accelerate recovery from preeclampsia-eclampsia? A randomized controlled trial. Arch Gynecol Obstet. 2013 Nov;288(5):1035-8.

65. Roes EM, Raijmakers MT, Boo TM, Zusterzeel PL, Merkus HM, Peters WH, et al. Oral N-acetylcysteine administration does not stabilise the process of established severe preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006 Jul;127(1):61-7.

66. Rossouw HJ, Howarth G, Odendaal HJ. Ketanserin and hydralazine in hypertension in pregnancy--a randomised double-blind trial. S Afr Med J. 1995 Jun;85(6):525-8.

67. Rytlewski K, Olszanecki R, Lauterbach R, Grzyb A, Basta A. Effects of oral L-arginine on the foetal condition and neonatal outcome in preeclampsia: a preliminary report. Basic Clin Pharmacol Toxicol. 2006 Aug;99(2):146-52.

68. Sahin HG, Sahin HA, Kocer M. Induction of labor in toxemia with misoprostol. Acta Obstet Gynecol Scand. 2002 Mar;81(3):252-7.

69. Samangaya RA, Mires G, Shennan A, Skillern L, Howe D, McLeod A, et al. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. Hypertens Pregnancy. 2009 Aug;28(4):369-82.

70. Sanchez-Ramos L, Adair CD, Kaunitz AM, Briones DK, Del Valle GO, Delke I. Calcium supplementation in mild preeclampsia remote from term: a randomized double-blind clinical trial. Obstet Gynecol. 1995 Jun;85(6):915-8.

71. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. Am J Obstet Gynecol. 1999 Oct;181(4):862-6.

72. Sharma R, Mir, S, Rizvi, M, Akthar, S. Efficacy of magnesium sulphate versus phentoin in seizure control and prophylaxis in patients of eclampsia and severe pre-eclampsia. JK Science. 2008;10(4):181-5.

73. Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol. 1987 Sep;70(3 Pt 1):323-7.

74. Sibai BM, Barton JR, Akl S, Sarinoglu C, Mercer BM. A randomized prospective comparison of nifedipine and bed rest versus bed rest alone in the management of preeclampsia remote from term. Am J Obstet Gynecol. 1992 Oct;167(4 Pt 1):879-84.

75. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. Am J Obstet Gynecol. 1994 Sep;171(3):818-22.

76. Staff AC, Berge L, Haugen G, Lorentzen B, Mikkelsen B, Henriksen T. Dietary supplementation with L-arginine or placebo in women with pre-eclampsia. Acta Obstet Gynecol Scand. 2004 Jan;83(1):103-7.

77. Toppozada T, Barakat S, Shaala S, Ismail AA. Management of severe pre-eclampsia with prostaglandin A, a useful therapeutic approach. J Obstet Gynaecol. 1989;9(3):184-8.

78. van Schie DL, de Jeu RM, Steyn DW, Odendaal HJ, van Geijn HP. The optimal dosage of ketanserin for patients with severe hypertension in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2002 May 10;102(2):161-6.

79. Verma R, Lahon K, Tonpay S, Kale VJ, Jain DK. A comparative randomised controlled parallel group study of efficacy and tolerability of labetalol versus methyldopa in the treatment of new onset hypertension during pregnancy. Int J Life Sci Pharma Res. 2012;2(1):23-31.

80. Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC, et al. Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. Eur J Obstet Gynaecol Reprod Biol. 2006;128(1-2):157-62.

81. Vigil-De Gracia P, Reyes Tejada O, Calle Minaca A, Tellez G, Chon VY, Herrarte E, et al. Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. Am J Obstet Gynecol. 2013;209(5):425.e1-8.

82. Wacker JR, Wagner BK, Briese V, Schauf B, Heilmann L, Bartz C, et al. Antihypertensive therapy in patients with pre-eclampsia: A prospective randomised multicentre study comparing dihydralazine with urapidil. Eur J Obstet Gynaecol Reprod Biol. 2006;127(2):160-5.

83. Wichmana K, Karlberga BE, Rydéna G. Metoprolol in the Treatment of Mild to Moderate Hypertension in Pregnancy-Effects on the Mother. Hypertens Pregnancy. 1985;4(2-3).

84. Wide-Swensson DH, Ingemarsson I, Lunell NO, Forman A, Skajaa K, Lindberg B, et al. Calcium channel blockade (isradipine) in treatment of hypertension in pregnancy: a randomized placebo-controlled study. Am J Obstet Gynecol. 1995 Sep;173(3):872-8.

85. Witlin AG, Friedman SA, Sibai BM. The effect of magnesium sulfate therapy on the duration of labor in women with mild preeclampsia at term: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 1997 Mar;176(3):623-7.

86. Simon J, Gray A, Duley L. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial. Bjog. 2006 Feb;113(2):144-51.

87. van Baaren GJ, Broekhuijsen K, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. An economic analysis of immediate delivery and expectant monitoring in women with hypertensive disorders of pregnancy, between 34 and 37 weeks of gestation (HYPITAT-II). Bjog. 2017 Feb;124(3):453-61.

88. Vijgen SM, Koopmans CM, Opmeer BC, Groen H, Bijlenga D, Aarnoudse JG, et al. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). Bjog. 2010 Dec;117(13):1577-85.

89. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at 2 years. Bjog. 2007 Mar;114(3):300-9.

90. Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. CLASP collaborative group. British journal of obstetrics and gynaecology. 1995 Nov;102(11):861-8.

91. Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. Lancet. 2014 Jan 11;383(9912):101-4.

92. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. Bmj. 2010;340:c365.

93. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. Bmj. 2014;349:g6501.

94. Duffy JMN, Bhattacharya S, Herman M, Mol B, Vail A, Wilkinson J, et al. Reducing research waste in benign gynaecology and fertility research. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(3):366-9.

95. Hua M, Wunsch H. Reporting data on long-term follow-up of critical care trials. Thorax. 2016 May;71(5):395-6.

96. Hirsch M, Duffy JMN, Kusznir JO, Davis CJ, Plana MN, Khan KS, et al. Variation in outcome reporting in endometriosis trials: a systematic review. American Journal of Obstetrics & Gynecology.214(4):452-64.

97. Tirlapur SA, Ni Riordain R, Khan KS. Variations in the reporting of outcomes used in systematic reviews of treatment effectiveness research in bladder pain syndrome. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:61-7.

98. Al Wattar BH, Placzek A, Troko J, Pirie AM, Khan KS, McCorry D, et al. Variation in the reporting of outcomes among pregnant women with epilepsy: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2015 Dec;195:193-9.

99. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. BJOG. 2014 Sep;121(10):1181-2.

100. Duffy JMN, McManus RJ. Influence of methodology upon the identification of potential core outcomes. Recommendations for core outcome set developers are needed. BJOG. 2016 Jul 18;123(10):1599.

101. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13:132.

102. Hirsch M, Duffy JMN, Barker C, Hummelshoj L, Johnson NP, Mol B, et al. Protocol for developing, disseminating and implementing a core outcome set for endometriosis. BMJ Open. 2016;6(12).

103. Whitehouse KC, Kim CR, Ganatra B, Duffy JMN, Blum J, Brahmi D, et al. Standardizing abortion research outcomes (STAR): a protocol for developing, disseminating and implementing a core outcome set for medical and surgical abortion. Contraception.

104. Duffy JMN, van ’t Hooft J, Gale C, Brown M, Grobman W, Fitzpatrick R, et al. A protocol for developing, disseminating, and implementing a core outcome set for pre-eclampsia. Pregnancy Hypertension. 2016;6(4):274-8.

105. Duffy J, van ’t Hooft J, Gale C, Brown M, Grobman W, Fitzpatrick R, et al. JP228 A pre-eclampsia core outcome set developed by 283 healthcare professionals, 41 researchers, and 112 patients from 55 countries. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124(S1):151-2.

106. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS medicine. 2011 Jan 25;8(1):e1000393.

107. van 't Hooft J, Duffy JM, Daly M, Williamson PR, Meher S, Thom E, et al. A Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth. Obstet Gynecol. 2016 Jan;127(1):49-58.