Title: Effectiveness of nitric oxide agents in preventing the early onset of pre-eclampsia and possible modification of metabolic factors in high-risk pregnancies: a systematic review protocol

ABSTRACT

Objectives: To determine the effectiveness of nitric oxide agents in modifying the metabolic factors of pre-eclampsia and its effectiveness in preventing the onset of pre-eclampsia in high-risk pregnancies.

Introduction: Pre-eclampsia is a major cause of maternal death during the prenatal and neonatal periods. Nitric oxide is a vasodilator and platelet aggregation inhibitor responsible for the vascular adaptation of the placenta. Although various studies have established that nitric oxide is effective in preventing complications from pre-eclampsia, there is limited evidence to show that administering nitric oxide agents to the high-risk women before 20 weeks' gestation will prevent the onset of pre-eclampsia.

Inclusion criteria: This review will consider randomized controlled trials that compare nitric oxide donors and precursors with a placebo or no intervention on pregnant women (18 to 44 years) with ≤ 20-week gestational age that are at high risk of pre-eclampsia. The primary outcome of interest will be the onset of pre-eclampsia. Secondary outcomes include increased systolic and diastolic blood pressure, elevated asymmetric dimethylarginine levels, decreased endothelial nitric oxide synthase activity, reduced maternal placental vasculature, and abnormal Doppler ultrasound waveforms.

Methods: Data sources will be drawn up from MEDLINE, CINAHL, ProQuest (Health and Medicine) and Web of Science from inception till current date. No language restrictions will be applied in the search strategy. Selected studies will be assessed against the JBI critical

appraisal checklist, and the certainty of evidence and strength of recommendations from findings will also be ascertained.

Systematic review registration number: CRD42018099298

Keywords: Asymmetric dimethylarginine; high-risk pregnancy; nitric oxide; placental growth factor; pre-eclampsia

JBI Evid Synth 2020;18(?):1-8

INTRODUCTION

Pre-eclampsia is a pregnancy-specific condition which affects about 8% of pregnancies.[1] It is the major cause of fetal growth restriction and pre-term birth, which results in infants who are small for gestational age, with increased risk of chronic ill health due to delayed organ development.[2] Other affects include the subsequent financial burdens on health systems both in developed and less-developed nations.[3] Studies have reported predictive factors for pre-eclampsia as primigravida pregnancy, family history of hypertension and pre-eclampsia, diabetes, renal disease, body-mass index (BMI) above 30 kg/m², hormone imbalance, autoimmune disorders such as systemic lupus erythematosus or antiphospholipid syndrome, multiple birth pregnancy, pregnancy interval greater than 10 years, and pregnancy at 40 years and over.[4,5]

Serum concentrations of the proangiogenic maternal placental growth factor (PlGF) have been reported to decrease in the blood five weeks before a diagnosis of pre-eclampsia.[2,5] Alternatively, the antiangiogenic soluble fms-like tyrosine kinase-1 (sFLT-1) known as vascular endothelial growth factor receptor-1 increases with respect to decreased PlGF.[2] The circulating anti-angiogenic protein antagonizes PlGF, which plays a major role in the pathogenesis of pre-eclampsia.[6]

Dastur and Tank[7] earlier hypothesized that there is a likelihood of the disease already progressing when biomarkers become visible, and measures taken at this stage may be inclined towards preventing the outcomes rather than the onset of the syndrome. Likewise, a study by Zeisler *et al*.[8] revealed that there is elevated sFLT-1/PlGF in pregnant women before clinical diagnosis. Kahhale *et al*.[9] further suggested that biomarkers such as circulating PlGF, sFLT-1, and soluble endothelin and pregnancy-associated plasma protein-A in maternal blood differ significantly before 20 weeks' gestation, which makes it possible to predict pre-eclampsia. Therefore, researchers recommend managing clinical conditions that increase the risk of pre-eclampsia before 20 weeks.[5]

Bartsch *et al*.[10] suggested that nulliparity is a common risk factor associated with pre-eclampsia, followed by BMI >30 kg/m², and prior pre-eclampsia. A relationship between nulliparity, Doppler indices, levels of circulating antiangiogenic protein sFLT-1, and placental growth factor PlGF in pre-eclampsia has been well-established. [6] Nulliparous pregnancies have higher circulating sFLT-1 levels and sFLT-1/PlGF ratios than multiparous pregnancies; and this increase/decrease in circulating angiogenic proteins is associated with pre-eclampsia.[6] Although the first-trimester uterine artery Doppler ultrasound is reported to have a low sensitivity for predicting the early onset of pre-eclampsia,[11] Myatt *et al*.[12] suggested that a combination of biomarkers, clinical risk factors, and Doppler ultrasound in the second trimester may be more accurate in predicting pre-eclampsia. This multiple approach may not be applicable in clinical practice due to the expensive nature of the tests; nevertheless, many researchers hold the view that a high uterine artery resistive index is proportional to poor vascular function, which signifies an elevation in sFLT-1.[13] Thus, a combination of these biomarkers could serve as possible predictors of pre-eclampsia.

Owing to the poor knowledge of its pathophysiology, preventive measures of pre-eclampsia are based on established links between reduced placental perfusion due to impaired trophoblast differentiation and invasion of the spiral arteries that results in oxidative stress and thrombophilia from an increased inflammatory response.[14] Proposed interventions are intended to minimize endothelial dysfunction and oxidative stress within the maternal blood vessels, which causes vasoconstriction, platelet activation, thrombosis, and reduced blood supply to the placenta and maternal organs.[2,14] Studies on low-dose aspirin, low molecular weight heparin, calcium, vitamins and nutritional supplementation, antioxidants, magnesium, lifestyle modification, and physical activity show potential benefits in preventing the onset of pre-eclampsia and its complications.[4] However, further research is needed to determine their effectiveness and safety.[15] The benefits of low-dose aspirin for the prophylaxis of hypertension has been a point of contention in recent studies.[16,17]

Nitric oxide is synthesized by a Ca^{2+} dependent endothelial nitric oxide synthase (eNOS) from molecular oxygen and nitrogen from L-arginine.[18] Nitric oxide diffuses into adjacent vascular smooth muscle cells after its synthesis where it increases the second messenger, cyclic guanosine monophosphate, which mediates its effects in the endothelial cells.[9,18] Though there are no recorded teratogenic effects in human, the clinical use of nitric oxide (NO) agents such as glyceryl trinitrate and isosorbide mononitrate are often limited to the prophylaxis of angina.[19] Their mechanism of action and therapeutic application in ischemia provides a basis for research into NO agents for the regulation of blood flow along the placenta. The role of NO in the pathogenesis of pre-eclampsia is linked to its ability to mediate the functions of the endothelium, such as vasodilatation and inhibition of platelet aggregation, which is essential for the vascular adaptation of the placenta and maternal organs in pregnancy,[20] and regulation of blood capillary flow.[9,18]

After conception, epithelial trophoblast is generated on the lining of the placenta, which facilitates the attachment of the fetus to the uterine wall, and decidualization of the endometrium and myometrium.[21] To promote the adaption of the maternal uterine blood vessels, the endovascular trophoblasts also invade the spiral artery, which widens its diameter, thereby minimizing resistance to blood flow and increased placental perfusion.[22] Invasion of the endovascular trophoblast occurs in two waves: the first is the invasion of the decidual segments of spiral arteries between eight and 10 weeks' gestation; and the second with the myometrial segments between 16 and 18 weeks' gestation.[22] Trophoblast invasion is associated with the flow of oxygenated maternal blood through the placenta; therefore, partially modified vessels cause severe damage from oxidative stress and thrombophilia.[21,23] It has been reported that placental oxygenation from trophoblast invasion and transformation of blood vessels is dependent on the oxygen tension and PlGF expression in the placenta.[21,24]

It is now well established that the expression of antiangiogenic factors and invasion of the myometrium by the trophoblast during placentation would be complete by 18 weeks' gestation.[21,22] One possible implication of this is that NO agents may be more beneficial for the prophylaxis of pre-eclampsia if administered before 20 weeks' gestation. Furthermore, a relationship between increased levels of homocysteine, ADMA, PlGF, and sFLT-1 before 16 weeks' gestation and early prediction of pre-eclampsia have also been proposed.[13,24] This could be due to the inhibition of eNOS and possible decrease in NO.

Although preventive interventions that rely on the metabolic progression of the disease look promising, the evidence base is unclear for NO, thus requiring incorporation of further analysis of research into existing treatment protocols for pre-eclampsia. In addition, a study by Bartsch *et al*.[10] shows that clinical risk factors of pre-eclampsia can be diagnosed before 16 weeks' gestation. This indicates the potential for NO agents to modify these risk factors, thereby signifying a cost-effective preventive measure when administered early enough.

In a previous review by Meher and Duley,[25] the NO agent L-arginine was found to show potential benefit in the prophylaxis of pre-eclampsia; however, this study is statistically insignificant due to insufficient trials at that time. Notwithstanding, studies that have not yet been synthesized together and meet the proposed review's inclusion criteria have been identified (Nnate DA, 2018, unpublished data). [26] In addition, the study by Meher and Duley,[25] also evaluated the effectiveness of NO on the complications of pre-eclampsia. However, there is evidence suggesting that NO intervention may be less effective when pre-eclampsia has been diagnosed.[21,22,24] This implies that the administration of NO at this stage in high-risk pregnancies increases the chances of maternal and perinatal morbidity and mortality. This study will aim to investigate the effectiveness of NO agents in preventing the early onset of pre-eclampsia. A preliminary search was conducted in PROSPERO, Cochrane Database, CINAHL, MEDLINE, Google Scholar, and Web of Science, and no existing or in-progress systematic reviews on the topic was identified.

REVIEW QUESTION

Is there evidence that NO agents can prevent the early onset of pre-eclampsia when administered before 20 weeks' gestation by modifying metabolic precursors such as elevated ADMA levels, eNOS activity, placental vascular function, and Doppler ultrasound waveforms?

INCLUSION CRITERIA

Population

This review will consider studies with participants aged 18 to 44 years with ≤ 20-week gestational age at study entry with at least one risk factor from a previous pregnancy (history of pre-eclampsia, eclampsia, intrauterine growth restriction, placental abruption, or stillbirth)

or from current pregnancy (nulliparity or primigravidae, age > 40 years, BMI > 30 kg/m², gestational hypertension, chronic hypertension, pre-pregnancy type I or II diabetes mellitus, chronic kidney disease, or autoimmune diseases such as systemic lupus erythematosus, and antiphospholipid antibody syndrome), family history of pre-eclampsia, multiple pregnancy, or pregnancy interval >10 years. Either one or a combination of any of these risk factors has been recommended to identify women who are at high-risk of developing pre-eclampsia.[4,10] Studies on women with existing pre-eclampsia will be excluded.

Interventions

This study will consider research examining any molecule that mediates the effects of NO in the body, such as nitrate, NO donors (nitroglycerin, also known as glyceryl trinitrate, pentaerythritol tetranitrate, isosorbide mononitrate, isosorbide dinitrate, S-nitroso glutathione and sodium nitroprusside), and NO precursors (L-arginine, L-citrulline). The study will also consider interventions administered within the second trimester and before 20 weeks' gestation. While a specific dosage will not be considered, the intervention must conform with the pharmaceutical reference guideline associated with a study setting such as the National Institute for Health and Care Excellence (NICE) British National Formulary[27] (UK) and Prescribers' Digital Reference (PDR) Drug Information[28] (US).

Comparator

The proposed systematic review will consider studies that compared NO with placebo or no intervention. Studies combining NO alongside other interventions will not be considered to ensure that the observed effects are exclusively a result of NO.

Outcomes

The primary outcome will be the incidence of pre-eclampsia. This review will likewise consider secondary outcomes such as:

i) increased systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg;

ii) elevated asymmetric dimethylarginine (ADMA) levels and endothelial nitric oxide synthase (eNOS) activity, measured by arginine/ADMA ratio (A ratio <1 will signify impaired eNOS activity);

iii) significant changes in placental vascular function from decreased level of pregnancy-associated plasma protein-A and PlGF measured by sFLT-1/PlGF ratio (sFlt-1/PlGF ratio >38 represents a clinical onset of pre-eclampsia)[8];

iv) abnormal uterine artery (UtA) and middle cerebral arteries (MCA) Doppler ultrasound waveforms, such as pulsatility index (PI) and resistive index (RI), mean arterial pressure, systolic/diastolic ratio, peak systolic velocity, end-diastolic velocity, presence of diastolic notching, and cerebroplacental ratio (ratio of MCA PI and UtA PI). The cut-off values for abnormal second trimester Doppler ultrasound waveforms of the UtA and MCA were in accordance with the International Society of Ultrasound in Obstetrics and Gynecology and the Fetal Medicine Foundation. Abnormal waveforms will be described as RI > 95th percentile, PI > 95th percentile (not within the 50th percentile), presence of bilateral notch, MCA PI < 5th percentile, and absent or reverse end-diastolic velocity. Mean systolic/diastolic ratio ≥ 2.7 (average of right and left uterine arteries) will be considered abnormal.[29] A cerebroplacental ratio value < 1 will be regarded as abnormal.[30]

Any reported side effects of NO agents will also be analyzed. Where studies report the early onset of pre-eclampsia along with other outcomes not stated within our inclusion criteria, then only the incidence of pre-eclampsia will be considered for analysis.

Types of studies

This review will consider published randomized control trials that investigate the use of NO agents to prevent the onset of pre-eclampsia. The authors decision to include only RCTs for

the systematic review is aimed at selecting quality experimental studies in order to maintain a high level of evidence base in line with JBI levels of evidence.[31] This is to ensure that included studies meet the ethical requirements for human participants and adhere to the consolidated standards of reporting trials (CONSORT) guidelines as recommended in the JBI critical appraisal checklist for randomized control trials.[32]

METHODS

The protocol is developed in accordance with JBI methodology for systematic reviews of effectiveness evidence.[32]

Search strategy

An initial search on the Cochrane Database was undertaken to identify articles on the topic (Nnate DA, 2018, unpublished data).[26] The second step will involve the development of search strings from an analysis of text words from the title, abstract, and index terms used to describe the articles. This strategy will then be utilized for a full search on MEDLINE from inception (Appendix I) and then adapted for each included information source. The reference lists of included studies will be searched as will reviews and meta-analysis for relevant studies. Titles and abstracts of studies not available in English will be first translated using Google Translate to determine their eligibility. Thereafter, the authors and journal publishers of relevant studies not published in English will be contacted regarding the availability of an English version. However, where none is available, the study will be excluded.

Information sources

Data sources will include MEDLINE via Ovid; CINAHL via EBSCOhost; ProQuest (Health and Medicine) and Web of Science via Clarivate Analytics. Relevant studies will also be extracted from Google Scholar, NICE Evidence search, Health Management Information Consortium, Cochrane CENTRAL, and National Institute for Health Research (NIHR)

journal library. Manual searches will also be carried out on ClinicalTrials.gov and journals related to obstetrics and gynecology. The authors of unpublished studies found in any of the databases that reported similar outcomes of interest will be contacted to ensure the reviewers have access to the most salient literature. Furthermore, characteristics and results of unpublished studies will be recorded within the appendix in case of further updates to the systematic review.

Study selection

Identified citations will be collated and uploaded into EndNote vX9 (Clarivate Analytics, PA, USA). Duplicates will be removed to avoid overestimation of treatment effect. Titles and abstracts of all identified studies from the searched databases will be screened independently by two reviewers against the inclusion and exclusion criteria. The citation details of potentially relevant studies will be entered into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). Any conflict encountered during the initial screening of titles and abstracts will be resolved via discussion between the two authors or through a third reviewer who will perform an additional independent evaluation. The result of each stage of the search will be recorded using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram with the following details: number of studies found, number of duplicates removed, and excluded studies;[33] and reasons for exclusion provided in an appendix in the final systematic review report.

Assessment of methodological quality

The quality of each study will be independently assessed prior to inclusion by two reviewers using the JBI critical appraisal checklist for RCTs.[32] Where studies are rated "no" or "unclear," an agreement will be reached between the authors or with a third reviewer, who

will perform an additional independent evaluation. However, studies that record a "no" to “randomization of participants to treatment groups” will be excluded. Where quality of study is unclear, corresponding authors will be contacted for more details.

Data extraction

Characteristics of included studies will be recorded independently by both reviewers using a standard JBI quantitative data extraction tool.[32] Extracted data will include: study characteristics (name of authors, year of publication, country of origin, objectives, context, description of interventions and study design); participants characteristics (number of participants, BMI, gestational age, and risk factors at enrolment); and study results based on outcomes.

Data synthesis

Studies will, where possible, be pooled with statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as risk ratios (for dichotomous data) or weighted final post-intervention mean differences (for continuous data) and their 95% confidence intervals calculated for analysis. The treatment effect across subgroups of the various nitric oxide agents will be determined; and heterogeneity will be measured by checking if the confidence intervals overlap using the standard Q and I^2 statistic. The pooled effect and variabilities among studies will be analyzed to prevent the likelihood of drawing conclusions from variables that cannot be attributed to chance, and the results represented as forest plots. Statistical analyses will be performed using random effects model.[33] A sensitivity analysis will also be conducted to ascertain how likely the results are to change from the inclusion of studies of lower methodological quality in meta-analyses. In addition, a funnel plot will be generated using JBI SUMARI to assess publication bias if there are 10 or more studies included in a meta-analysis, and statistical tests for funnel plot asymmetry will be performed where appropriate.[30]

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed,[34, 35] and a Summary of Findings will be created using the GRADEPro guideline development tool (McMaster University, ON, Canada). The Summary of Findings will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the Summary of Findings will address the incidence of pre-eclampsia.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening. JAMA. 2017;317(16):1668.

2. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016;387(10022):999–1011.

3. World Health Organization. WHO recommendations non-clinical interventions to reduce unnecessary caesarean sections [Internet]. WHO: 2018 [cited 2020 March 27]. Available from https://www.who.int/reproductivehealth/publications/non-clinical-interventions-to-reduce-cs/en/.

4. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. Clinical guideline CG107 [Internet]. UK; NICE: 2017 [cited 2020 March 27]. Available from:

https://www.nice.org.uk/guidance/cg107/evidence/appendix-a-summary-of-new-evidence-pdf-2736422318.

5. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis and management recommendations for international practice. Pregnancy Hypertens. 2018;72(1):24–43.

6. Bdolah Y, Elchalal U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, et al. Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertens Pregnancy. 2014;33(2):250–9.

7. Dastur AE, Tank PD. The pharmacology of preventing preeclampsia. J Obstet Gynecol India. 2010;60(6):486–93.

8. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. Obstet Gynecol Surv. 2016;71(5):273–4.

9. Kahhale S, Francisco RPV, Zugaib M. Endothelial mechanisms in preeclampsia. In: Da Luz P, Libby P, Laurindo F, Chagas A, editors. Endothelium and cardiovascular diseases: vascular biology and clinical syndromes. 1st ed. Massachusetts: Academic Press; 2018. p. 655–64.

10. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353(i1753).

11. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55 974 women. Ultrasound Obstet Gynecol. 2014;43(5):500–7.

12. Myatt L, Clifton RG, Roberts JM, Spong CY, Wapner RJ, Thorp JM, et al. Can changes in angiogenic biomarkers between the first and second trimesters of pregnancy predict development of pre-eclampsia in a low-risk nulliparous patient population? BJOG. 2013;120(10):1183–91.

13. Maged AM, Saad H, Meshaal H, Salah E, Abdelaziz S, Omran E, et al. Maternal serum homocysteine and uterine artery Doppler as predictors of preeclampsia and poor placentation. Arch Gynecol Obstet. 2017;296:475–82.

14. Myers JE. What are the metabolic precursors which increase the risk of pre-eclampsia and how could these be investigated further. Placenta. 2017;60:110–4.

15. World Health Organization. WHO recommendations on maternal health [Internet]. WHO/MCA/17.10. 2017 [cited 2020 March 27]. Available from: http://apps.who.int/iris/bitstream/handle/10665/259268/WHO-MCA-17.10-eng.pdf?sequence=1.

16. Huang W-Y, Saver JL, Wu Y-L, Lin C-J, Lee M, Ovbiagele B. Frequency of intracranial hemorrhage with low-dose aspirin in individuals without symptomatic cardiovascular disease. JAMA Neurol. 2019;76(8):906-14.

17. Christiansen M, Grove E, Hvas A-M. Primary prevention of cardiovascular events with aspirin: toward more harm than benefit—a systematic review and meta-analysis. Semin Thromb Hemost. 2019;45(5):478=89.

18. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev. 1991;43(2).

19. Joint Formulary Committee. British National Formulary [78]. London: BMJ Group and Pharmaceutical Press. 2019.

20. Maruta E, Wang J, Kotani T, Tsuda H, Nakano T, Imai K, et al. Association of serum asymmetric dimethylarginine, homocysteine, and L-arginine concentrations during early pregnancy with hypertensive disorders of pregnancy. Clin Chim Acta. 2017;475:70–7.

21. Knöfler M, Haider S, Saleh L, Pollheimer J, Gamage TKJB, James J. Human placenta and trophoblast development: key molecular mechanisms and model systems. Cell Mol Life Sci. 2019;1–18.

22. Lyall F, Bulmer JN, Duffie E, Cousins F, Theriault A, Robson SC. Human trophoblast invasion and spiral artery transformation: the role of PECAM-1 in normal pregnancy, preeclampsia, and fetal growth restriction. Am J Pathol. 2001;158(5):1713–21.

23. Jauniaux E, Watson A, Burton G. Evaluation of respiratory gases and acid-base gradients in human fetal fluids and uteroplacental tissue between 7 and 16 weeks' gestation. Am J Obstet Gynecol. 2001;184(5):998–1003.

24. Bian Z, Shixia C, Duan T. First-Trimester Maternal Serum Levels of sFLT-1, PGF and ADMA Predict Preeclampsia. PLoS One. 2015;10(4):e0124684.

25. Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Cochrane database Syst Rev. 2007;(2):CD006490.

26 Nnate DA. A systematic review on the effectiveness of nitric oxide agents in the prevention of preeclampsia and its complications in high-risk pregnancies: research proposal. NM7069 Research, Faculty of Health and Social Care, University of Chester. 2018

27. National Institute for Health and Care Excellence (NICE). NICE British National Formulary (BNF) [internet]. UK: NICE; 2020 [cited 2020 March 27].

https://bnf.nice.org.uk/treatment-summary/nitrates.html.

28. Prescribers' Digital Reference (PDR). Drug information [internet]. USA: PDR; 2020 [cited 2020 March 27]. https://www.pdr.net/browse-by-drug-name.

29. Magriples U. Intrauterine growth restriction. In: Copel JA, D'Alton ME, Feltovich H, Gratacós E, Krakow D, Odibo AO, et al., editors. Obstetric imaging: fetal diagnosis and care. 2nd ed. Elsevier; 2018. p. 466-472.e1.

30. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Vol. 213, American Journal of Obstetrics and Gynecology. Mosby Inc.; 2015. p. 5–15. ***

31. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017.

32. Aromataris E, Munn Z. Chapter 1: JBI Systematic Reviews. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017.

33. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med. 2009;6(7):1–28.

34. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc. 2015;13(3):196–207.

35. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent

approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.

Appendix I: Search strategy

Database: Ovid MEDLINE (R) [1946 to May Week 2 2020], searched 16 May 2020.

Search	**Query**	**Results**
#1	(Nitrate OR "nitric oxide" OR OR arginine OR citrulline OR OR "isosorbide mononitrate" OR "isosorbide dinitrate" OR "glyceryl trinitrate" OR "sodium nitroprusside" OR "nitrosoglutathione" OR "pentaerythritol tetranitrate").mp	298,161
#2	(Pre*eclampsia OR "Chronic hypertension" OR "pregnancy-induced hypertension" OR "impaired utero-placental perfusion").mp	22,660
#3	"Asymmetric dimethylarginine".mp	2,417
#4	(Endothelial growth factor OR placental growth factor).tw,kw.	52,650
#5	Doppler test.mp	101
#6	#3 OR #4 OR #5	55,142
#7	Pregnancy.mp	91,5614
#8	"high*risk pregnancy".mp	3
#9	primigravidae.mp	1,128
#10	nullipar*.mp	11,013
#11	#7 OR #8 OR #9 OR #10	918,673
#12	#2 OR #6 OR #11	972,128

#13	#1 AND #12	11,393
#14	clinical trial* OR "Random* controlled trial*" OR rct*	1,307,294
#15	#13 AND #14	744
No language limits, No limits on date, No limit on age		