



Pharmacological Interventions and Dietary Supplementations to Prevent Preeclampsia: A Systematic Literature Review

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Abstrak

Preeklampsia adalah kelainan kehamilan yang dapat meningkatkan risiko konsekuensi kesehatan jangka panjang bagi ibu dan anak, dan jika tidak diobati dapat menjadi penyebab kematian ibu dan janin. Namun, pengeluaran plasenta adalah satu-satunya penanganan, sehingga pencegahan untuk kondisi ini sangat diperlukan. Penelitian ini bertujuan untuk melakukan tinjauan sistematis tentang efektivitas intervensi farmakologis dan suplementasi diet untuk mencegah preeklampsia. Kami menggunakan MEDLINE dan ProQuest untuk melakukan pencarian sistematis publikasi peer-review tentang pencegahan preeklampsia. Kami memilih studi yang dilakukan pada manusia dan diterbitkan dalam bahasa Inggris dari tahun 2010 hingga 2020, tentang: i) jenis intervensi; ii) kualitas studi dan keterbatasan penelitian. Tiga jenis intervensi farmakologis dan delapan jenis suplementasi diet diidentifikasi. Donor Nitrat Oksida dengan Isosorbide Mononitrate (IMN), dan aspirin telah terbukti efektif, sementara donor Nitric Oxide dengan Pentaerythritol Tetranitrate (PETN), selenium, kalsium, vitamin D, konsentrat minyak ikan kaya DHA, tembaga, fitonutrien, asam folat, vitamin C dan E dan magnesium belum terbukti efektif untuk mencegah preeklampsia. Meskipun semua penelitian menunjukkan kualitas penelitian yang baik, mereka memiliki beberapa keterbatasan. Keterbatasan yang paling umum adalah kurang awalnya pemberian terapi, kurangnya dosis, dan jumlah sampel yang tidak memadai untuk mendeteksi efek yang kecil. Meskipun upaya intervensi telah banyak dilakukan untuk mencegah preeklampsia, namun efeknya tidak besar. Diperlukan lebih banyak penelitian sebelum intervensi dapat diterapkan dalam praktik klinis di lapangan.

Kata kunci: tinjauan pustaka sistematis; intervensi pencegahan; preeklampsia

Abstract

Preeclampsia is a disorder of pregnancy that increases risk for long-term health consequences for both mother and child, and if left untreated is one of the main causes of maternal and fetal mortality. However, delivery of the placenta is the only cure, making prevention options for this condition needed but little consensus exist on their effectiveness. Thus, we conducted a systematic literature review on the effectiveness of pharmacological interventions and dietary supplementations to prevent preeclampsia. We used MEDLINE and ProQuest to conduct a systematic search for peer-review publications on prevention of preeclampsia. We selected studies conducted in human and published in English from 2010 through 2020 on: i) types of interventions; ii) quality of studies and limitations. We selected 22 articles to be reviewed. Three types of pharmacological interventions and eight types of dietary supplementations were identified. Nitric Oxide-donors with Isosorbide Mononitrate (IMN), and aspirin have

been shown to be effective, while selenium, calcium, vitamin D, DHA-rich fish oil-concentrate, copper, phytonutrient, Nitric Oxide-donors with Pentaerythryl Tetranitrate (PETN), folic acid, vitamins C and E and magnesium have not been proved effective to prevent preeclampsia. Although all studies presented good quality of evidence, they had several limitations, the most common limitations are lack of initial therapy, lack of dosage, and inadequate sample size to detect small effect. Despite the growing evidence of treatments to prevent preeclampsia, their effect is not large. More research is needed in the field before prevention treatments are prescribed in clinical settings.

Keywords: *systematic literature review; preventive intervention; preeclampsia*

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INTRODUCTION

Hypertensive disorders have been described as one of the main causes of maternal mortality worldwide (1), especially in low-income and middle-income countries (2). Preeclampsia is one of these disorders and estimated affect 4,6% of all deliveries and ranging from 1.0% in the Eastern Mediterranean (EMRO) Region to 5.6% in the African (AFRO) Region (3).

Preeclampsia is a condition develop during pregnancy and diagnosed by the presentation of high blood pressure and proteinuria. This health disorder imposes risks for both mother and offspring. Preeclampsia is significantly associated with an increased incidence of low birth weight (LBW) and prematurity (4,5), the most common causes of neonatal and infant death.

Preeclampsia can also cause long-term health problems which can affect mother's and baby's quality of life in the future. Mothers who have preeclampsia are at increased risk for developing hypertension, stroke, ischemic heart disease, thromboembolism, type 2 diabetes mellitus and metabolic syndrome (6–10) cardiovascular risk factors were compared between women with a history of HTP (HTP cohort, n = 306. Meanwhile, babies born to mothers who suffered from preeclampsia in their pregnancy have a high risk

for cardiovascular disease, cognitive function disorders, and cerebral palsy in the next phase of life, and are at risk for ischemic heart disease, diabetes mellitus and impaired glucose tolerance if the baby experienced intra Uterine Growth Retardation (IUGR) while in the womb (11–13) but little is known about their long-term health. We hypothesized that pre-eclampsia would lead to an increased risk of cardiovascular disease in the offspring. Methods-We traced 6410 babies born in Helsinki, Finland, from 1934 to 1944. We used the mothers' blood pressure levels and the presence of proteinuria during pregnancy to define pre-eclampsia and gestational hypertension without proteinuria according to modern criteria. Results-Two hundred eighty-four of the pregnancies were complicated by pre-eclampsia (120 with nonsevere and 164 with severe disease.

Given the magnitude of the health complications, preventive measures are needed to decrease the incidence of preeclampsia in pregnant women. Several interventions have been studied to find the effective measures to prevent preeclampsia, among them, the administration of pharmacotherapy (i.e. aspirin) and dietary supplementation (i.e. calcium) were the interventions that showed the most promising

results(14). However, there is no recent study investigating the extent to which researches on both interventions have been conducted. Therefore, in this systematic literature review, we aimed to identify, evaluate and interpret the most recent studies on the use of pharmacological interventions and dietary supplementations for preventing preeclampsia to answer two following questions: 1) What forms of pharmacological interventions and dietary supplementations have been studied to prevent preeclampsia, and how effective are these therapies? 2) What is the quality of the current evidence and the limitation?

MATERIALS AND METHODS

We used the Population, Intervention, Comparison and Outcome (PICO) framework to determine inclusion and exclusion criteria for review. The “population” was defined as pregnant women, either low-risk or high-risk for preeclampsia; “intervention” was defined as pharmacological interventions and dietary supplementations that was given to prevent the occurrence of preeclampsia; “comparison” was placebo or no therapy; and “outcome” was the incidence of preeclampsia.

We selected search terms through two stages. We first searched for articles with keywords relevant to the PICO framework and based on medical subject heading (MeSH). Then, we drew relevant keyword from articles we found in the first stage and combined all keywords with Boolean operators. The final search terms were: (((supplementation OR “prophylactic treatment” OR aspirin OR “nitric oxide” OR “isosorbide mononitrate” OR “multiple micronutrient” OR calcium OR selenium OR “vitamin B6” OR “vitamin D” OR “vitamin C AND E” OR lycopene OR antioxidant)) AND (preeclampsia OR pre-eclampsia OR “gestational hypertensive disorder”)) AND (reduction OR Prevention OR Preventive OR Control OR “disease management” OR management OR treatment)) AND (pregnant OR pregnancy). We used two electronic databases

- MEDLINE and ProQuest - to identify studies meeting the search terms. For inclusion in this systematic literature review, studies had to be: met PICO criteria, conducted in human, used English language, from the last ten years (2010 to 2020) and published in first or second quartile journal based on Scimago Journal Rank (SJR). We found 994 articles from all databases, and after reviewed by researcher from title, abstract and fulltext assessment for eligibility, we obtained 26 selected studies. We appraised the quality of evidence in the selected studies with Joanna Briggs Institute (JBI) tool for Randomized Controlled Trial (RCT) (15) beyond the protein-coding portion, often relies on signals of conservation across species. The Human Accelerated Regions (HARs), and excluded four studies because did not meet 50% of all criteria questioned in that assessment tool. The process of critical appraisal is overviewed in table 1. After excluded by critical appraisal, twenty-two studies were selected to be analyzed and synthesized for the following characteristics: type of intervention, dose, and time administration of the treatment, the criteria and size of the sample, findings, the quality of evidence and limitations of the study. The study selection process is detailed in figure 1.

RESULT AND DISCUSSIONS

Description of the studies

The 22 studies found in this paper were conducted in single centre; Australia (16), United Kingdom (17) as assessed by biomarkers of pre-eclampsia. In a double-blind, placebo-controlled, pilot trial, we randomised 230 primiparous pregnant women to Se (60 µg/d, as Se-enriched yeast, United States of America (18–24), Iran (25), Egypt (26) fetal, and neonatal outcome in both groups. Results: The study group had significant lower incidence of preeclampsia, preterm birth, intrauterine growth restriction and of neonatal admission to the intensive care ($p < 0.05$, Germany (27), Spain (28,29), Uganda (30), and Brazil

Table 1. Critical Appraisal Of The Selected Studies Using Joanna Brigg Institute (JBI) Tool For RCT

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	Total*
Scazzocchio et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	92%
Bakhti et al.	Y	N	Y	N	U	N	U	N	Y	Y	U	Y	Y	46%
Ayala et al.	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	85%
Abramovici et al.	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	85%
Odibo et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	92%
Poon et al.	U	U	Y	U	U	U	U	N	U	Y	U	Y	Y	31%
Rolnik et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	92%
Villa et al.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	92%
Sablok et al.	Y	U	U	U	U	U	Y	Y	N	Y	U	Y	Y	46%
Wen et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	Y	85%
Razik et al.	Y	Y	Y	U	U	U	Y	Y	Y	Y	U	Y	Y	69%
Schleussner et al.	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	85%
Kashanian et al.	Y	Y	Y	Y	Y	Y	Y	N	U	Y	U	Y	Y	77%
Rayman et al.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	92%
Parrish et al.	Y	Y	Y	Y	Y	U	Y	Y	N	Y	U	Y	Y	77%
Zhou et al.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	92%
Kiondo et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	Y	85%
Roberts et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	Y	85%
Xu et al.	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	92%
Abramovici et al.	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y	Y	85%
Kalpdev et al.	Y	N	Y	N	N	U	Y	N	U	Y	U	Y	Y	46%
Cantu et al.	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	85%
Moore et al.	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	85%
McCance et al.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	92%
Hofmeyr et al.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	92%
Araújo et al.	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	84%

Y= Yes, N=No, U=Unclear, * =total percentage of "Yes" answer

(31) and multicentre; Canada, Argentina, Australia, Jamaica, and United Kingdom (32), Canada and Mexico (33), Ireland, Scotland and Northwest England (34)but the effect in women with diabetes is unknown. We aimed to assess whether supplementation with vitamins C and E reduced incidence of pre-eclampsia in women with type 1 diabetes. Methods We enrolled women from 25 UK antenatal metabolic clinics in a multicentre randomised placebo-controlled trial. Eligibility criteria were type 1 diabetes preceding pregnancy, presentation between 8 weeks' and 22 weeks' gestation, singleton pregnancy, and age 16 years or older. Women were randomly allocated in a 1:1 ratio to receive 1000 mg vitamin C and 400 IU vitamin E (α -tocopherol, South Africa, Zimbabwe, and Argentina (35)the effect of calcium supplementation during placentation

is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation and UK, Spain, Italy, Belgium, Germany and Israel (36).

Type of Interventions to Prevent Preeclampsia **Pharmacological interventions**

Ten studies investigated pharmacological interventions to prevent preeclampsia, from which three types of intervention were identified: Aspirin (19–22,28,29,37,38), Pentaerythrityl-tetranitrate (PETN) (27), and isosorbide mononitrate (IMN) (26)fetal, and neonatal outcome in both groups.Results: The study group had significant lower incidence of preeclampsia, preterm birth, intrauterine growth restriction and of neonatal admission to the intensive care ($p < 0.05$. From those interventions, we found

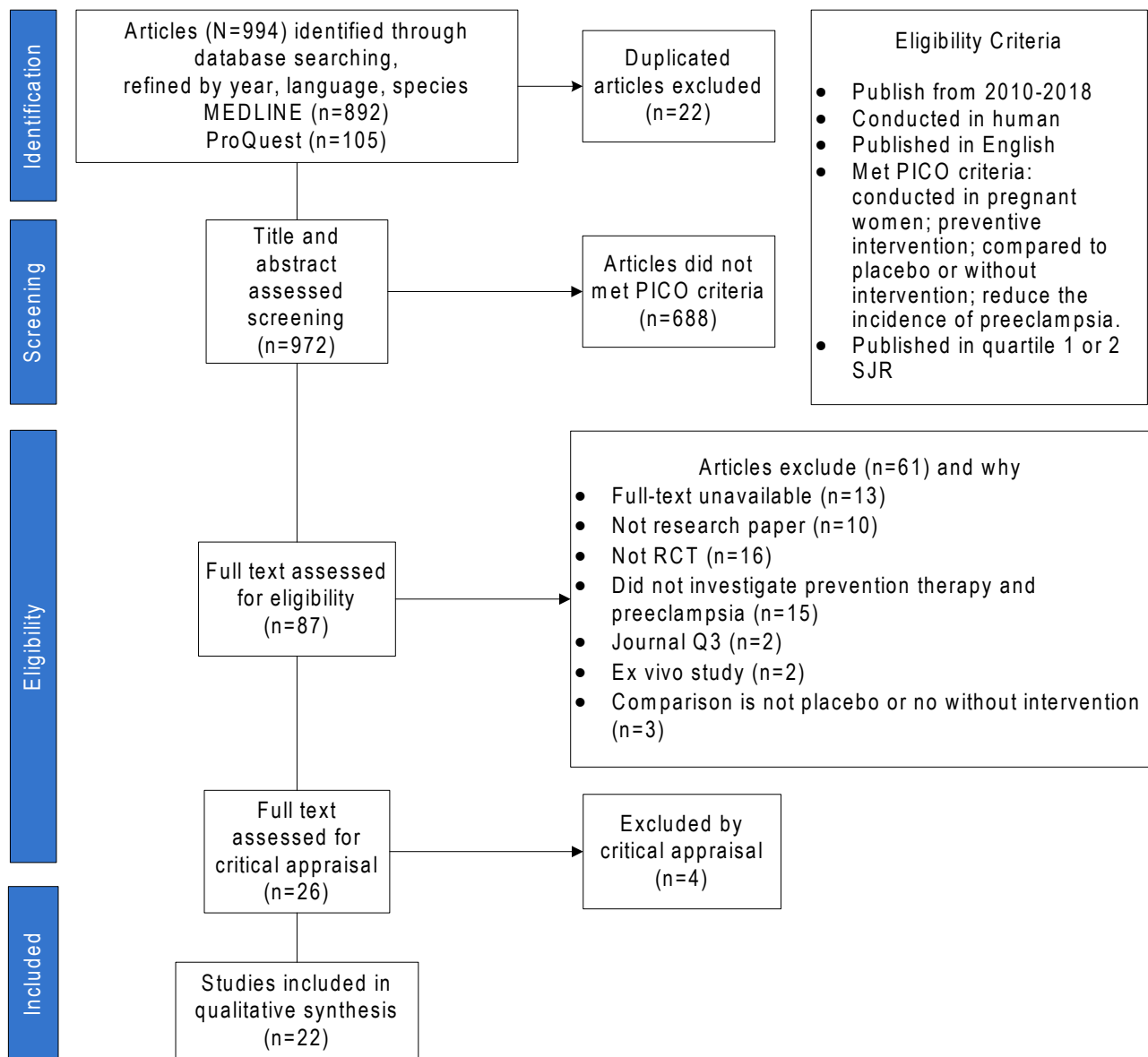


Figure 1. Article selection proces

two treatments associated with a lower risk of preeclampsia that were IMN and aspirin. IMN was found in one study that showed its effectivity to reduce the risk of preeclampsia (RR= 0.14 [0.02–0.75]). Meanwhile, aspirin was found in eight studies, from which one study showed significant effect on reducing preeclampsia (RR= 0.49 [0.25-0.99]) (39), one other study showed significant effect only on preterm preeclampsia (RR= 0.38 [0.20 - 0.74]) but not for preeclampsia in general (37), and the remaining six study showed no significant effect on preeclampsia (19–22,29,38). All interventions were targeted for pregnant women with high risk for preeclampsia

which was characterized by abnormalities in the uterine arteries, or having high risk conditions of causing preeclampsia such as suffered from diabetes mellitus, chronic hypertension, multiple pregnancy, having previous history of preeclampsia and others. The characteristic of each study is detailed in table 2.

Dietary Supplementations

Twelve studies investigated dietary supplementations to prevent preeclampsia, from which ten types of supplementation were identified: calcium (35)the effect of calcium supplementation during placentation is not

Table 2. Pharmacological Intervention To Prevent Preeclampsia In Pregnant Women

Author	Type of intervention, dose and time of administration	Participant, Sample size (Intervention: Control)	Relative Risk (95% CI)	Quality of evidence ^a	Limitation
Ayala, et.al (28)	Aspirin 100mg/d, ≤ 16 WG until delivery	Pregnant women with high risk PE, 176:174	0.41 (0.25 - 0.99) ^b	85%	Lack Information about drop out reason
Villa, et.al (38)	Aspirin 100mg/d, 12 ⁺⁰ -13 ⁺⁶ WG until 35WG	Women with risk factors for PE and abnormal uterine artery based on doppler velocimetry, 61:60	0.7 (0.3 – 1.7)	92%	Small sample size. Did not reveal how doppler ultrasound measurement performed in prediction of pre-eclampsia
Scazzocchio, et.al (29)	Aspirin 150mg/d, 11-14WG until 28WG	Women with abnormal uterine artery based on doppler velocimetry, 75:80	1.25 (0.29 - 5.40)	92%	Participant recruitment was slow. Women declined participation because they wanted to be guaranteed aspirin rather than placebo. The study was not primarily intended to evaluate the efficacy of aspirin in preventing preeclampsia
Cantu et.al (20)	Aspirin 60 mg/d, <16WG until delivery	Women with high-risk PE, 225:236	0.93 (0.67 - 1.31)	85%	Using retrospective data (secondary analysis)
Moore et.al (21)	Aspirin 60 mg/d, <17WG until delivery	Women with high-risk PE, 265:258	0.81 (0.60 - 1.09)	85%	Using retrospective data (secondary analysis) so that could not distinguish potentially relevant outcomes (e.g mild vs severe preeclampsia)
Abramovici, et.al (19)	Aspirin 60 mg/d, 13-26WG until delivery	Smoker pregnant women with high risk PE, 207:214	0.8 (0.51 – 1.26)	85%	Smoking habit was measured only at recruitment, and only rely to self-reported tobacco use
		Non-smoker pregnant women with high risk PE, 1041:1038	0.93 (0.78– 1.10)		
Odibo, et.al (22)	Aspirin 81mg/d, 11 ⁺⁰ -13 ⁺⁶ WG until 37WG	Pregnant women with high risk PE, 16:14	0.88 (0.21– 3.66)	92%	Small sample size. A significant dropout rate (43.3%) occurred
Rolnik, et.al (36)	Aspirin at night 150mg/d, 11 ⁺⁰ -13 ⁺⁶ WG until 36WG	Women with high risk for preterm PE, 878:898	0.95 (0.57– 1.57)	92%	The trial was not adequately powered for preeclampsia as preeclampsia is the secondary outcomes
Razik, et.al (26)	Isosorbide mononitrate (IMN) vaginal tablet 2mg/d, <24WG until delivery	Primigravida, aged 20 years or younger, had a diastolic notch in one or both uterine arteries, 20:20	0.14 (0.02– 0.75) ^b	69%	Small sample size
Schleussner, et.al (27)	Pentaerythrityl-tetranitrate (PETN) 160mg/day, 19 ⁺⁰ -23 ⁺⁶ WG until delivery	Pregnant women with bilateral or unilateral notching and increased mean resistance index more than 90 th percentile, 53:57	0.29 (0.06– 1.48)	85%	Small sample size

WG= week of gestation, PE=Preeclampsia

^a= Assessed using JBI

^b= Statistically significant

Table 3. Dietary Supplementations To Prevent Preeclampsia In Pregnant Women

Author	Type of interventions, dose and time of administration	Participant, Sample size (Intervention: Control)	Relative Risk (95% CI)	Quality of evidence ^a	Limitation
Hofmeyr, et.al (35)	Calcium elemental 500 mg in chewable tablet daily from pre pregnancy randomisation until 20 WG,	Parous women whose recent pregnancy had been complicated by preeclampsia or eclampsia, 296:283	0.80 (0.61–1.06)	92%	The sample size was underpowered to detect small effect, and participant compliance to the intervention was low.
Kashanian, et.al (25)	Copper supplement 1000mg/d, 17WG until delivery	Normal nullipara pregnant women, 127:111	4.32 (0.21 - 89.01)	77%	Preeclampsia was not primary outcome. The incidence of preeclampsia was very few, only 2 in intervention group, and 0 in control group
Zhou, et.al (16)	DHA-rich fish-oil concentrate 1500mg/d, 20WG until delivery	All singleton pregnant women regardless preeclampsia risk factor, 1197:1202	1.03 (0.71 – 1.48)	92%	Initial treatment began in the second half of pregnancy
Wen, et.al (42)	Folic acid 4mg/d, 8-16WG until delivery	Pregnant women with at least one risk factors for PE, 1227:1236	1.10 (0.90 – 1.34)	85%	Did not investigate baseline folic acid values, compliance, and levels during pregnancy in subgroups of high-risk factors for pre-eclampsia
Araújo, et.al (31)	Magnesium citrate capsule 300 mg daily from 12-20 WG until delivery	Low risk pregnant women with low level of magnesium and creatinine serum, 159:159	0.90 (0.48–1.69)	85%	The magnesium serum level after intervention was not evaluated, the sample size was underpowered to detect small effect.
Parrish, et.al (24)	Phytonutrient (7.5mg beta-carbonate, 234mg vitamin C, 30mg Vitamin E, 420mg folat, 60mg calcium) 2 tab/day, 12WG until delivery	Pregnant women without and with high-risk PE, 132:135	0.97 (0.56 – 1.69)	77%	Poor completion rate by the enrolled participants. The majority of those enrolled in both groups were African-American, the results should be interpreted with caution in areas where other ethnicities may be more predominant
Rayman et.al (17)	Selenium-enriched yeast 60µg/d, 12-14WG until delivery	Primiparous women, 115:114	0.42 (0.16-1.09)	92%	The trial was not adequately powered for preeclampsia as the secondary outcomes. Initial treatment was given too late. It may be beneficial if initiated from peri conception period or in early gestation
Kiondo, et.al (30)	Vitamin C 1000mg daily, 12-22WG until delivery	Healthy pregnant women without preeclampsia risk factor, 418:418	0.77 (0.37 – 1.56)	85%	The study was conducted in the national referral hospital in Uganda so that some findings may not be generalized to all pregnant women. The incidence of preeclampsia was lower than was initially anticipated

Xu, et.al (33)	Vitamin C 1000mg and vitamin E 400IU daily, 12-18WG until delivery	Pregnant women without and with high-risk PE, 1167:1196	1.04 (0.75 – 1.44)	92%	The trial was prematurely stopped before reached the initially planned sample size because of increased risk of certain adverse outcomes. 20% of assigned women were lost to follow-up
Roberts, et.al (23)	Vitamin C 1000mg and vitamin E 400IU daily, 9 ⁺⁰ -16 ⁺⁶ WG until delivery	Singleton pregnant women without preeclampsia risk factor, 5087:5065	1.07 (0.93 – 1.24)	85%	Sample may already have had adequate concentrations of vitamins C and E before therapy
McCance, et.al (34)	Vitamin C 1000mg and vitamin E 400IU daily, 8-22WG until delivery	Pregnant women with type 1 diabetes preceding pregnancy, 379:383	0.81 (0.59 – 1.12)	92%	The sample is too homogenous, only women with type I diabetes were recruited. Initial treatment was too late, it might be more effective if the supplementation was introduced before or around conception
Abramovici, et.al (18)	Vitamin C 1000mg and vitamin E 400IU daily, 9 ⁺⁰ -16 ⁺⁶ WG until delivery	Smoker nulliparous women with low risk PE, 763:788 Non-smoker nulliparous women with low risk PE, 4213:4205	1.15 (0.81 – 1.65) 1.06 (0.90 – 1.24)	92%	The large proportion of women identified as smokers smoked fewer than five cigarettes per day may contributed to the result. Smoking habit was measured only at recruitment.

WG= week of gestation, PE=Preeclampsia

^a= Assessed using JBI

known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation, copper (25), DHA-rich fish-oil concentrate (16), folic acid (40), phytonutrient (24), selenium (17) as assessed by biomarkers of pre-eclampsia. In a double-blind, placebo-controlled, pilot trial, we randomised 230 primiparous pregnant women to Se (60 µg/d, as Se-enriched yeast, magnesium (31) and vitamin C and E (18,23,30,33,34,41) placental abruption and low birthweight. We evaluated the relationship between prenatal Vitamin C and E (C/E. None of those supplementations were associated with a lower risk of preeclampsia. Two studies targeted singleton pregnant women without preeclampsia risk factor (23,30), three studies targeted all pregnant women regardless preeclampsia risk factors (16,24,33), and the remaining studies targeted pregnant women

with at least one of preeclampsia risk factor. The characteristic of each study is detailed in table 3.

Quality of evidence and limitation.

The quality of the study was assessed using Joanna Brigg Institute (JBI) tool for RCT. Nine studies had very good quality with the fulfilment of all criteria in that assessment tool reached 92 % (17,29,34–36,43–46)PFMC and maximum Valsalva. Results were then compared between women who were able to use vaginal pessary for 1 year and those whose pessary was expelled within 1 year. Results: The dataset of 255 women were analyzed with 147 (57.6%, and the remaining studies fulfilled 85% (18,30,32,47–49) placental abruption and low birthweight. We evaluated the relationship between prenatal Vitamin C and E (C/E, 77% (24,39,50) and 62% (26) fetal, and neonatal outcome in both

groups. Results: The study group had significant lower incidence of preeclampsia, preterm birth, intrauterine growth restriction and of neonatal admission to the intensive care ($p < 0.05$).

We found several limitations in the selected studies. Half of all studies did not report adverse events or side effect of treatment (18,24,26,29,39,45,47,51). Five studies had small sample size that inadequate to detect small effect size (22,26,27,29,38). Four studies investigated preeclampsia as the secondary outcome so that underpowered to detect the effect of intervention on preeclampsia (17,25,29,37). Two studies was assumed using lack dose of treatment (52,53), and two studies was late in initial administration (16,34).

Discussion

This SLR found two interventions that have been proven to reduce the risk of preeclampsia. Those interventions were aspirin (37,39) and Isosorbide mononitrate (IMN) (26) fetal, and neonatal outcome in both groups. Results: The study group had significant lower incidence of preeclampsia, preterm birth, intrauterine growth restriction and of neonatal admission to the intensive care ($p < 0.05$, both of which were included in pharmacotherapy category. While Isosorbide mononitrate (IMN) was only found in one study that had moderate evidence quality, aspirin was found to be effective in two studies that had high verification quality (38,40). However, one study from aspirin found that aspirin was only effective for preterm preeclampsia (preeclampsia that occurs before the 37-week study), but not for preeclampsia in general (38). According to the sample, both interventions were targeted to pregnant women with high risk for preeclampsia.

In IMN study, the risk of preeclampsia was confirmed by the presence of a diastolic notch in one or both uterine arteries in Doppler velocity waveform examination which indicated an increased resistance in the uterine arteries

(15). The vasodilator effect produced by IMN was considered to decrease the resistance and increase the utero-placental circulation. In addition, the release of NO generated by IMN administration was also known to inhibit platelet aggregation in blood vessels (54). Therefore, IMN was believed to give protective effect on preeclampsia in women with abnormal utero-placental circulation. This study was a pilot study that had moderate quality of evidence for RCT, as the participants, those delivering the treatments and the assessors were not blinded to the treatment and only involved 20 participants in each arm. More recent study investigating the effect of IMN on preeclampsia prevention had been conducted and showed different result with this study (55). That study used more robust research method with double-blinded RCT and larger sample size with 50 pregnant women in each arm, but did not investigate preeclampsia as a separate outcome variable from hypertensive disorders. In addition, that study did not administered IMN as single therapy to prevent preeclampsia, but was an extra therapy beside aspirin prophylaxis that given for all participants in both arms.

There were eight studies in this SLR that investigated the effect of aspirin on preeclampsia prevention, but only two studies showed favourable result. Aspirin was chosen as preventive therapy for preeclampsia in pregnant women with high risk preeclampsia because it could reverse the imbalance of Thromboxane A₂ / Prostaglandin I₂ (TXA₂ / PGI₂) which usually occurs in pregnant women with high risk for preeclampsia without changing the PGI₂ secretion so that beneficial for the systemic vasodilation. TXA₂ was a platelet product that is responsible for vasoconstriction, induction of vascular remodelling, and increasing platelet aggregation and adhesion while PGI₂ was in the opposite way. In addition, aspirin in hypoxic conditions can also inhibit sFIT-1 which plays a

role in the process of vascular endothelial cell dysfunction (56). The finding that the majority of the studies showed insignificant effect of aspirin on preeclampsia in this SLR was accordance with a systematic review which stated that administering aspirin with a dose of ≥ 100 mg per day in pregnant women with gestational age ≤ 16 weeks can reduce the risk of preterm preeclampsia, but not for term preeclampsia (Roberge, Bujold, & Nicolaides, 2018).

In contrast to above two pharmacological interventions, donor nitric oxide in the form of pentaerythryl-tetranitrate showed no significant effect on preeclampsia (RR= 0.29 [0.06–1.48]) (27). Nitric oxide is identified as the dominant vasodilation substance produced by endothelium in response to mechanical and chemical stimuli which causes relaxation of vascular smooth muscle cells(57). However, a review from cochrane library also stated that there is insufficient evidence to draw reliable conclusions about whether NO could prevent preeclampsia (58).

None of dietary supplementations in this SLR that showed a significant effect on preeclampsia prevention. Calcium supplementation that was given pre pregnancy until 20 weeks gestation did not show significant effect on preeclampsia (RR= 0.80 [0.61–1.06]) (35) the effect of calcium supplementation during placentation is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation. That result was not significant might because all participants in the intervention and control groups received higher dose of calcium after 20 weeks gestation until delivery that have more effect on preeclampsia. Cochrane systematic review revealed that high doses of calcium (g1 g per day) in women with low calcium diets could reduce the incidence of preeclampsia (RR = 0.45 [CI 0.31-0.65]) (59). The rationale was calcium could prevent endothelial cell activation

caused by trophoblastic debris from the ischemic placenta (60).

Copper was also showed not effective to prevent preeclampsia (RR= 4.32 [0.21 - 89.01]) (25). A meta-analysis study concluded that higher copper concentrations in plasma serum were significantly associated with an increased risk of preeclampsia, but not so with the Cu / Zn ratio (61). Another study revealed that copper itself (which does not bind to any compound) had a pro-redox effect that can trigger oxidative stress causing preeclampsia, but it turned out to provide a protective effect against radicals (antioxidants) if it was compounded with zinc in the form of zinc-superoxide dismutase (62). Therefore, it can be concluded that supplementation of copper alone cannot provide preventive effect in preeclampsia.

Two studies investigated folic acid also did not show a significant effect on the prevention of preeclampsia (RR= 1.10 [0.90 – 1.34]). In theory, folic acid can prevent preeclampsia through the homocysteine pathway (63). Folic acid had been shown to reduce blood homocysteine levels (hyperhomocysteinemia). While, Hyperhomocysteinemia can result in oxidative stress, endothelial dysfunction and thrombosis that can cause preeclampsia (64). Other studies show mixed results with both of those studies in this SLR (65) (66) (67).

LCPUFA also did not show significant effect on the incidence of preeclampsia (RR=1.03 [0.71 – 1.48]) (16), even though a study revealed that LCPUFA has a modulating effect on inflammatory and vascular functions, which very important in the process of preeclampsia (16). LCPUFA is also known from other study to have anti-thrombotic effects and can cause endothelial relaxation (68). A review written by Burchakov, et.al (2017), reveals that there were several issues which are often disregarded by researchers that might be the reason why the results of the existing studies concluded LCPUFA therapy does not have a significant effect on the

incidence of preeclampsia. These issues were the neglect of heterogeneity of inclusion and exclusion criteria, research methods such as type and dose of supplement and the different of follow-up periods in systematic review or meta-analysis studies. The neglect of confounding variables such as fetal sex and smoking status, and the neglect of accurate time for starting the drug administration in individual studies also should be regarded (69).

Magnesium also showed no significant effect on preeclampsia prevention (RR= 0.90 [0.48–1.69]) (31). The theory underlying this intervention is because it has significant effect on vascular tone, contractility, and reactivity by relaxing vascular muscle (70) training, and anthropometric indices of sportspersons from different sports discipline can aid in improving sports performance. This study sought to evaluate the association between urine creatinine concentration (UCR). However, the insignificant result of that study was strengthened by another study that reveals magnesium supplementation was not proven to be effective in preventing increased blood pressure in pregnant women (71).

Phytonutrients therapy also had no significant effect to the incidence of preeclampsia (RR= 0.97 [0.56 – 1.69]) (24). It was explained that one of the possibilities why the conclusions did not show a significant effect was because most of the phytonutrient therapy was given to the respondents at gestational age more than 13 weeks. This may reduce the effectiveness of therapy because the times when free radicals are produced at the highest level in uteroplacental blood vessels have been missed.

Selenium (Se) had a significant effect to prevent the incidence of preeclampsia and Pregnancy-induced Hypertension (PIH) in combination but not for preeclampsia alone when the data analysis adjusted for the baseline Se concentration and baseline haematocrit

(RR= 0.42 [0.16-1.09]) (17) as assessed by biomarkers of pre-eclampsia. In a double-blind, placebo-controlled, pilot trial, we randomised 230 primiparous pregnant women to Se (60 µg/d, as Se-enriched yeast. Other studies concluded different results, one of which concluded the effect of selenium therapy on preventing the incidence of preeclampsia was insignificant (72), but another of which that was meta-analysis study concluded that selenium supplementation could reduce the incidence of preeclampsia with RR = 0.28 (CI 0.09-0.84) and *p* value = 0.02 (73) and to determine the effectiveness of selenium supplementation in preventing preeclampsia. We searched PubMed, ScienceDirect, the Cochrane Library, and relevant references for English language literature up to November 25, 2014. Mean difference from observational studies and relative risk from randomized controlled trials were meta-analyzed by a random-effect model. Thirteen observational studies with 1515 participants and 3 randomized controlled trials with 439 participants were included in the meta-analysis. Using a random-effect model, a statistically significant difference in blood selenium concentration of -6.47 µg/l (95 % confidence interval (CI).

Five studies investigating the use of Vitamin C and E to prevent preeclampsia also failed to show beneficial effect, with RR= 0.77 – 1.15 (18,30,34,46,49) placental abruption and low birthweight. We evaluated the relationship between prenatal Vitamin C and E (C/E). The theory underlying the idea of using vitamins C and E is vitamins C and E are antioxidants that may be able to provide a protective effect against preeclampsia. Similar result with those studies was also found in a Cochrane systematic review conducted by Rumbold et al. (2016) which concluded that data from existing studies did not support the use of vitamin C and E in single form or in combination with other supplements for therapy in prevention of preeclampsia

(74,75) such as pre-eclampsia. There is a need to evaluate the efficacy and safety of vitamin E supplementation in pregnancy. Objectives: To assess the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes, adverse events, side-effects and use of health services. Search methods: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (23 June 2004).

This study has several limitations. Firstly, we only used two databases to search articles so that there might still be a lot of studies on preeclampsia prevention therapy that are unidentified. Secondly, the articles discussing therapies that have a significant effect on reducing the incidence of preeclampsia are too small, specifically for the treatment that investigated IMN, so that other studies are indispensable to strengthen that evidence.

CONCLUSION AND RECOMMENDATION

There are three types of pharmacological interventions and eight types of dietary supplementations that were identified in this SLR. Nitric Oxide-donors with Penthaerythryl Tetranitrate selenium, calcium, vitamin D, DHA-rich fish oil-concentrate, copper, phytonutrient, (PETN), folic acid, vitamins C and E and magnesium have not been proved effective, while Nitric Oxide-donors with Isosorbide Mononitrate (IMN) and aspirin have been shown effective to prevent preeclampsia. Although all studies presented good quality of evidence, their effect is not large. More research is needed in the field before prevention treatments are prescribed in clinical settings.

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