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Review Article

Factors effective in the prevention of Preeclampsia:A systematic review

Fatemeh Alsadat Rahnemaei [a], Mahta Abbasi Fashami [a], Fatemeh Abdi [b, *], Mahmoud Abbasi [b]

[a] Student Research Committee, Nursing and Midwifery Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Medical Ethics and Law Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Due to the morbidity and mortality of mothers and fetuses developed by preeclampsia, preventive approaches have always been taken into account in high risk individuals. Systematic review studies contribute to make a better decision about the results of such studies. Accordingly, this study strived to systematically study the factors effective in the prevention of preeclampsia. The MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, and Proquest databases were systematically reviewed between January 2000 and May 2019. The quality of the studies was analyzed using the CONSORT checklist. A study was conducted on 29 quality interventional studies; 28 of which were RCT type, and on various factors such as anticoagulants (heparin, enoxaparin, Dalteparin and Nadroparin), aspirin, paravastatin, nitric oxide, yoga, micronutrients Such as L-Arginine, Folic Acid, Vitamin E and C, Phytonutrient, Lycopene and Vitamin D alone or in combination with Calcium. The results of this study showed that low molecular weight heparin, enoxaparin, PETN, yoga, L arginine, folic acid, vitamin D prevented preeclampsia alone or combined with calcium.

Introduction

Preeclampsia is a unique disorder of gestation and multiple system associated with elevated systolic blood pressure of 140 mmHg and diastolic blood pressure of 90 mmHg and along with proteinuria of 1+ or more (0.3 g per 24 h). This disorder occurs at about the 20th week of pregnancy and has an estimated 14.1% prevalence and is one of the most common complications of pregnancy among women [2]. This disorder is associated with complications such as fetal loss, preterm delivery, impotence in the neonate, early pruritus, and high rates of morbidity and mortality and is one of the five main causes of the death of pregnant mothers in developed countries [3–5]. Reduced maternal mortality has also been identified as one of the main goals of the Millennium Development Goals [6]. Disruptions in the restoration of placenta vessels and decreasing blood flow to the placental cause preeclampsia [7]. Women with a history of preeclampsia are more likely to have vascular disorders in the future [8]. Diagnosis of preeclampsia is especially difficult in women who have vascular problems or chronic protein excretion [9]. Other major complications of preeclampsia include liver failure, renal failure, coagulation disorders, neurological complications, and abnormal placental pulmonary function and fetal death [10–12]. However, no definitive treatment for preeclampsia has so far been identified so as to reduce maternal and fetal complications [13]. Most existing therapeutic approaches are for the time when preeclampsia has already been diagnosed and are applied to help relieve maternal and fetal complications. Considering the pathogenesis of the disease, a preventive approach can be made to the pathogenesis of the disease, as well as to the prevalence of clinical disease.

Preeclampsia prevention, especially in high risk individuals, can prevent maternal mortality and maternal and fetal morbidity, such as maternal mortality, fetal death, preterm labor, growth constraints, hospitalization in NICU, etc. and result in safe pregnancy and childbirth for mothers and fetuses as well [14]. Various review studies have also been conducted to evaluate anti-inflammatory drugs such as aspirin on the prevention of preeclampsia in high-risk women/it should be noted that the results are quite contradictory [15,16]. In addition, the role of antioxidants with an emphasis on lipid oxidation hypothesis in preventing preeclampsia

* Corresponding author.
E-mail address: abdi@sbmu.ac.ir (F. Abdi).

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and also anticoagulant drugs such as low molecular weight heparin with vascular activity in the maternal compartment of the vascular system of systemic vessel disorders, which is a major characteristic of preeclampsia [17,18].

Systematic review studies summarize the results reported to explicitly outline the goals and outcomes and thus provide a broader picture of the results [19]. Based on the findings, there is dearth of systematic review that examines different preventive approaches to preeclampsia in high-risk or low-risk populations to achieve a comprehensive outcome in this respect. Therefore, the present study was conducted with the aim of systematically studying the effective factors in preventing preeclampsia. It is hoped that the results of this study will be able to decide on the best decisions to prevent preeclampsia.

Methods

Search strategy

This study was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In order to collect data, valid databases, i.e. MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, and Proquest were systematically searched.

Inclusion and exclusion criteria

Inclusion criteria were: Persian and English studies published between January 2000 and May 2019, randomized interventional studies, and non-randomized studies, pregnant women with different gestational age, high risk women such as older age, greater body mass index equal to 30, previous history of preeclampsia, embryonic growth limitation, preterm labor, multiple pregnancy, history of decolonization of the placenta, chronic underlying conditions of the mother such as chronic blood, cardiovascular, vascular and renal disease, or evidence of preeclampsia such as uterine doppler examination or human chorionic gonadotropin hormone as well as low-risk nulliparous women.

Exclusion criteria: studies outside the mentioned time period, studies in languages other than Persian and English, studies other than interventional studies, protocol, thesis documentations, and lack of access to full text articles, history of drug allergy of participants to Anticoagulants, nonsteroidal anti-inflammatory drugs, vitamins and non-compliance with therapeutic protocols.

Study selection

The initial search yielded 2862 results. The eligibility of these articles was independently evaluated by two authors and any cases of disagreement were resolved through consensus. During this stage 1868 articles were found to be irrelevant or duplicate and were thus excluded. After reviewing the titles and abstracts of the remaining articles, 868 more papers that was not related to the purpose of this study were excluded. In the evaluation of the full texts, 53 out of the remaining 126 articles were found ineligible and were thus excluded. As a result, a total of 29 eligible articles were finally reviewed (Fig. 1).

Quality assessment

The quality of quantitative studies was determined by evaluating their adherence to the Strengthening the CONSORT Statement comprises a 25-item checklist. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted.

Data extraction

Two authors independently performed the study selection and validity assessment and resolved any cases of disagreement by consulting a third researcher. The first author's name, publication year, country, sample size, gestational age, Consort score, Participant condition, Intervention, control, results were extracted and entered the analysis (see Table 1).

Results

According to the review on the studies shown in Figs. 1, 29 quality intervention studies were selected according to the CONSORT check-list, of which 28 ones were of RCTs and one of clinical trial (Meiri2014). The CONSORT scores are between 19 and 23. The total number of participants in the studies were 15,328 high-risk women in terms of preeclampsia or healthy nulliparous. Studies in different countries included Iran [3], Finland [1], UK [3], France [2], India [4], Mexico [2], Italy [1], Spain [1], Netherland [4], USA [7], Israel [1], Germany [1], China [1], Egypt [1], Belgium [1], Canada [1], Australia [3], Argentina [1], New Zealand [1], Sweden [1]. The results of the study are presented in Table 2 as well. Studies have been done on various factors and their effect on the pathogenesis of preeclampsia in order to prevent its occurrence. Interventions included anticoagulant drugs (low molecular weight heparin = 2, enoxaparin = 2, Dalteparin = 1, nadoparin = 1), aspirin = 11, paravastatin 1, nitric oxide = 1, yoga = 1, and micronutrients (L-Arginine = 2, Vit E, C = 3, Folic Acid = 2, Phytonutrient = 1, Lycopene = 1, Vit D = 1, VtD + Calcium = 1). The summary of these factors and the results of studies are presented in Table 3, below (see Fig. 3).

Among the four anticoagulants evaluated in studies, molecular weight heparin and then enoxaparin had a positive effect on decreasing preeclampsia. Concerning the use of aspirin at different doses, there were controversial results in reducing the incidence of preeclampsia. Eleven studies were conducted on this subject. Low-dose aspirin (LDA) was studied in three studies, with two studies of its effect on a total of 575 participants compared to placebo in reducing the incidence of preeclampsia. However, another study with a sample size of 2503 patients showed no difference in the incidence of pre-eclampsia before and after the intervention compared to placebo. Out of eight other studies performed on different doses of aspirin, four reported a reduction in preeclampsia occurring in total for 1980 women, while four other studies reported an ineffectual effect of aspirin on 4060 patients. As a lipid lowering agent for primary and secondary prevention of preeclampsia used in 21 patients, Paravastatin had an effect on preeclampsia compared with placebo (only 4 cases of preeclampsia was observed in placebo group).

NO-Donor Pentaerythritol Tetranitrate (PETN) with endothelial dysrhythmia and improvement of uterine paired blood flow with prophylaxis in reducing the risk of complications such as preeclampsia on 110 high risk women showed that this substance can play a role in preventing preeclampsia.

The effect of folic acid on the prevention of preeclampsia had been evaluated in two studies. The use of folic acid with early onset of pregnancy and at a dose of 4 mg on 3064 women with different nationalities in a study that was observed could play a role in preventing preeclampsia. Meanwhile, in another study, the combination of folic acid with aspirin on 202 women did not have any effect.

Vitamin E and C had been analyzed in three studies. One study reported its effect on reducing the incidence of preeclampsia on 200 female participants, while two other studies showed no effect on a total of 1173 female participants.

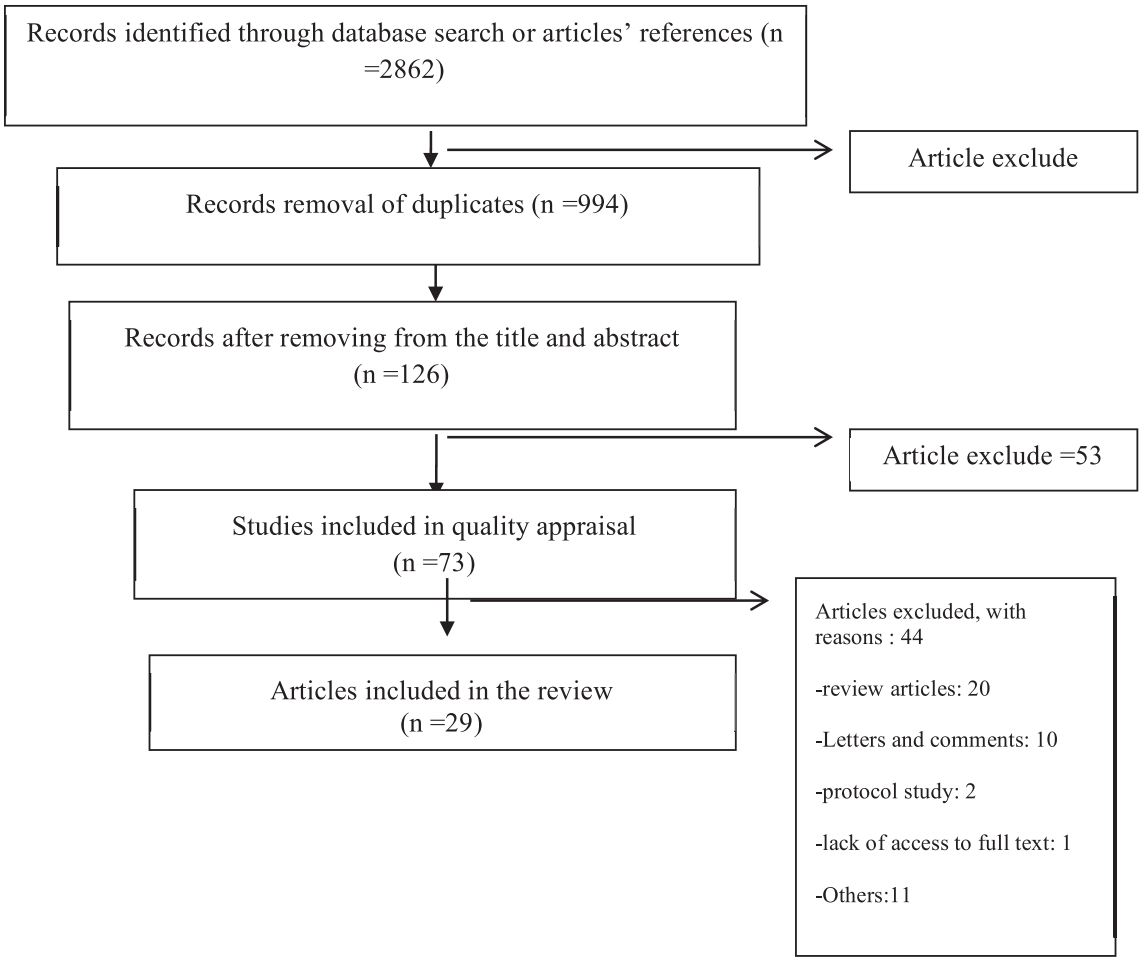

Fig. 1. Search flow diagram.

Other interventions included yoga, L-arginine, vitamin D alone or combined with calcium that was effective in reducing pre-eclampsia. However, Phytonutrient, lycopene was not effective in preventing preeclampsia.

The total number of participants participating in each of the approaches are given in Chart 2 and the impact of these preventive approaches is also presented in Fig. 2, below.

Discussion

The results of this systematic review showed that low molecular weight heparin, enoxaparin, PETN, yoga, and micronutrients such as L arginine, folic acid, vitamin D alone or combined with calcium prevented preeclampsia. In the case of aspirin: however, the results of the existing studies were controversial.

Aspirin is a drug that has been introduced in the prevention of preeclampsia. In a study conducted on 1760 with low dose aspirin (LDA) before 16 weeks of gestation, it was shown that early administration of LDA can be associated with a low preeclampsia prevalence and is a cost-effective way of preventing it [47]. In another study on double-twin pregnancies and with an increase in the level of low dose dopamine gonadotropin to prevent pre-eclampsia, a positive effect of this drug on the prevention of preeclampsia was observed [22]. However, in other studies, no beneficial effects of administering low-dose aspirin or aspirin generally have been observed in preventing preeclampsia and cannot prevent preeclampsia in primiparous women [27,28,44]. Ting–ting et al., in their meta-analysis study, evaluated the effect of low-dose aspirin on the prevention of preeclampsia in high-risk women. They analyzed 29 randomized clinical trials and eventually observed that low-dose aspirin before 16 weeks of gestation could be effective in preventing preeclampsia [14]. In this regard, Yao et al. also studied the effect of early intervention with aspirin

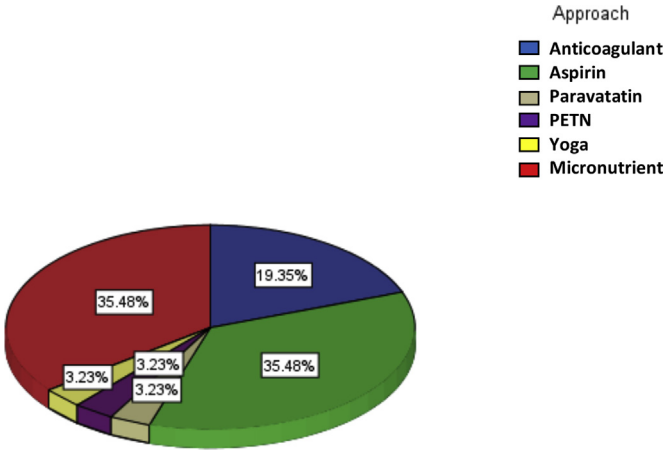

Fig. 2. The total number of participants in each study in terms of preventive approaches.

Table 1
Search strategy.

	Search term
#1	'preeclampsia' [tiab], OR 'pregnancy toxemia' [tiab], OR 'EPH complex' [tiab], OR 'EPH gestosis' [tiab]
#2	'preventing' [tiab], OR 'prevention' [tiab], OR 'prophylaxis' [tiab]
#3	'Aspirin' [tiab], OR 'Anticoagulants' [tiab], OR 'vitamins' [tiab], OR 'antioxidant' [tiab], OR 'acid folic' [tiab]
#1 AND #2	Combination of first AND second's keywords
#1 AND #3	Combination of first AND third's keywords
#1 AND #2 AND #3	Combination of first AND second AND third's keywords

(beginning before 16 weeks of pregnancy) in another meta-analysis study. After reviewing five clinical trials and a total of 860 high risk pregnant women, the incidence of biliary obstruction was lower in the intervention group compared to the control group [48]. Similar results from the above studies in another meta-analysis of 10 clinical trial studies showed that using low dose aspirin at ≤16 weeks of pregnancy can play a proactive role in preeclampsia [49]. In a study that was conducted on high-risk women for preeclampsia to prevent it with paravastatin, the results of the study showed that the use of this drug reduced the risk of preeclampsia [23]. Esteve-Valverde et al. reviewed the effect of paravastatin on the prevention of preeclampsia in a systematic review study and reported the results of a review of 84 articles. Accordingly, the studies did not have the proper quality to conclude, but the positive role of paravastatin in the prevention and treatment of preeclampsia without increasing congenital anomalies was reported [50].

Low molecular weight heparin (LMWH) has been evaluated for the prevention of various placenta-mediated pregnancy complications, including severe preeclampsia and recurrent miscarriage. Multiple trials and systematic reviews have concluded that LMWH reduces the incidence of recurrent severe preeclampsia in high-risk women [18].

In a study to investigate the effect of low molecular weight heparin (LMWH) on endothelial function in women at risk of preeclampsia, intervention was performed on 45 high-risk women with gestational age of 26 to 22 weeks. Finally, serum levels of yhe secreted growth factor of placenta 1 and 2 (PIGF1 and PIGF2) was reduced in comparison with the control group, and the risk of preeclampsia was also reduced and endothelial function improved [18,38]. In a systematic review of 5 studies (484 women) shown that while treatment with heparin for women considered to be at particularly high risk of adverse pregnancy complications secondary to placental insufficiency was associated with a statistically significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 weeks' gestation, and infant birth weight below the 10th centile for gestational age when compared with no treatment for women considered at increased risk of placental dysfunction [51].

In a study that evaluated the effect of enoxaparin to prevent preeclampsia in pregnancy at 149 high risk women with single-twin pregnancy, there was no clear evidence of the effect of enoxaparin on prevention of preeclampsia [20]. However, in another study, the effect of enoxaparin in combination with aspirin on prevention of preeclampsia was observed. This drug is a safe, cost-effective and non-adverse one [42].

Women with a history of early-onset hypertensive disorders of pregnancy and/or SGA, who also have acquired thrombophilia with consistently positive titres of antiphospholipid antibodies, showed no benefit from combination treatment with dalteparin and aspirin started before the second trimester of pregnancy. On the other hand, early initiation of aspirin treatment in such women reduced subsequent recurrence of complications considerably, although it did not completely prevent complications before 34 weeks gestation [21]. Antithrombotic prophylaxis with nadroparin (a low-molecular-weight heparin recommended by the Italian Society for Hemostasis and Thrombosis) in addition to medical surveillance failed to decrease the number of late pregnancy complications compared with medical surveillance alone in women with a previous history of preeclampsia, eclampsia, HELLP syndrome, intrauterine fetal death, FGR, or placental abruption [37]/In another study, the effect of nitric oxide on the prevention of preeclampsia was investigated and it was observed that before and after intervention preeclampsia was reduced in preeclampsia early on in high-risk individuals [31].

Other preventive approaches to preeclampsia are interventions that are carried out by vitamins and minerals. In a study, the effect of vitamin E and C supplementation on preventing preeclampsia was observed. The incidence of severe preeclampsia was 2% in the intervention group and 7% in the control group, indicating a positive effect of the two vitamins in the prevention of preeclampsia [25]. While the lack of effect of these two vitamins was observed in another study on the prevention of preeclampsia [52]. In a study that evaluated the effect of lycopene on preventing preeclampsia in 54 pregnant women aged 14–28 weeks, there was no evidence of a positive and sufficient effect on the prevention of preeclampsia [41].

In a meta-analysis study, 16 clinical trials were conducted to evaluate the effect of antioxidants on the prevention of premature ejaculation. The use of vitamin C, vitamin E, lycopene, selenium, and red palm oil in the intervention group was significantly different in the control group You do not have to prevent preeclampsia [53]. In another systematic review, the effect of these antioxidants on the prevention of preeclampsia was not reported [17]. Consumption of calcium and vitamin D supplements with aspirin can play a significant role in the prevention and reduction of preeclampsia [46]. In a meta-analysis study conducted on 16 clinical trials, the use of excess calcium in high-risk pregnant women could be effective in preventing preeclampsia [54]. Also, the role of amino acid L-arginine in the prevention of preeclampsia can be mentioned, whose positive effect on prevention of preeclampsia has been observed in a study [24]. In another study, there was a positive effect of L-arginine and antioxidant vitamins in preventing preeclampsia in high-risk women [39]. Physical activity was one of the other approaches used to prevent preeclampsia, and there were different results that require counseling-based decision within prenatal period [55]. Also, in another study, doing yoga in high risk women could be effective in preventing preeclampsia [36].

Conclusion:Low molecular weight heparin, enoxaparin, PETN, yoga, L-arginine, folic acid, vitamin D alone or combined with calcium can be used as cost-effective, available, and acceptable factors to prevent preeclampsia. Thus, maternal and fetal complications of preeclampsia can be prevented and consequently costs associated with preeclampsia can be haltered. However, the treatments that mentioned in this review study can be potential preventative interventions in the future. It is recommended that further studies be needed in this area.

Limitations:One of the limitations of this study was the low number of participants in some studies, or small number of articles that focused on some approaches which made it difficult to generalize the outcomes of preeclampsia prevention factor. The other limitations is not access full text of some articles that met the inclusion criteria. A similar study using meta-analysis approach is proposed to be carried out in this regard.

Table 2
Characteristics of the studies included in the systematic review.

Author (year)	Country	Sample size	gestational age (weeks)	Consort score	Participant condition	Intervention	Control	Results
McLaughlin (2017) [18]	USA	45 Intervention = 25 Control = 20	22–26	22	high risk of preeclampsia	Low molecular weight heparin (LMWH)	saline placebo	- LMWH improves maternal endothelial function through increased placental growth factor bioavailabilityin high risk women.
Groom (2017) [20]	Australia, New zealand, Netherland	149 Intervention = 72 Control = 77	6–16 until 36 w or delivery	23	high risk of preeclampsia and/or small for gestational age	Enoxsaparin 40 Mg (4000 IU) +High Risk Care	High risk care (High Risk Antenatal Service+100 mg Aspirin+1000 or1500 mg Calcium)	- Enoxsaparin have no effect on Prevention of PE
Van (2016) [21]	Netherland, Australia, Sweden	32 Intervention = 16 Control = 16	6–12 until delivery	22	1 History of hypertensive disorders of pregnancy (PE, eclampsia, Hellp syndrome) or SGA 2 anti phospholipid syndrome	Dalteparin 5000 IU(Person weight> 80: 7500 IU. Person weight<50: 2500 IU + Aspirin 80mg/daily	Asperin 80mg/daily	- Dalteparin + Aspirin have no effect on PE - there are no different between alone Aspirin and combine therapy.
Euser (2016) [22]	USA	225 Intervention = 106 Control = 119	12–26	21	one risk factor for preeclampsia (multiple gestation, chronic hypertension, insulin-dependent diabetes or pre-eclampsia in a prior pregnancy)	Low dose of Aspirin	Placebo	- Preeclampsia incidence was lower with LDA than with placebo
Costantine (2016) [23]	USA	20 Intervention = 10 Control = 10	12–26 Until delivery	21	History of sever PE + delivery before 34w	Paravastatin 10 mg/Dail	placebo	- use of pravastatin for preventing preeclampsia in high-risk pregnant women is beneficial.
Camarena (2016) [24]	Mexico	96 Intervention = 49 Control = 47	Beginning from 20	21	High risk for PE (nulipar, history of PE, HTN, BMI>30)	L-arginine 3 gr/daily	Placebo	- L-arginine can decrease the incidence of PE.
Cardoso (2016) [25]	India	200 Intervention = 100 Control = 100	2nd & 3rd trimester	20	Normal pregnant women	Vit C 500 mg Vit E 400 IU Daily	Without intervention	- There was 46% reduce in PE incidence.
Odibo (2015) [26]	USA	30 Intervention = 16 Control = 14	11–13 w + 6 d To 37 or delivery	22	High risk for PE (history of PE, HTN,+DM + low PPAPA + BMI>30)	Aspirin 81mg/dail	Placebo	- Aspirin in this study has no effect on PE
Hassan (2015) [27]	Egypt	202 Aspirin = 68 Folic acid = 67	22–24	22	High risk of developing PE (history of PE, HTN, BMI>30, DM) with uterine doppler analysis)	1 Aspirin75mg/daily 2 folic acid 500μg/daily	Without intervention	- between aspirin and control the aspirin can reduce the incidence of PE. - There was no different between aspirin and folic acid group. - aspirin has no effect on sever PE.
Cantu (2015) [28]	USA	2503 Intervention = 1254 control = 1249	from randomization until deliver	20	High risk for PE	LDA (60 mg/daily)	Placebo	- women who initiated LDA<16 weeks. LDA effect was not better

(*continued on next page*)

Table 2 (*continued*)

Author (year)	Country	Sample size	gestational age (weeks)	Consort score	Participant condition	Intervention	Control	Results
								when initiated<16 weeks versus ≥16 weeks - LDA effect was not better in non-obese versus obese women.
Qian (2015) [29]	China	60 Intervention = 30 Control = 30	20–32	19	at risk for PE according to abnormal uterine artery Doppler wave	daily dose of 2000 IU vitamin D	Placebo	- vitamin D3 supplementation can prevent preeclampsia
Talari (2014) [30]	Iran	80 Intervention = 40 Control = 40	12–16	22	1 high-risk (history of PE, HNT, family history underlying vascular disorder, GDM, age <20 or >40 2 Abnormal Uterine Artery Blood Flow	ASA 80 mg/daily	placebo	ASA reduced the risk of preeclamp-sia.
Schleussner (2014) [31]	Germany	110 Intervention = 53 Control = 57	19–23 until 35 w	23	abnormal uterine artery Doppler	nitric oxide-donor pentaerythrityltetranitrate 80 mg Twice a day	Placebo	There was no difference in the risk of developing PE between the groups but early onset PE was reduced in trend in the high risk group
Meiri (2014) [32]	Israel	820	14–35	21	First Trimester PP13 level </ = 0.4 multiple of the median (MoM) and/or at least one major risk factor for PE	Aspirin (75mg/daily) + routine care	routine care	PE risk is determined by low first trimester PP13 or by combined low PP13 and RFs, prevention with aspirin is warranted.
Wen (2013) [33]	Canada, Australia, Argentina, UK, Netherlands, Brazil, West Indies, and United States	3064 Intervention = 1532 Control = 1532	8–16 until delivery	21	high risk for PE	folic acid (4mg/daily)	Placebo	supplementation with 4 mg folic acid starting in early pregnancy until delivery is effective in preventing PE
Parrish (2013) [34]	USA	267 Intervention = 132 Control = 135	12 until delivery	22	Low-risk group And high risk	Phytonutrient2cap daily	Placebo	Initiation of antioxidant/ phytonutrient supplementation in the first trimester did not decrease rates of preeclampsia
Ayala (2012) [35]	Spain	350 Intervention = 176 Control = 174	12–16 Until delivery	19	High risk	ASA 100mg/daily + chronotherapy at the time of using the cap	Placebo	low-dose ASA ingested at bedtime, significantly regulates ambulatory BP and reduces the incidence of preeclampsia
Rakhshani (2012) [36]	India	68 Intervention = 30 Control = 38	12–28	23	High risk women	Yoga 1 h session/3 time in week	Walking Half of hour	yoga can potentially be an effective therapy in reducing hypertensive related complications of pregnancy
Martinelli (2012) [37]	Italy	128 Intervention = 63 Control = 65	From 12	22	history of 1.preeclampsia, 2.hemolytic anemia, 3.elevated liver enzymes 4.low platelet count syndrome, 5.IUFD 6.IUGR 7. Placental abruption	Nadroparin (3800 IU daily subcutaneous injections+medical surveillance (monthly visits and controls of maternal weight, blood pressure, Aspirin intake, abdominal growth, and ultrasound	medical surveillance	Nadroparin did not prevent late-pregnancy complications in women at risk of recurrence

						evaluation of fetal biometry)		
Vries (2012) [38]	Netherland	139 Intervention=70 Control=69	6-12until the onset of labor	23	1 inheritable thrombophilia without antiphospholipid antibodies. 2 Previous delivery< 34 weeks gestation with HD and/or SGA	LMWH 5000 IU (Person weight> 80: 7500 IU. Person weight<50: 2500 IU + Aspirin 80 mg/daily	Aspirin 80 mg/daily	Adding LMWH to aspirin at < 12 weeks gestation reduces recurrent HD onset <34 weeks gestation in high risk womens
Vadillo (2011) [39]	Mexico	450 Intervention=228 Control=222	14-32	22	High risk of PE	L-arginine 5.4 g + antioxidant vitamins	Placebo	L-arginine and antioxidant vitamins reduced the incidence of preeclampsia.
Rahmanian (2011) [40]	Iran	424 Intervention = 212 Control = 212	14–22 to end of pregnancy	22	Nulliparous	Vit C 1000 mg + Vit E 400ui + Fe + folic acid	Fe + folic acid	This intervention have no effect on the incidence of PE
Antartani (2011) [41]	India	48 Intervention = 20 Control = 28	14–28 to end of pregnancy	19	history of preeclampsia, IUGR, perinatal death, multifetal gestation and chronic hypertension	Lycopene 2 mg twice a day	Without intervention	Lycopene supplementation does not decrease the incidence of preeclampsia in high risk women.
McCance (2010)	UK	749 Intervention = 375 Control = 374	8–22 to end of pregnancy	22	type 1 diabetes	Vit C 1000 mg + Vit E 400ui	Placebo	vitamins C and E did not reduce risk of preeclampsia in women with type 1 diabetes.
Gris (2010) [42]	France	160 Intervention = 80 Control = 80	12–36 or end of pregnancy	23	History of PE	Enoxaparin 4000 UI Aspirin 100 mg/day	Aspirin 100 mg/day	Enoxaparin reduce the occurrence of PE
Yu(2003) [43]	UK	554 Intervention = 276 Control = 278	22–24 To 36	21	high-risk in color Doppler (Women with a mean PI above 1.6, which was the 95th centile)	Aspirin 150 mg/day	Placebo	This intervention have no effect on PE
Subtil (2003) [44]	France & Belgium	3274 Intervention = 1634 Control = 1640	14–20 w to 34 w	22	Nulliparous high risk by a uteroplacental artery Doppler examination	Aspirin 100 mg/day	Placebo	Aspirin at a dose of 100 mg does not reduce the incidence of preeclampsia
Vainio (2002) [45]	Finland	90 Intervention = 45 Control = 45	12–14 until delivery	20	risk of preeclampsia or intrauterine growth retardation	acetylsalicyclic acid (0.5 mg/kg/daily)	Placebo	low-dose acetylsalicyclic acid given to high risk women reduced the incidence of PE.
Taherian (2002) [46]	Iran	990 Aspirin = 330 Ca + VitD = 330 Control = 330	20 w until delivery	20	healthy Nulliparous	1 Aspirin 75 mg/daily 2 calcium-D (500 mg calcium carbonate + 200 IU vitamin D)	Without intervention	low-dose aspirin or calcium-D is effective in reducing the occurrence of preeclampsia.

LMWH: low molecular weight Heparin, PE: preeclampsia, HTN: hypertension, LDA: low dose aspirin, ASA: Acetyl salicylic acid, Fe: Chemical symbol for Iron.

Table 3
Summarized the results of prevention factors of preeclampsia.

Treatment approaches	Related studies	Using in Pregnancy trimester	Results
Anticoagulants			
Low molecular weight heparin	McLaughlin (2017), Vries (2012)	T1 & T2	It is effective in reducing the incidence of PE alone or in combination with aspirin.
Enoxaparin	Groom (2017), Gris (2010)	T1 until delivery	No difference was not seen alone, but in combination with aspirin, it was involved in preventing PE.
Dalteparin	Van (2016),	T1 until delivery	Separately or in combination with aspirin, there was no difference in the incidence of PE.
Nadroparin	Martinelli (2012)	T1 until delivery	It did not affect the incidence of PE.
Nonsteroidal anti-inflammatory drugs			
Aspirin	Euser (2016), Odibo (2015), Hassan (2015), Cantu (2015), Talari (2014), Meiri (2014), Ayala (2012), Yu(2003), Subtil (2003), Vainio (2002), Taherian (2002)	T1 until delivery	Of the 11 studies in this field, 6 studies reported a decrease in incidence of PE and 5 studies reported no change in the incidence of PE.
Blood lipid lowering drugs			
Paraavastatin	Costantine (2016),	T1 until delivery	Reduces the incidence of PE.
Vasodilator			
NO-donor pentaerithrityl-tetranitrate (PETN)	Schleussner (2014),	T2 until T3	Early onset of PE decreased
physical activity			
yoga	Rakhshani (2012)	T1 to T3	It can regulate blood pressure disorders.
Micronutrients			
L-arginine	Camarena (2016), Vadillo (2011)	T2 & T3	Reduces the incidence of PE.
Vit E,C	Cardoso (2016), Rahmanian (2011), McCance (2010)	T1 until delivery	1 study showed reduction and 2 studies revealed no effect on the incidence of PE.
Folic acid	Wen (2013), Hassan (2015)	T1 until delivery	One study showed that early onset could play a role in preventing PE, but in combination with aspirin, no difference in incidence was observed.
Phytonutrient	Parrish (2013)	T1 until delivery	There was no effect on the incidence of PE.
Lycopene	Antartani (2011)	T1 to T3	There was no effect on the incidence of PE.
Vit D	Qian (2015)	T2 to T3	Reduces the incidence of PE.
VtD + Calcium	Taherian (2002)	T2 until delivery	Reduces the incidence of PE.

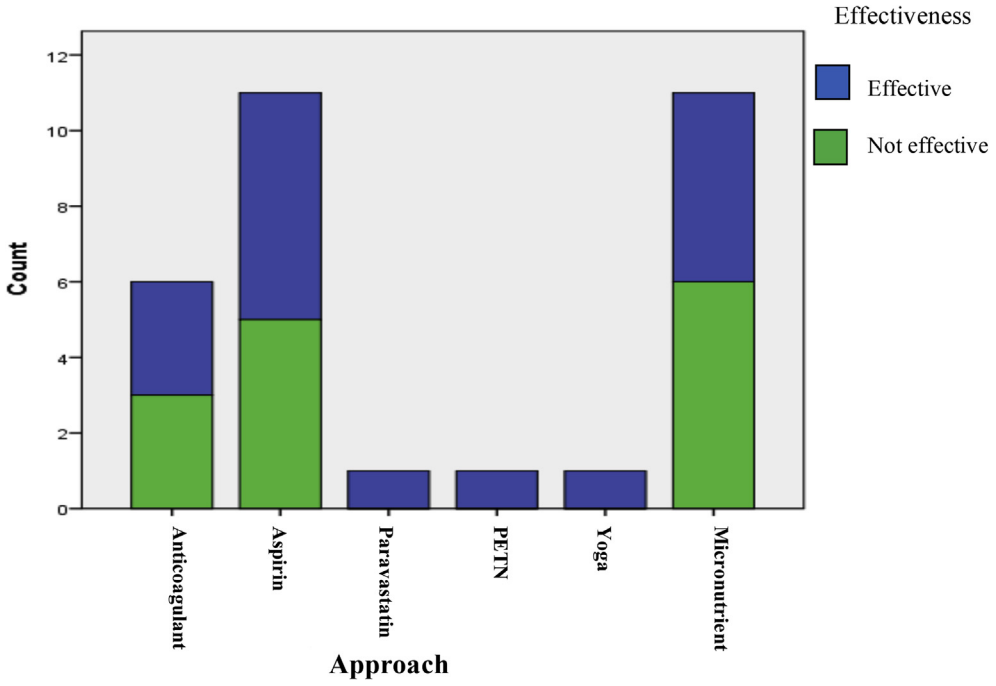

Fig. 3. The Effectiveness of preeclampsia preventive approaches.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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