Review Article

Prevention of preeclampsia by aspirin consumption in high-risk pregnancies that can be complicated with preeclampsia: A systematic review

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Background: For a long time, it has been proposed that aspirin might have a preventive property to reduce the risk of preeclampsia; however, recent assessments have changed the insights toward this medication. The current qualitative systematic review aims to thoroughly assess the outcomes of treatment with aspirin in high-risk preeclampsia women. **Materials and Methods:** The scope of this study was to evaluate: (1) the preventive role of treatment with aspirin on high-risk pregnancies for preeclampsia, (2) the applied dose on the incidence of preeclampsia, (3) the outcome of using aspirin alone versus in combination with an anticoagulant, and (4) the outcome of aspirin discontinuation on the incidence of preeclampsia. PubMed, Scopus, Web of Science, and Embase databases were searched from January 1, 2015, to December 31, 2023. English-written studies with trial designs (randomized or nonrandomized) assessing the use of aspirin on preeclampsia prevention among high-risk women for this phenomenon were included. Three authors independently surfed the databases and selected the studies; in case of any disagreement, the problem was resolved by the fourth author. Then, the papers were fully screened and those that met the study criteria were individually evaluated. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials was applied categorizing the studies into low-moderate and high risk of bias. **Results:** Finally, data from twenty-three studies on 15,764 high-risk preeclampsia individuals with singleton pregnancies were extracted. Fourteen, 4, and 5 studies had low, moderate, and high risk of bias. Aspirin use regardless of its dosage was not remarkably associated with reduced risk of preeclampsia in the majority of studies. Besides, the time of initiation or discontinuation did not affect the outcomes. Moreover, aspirin combination with anticoagulant was not necessarily superior over aspirin alone. **Conclusion:** Based on our findings, the body of evidence majorly found no remarkable role for prophylactic aspirin use to prevent preeclampsia incidence at any time during pregnancy; however, promising data, particularly in higher doses and earlier initiation of aspirin, have been noted.

Key words: Aspirin, high-risk pregnancy, preeclampsia, pregnancy, treatment outcome

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INTRODUCTION

Preeclampsia is a life-threatening multisystem disorder affecting 2%–4% of all pregnancies worldwide.[1] It is estimated that preeclampsia is responsible for over 70000 maternal and 500000 fetal deaths around the globe.[2]

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This phenomenon is generally characterized by the development of hypertension and proteinuria initiated after the 20th gestational week. Preeclampsia is classified as early preterm, preterm, and term considering the initiation of the disorder, i.e., <34th, <37th, and >37th week of pregnancy, respectively. Besides, it can lead to complications including preterm birth, fetal growth

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restriction, placental abruption, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, seizures (eclampsia), and other end organ damage (acute kidney injury, stroke, myocardial infarction, pulmonary edema, retinal detachment, and hepatic dysfunction), especially with onset at earlier gestational ages.[3]

Once preeclampsia occurs, it progressively continues to worsen, and termination is the only way to treat preeclampsia if gets severe. This is while termination before the 37th gestational week is a challenging issue due to prematurity and its related complications.[4] On the other hand, continuation of a preeclamptic pregnancy might be fatal for both the mother and the fetus. Given that, preeclampsia prevention plays a critical role in the management of individuals at high risk for developing preeclampsia.[5]

A variety of drugs have been experimented to prevent or treat preeclampsia; among which, aspirin is the most common one with the most promising prophylactic effects. The major property by which aspirin exerts its effect is dependent on cyclooxygenase, which inhibits thromboxane A2 production in platelets and subsequently reverses the preeclampsia patients' thromboxane A2/prostaglandin I2 imbalance, thereby improving placental function by favoring systemic vasodilatation and inhibiting the platelet aggregation, which is abnormally activated in preeclampsia.[6]

The prophylactic use of aspirin was primarily proposed in 1978,[7] while the first randomized clinical trial was published in 1985.[8] Since then, numerous trials presented promising outcomes regarding the use of low-dose aspirin to prevent preeclampsia in low-risk women. In 2004, the first meta-analysis presented that the use of aspirin in high-risk women could reduce the rate of preeclampsia by 19%.[9] Given that, the guidelines recommended applying low-dose aspirin in high-risk females to minimize the probability of preeclampsia development. Nevertheless, the protocols remarkably vary over the countries.[2,5,10-12] For instance, one of the most prominent guidelines which has emphasized on the significance of low-dose aspirin therapy for preeclampsia prevention is the American College of Obstetricians and Gynecologists (ACOG) which recommended daily low-dose aspirin initiated between 12th and 28th week of gestation, optimally before 16th week.[5] The recommended time of aspirin imitation by the World Health Organization is before the 20th week, while the Royal College of Obstetricians and Gynaecologists (RCOG) provides a scoring system by which the risk of preeclampsia is evaluated, and then, the decision to treat with aspirin is made.[13]

Nevertheless, a growing body of evidence has shown no beneficial effect of aspirin to reduce preeclampsia,[12,14] while others have presented a dose-dependent effect of aspirin use to reduce the risk of preeclampsia.[15] Although the reason for this controversy is not well-elucidated, it might have occurred due to the screening test of the large population, the inclusion of pregnant women who are at lower risk of preeclampsia, the diversity in gestational age to initiate aspirin treatment, and the definitions made for high risk for preeclampsia.[12,16-18] Moreover, it may be because of the underreporting of other smaller negative trials.[16] Some studies have presented a dose-dependent role for aspirin in reducing the risk of preeclampsia. Considering the trace of platelet activity in the pathogenesis of preeclampsia, it seems that higher doses might have deeper effects on platelet activity.[19,20] Moreover, response to aspirin is heterogeneous, and this heterogeneity might be related to ethnicity and race which can be attributed to the conclusion made by different studies.[21] Accordingly, we aimed to investigate the current systematic review to explore studies from 2015 to 2023 assessing the efficacy of aspirin use in reducing preeclampsia incidence in high-risk pregnancies.

MATERIALS AND METHODS

Research strategy

We aimed to conduct a systematic review based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[22] To carry out an exhaustive search, the PubMed, Scopus, Web of Science (WOS), and Embase databases were used from January 1, 2015, to December 31, 2023. Based on our primary research, 746 articles were extracted.

The searched keywords included ("Aspirin") OR ("ASA") OR ("acetylsalicylic acid") AND ("pregnancy") AND ("preeclampsia") OR (pre-eclampsia) OR (pregnancy complications) AND (Randomized Clinical trial) OR (Clinical Trial) OR (trial) OR ("RCT").

Inclusion criteria

The included studies for this systematic review met the following criteria: (1) written in English, (2) designed in trial format, either randomized or non-randomized, (3) conducted on human samples, (4) receiving aspirin at any dose, and (5) commencing aspirin treatment at any point during pregnancy.

Exclusion criteria

Studies that were excluded from this systematic review included those that did not have sufficient data for analysis, those that reported pregnancy complications other than preeclampsia, the investigations that were designed in other formats than trial, studies for which the full texts were not accessible, and the ones that were written in languages other than English.

Study selection

The authors independently surfed the mentioned databases and selected the studies; in case of any disagreement, the problem was resolved by another author. Then, the papers were fully screened regarding duplication, and the double-selected ones were eliminated. Subsequently, those articles that met the study criteria were individually evaluated. Finally, all those articles that met the eligibility criteria were identified and included in the qualitative analysis.

Population, intervention, comparison, outcome components

Population: high risk for preeclampsia pregnant women [Table 1]; Intervention: treatment with aspirin; Comparison: (1) different doses of aspirin, placebo versus aspirin, other therapeutic agents versus aspirin, the effect of aspirin continuation, or discontinuation on pregnancy outcomes; Outcome: the incidence of preeclampsia in any point during pregnancy.

Data extraction

The authors independently extracted the data from the included papers including the first author and year of publication, the studied population, the design of the study, the strategy to prevent preeclampsia, the span of time in which medication was initiated and discontinued, and the incidence of preeclampsia at any point during pregnancy.

RESULTS

Study selection

The literature search strategy yielded 746 records, and 586 have remained after duplicates' removal. After initial screening according to the titles and abstracts, 158 full-text articles were saved and assessed. Ultimately, 23 studies were included in the qualitative assessment as shown in the PRISMA flow diagram in Figure 1.

The sample size of the study includes 15,764 individuals. From all the 23 studies, we extracted 41 studies because of each study may have had more than one outcome measurements [Table 1].

The main reported characteristics and data in the included articles are demonstrated in Table 1. All the included studies were designed in randomized clinical trials and have been

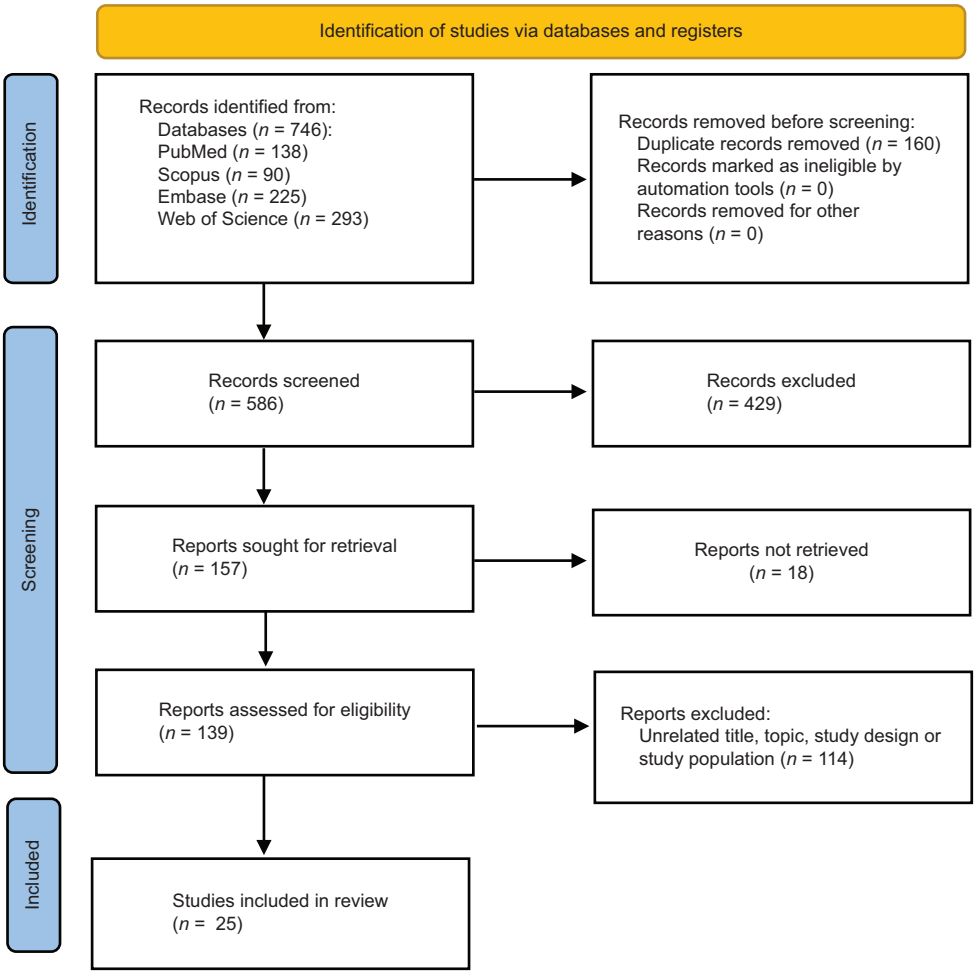

Figure 1: Flowchart of study selection for systematic review

Table 1: The included studies

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Rolnik *et al.*[23]	2017	England	Randomized clinical trial	1776	High risk for PE and singleton pregnancy	Maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum PAPP-A and placental growth factor	798 in the intervention group received 150 mg aspirin versus 822 in the control group	11:14	36	13 (1.6%) in the intervention group versus 35 (4.3%) in the control group	Decreased preterm PE
ASA treatment	Rolnik *et al.*[23]	2017	England	Randomized clinical trial	1776	High risk for PE and singleton pregnancy	Maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum PAPP-A and placental growth factor	798 in the intervention group received 150 mg versus 822 in the control group	11:14	36	53 (6.6%) in the intervention group versus 59 (7.9%) in the control group	No difference for PE
ASA treatment	Huai *et al.*[24]	2021	China	Randomized clinical trial	190	High risk for PE and singleton pregnancy	History of PE, preexisting diabetes, or chronic hypertension; or presence of ≥2 intermediate-risk factors of obesity (BMI ≥28 kg/m^2), advanced maternal age (≥35 years), family history of PE, or nulliparity	95 in the intervention group received 100 mg aspirin versus 95 in the control group	<16	-	1 (1.1%) in the intervention group versus 4 (4.2%) in the control group	No difference for preterm PE
ASA treatment	Huai *et al.*[24]	2021	China	Randomized clinical trial	190	High risk for PE and singleton pregnancy	History of PE, preexisting diabetes, or chronic hypertension; or presence of≥2 intermediate-risk factors of obesity (BMI ≥28 kg/m^2), advanced maternal age (≥35 years), family history of PE, or nulliparity	95 in the intervention group received 100 mg aspirin versus 95 in the control group	<16	-	3 (3.2%) in the intervention group versus 2 (2.1%) in the control group	No difference for PE
ASA treatment	Huai *et al.*[24]	2021	China	Randomized clinical trial	93	High risk for PE and singleton pregnancy and chronic hypertension	History of PE, preexisting diabetes, or chronic hypertension; or presence of ≥2 intermediate-risk factors of obesity (BMI ≥28 kg/m^2), advanced maternal age (≥35 years), family history of PE, or nulliparity	44 in the intervention group received 100 mg aspirin versus 49 in the control group	<16	-	2 (4.5%) in the intervention group versus 10 (20.4%) in the control group	Decreased preterm PE

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Table 1: Contd...

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Huai *et al.*[24]	2021	China	Randomized clinical trial	93	High risk for PE and singleton pregnancy and chronic hypertension	History of PE, preexisting diabetes, or chronic hypertension; or presence of ≥2 intermediate-risk factors of obesity (BMI≥28 kg/m^2), advanced maternal age (≥35 years), family history of PE, or nulliparity	44 in the intervention group received 100 mg aspirin versus 49 in the control group	<16	-	1 (2.3%) in the intervention group versus 5 (10.2%) in the control group	No difference for PE
Discontinuation	Mendoza *et al.*[3]	2023	Spain	Randomized clinical trial	936	High risk for PE and singleton pregnancy	High risk of preterm PE (≥1/170) in the first-trimester screening (11–13 weeks of gestation) according to the screening algorithm	473 in the intervention group received 150 mg aspirin until delivery versus 463 received 150 mg aspirin until 24–28th gestational weeks	<16	24–28	7 (1.48%) in the intervention group continuing aspirin until delivery versus 8 (1.73%) in those who discontinued treatment within 24–28th gestational week	No difference for preterm PE
Discontinuation	Mendoza *et al.*[3]	2023	Spain	Randomized clinical trial	936	High risk for PE and singleton pregnancy	High risk of preterm PE (≥1/170) in the first-trimester screening (11–13 weeks of gestation) according to the screening algorithm	473 in the intervention group received 150 mg aspirin until delivery versus 463 received 150 mg aspirin until 24–28th gestational weeks	<16	24–28	30 (6.34%) in the intervention group continuing aspirin until delivery versus 40 (8.64%) in those who discontinued treatment within 24–28th gestational week	No difference for PE
ASA treatment	Tolcher *et al.*[21]	2020	USA	Randomized clinical trial	3134	High risk for PE and singleton pregnancy	Pregestational insulin-treated diabetes mellitus, chronic hypertension, multiple gestations, or a history of PE	1570 in the intervention group received 60 mg aspirin versus 1564 in the control group	13:26	-	69 (4.39%) in the intervention group versus 94 (6.09%) in the control group	No difference for PE

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Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Tolcher *et al.*[21]	2020	USA	Randomized clinical trial	2539	High risk for PE and singleton pregnancy	Pregestational insulin-treated diabetes mellitus, chronic hypertension, multiple gestations, or a history of PE	1273 in the intervention group received 60 mg aspirin versus 1266 in the control group	13:26	-	231 (18.14%) in the intervention group versus 254 (20.06%) in the control group	No difference for PE
ASA treatment	Lin *et al.*[6]	2022	China	Randomized clinical trial	898	High risk for PE and singleton pregnancy	At least 1 high risk factor, namely, history of PE, diabetes mellitus (type 1 or 2), or chronic hypertension; or At least 2 of the following intermediate risk factors, including obesity (prepregnancy body mass index [pre-BMI] 28 kg/m^2), advanced maternal age (35 years), family history of PE (mother or/and sister) or nulliparity	464 in the intervention group received 100 mg aspirin versus 434 in the control group	12:20	34	78 (16.8%) in the intervention group versus 74 (17.1%) in the control group	No difference for PE
Dose	Gu *et al.*[25]	2020	China	Randomized clinical trial	1105	High risk for PE and singleton pregnancy	History of PE or gestational hypertension, chronic hypertension, multiple pregnancies, kidney disease, type 1 or type 2 diabetes and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome	284 in the intervention group recieved 25 mg aspirin, 272 in the intervention group received 50 mg aspirin, 278 in the intervention group received 75 mg aspirin and 271 in the group receiving nothing	<12	-	51 (18%) in the intervention group treated with 25 mg aspirin, 37 (13.6%) in the intervention group treated with 50 mg aspirin, 28 (10.1%) in the intervention group treated with 75 mg aspirin and 26 (9.6%) in the intervention group receiving no treatment	Higher dose significantly decreased PE
ASA treatment	Diguisto *et al.*[32]	2022	France	Randomized clinical trial	1100	High risk for PE and singleton pregnancy	A lowest pulsatility index≤1.7 for both uterine arteries or bilateral protodiastolic notching	550 in the intervention group received 160 mg aspirin versus 550 in the control group	11:14	34	88 (16%) in the intervention group versus 79 (14.4%) in the control group	No difference for PE

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Table 1: Contd...

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA versus anticoagulant treatment	Haddad *et al.*[31]	2016	France	Randomized clinical trial	244	Previous history of PE	A confirmed history of previous severe PE diagnosed before 34 weeks of gestation	122 in the intervention group received 100 mg aspirin versus 122 in the intervention group received 100 mg aspirin plus 4000 IU enoxaparin	<16	35	27 (22.1%) in the intervention group versus 22 (18%) in the control group	No difference for PE
ASA treatment	Liu *et al.*[27]	2016	China	Randomized clinical trial	98	High risk for PE and singleton pregnancy	Age ≥40, BMI ≥35 kg/m^2, PE family history, multiple pregnancy history, previous hypertensive disease, chronic nephrosis, autoimmune disease like systemic lupus erythematosus and antiphospholipid syndrome, type 1 or type 2 diabetes, chronic hypertension	50 in the intervention group received 100 mg aspirin versus 48 in the control group	-		3 (6%) in the intervention group versus 10 (20.8%) in the control group	Decreased PE
ASA treatment	Mone *et al.*[33]	2018	Ireland	Randomized clinical trial	546	High risk for PE and singleton pregnancy	Chronic kidney disease; autoimmune disease, e.g., systemic lupus erythematosus, diabetes mellitus and chronic hypertension	192 in the intervention group received 75 mg aspirin versus 354 in the control group	11:14	36	8 (4.16%) in the intervention group versus 7 (1.97%) in the control group	Decreased PE
ASA treatment	Odibo *et al.*[28]	2015	USA	Randomized clinical trial	30	High risk for PE and singleton pregnancy	Chronic hypertension, history of prior PE, diabetes mellitus, obesity (BMI>30), bilateral uterine artery notches, low PAPP-A (<0.52 MoM)	16 in the intervention group received 81 mg aspirin versus 14 in the control group	11:14	37 or delivery	3 (18.75%) in the intervention group versus 3 (21.42%) in the control group	No difference for PE
ASA versus anticoagulant treatment	van Hoorn *et al.*[34]	2016	Netherlands	Randomized clinical trial	32	High risk for PE and singleton pregnancy	History of uteroplacental insufficiency and delivery before 34 weeks of gestation (hypertensive disorders of pregnancy and small for gestational age infant), anticardiolipin antibodies present and/or lupus anticoagulant present	16 in the intervention group received 80 mg aspirin versus 16 received 80 mg aspirin plus 2500–7500 IU dalteparin	6:12	36	2 (12.6%) in the intervention group received 80 mg aspirin versus 0 (0%) in the intervention group received 80 mg aspirin plus 2500–7500 IU dalteparin	No difference for PE

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Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA versus anticoagulant treatment	van Hoorn *et al.*[34]	2016	Netherlands	Randomized clinical trial	32	High risk for PE and singleton pregnancy	History of uteroplacental insufficiency and delivery before 34 weeks of gestation (hypertensive disorders of pregnancy and small for gestational age infant), anticardiolipin antibodies present and/or lupus anticoagulant present	16 in the intervention group received 80 mg aspirin versus 16 received 80 mg aspirin plus 2500–7500 IU dalteparin	6:12	36	1 (6.3%) in the intervention group received 80 mg aspirin versus 0 (0%) in the intervention group received 80 mg aspirin plus 2500–7500 IU dalteparin	No difference for preterm PE
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	523	High risk for PE and singleton pregnancy	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	265 in the intervention group received 60 mg aspirin versus 258 in the control group	<12	37	59 (22.26%) in the intervention group versus 71 (27.52%) in the control group	No difference for PE
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	523	High risk for PE and singleton pregnancy	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	265 in the intervention group received 60 mg aspirin versus 258 in the control group	<12	37	13 (4.91%) in the intervention group versus 8 (3.10%) in the control group	No difference for preterm PE
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	191	High risk for PE and singleton pregnancy and diabetes mellitus	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	94 in the intervention group received 60 mg aspirin versus 97 in the control group	<12	37	17 (18.9%) in the intervention group versus 21 (21.65%) in the control group	No difference for PE
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	191	High risk for PE and singleton pregnancy and diabetes mellitus	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	94 in the intervention group received 60 mg aspirin versus 97 in the control group	<12	37	5 (5.32%) in the intervention group versus 3 (3.09%) in the control group	No difference for preterm PE
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	186	High risk for PE and singleton pregnancy and chronic hypertension	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	93 in the intervention group received 60 mg aspirin versus 93 in the control group	<12	37	23 (24.73%) in the intervention group versus 32 (34.41%) in the control group	No difference for PE

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Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Moore *et al.*[29]	2015	USA	Randomized clinical trial	186	High risk for PE and singleton pregnancy and chronic hypertension	Preexisting diabetes mellitus, chronic hypertension or a history of PE in a previous pregnancy	93 in the intervention group received 60 mg aspirin versus 93 in the control group	<12	37	6 (6.45%) in the intervention group versus 3 (3.23%) in the control group	No difference for preterm PE
Dose	Tapp *et al.*[35]	2020	Canada	Randomized clinical trial	107	High risk for PE and singleton pregnancy	Previous history of PE	54 in the intervention group received 80 mg aspirin versus 53 received 160 mg aspirin	10:16	36	6 (12%) in the intervention group received 80 mg aspirin versus 8 (15%) received 160 mg aspirin	No difference for PE
Dose	Tapp *et al.*[35]	2020	Canada	Randomized clinical trial	107	Previous history of PE	Previous history of PE	54 in the intervention group received 80 mg aspirin versus 53 received 160 mg aspirin	10:16	36	0 (0%) in the intervention group received 80 mg aspirin versus 1 (2%) received 160 mg aspirin	No difference for preterm PE
Dose	Tapp *et al.*[35]	2020	Canada	Randomized clinical trial	107	Previous history of PE	Previous history of PE	54 in the intervention group received 80 mg aspirin versus 53 received 160 mg aspirin	10:16	36	0 (0%) in the intervention group received 80 mg aspirin versus 1 (2%) received 160 mg aspirin	No difference for early preterm PE (<34 weeks)
Dose	Muldoon *et al.*[36]	2023	Canada	Randomized clinical trial	660	High risk for PE and singleton pregnancy	-	548 in the intervention group received<81 mg aspirin versus 112 received 81–150 mg aspirin	<16	Delivery	99 (15%) in the intervention group received<81 mg aspirin versus 33 (5%) received 81–150 mg aspirin	Higher dose significantly decreased PE
Dose	Muldoon *et al.*[36]	2023	Canada	Randomized clinical trial	660	High risk for PE and singleton pregnancy	-	548 in the intervention group received<81 mg aspirin versus 112 received 81–150 mg aspirin	<16	Delivery	41 (6.21%) in the intervention group received<81 mg aspirin versus 19 (2.88%) received 81–150 mg aspirin	Higher dose significantly decreased preterm PE

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Table 1: Contd...

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Euser *et al.*[30]	2016	USA	Randomized clinical trial	225	High risk for PE and singleton pregnancy	Multiple gestation, chronic hypertension, insulin-dependent diabetes or preeclampsia in a prior pregnancy	106 in the intervention group received 80 mg aspirin versus 119 in the control group			6 (6%) in the intervention group versus 19 (16%) in the control group	Decreased PE
ASA versus anticoagulant treatment	Baiazid and Hraib[37]	2022	Syria	Randomized clinical trial	14	Antiphospholipid syndrome	Clinical criteria 1. Vascular thrombosis 2. Pregnancy morbidity a. 1 or more late termination spontaneous miscarriages of a morphologically normal fetus (≥10 weeks of gestation). Or b. 1 or more premature births of a morphologically healthy neonate (≤34 weeks of gestation) due to severe placental insufficiency or severe PE or eclampsia or c. 3 or more unexplained, consecutive, spontaneous miscarriages (<10 weeks of gestation) Laboratory criteria on 2 or more occasions at least 12 weeks apart 1. LA 2. Medium to high levels of aCL antibody of IgG and/or IgM isotype 3. Anti-b2 glycoprotein-I antibody (anti-β2GPI) of IgG and/or IgM isotype	5 in the intervention group received 100 mg aspirin versus 9 received 100 mg aspirin plus 5000 IU heparin			0 (0%) in the intervention group received 100 mg aspirin versus 0 (0%) received 100 mg aspirin plus 5000 IU heparin	No difference for PE
ASA treatment	Abdi *et al.*[38]	2020	Iran	Randomized clinical trial	86	Previous history of PE	Previous history of PE	43 in the intervention group received 80 mg aspirin versus 43 in the control group	12:15	36	15 (39.9%) in the intervention group versus 26 (60.5%) in the control group	Decreased PE

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Table 1: Contd...

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
ASA treatment	Xiao *et al.*[26]	2023	China	Randomized clinical trial	266	High risk for PE and singleton pregnancy	≥1 high-risk factor or≥2 intermediate-risk factors for PE according to the 2019 ACOG guidelines	115 in the intervention group received 75 mg aspirin versus 151 in the control group	12:24	36	12 (10.43%) in the intervention group versus 34 (2.52%) in the control group	Decreased PE
ASA treatment	Andrade *et al.*[39]	2022	Brazil	Randomized clinical trial	277	High risk for PE and singleton pregnancy	-	139 in the intervention group received 100 mg aspirin versus 138 in the control group	11:14	34	5 (5.8%) in the intervention group versus 14 (10.2%) in the control group	No difference for PE
ASA treatment	Anjum *et al.*[40]	2022	Pakistan	Randomized clinical trial	140	Previous history of PE	Previous history of PE, hypertension or diabetes	119 in the intervention group received 80 mg aspirin versus 121 in the control group		36	2 (1.6%) in the intervention group versus 5 (4.1%) in the control group	Decreased PE
ASA treatment	Anjum *et al.*[40]	2022	Pakistan	Randomized clinical trial	140	Previous history of PE and preexisting hypertension	Previous history of PE, hypertension or diabetes	119 in the intervention group received 80 mg aspirin versus 121 in the control group		36	16 (13.4%) in the intervention group versus 19 (15.7%) in the control group	No difference for PE
ASA treatment	Anjum *et al.*[40]	2022	Pakistan	Randomized clinical trial	140	High risk for PE and singleton pregnancy and diabetes mellitus	Previous history of PE, hypertension or diabetes	119 in the intervention group received 80 mg aspirin versus 121 in the control group		36	8 (6.7%) in the intervention group versus 8 (6.6%) in the control group	No difference for PE
Dose	Kumar *et al.*[15]	2020	India	Randomized clinical trial	178	High risk for PE and singleton pregnancy	A calculator assessing history of PE, BMI, medical disorders, mean arterial pressure and uterine artery pulsatile index	91 in the intervention group received 75 mg aspirin versus 87 received 150 mg aspirin	11:14	36	6 (6.5%) in the intervention group received 75 mg aspirin versus 15 (17.2%) received 150 mg aspirin	Higher dose significantly decreased PE
Dose	Kumar *et al.*[15]	2020	India	Randomized clinical trial	178	High risk for PE and singleton pregnancy	A calculator assessing history of PE, body mass index, medical disorders, mean arterial pressure and uterine artery pulsatile index	91 in the intervention group received 75 mg aspirin versus 87 received 150 mg aspirin	11:14	36	1 (1%) in the intervention group received 75 mg aspirin versus 5 (5.7%) received 150 mg aspirin	No difference for preterm PE

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Table 1: Contd...

Title	Author	Year	Country	Study design	*n*	Eligibility	Definition of high risk for PE	The intervention groups	Time of initiation	Time of discontinuation	The PE occurrence	Outcome
Dose	Kasraeian *et al.*[18]	2022	Iran	Randomized clinical trial	190	High risk for PE and singleton pregnancy	High resistance UAPI >95th centile in Doppler ultrasound plus the history of previous high-risk pregnancies including the history of hypertension, preterm birth, PE, diabetes, fetal growth restriction, or preterm rupture of membrane	101 in the intervention group received 80 mg aspirin versus 89 received 150 mg aspirin	11:14	36	18 (17.8%) in the intervention group received 80 mg aspirin versus 3 (3.4%) received 150 mg aspirin	Higher dose significantly decreased PE

UAPI=Uterine Artery Pulsatility Index; BMI=Body mass index; ACOG=American College of Obstetricians and Gynecologists; PE=Preeclampsia; LA=Lupus anticoagulant; aCL=Anticardiolipin; PAPP-A=Pregnancy-associated plasma protein A; Ig=Immunoglobulin

conducted on human samples. The recruited studies were from England,[23] China,[6,24-27] Spain,[3] USA,[21,28-30] France,[31,32] Ireland,[33] Netherlands,[34] Canada,[35,36] Syria,[37] Iran,[18,38] India,[15] Brazil,[39] and Pakistan[40] [Table 1].

The scope of this study was to evaluate (1) the preventive role of treatment with aspirin on high-risk pregnancies for preeclampsia, (2) the applied dose on the incidence of preeclampsia, (3) the outcome of using aspirin alone versus in combination with anticoagulant on the incidence of preeclampsia, and (4) the outcome of aspirin discontinuation on the incidence of preeclampsia.

The definition of high-risk for preeclampsia variably differed among the studies and is presented in detail in Table 1. Besides, preeclampsia was categorized into three groups of term, preterm, and early preterm defined as the incidence of preeclampsia >37th, <37th, and <34th week of pregnancy, respectively.

Risk of bias

The revised JBI critical appraisal tool for the assessment of the risk of bias for randomized controlled trials was applied to determine the risk of bias.[41] Given that, two of the authors (S. A. and H. Gh. T.) evaluated the studies one by one to score their risk of bias. Then, their idea about each study was discussed, and the level of bias was concluded. This assessment revealed that 14,[3,15,18,23,25,27-33,35,39] 4,[6,21,24,38] and 5[26,34,36,37,40] studies had low, moderate, and high risk of bias, respectively [Table 2].[41]

Outcomes

Aspirin preventive role on the incidence of preeclampsia

Data from 26 investigations extracted from 14 studies for the assessment of applying ASA to prevent preeclampsia incidence, including 12,298 patients, were incorporated in this systematic review.

Twelve studies[6,21,23,24,26-30,32,33,39] evaluated the preventive outcome of aspirin use on preeclampsia, in which 11602 high-risk women for preeclampsia with singleton pregnancy were included. The utilized daily doses of aspirin were 60,[21,29] 75,[26,33] 81,[28] 100,[6,24,39] 150,[23] and 160[32] mg. The majority of studies commenced their intervention in the 11th to 13th + 6 days of pregnancy;[23,28,32,33,39] however, the others reported ASA initiation before the 12th,[29] before the 16th,[24] 12th to 23th + 6 days,[26] and 13th to 25th + 6 days,[21] as well. In addition, most of the investigations continued aspirin until the end of the 36th week[23,26,33] of pregnancy. Nevertheless, the others reported 34th[6,32,39] or 37th[28,29] weeks, as well.

The major body of evidence presented no role for aspirin in the reduction of either preterm preeclampsia[24,29] or

Table 2: Risk of bias

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	Outcomes
Rolnik *et al.*[23]	2017	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Huai *et al.*[24]	2021	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Mendoza *et al.*[3]	2023	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Tolcher *et al.*[21]	2020	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Lin *et al.*[6]	2022	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Gu *et al.*[25]	2020	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Diguisto *et al.*[32]	2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Haddad *et al.*[31]	2016	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Liu *et al.*[27]	2016	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Low
Mone *et al.*[33]	2018	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Odibo *et al.*[28]	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
van Hoorn *et al.*[34]	2016	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Moore *et al.*[29]	2015	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Low
Tapp *et al.*[35]	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Muldoon *et al.*[36]	2023	Unclear	Unclear	No	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	High
Euser *et al.*[30]	2016	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Baiazid and Hraib[37]	2022	Yes	No	Yes	No	Unclear	N/A	No	Yes	Yes	Yes	N/A	Yes	No	High
Abdi *et al.*[38]	2020	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Xiao *et al.*[26]	2023	Yes	N/A	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Andrade *et al.*[39]	2022	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Anjum *et al.*[40]	2022	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	High
Kumar *et al.*[15]	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Kasraeian *et al.*[18]	2022	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

N/A=Not available

preeclampsia.[6,21,23,24,28,29,32,39] However, despite preeclampsia, the assessments of Rolnik *et al*. on preterm preeclampsia were promising for aspirin.[23] Other positive outcomes for aspirin use to prevent preeclampsia incidence were published by Liu *et al*.,[27] Mone *et al*.,[33] Euser *et al*.,[30] and Xiao *et al*.[26]

Huai and colleagues evaluated aspirin use at a daily dose of 100 mg on 44 high-risk preeclampsia women with singleton pregnancy and preexisting hypertension versus 49 normal individuals and presented a decreased risk of preterm preeclampsia incidence; however, their investigation on term preeclampsia revealed no effect.[24] Similar outcomes for both preterm and delayed preeclampsia were presented in the study of Moore *et al*.,[29] as well.

Furthermore, the assessments on high-risk preeclampsia women with singleton pregnancy and preexisting diabetes mellitus were accompanied by no preventive role for aspirin use.[29,40]

Anjum and colleagues also evaluated the use of aspirin on two other critical groups including those who had a previous history of preeclampsia with or without preexisting hypertension and presented a statistically significant reduction in the incidence of preeclampsia among those who did not have preexisting hypertension, but not for those with the history of hypertension in their past medical history.[40] Another assessment conducted on individuals with a previous history of preeclampsia was conducted in Iran concluding that aspirin use at an 80 mg daily dose led to a remarkable decrease in the incidence of preeclampsia.[38]

Detailed data are presented in Table 1.

Aspirin daily dose and the incidence of preeclampsia

Data from 9 investigations were extracted from 5 studies assessing the outcomes of different aspirin doses on the incidence of preeclampsia incidence. The number of included patients was 2240 women.

Tapp *et al*. evaluated high-risk preeclampsia women with singleton pregnancies in two groups of 80 mg versus 160 mg daily aspirin use initiated between the 10th and 15th + 6 day of pregnancy and continued until the 36th week. They presented 12% versus 15% of preeclampsia incidence with no significant difference.[35] Similar outcomes were presented by Kumar *et al*. who compared 75 mg versus 150 mg aspirin use between the 11th −13th + 6 days and 36th week of pregnancy with no remarkable effect on the incidence of preterm preeclampsia.[15]

Nevertheless, there is evidence regarding the benefits of higher doses of aspirin on the incidence of preeclampsia. Kasraeian *et al*. compared 80 mg daily dose with 150 mg commenced between the 11th −13th + 6 days and 36th week of pregnancy and concluded in favor of the higher dose.[18] Kumar and colleagues also reported the superiority of 150 mg aspirin over 75 mg in the incidence of preeclampsia.[15] Similar outcomes were presented for both preterm and term preeclampsia and compared <81 mg aspirin with 81–150 mg daily aspirin.[36] The other study by Gu *et al*. compared 25, 50, and 75 mg daily doses of aspirin initiated before the 12th week of pregnancy. Although they did not report the time of aspirin discontinuation, they concluded that higher doses significantly decreased preeclampsia.[25]

The evaluation of different doses of 80 versus 160 mg aspirin on individuals with a previous history of preeclampsia revealed no significant difference.[35]

Detailed data are presented in Table 1.

The time of aspirin initiation and discontinuation

The time of ASA treatment initiation variably differed over the studies. Nevertheless, the majority of the studies on high-risk individuals for preeclampsia with singleton pregnancy commenced the treatment before week 16;[6,15,18,21,23-40] however, a rarity of studies reported aspirin initiation even in week 20,[6] 24,[26] or 26.[21] On the other hand, van Hoorn *et al*. reported that daily ASA was prescribed for their patients as early as the 6th week of gestation.[34]

Week 36 was the most common time to cease aspirin use.[15,18,23,26,33-35,38,40] Other studies reported weeks 34,[6,32,39] 35,[31] 37,[28,29] or until delivery.[28,36]

Detailed information is shown in Table 1.

Aspirin alone versus in combination with an anticoagulant to prevent preeclampsia

Data from 4 investigations extracted from 3 studies on 290 individuals evaluated ASA alone or in combination with anticoagulant to prevent preeclampsia incidence.

Van Hoorn and colleagues assessed high-risk for preeclampsia women with singleton pregnancies and presented no difference between 80 mg aspirin use alone or combined with 2500–7500 IU dalteparin initiated on the 6th to 11th + 6 day of pregnancy and continued until the 36th week either for the incidence of preterm preeclampsia or term preeclampsia.[34] Similar findings were concluded in the study of Haddad *et al*. who compared daily dose of 100 mg aspirin versus 100 mg aspirin plus 4000 IU enoxaparin started before week 16th of pregnancy and discontinued at week 35th + 6 days.[31] The other in-line outcome was published in a study conducted on women with antiphospholipid syndrome divided into a group

receiving 100 mg aspirin only versus 100 mg aspirin plus 5000 IU heparin[37] [Table 1].

Early aspirin discontinuation and the incidence of preeclampsia

Data from 2 investigations extracted from a study on 936 individuals with singleton pregnancy who were at high risk for preeclampsia revealed no difference in the incidence of both preterm versus term preeclampsia between the cases who continued 150 mg daily aspirin until 36th week of pregnancy versus those who discontinued it within the 24th–28th weeks of pregnancy[3] [Table 1].

DISCUSSION

We observed that data regarding the use of aspirin for preeclampsia prevention are remarkably variable. This variety includes several points including whether or not to apply aspirin, the subpopulation for whom aspirin should be considered, the dosage of aspirin, the time of ASA initiation, the time of cessation, the use of aspirin alone or in combination with anticoagulants, and the benefits of early aspirin discontinuation rather that its use until the late days of the third trimester.

In the studies assessing the benefits of ASA treatment for preeclampsia, only 8 out of 42 extracted studies presented promising data regarding the use of aspirin to prevent either preeclampsia in general or preterm preeclampsia.[23,24,26,27,30,33,38,40] The majority of these trials were conducted on high-risk preeclampsia individuals who were singleton pregnant except the studies performed by Abdi *et al*.[38] and Anjum *et al*.[40] who included patients with a previous history of preeclampsia. These investigations with a positive notion regarding the use of aspirin applied doses ranged from 75 to 150 mg per day and commenced ASA use ranging from the 11th week of pregnancy to the 23rd + 6 day and discontinued it until the 36th week.

In contrast, the majority of the trials did not show any benefit, representing no role for aspirin use in different doses and with wide ranges of duration of use in pregnancy to decrease the probability of preeclampsia incidence. These studies were conducted on high-risk preeclampsia individuals without preexisting chronic disease,[6,21,23,24,28,29,32,39] those who had a positive history of hypertension[24,29] or diabetes mellitus,[29,40] as well as the individuals who had a previous history of preeclampsia in their prior pregnancies.[40] The initiation of aspirin administration in the studies ranged from week 6 to 26, and the time of cessation was between weeks 34 and delivery.[6,21,23,24,28,29,32,39,40]

Nevertheless, some data assessing the preventive effect of different doses of aspirin on preeclampsia concluded that higher doses were accompanied by less incidence of this phenomenon.[15,18,25,36] The highest daily applied dose in these studies is 150 mg;[15,18,36] however, Gu *et al*. made this conclusion by comparing 25, 50, and 75 mg.[25] This is while the lowest dose in other studies was 75 mg.[15,18,36] The basis of the theory on higher doses of aspirin to prevent preeclampsia stands on two perspectives. Primarily, it is assumed that considering the role of platelet activation and aggregation in the pathogenesis of preeclampsia, platelet inactivation by aspirin might be mightier using higher doses. Secondarily, response to aspirin might differ in different ethnicities and races; therefore, higher doses can induce more efficacy. Nevertheless, the most appropriate dose is a matter of debate yet.[18-20]

Contrarily, Tapp and colleagues found no preventive role for aspirin to reduce preeclampsia in general, early preterm, and preterm preeclampsia either in high-risk individuals or among those with a previous history of this condition.[35] Kumar's[15] conclusion about preterm preeclampsia was in agreement with the latter. The period when aspirin was prescribed and the compared doses were relatively similar between the studies presenting data in favor of aspirin use and those who opposed it.

The time of aspirin initiation to prevent preeclampsia incidence variable differed over the studies. Van Hoorn *et al*. reported very early initiation of ASA therapy since the 6th week of gestation.[34] Nevertheless, the studies mostly presented aspirin treatment initiation before week 16,[6,15,18,21,23-40] while there were 3 ones representing to begin aspirin in weeks 20,[6] 24,[26] or 26.[21]

Aspirin discontinuation to a lesser extent was a matter of debate. Given that, most of the authors recommended ceasing its use in the 36th gestational week.[15,18,23,26,33-35,38,40] However, weeks 34,[6,32,39] 35,[31] 37,[28,29] or until delivery[28,36] have been proposed, as well.

Surfing the literature led to finding 3 studies assessing aspirin alone or in combination with anticoagulants for the prevention of preeclampsia including a study on high-risk preeclampsia patients,[34] one of those with a previous history of preeclampsia[31] and one on the individuals with antiphospholipid syndrome.[37] All the assessments unanimously presented no benefit to adding any anticoagulant to aspirin compared with ASA use alone, even if aspirin was initiated very early, within the 6th week of pregnancy.[34]

Further search on our investigation was done to find the benefit of early aspirin discontinuation within the 24th–28th week of pregnancy, representing no difference in the incidence of preeclampsia among those who ceased

aspirin use in the mentioned period or continued it until the 36th week of pregnancy.[3]

Considering the diversities and inconsistency between the data of various studies in this issue, further investigations with meta-analysis design on measures were done including the following: (1) whether to use aspirin for preeclampsia prevention in high-risk pregnant women or not, (2) the dose of aspirin to reduce preeclampsia, and (3) the definition of high risk for preeclampsia can open windows to approach women who are at risk of preeclampsia development.

Strength

This systematic review has included a wide range of women at high risk for developing preeclampsia. Given that, the patients who were at high risk of preeclampsia were included as well as those with preexisting chronic conditions including hypertension and diabetes mellitus and those who had a previous history of preeclampsia. Moreover, the included sample population in our investigation accounted for 27,643 individuals which is remarkably high and improves the generalizability of the extracted data. This study was conducted using rigorous methodology resulting in a comprehensive qualitative assessment. We highlight an important area for future research.

Limitations

Five out of 24 studies were at a high risk of overall bias. In addition, there were differences in definitions of outcomes between studies, which is an important caveat when interpreting pooled results. The meta-analysis design of the study could reinforce the outcomes considering presenting the outcomes based on analytical assessments.

CONCLUSION

The findings of this systematic review led to some controversial outcomes. On a hand, the majority of studies found no remarkable role for prophylactic aspirin use to prevent preeclampsia incidence at any time during pregnancy. However, on the other hand, those studies that promise prophylactic aspirin to prevent preeclampsia indicated that higher doses and earlier aspirin initiation could lead to better outcomes. Given that, further trials on three fields of (1) whether or not to use aspirin, (2) the dose, and (3) the time of aspirin use can improve our knowledge regarding aspirin use for the prevention of preeclampsia. Besides, conducting studies in meta-analysis can help make a more precise conclusion as well as generalize the outcomes.

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Conflicts of interest

There are no conflicts of interest.

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