Review

PACNJ

The Effect of Supplementation in Pregnancy for Preventing Preeclampsia: A Literature Review

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ARTICLE INFO
Article history:
Received 30-07-2020
Received in revised from 06-08-2020
Accepted 08-08-2020

Keyword:
Folic acid, L-arginine, phytonutrient, preeclampsia, vitamin D

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ABSTRACT
Background: Preeclampsia increases maternal and perinatal morbidity and mortality. Recently, there have been many studies to reduce the risk of preeclampsia, one of which is the finding that vitamin D, L-arginine, folic acid, or phytonutrient in supplementation form play a role in reducing preeclampsia incidence.
Objective: This study aimed to investigate the effect of supplementation on pregnancy for preventing preeclampsia.
Method: The search strategy was conducted through CINAHL and Medline databases. Five hundred twenty-two articles were retrieved using 'preeclampsia in pregnancy' and 'prevention' keywords. Further, screening was carried out and resulted in 47 articles. In the end, five articles were included. To be eligible, the articles should be research articles, published from 2009-2019, and published in English.
Results: This review found that vitamin D, L-arginine, and folic acid can prevent preeclampsia. Meanwhile, phytonutrient did not decrease the incidence of preeclampsia.
Conclusion: Prescribing vitamin D, L-arginine, and folic acid to pregnant women is more likely to reduce preeclampsia incidence.

Introduction

Preeclampsia is one of the three highest causes of mother and fetal morbidity and mortality worldwide, with prevalence rates reaching 2-8% of all pregnancies (Behjat Sasan et al., 2017; Fu et al., 2018; Mirzakhani et al., 2016). Preeclampsia is a specific syndrome in pregnancy that is identified by an increase in blood pressure greater than 140/90 mmHg at two examinations within 6 hours and the presence of proteinuria higher than 2+ on dipstick or greater than 300 mg in 24-hour urine collection, found after 20 weeks' gestation (Behjat Sasan et al., 2017; Phipps et al., 2016; Wen et al., 2016).

The pathogenesis of preeclampsia is not fully known. However, in the last decade, there have been advances in research results that show the role of the placenta in the etiology of preeclampsia (El-Sayed, 2017; Phipps et al., 2016). Results of the placenta's examination in preeclampsia pregnancy often indicate placental infarction and narrowing of the sclerotic artery. Based on this evidence, "the pathogenesis of preeclampsia: a two-stage model" was developed, namely incomplete spiral arterial remodeling in the uterus causing placental ischemia (stage 1) and the release of antiangiogenic factors from the ischemic placenta into the maternal circulation that contributes to the maternal circulation which contributes to the endothelial damage (stage 2) (Phipps et al., 2016).

During the implantation process, trophoblast tissue in the placenta invades the uterus and induces a spiral artery to perform remodeling (El-Sayed, 2017; Phipps et al., 2016). The spiral arteries can accommodate increased blood flow from the maternal circulation to nourish fetal development through the placenta (El-Sayed, 2017; Phipps et al., 2016). However, the disruption of the remodeling process can decrease the possibility of blood flow to the placenta (El-Sayed, 2017; Phipps et al., 2016). The placenta's impact will experience a lack of oxygen and trigger the emergence of tissue ischemia and increased oxidative stress. The failure of the spiral artery remodeling process was discovered more than five decades ago in pregnant women with hypertension (El-Sayed, 2017; Phipps et al., 2016).

Further manifestations that can occur in pregnant women with preeclampsia include hypertension, proteinuria, acute kidney injury, capillary leak, pulmonary edema, headache, seizures, posterior reversible encephalopathy syndrome, increased liver function test, hepatic infarction, activated coagulation system, and thrombocytopenia (Fu et al., 2018; Phipps et al., 2016). Therefore, appropriate management efforts are needed for preeclampsia so that it does not develop further, even in prevention, to avoid preeclampsia.

Recently, research results reveal the role of supplements such as vitamin D, folic acid, L-arginine, and phytonutrients to prevent preeclampsia. This supplementation has a biological influence in inhibiting preeclampsia's pathogenesis by preventing placental ischemia, maintaining endothelial cell function, improving the response of the inflammatory system, and maintaining feto-maternal vascularization (El-Sayed, 2017; Fu et al., 2018; Phipps et al., 2016).

Method

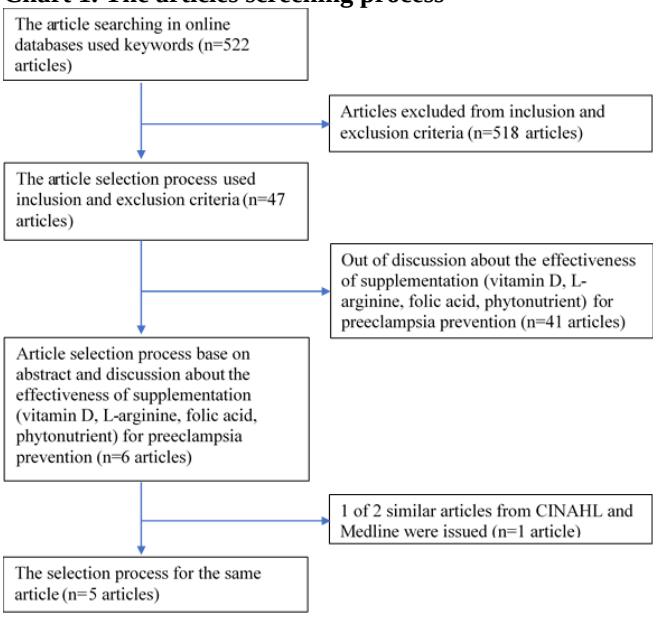
This study was a literature review with a narrative review approach, and it aimed to provide a perspective on preeclampsia and illustrate the prevention of preeclampsia. The first step taken was identifying clinical information related to preeclampsia using the PICO method (P = patient, population, problem; I = intervention, prognostic factor, exposure; C = comparison, control; and O = outcome) method. In this study, 'P' was pregnant women with preeclampsia, 'I' was supplementation to prevent preeclampsia, and 'O' was supplementation's effectiveness to prevent preeclampsia. Meanwhile, the author did not specify any phrase for 'C' in the PICO method.

The next step was literature searching in online databases, namely CINAHL and Medline. 'Preeclampsia in pregnancy' AND 'prevention' were used as keywords in a literature search and found 522 articles. Furthermore, the authors select articles based on inclusion and exclusion criteria. The inclusion criteria used included research

articles, published in English, and published in 2009-2019. While the exclusion criteria in this study were the study sample were preeclampsia mothers with comorbidities. The ranking of articles based on inclusion and exclusion criteria resulted in 47 articles.

In the final step, the authors screened the article manually by looking at the title and abstract of the article, which discussed the effectiveness of supplementation for preeclampsia prevention, and obtained six articles from CINAHL and Medline. After the manual screening process, there are still two articles with the same contents so that one of the same two articles was excluded from the articles filtering. In the end, five articles were found that deserve to be analyzed and discussed in this literature study. The overall article screening process was displayed in chart 1.

Chart 1. The articles screening process



Results

Management of preeclampsia consists of various management, including prevention and treatment, both with pharmacological and non-pharmacological therapies and appropriate postpartum follow-up. In this literature study, five articles found the effect of supplementation on case prevention and reduction in the incidence of preeclampsia, shown in Table 1.

This literature study found that pregnant women can experience preeclampsia in developing and developed countries. Table 1 shows that four articles originated from America, and 1 article originated from Asia, which was published in 2013-2017.

All articles analyzed were research articles with a randomized controlled trial (RCT) study design (4 articles) and prospective cohort studies (1 article). The study population in the articles obtained were pregnant women with or without history and/or risk of preeclampsia (2 articles), pregnant women at risk of preeclampsia (2 articles), and pregnant women with a history of preeclampsia (1 article). Simultaneously, the sample in all studies consisted of 2 groups: the intervention group (the group that received pharmacological supplementation) and the control group (the group that received the placebo).

Table 1. The effectiveness of pharmacological supplements on preeclampsia prevention

Title	Author, Year	Population dan Sample	Method	Intervention	Results
The effect of vitamin D supplement on prevention of recurrence of preeclampsia in pregnant women with a history of preeclampsia.	(Behjat Sasan et al., 2017)	Population: pregnant women with a history of preeclampsia in a previous pregnancy in Besat Hospital, Sananjad City, Iran. Sample: 72 patients in the control group and 70 patients in the intervention group. Inclusion criteria: if 25-hydroxy vitamin D of the pregnant woman was ≥ 25 ng/ml. Exclusion criteria: the pregnant woman with the comorbid disease.	RCT	The intervention group was given 50000 IU of pearl vitamin D3, one time per 2 weeks, up to 36 weeks gestational age. In contrast, the control group was only given a placebo.	Patients in the control group were more likely to develop preeclampsia than patients in the intervention group (p-value = 0.036). The risk of preeclampsia in the control group was 1.94 times higher than in the intervention group. This could be influenced by low serum vitamin D levels in patients in the control group.
Folic acid supplementation in pregnancy and the risk of pre-eclampsia-a cohort study.	(Wen et al., 2016)	Population: pregnant women with a risk of preeclampsia with a gestational age of fewer than 20 weeks in Ottawa Region and Kingston General Hospital, from 1 September 2002 to 31 August 2008. Sample: 404 patients did not receive folic acid, and 7265 patients received folic acid.	Prospective cohort study	Patients get or do not get supplementation of a single form of folic acid or folic acid in other multivitamins.	The rate incidence of preeclampsia in the group that received folic acid supplementation was lower than the group that did not get folic acid supplementation. This difference is statistically significant in patients at high risk of preeclampsia (OR=0.17; 95% CI 0.03, 0.95)
Efficacy of L-arginine for preventing preeclampsia in high-risk pregnancies: a double-blind, randomized, clinical trial.	(Camarena Pulido et al., 2016)	Population: pregnant women with a high risk of preeclampsia in the Department of Gynecology and Obstetrics Outpatient Department of the Dr. Juan I. Menchaca Civil Hospital of Guadalajara, Jalisco, Mexico. Sample: 50 patients in the control group and 50 in the intervention group.	A randomized, placebo-controlled, double-blind trial	The intervention group was given 3 grams of L-arginine in a 600 mg capsule, once per day via oral, from 20 weeks' gestation. In comparison, the control group was given a homologated placebo.	The incidence of preeclampsia in the control group (11/47) was higher than in the intervention group (3/49) (p-value = 0.01).

Early pregnancy vitamin D status and risk of preeclampsia.	(Mirzakhani et al., 2016)	Population: pregnant women in Obstetric Clinic in The United States (Boston University Medical Center in Boston Massachusetts, Washington University di St. Louis Missouri, and Kaiser Permanente Southern California Region in San Diego California). Sample: 408 patients in the control group and 408 patients in the intervention group. Inclusion criteria: have a history of asthma, eczema, or allergic rhinitis; 18-39 years old; 10-18 weeks of gestational age; do not smoke; speak English or Spanish; able to participate intensely. Exclusion criteria: have comorbidities; consume > 2,000 IU/day of vitamin D; multiple pregnancy; pregnancy achieved by assisted reproductive techniques (e.g., IUI, IVF); consume illicit drugs; involved in this study in the previous period; patient health questionnaire depression scale of 15 or higher.	RCT	The intervention group received 4400 IU of vitamin D from the beginning of pregnancy (10-18 weeks' gestation) to delivery, while the control group received a 400 IU placebo.	There was no significant difference between the incidence of preeclampsia in the intervention group (8.08%) and the control group (8.33%) (RR 0.97; 95% CI, 0.61-1.53).
Randomized, placebo controlled, double blind trial evaluating early pregnancy phytonutrient supplementation in the prevention of preeclampsia.	(Parrish et al., 2013)	Population: pregnant women in the area of the University of Mississipi Medical Center. Sample: 135 patients in the control group and 132 patients in the intervention group. Inclusion criteria: nulliparous or multiparous with single gestation and no history of systemic vascular disease.	A randomized, placebo-controlled, double-blind trial	The intervention group received two times two capsules of phytonutrient supplementation every day, from 12 weeks' gestation to delivery. At the same time, the control group received two capsules of placebo twice daily, from 12 weeks' gestation to delivery.	There was no significant difference between the incidence of preeclampsia in the intervention group (15.9%) and the control group (16.3%) (RR 0.97; 95% CI, 0.56-1.69).

Discussion

This literature study indicates that there are 4 pharmacological supplements used as independent variables to prove the effectiveness of pharmacological supplementation for the prevention of preeclampsia, namely, vitamin D, folic acid, L-arginine, and phytonutrient.

Vitamin D

A meta-analysis revealed a correlation between vitamin D deficiency and preeclampsia, premature birth, and gestational diabetes (Arain et al., 2015). In this literature study, two studies found the effect of vitamin D on the decrease in the probability of preeclampsia. Both of them used the RCT research design, with one of the inclusion criteria: the patient had an examination of 25-hydroxy vitamin D level ≥ 25 ng/ml (Behjat Sasan et al., 2017), and the exclusion criteria were that the patient had the comorbid disease (Behjat Sasan et al., 2017; Mirzakhani et al., 2016).

The study (Behjat Sasan et al., 2017) showed that the group that received vitamin D had a lower likelihood of experiencing preeclampsia than the placebo group (p-value = 0.036). That result was in line with the evidence which states that 1.25 dihydroxy vitamin D3, as an active form of vitamin D influences preeclampsia. 1.25 dihydroxy vitamin D3 has a role in adjusting transcription and related gene function in the process of normal implantation, placental invasion, and angiogenesis. Also, 1.25 dihydroxy vitamin D functions as an immunomodulator that can prevent abnormal implantation, where abnormal implantation can be triggered by an abnormal immune response between mother and fetal.

Meanwhile, previous studies showed no significant difference in the incidence of preeclampsia between the intervention group and the placebo group (Mirzakhani et al., 2016). Preeclampsia occurred in 33 women in the vitamin D group (8.08%) and 34 women in the placebo group (8.33%) (relative risk [RR], 0.97; 95% CI, 0.61-1.53). That could be due to the research conducted on women with gestational age reaching 10-18 weeks, while placental implantation that embraces the adequacy of vitamin D has occurred earlier than the time of the study. Besides, researchers consider that the sample size used is too small for the research design they use.

However, women who had sufficient vitamin D levels (at least 30 ng/ml) at the beginning and end of pregnancy showed a significantly lower incidence of preeclampsia than those with vitamin D deficiency (Mirzakhani et al., 2016). That result was in line with the results of other studies that found a decrease in the incidence of preeclampsia in women who had vitamin D levels of 40 ng/ml despite being given vitamin D treatment after 12-16 weeks' gestation (Hollis et al., 2011). The researchers concluded that larger sample size, earlier gestational age, high vitamin D levels in women since preconception, and the dose of vitamin D administered had a role in decreasing preeclampsia incidence. Besides that, the two research results analyzed in this review revealed no adverse effects of giving vitamin D to pregnant women.

Folic Acid

The previous evidence has proven that folic acid has a crucial role in the prevention of preeclampsia. Studies of Caucasian Women with the risk of preeclampsia show that folic acid supplementation was associated with increased red blood count (RBC) folate levels (Wen et al., 2016). RBC folate level was higher in the group that received supplementation (both supplementation containing folic acid only and supplementation containing folic acid and other vitamins) than the group that did not receive supplementation (p-value = 0.0002).

The results of subsequent analyzes found the incidence rate of preeclampsia in the supplementation group was lower than that of the group that did not receive supplementation, with statistically significant differences found in women with an increased risk of preeclampsia (Wen et al., 2016). The study results were estimated due to the discrepancy of the dose given in the study sample. So the researchers tested the additional hypothesis by giving higher doses to

women with an increased risk of preeclampsia. The results showed that giving folic acid with higher doses gave significantly better benefits to women with an increased risk of preeclampsia.

L-arginine

Endothelial dysfunction is the impact of abnormal placental implantation, which is often linked to the pathogenesis of preeclampsia (El-Sayed, 2017; Phipps et al., 2016). Endothelial dysfunction can inhibit the production of vasodilator molecules such as nitric oxide (NO), which causes increased blood vessel resistance, platelet aggregation, and activation of the coagulation system (Vadillo-Ortega et al., 2011). In contrast, L-arginine is a primary amino acid precursor that can increase NO formation.

The results of the study (Camarena Pulido et al., 2016) showed a significantly higher incidence of preeclampsia in the placebo group (23.4%) compared to the L-arginine group (6.1%) with a p-value = 0.016. Likewise, severe preeclampsia incidence was significantly higher in the placebo group (n = 7) compared to the L-arginine group (n = 1) with p-value = 0.02.

Different results on systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), perinatal outcome, medical complication, and adverse effects were also found in the study (Camarena Pulido et al., 2016). Systolic blood pressure, diastolic blood pressure, and MAP were significantly lower in the group receiving L-arginine than in the placebo group (p = 0.022, p = 0.035, and p = 0.023 respectively). Birth weight was higher in the L-arginine group compared to the placebo group (p = 0.03). The prematurity level was significantly lower in the L-arginine group than in the placebo group (p = 0.04). Besides, the study found adverse effects of L-arginine in the form of dyspepsia, vomiting, diarrhea, and abdominal pain.

Phytonutrient

The recent evidence found that giving antioxidant/phytonutrient supplements to first-trimester pregnant women and continuing throughout pregnancy can significantly reduce or reduce the number of preeclampsia. Providing whole-food supplements rich in antioxidants for pregnant women can reduce the effects of oxidative stress on the mother's placenta and blood vessels. (Parrish et al., 2013)conducted research by giving juice plus products a phytonutrient supplement containing vitamins C and E, which can provide more robust antioxidant defenses. Juice plus is known to increase antioxidant activity and folate levels, reduce homocysteine levels, increase vasodilatory effects, increase cholesterol profiles, have a positive effect on blood pressure, and reduce calcium deposition in coronary arteries.

The study (Parrish et al., 2013) showed no significant changes in the incidence of preeclampsia and placental derived morbidity after the administration of phytonutrients in the intervention group. The study results can be influenced by differences in the demographics of respondents in the study with other studies that can affect the absorption of phytonutrients by the body. In that study, it was known that the placebo group had a history of preterm delivery that was significantly higher than the intervention group. The placebo group had received a multivitamin before becoming a research respondent to prevent complications in her pregnancy. History of consumption of a multivitamin in the placebo group can be biased towards phytonutrient administration in the intervention group.

Based on an analysis of the method and the results of his research, (Parrish et al., 2013) still concluded that phytonutrients should still be given to pregnant women even since the pre-conceptual period.

Conclusions

This literature study shows that vitamin D, folic acid, and L-arginine influence the prevention of preeclampsia. At the same time, phytonutrients do not provide significant effectiveness in the prevention of preeclampsia. This literature study indicates that the administration of vitamin D, folic acid, and L-arginine to pregnant women since early pregnancy can be used as a prevention against preeclampsia. The researchers suggest vitamin D, folic acid, and phytonutrients should be

given since preconception (before pregnancy) and at 19-20 weeks of gestation for L-arginine.

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