The Effect of Aspirin on Preeclampsia: A Systematic Review

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Abstract

Background: Preeclampsia is one of the most common causes of maternal mortality. This complication has been attempted to prevent preeclampsia. Many drug treatments have also been tested, including aspirin, one of the drugs prescribed to prevent preeclampsia. Therefore, the present study was designed to summarize the findings and conclusions for the effect of aspirin on preeclampsia.

Materials and Methods: In this systematic review, databases of Iran Doc, IRCT, SID, ProQuest, Medline, Scopus, and Cochrane were reviewed until October 2019. The keywords "Aspirin, Preeclampsia, hypertension, acetylsalicylic acid, ASA, Iran and clinical trials" were searched for references in the literature and their possible combinations in the title and abstract. Qualitative analysis of studies was performed according to the Evidence-Based Medicine Checklist for therapeutic studies.

Results: Six clinical trials including 1,765 pregnant women were studied. In four studies, aspirin had a significant effect on the prevention of preeclampsia. In two studies, calcium-D had a significant effect on reducing the incidence of preeclampsia. Results regarding the effect of aspirin on infant birth weight, preterm labor and intrauterine growth restriction are inconsistent.

Conclusion: The results showed that aspirin (within the lowest daily dose of 75mg) has a positive effect on the prevention of preeclampsia (pregnant women at risk of preeclampsia) among most of the studies and positive results. Judging the definitive efficacy of aspirin in relation to other variables such as neonatal birth weight, preterm labor and intrauterine growth restriction requires more and more detailed studies with a sufficient sample size.

Key Words: Aspirin, Iran, Preeclampsia.

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1- INTRODUCTION

Preeclampsia (PE) is one of the most common causes of maternal morbidity and mortality (1). It is directly responsible for more than 70,000 maternal deaths annually worldwide (2). The pathophysiology of PE is not completely understood, but for placental uterine blood flow during normal pregnancy, trophoblast invasion and spiral artery transformation occur without any problems, leading to reduced vascular resistance and the normal activity of coagulation factors. But both invasion and abnormal vascular changes occur in the PE, resulting in vascular spasm followed by endothelial damage and activated coagulation factors and their deposition in the vessel wall. This cascade of events reduces the uterine and placental perfusion, and the fetal-placental status as well as maternal health are most likely to be at risk (3). Preeclampsia is considered as one of the most serious emergencies in the maternity wards because women with PE may develop the HELLP (Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels) syndrome and coagulopathy, eclampsia and stroke (4). Hypoxia, intrauterine growth restriction (IUGR) and death are the most common fetal complications in PE (5).

Nowadays, however, several attempts have been made to prevent PE. Fish oil, vitamins, and calcium may not be an effective therapy for reducing the risk of PE (6). Aspirin can help prevent PE (7). Aspirin inhibits vasoconstriction and coagulation problems via reducing thromboxane A2 without changing the prostacyclin levels. In addition, there are no serious side effects for both the mother and the fetus related to aspirin use during pregnancy (8). However, studies have reported conflicting results. Some studies have suggested that aspirin has a significant reduction in the incidence of PE (9, 10), while others have demonstrated its effects on the prevention of PE which can act as something like a placebo (11). Given than the prevention of PE is more important than its treatment due to its potential risks for both the mother and the fetus, and also aspirin which is safe and available can be recommended for individuals at risk, therefore, we review the most recent evidence of the effect of aspirin on the prevention of PE in Iran.

2- MATERIALS AND METHODS

2-1. Study design

This study was a systematic review of all clinical trials conducted on the effect of aspirin on preeclampsia. PICOT in the present study is as follows: Participants: pregnant women at risk of preeclampsia, Interventions: administration of aspirin, C: comparison with placebo or without treatment, O: Doppler sonography, pregnancy hypertension and pre-eclampsia occur more frequently after first week of pregnancy; 90/40 with proteinuria (protein excretion greater than 300 mg in 24 hours), and T (Time frame): between 2000 and October 2019.

2-2. Search strategy

Documentation published in ProQuest, Medline, EMBASE, Scopus, Cochrane databases and Web of Science as English databases and Iran doc, Magiran, IRCT and SID as Iranian databases, was reviewed. In English language database, keywords were selected according to MeSH and included "Aspirin", "Acetylsalicylic Acid", "Acylpyrin", "Easprin", "Polopirin", "Preeclampsia", "Pregnancy Toxemia", "Pregnancy-Induced hypertension", "Pregnancy Complications", "Iran", "Islamic Republic Of Iran", "Randomized Controlled Trial", "Randomized", and "Placebo". The keywords in the Persian databases included "Aspirin", "Acetylsalicylic Acid", "Preeclampsia", "Pregnancy Toxemia", "Randomized Controlled Trial", and

"Iran". The keywords were combined with AND, OR.

2-3. Study selection

To avoid bias, two researchers performed the search independently. The information form extracted by the researcher included first author, year of research, sample size, mean age, randomization technique, groups, onset duration treatment, treatment blinding, baseline comparability, main findings. Included studies: evaluate the effect of aspirin treatment on preeclampsia, place of study in Iran, type of clinical trial study, full text available. All studies that were not related to the subject, or were duplicate, were excluded. In general, our search rendered 120 articles, and eventually 6 articles were assessed based on the inclusion criteria (**Figure. 1**).
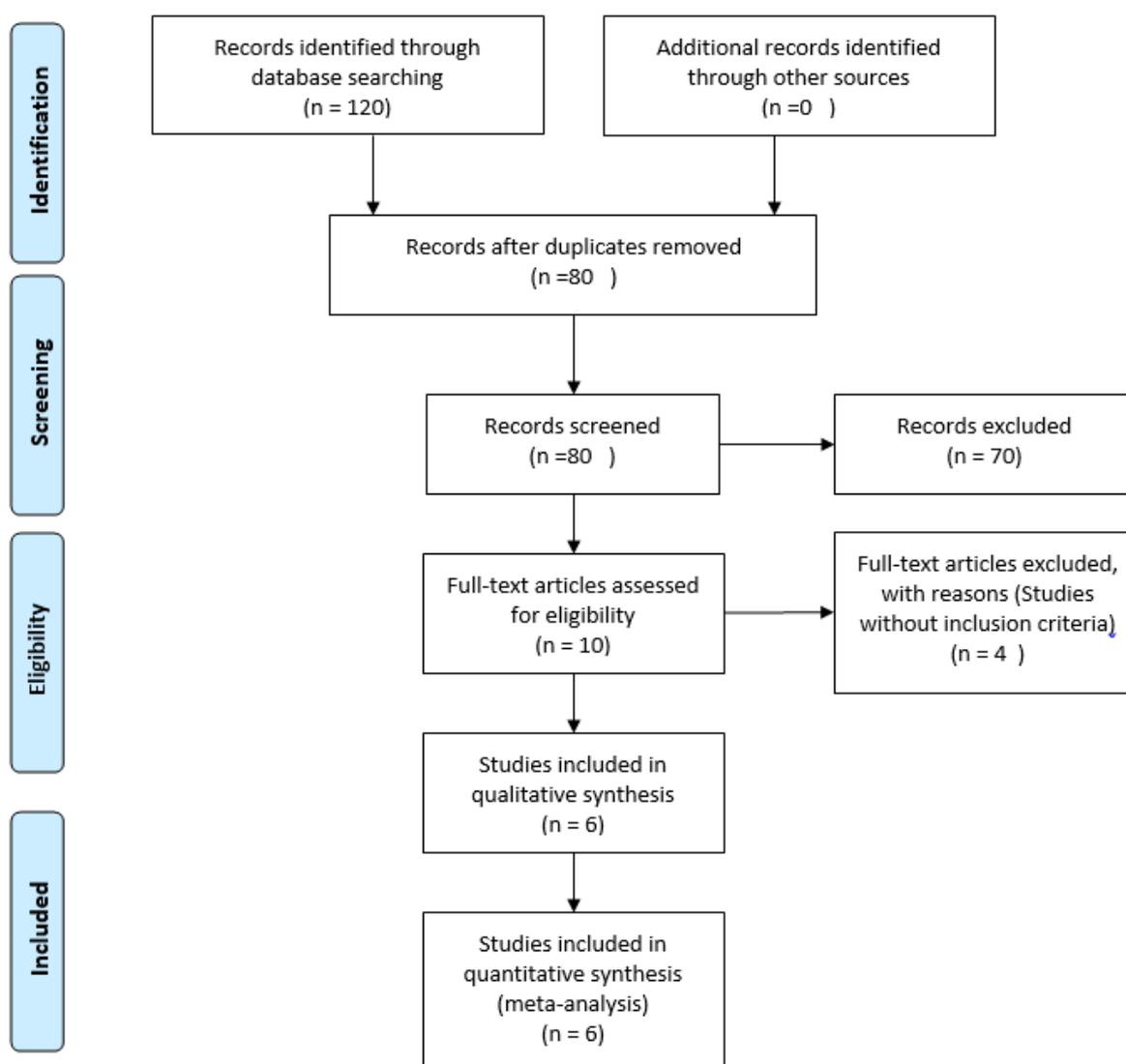

Fig.1: PRISMA flowchart of present study.

2-4. Quality Assessment of Studies

Quality Assessment was considered by two researchers independently. Evaluation of articles from Evidence-Based Medicine Checklist for Therapeutic Studies included blinded study, random assignment method,

withdrawal report, Intention-to-treat. In intent-to-treat items, random assignment, exclusion report, where the author of the article mentions these items, the answer is yes and no. In blinding, if the author of the article mentioned these items, the answer is yes, and if unclear information is not provided, the unclear answer is otherwise marked as no (12).

3- RESULTS

A total of 6 studies with 1,765 participants were included in the study. In this study, 4 studies reported aspirin has a positive effect on the prevention of preeclampsia (1, 8, 13, 14). Results regarding the effect of aspirin on infant birth weight, preterm labor and intrauterine growth restriction are inconsistent.

3-1. Preeclampsia

In this study, 4 studies reported aspirin had a positive effect on the prevention of preeclampsia (**Table. 1**) (*Please see the table.1 in the end of paper*). The results of these studies demonstrated that the use of aspirin significantly reduced the incidence of PE (1, 8, 13, 14). In a study conducted by Abdali et al. (2013), 64 women at risk for PE were randomly divided into four equal groups: (1) control group I receiving placebo in the morning, (2) control group II receiving placebo before bedtime, (3) experimental group I receiving 100 mg aspirin in the morning, and (4) experimental group II receiving 100 mg aspirin before bedtime. The results of the study showed that compared with placebo group, taking aspirin at night was more effective on 24-hour blood pressure mean reduction in women at risk of PE (1). In the study of Talari et al. (2014), 80 women at risk for PE were randomly divided into two experimental and control groups. The experimental group received aspirin 80 mg daily and control subjects received no treatment. The results of the study suggested that administration of aspirin reduced the incidence of PE in women at risk of PE compared to the controls (8). In the study of Asemi et al. (2012), 42 primiparous women at risk of preeclampsia were randomly divided into intervention and control groups. The intervention group received 500 mg carbonate calcium plus 80 mg aspirin per day and the controls received no treatment. The results of the study indicated that CRP, plasma TAC, GSH levels were significantly increased in intervention group compared to the controls. However, no significant differences in serum insulin levels and HOMA-IR scores were detected between the intervention and control groups (13).

In the study of Taherian et al. (2002), 990 primiparous women were selected using non probability convenience sampling and were divided into three groups. Group I received 75 mg aspirin each day, group II were treated with 500 mg calcium-D daily and the control group received no treatment. The results of the study demonstrated that the relative frequency of PE in the aspirin and calcium groups was significantly lower than that in the controls (14). In a study conducted by Atarod et al. (2003), 489 primiparous women were divided into intervention and control groups. All participants in the intervention group took 3/4 tablet of 100 mg aspirin per day and the control group received 3/4 tablet of placebo daily.

The findings of the study revealed that no significant difference in the relative frequency of PE was observed between the two groups (11). In the study of Movahed et al. (2017), 100 pregnant women were divided into case and control groups. The intervention group received 80 mg aspirin each day and the control subjects received one placebo tablet daily. The results of the study indicated that aspirin reduced the frequency of PE in the aspirin group compared to the placebo group, but this was not statistically significant (15).

3-2. Birth weight

The results of Taherian et al. (2002) demonstrated that the mean birth weight in the aspirin and calcium groups was significantly higher than that in the controls (14). In addition, the findings of Movahed et al. (2017) indicated that the mean birth weight in intervention group was significantly higher than that in control group (15), but the results of studies of Talari et al. (2014), and Atarod et al. (2003) suggested that no significant difference in the mean birth weight was detected between intervention and control groups (8, 11).

3-3. Preterm labor

The results obtained from studies conducted by Movahed et al. (2017), and Atarod et al. (2003) showed that there was no significant difference between the intervention and control groups in terms of in preterm labor (11, 15).

3-4. Intrauterine Growth Restriction (IUGR)

According to studies conducted by Talari et al. (2014), and Movahed et al. (2017), there was no statistically significant difference between intervention and control groups with respect to fetal growth restriction (8, 15).

4- DISCUSSION

The present study aimed to investigate the effect of aspirin on the prevention of PE in Iran. Of the 6 studies conducted, three investigated the efficacy of aspirin, one examined the effect of aspirin administration at different times of the day on 24-hour mean blood pressure, one compared the efficacy of aspirin and calcium use in the prevention of PE, and one investigated the effect of calcium supplement plus aspirin on hs-CRP, oxidative stress and insulin resistance in pregnant women at risk for PE (1, 8, 11, 13-15). The results of a review of studies conducted by Abdali et al., Taherian et al., Talari et al., and Asami et al. showed that aspirin use during pregnancy can reduce the incidence of PE (8, 11, 13, 14). This may be due to the fact that aspirin inhibits synthesis of thromboxane A2 and the balance between prostacyclin and thromboxane A2 as well as platelet aggregation via irreversible inhibition of cyclooxygenase in platelets, which in turn leads to a reduction in the incidence of PE (1, 14). The results from Abdali et al.'s study (2013) showed that 24-hour mean blood pressure variations for the group receiving aspirin before bedtime were significantly lower than those for the controls and the group taking aspirin in the morning (1), which was consistent with the study conducted by Hermida et al. (2005), suggesting that diurnal blood pressure was unchanged in subjects receiving aspirin on awakening but nocturnal BP increased and daytime and night-time blood pressure was reduced in subjects who received aspirin at bedtime (16). This may be due to the fact that the renin production increases during the night and aspirin may exert its greatest effect on the maximum activity of renin (1).

The results of the study of Taherian et al. (2002) demonstrated that the incidence of PE in the aspirin group was 4.6% and in the control group it was 10.1%, which was statistically significant (14). These results were consistent with the findings of the meta-analysis of Roberge et al. (2017) (2). The results from Talari et al.'s study (2014) showed that there was a significant difference between the aspirin and placebo groups in terms of the incidence of PE (2.5% versus 22.5%), and in fact, the PE incidence was lower in the aspirin-treated group (8), which was consistent with results found by Burchett et al., as cited in Mesdaghinia et al. (2011) showing that low-dose aspirin could reduce resistance to placental blood flow and prevent the PE (17).

However, these results were inconsistent with the study of Atarod et al. (2003), which might be due to differences in the aspirin initiation at 13 to 32 weeks of gestation (11). The results of Asemi et al.'s study (2012) indicated that consumption of calcium supplement plus aspirin during pregnancy for 9 weeks in pregnant women at risk for PE led to a significant difference in serum hs-CRP and increased levels of plasma TAC and total GSH as compared to the placebo group, but could not influence serum insulin levels and HOMA-IR score, which might be due to the mechanism of the effects of aspirin and calcium.

Due to elevated GSH concentration, the enzyme activity of catalase, suppression of parathyroid hormone (PTH), and nitric oxide inhibitor can improve inflammation/oxidative stress (13). However, according to the studies of Atarod et al., and Movahed et al., the use of aspirin did not did not reduce the incidence of PE, which might be due to the administration of aspirin at 13 to 32 weeks of gestation (11,15). A study conducted by YU et al. (2003) reported that administration of aspirin after 23 weeks of gestation did not prevent the subsequent development of PE (18). These results were consistent with Grab study showing that the daily administration of 80 mg aspirin after 18 weeks of gestation did not reduce the incidence of PE as compared with placebo (19).

Given the pathophysiology of normal pregnancy and the completion of the placental implantation process after 14 to 18 weeks of gestation, uterine arteries are transformed from high resistance to low resistance during this period. Aspirin seems to have a beneficial effect on the prevention of PE when initiated before 14 weeks' gestation(15). Bujold et al. performed a meta-analysis to examine the effect of aspirin initiation (at 16 weeks of gestation or less, 16 weeks of gestation or

more) on the prevention of PE in high-risk pregnant women with normal uterine artery Doppler. The results showed that aspirin initiation at 16 weeks or earlier was associated with a significant decrease in the PE (20). Mesdaghinia et al. (2011) performed a clinical trial to evaluate the effect of the daily administration of 80 mg aspirin at 12-16 weeks of pregnancy in women with uterine artery Doppler. The results showed a 9-fold reduction in the incidence of PE in the aspirin group (17).

According to many of the studies conducted and their positive results mentioned above, it can therefore be concluded that aspirin has a positive effect on the prevention of PE and contradictory findings regarding aspirin efficacy may be due to differences in time of aspirin use and gestational age at initiation of aspirin. There was inconsistency between studies conducted on the effects of aspirin on birth weight and IUGR. The results of studies conducted by Taherian et al., and Movahed et al., demonstrated that aspirin use did not increase birth weight, which was consistent with the findings of Decker, Schiff, and Wagon, as cited in Taherian et al., but it was inconsistent with the study of Mesdaghinia et al. (2011). This may be due to differences in the study inclusion criteria and sample size (14-15,17).

The results of studies conducted by Talari et al., and Atarod et al., showed that aspirin use did not increase birth weight (8, 11), which was in agreement with the results of Ebrashy et al. (2005) suggesting that there was a significant difference between the intervention and control groups in terms of birth weight (9). The results of studies of Talari et al., and Atarod et al., revealed that no significant difference in IUGR was detected between the two groups (8, 11). These results were in line with the study of Roberge et al. (2016), but were inconsistent with the study of Taherian et al. (2002), which might be due to the larger sample size (2,

14). The results of studies conducted on the effect of aspirin on preterm labor indicated that aspirin has no effect on preterm birth. The results of studies of Movahed et al., and Atarod et al., showed no significant difference between the two groups with respect to preterm labor, which was consistent with the findings of Taherian et al. (2002), Ebrashy et al. (2005), and Mesdaghinia et al. (2011) (9, 14, 17). Limitations of the present study are lack of access to unpublished papers and theses, inaccurate reporting of results, and method of study. Also, the limited literature on the effects of aspirin can prevent a more accurate and complete study from being performed. Given the limited number of studies investigating the effect of aspirin on birth weight, preterm labor and IUGR, it is therefore recommended that more extensive studies with a larger sample sizes need to be conducted to investigate the effect of aspirin on birth weight, preterm labor and IUGR. It is also recommended that more extensive studies with larger sample sizes should be performed to compare the effects of aspirin administration at two different times of the day (at 14 weeks of gestation or less, 14 weeks of gestation or more) on the prevention of PE in high-risk pregnant women worldwide.

5- CONCLUSIONS

The results showed that aspirin (within the lowest daily dose of 75mg) has a positive effect on the prevention of preeclampsia (Pregnant women at risk of preeclampsia) among most of the studies and positive results. Judging the definitive efficacy of aspirin in relation to other variables such as neonatal birth weight, preterm labor and intrauterine growth restriction requires more and greater detailed studies with sufficient sample size.

6- ABBREVIATION

PE: Preeclampsia, HELLP: Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels, IUGR: Intrauterine Growth Restriction, CRP: C-Reactive Protein, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, hs- CRP: high sensitivity C-reactive protein, TAC: Total Antioxidant Capacity, GSH: Total Glutathione, FPG: Fasting Plasma Glucose.

7- CONFLICT OF INTEREST: None.

8- ACKNOWLEDGMENTS

9- REFERENCES

1. Abdali K, Taghizadeh R, Amoei S, Tabatabai SHR. Comparison between aspirin and placebo on the mean of 24 hour blood pressure in pregnant women at preeclampsia risk, a double blind randomized controlled clinical trial. International Journal of Community Based Nursing and Midwifery. 2013;1(2):83-91.

2. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. American journal of obstetrics and gynecology. 2017;216(2):110-20. e6.

3. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams obstetrics, 24e: Mcgraw-hill; 2014.

4. Lam MTC, Dierking E. Intensive Care Unit issues in eclampsia and HELLP syndrome. International journal of critical illness and injury science. 2017;7(3):136.

5. Askar E, Selim S, Sibai H. Histological changes of human placenta in early intrauterine growth restriction with and without preeclampsia. Journal of Medical Histology. 2019;3(1):65-76.

6. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstetrics & Gynecology. 2008;112(2):359-72.

7. Atallah A, Lecarpentier E, Goffinet F, Doret-Dion M, Gaucherand P, Tsatsaris V. Aspirin for prevention of preeclampsia. Drugs. 2017;77(17):1819-31.

8. Talari H, Mesdaghinia E, Kalahroudi MA. Aspirin and preeclampsia prevention in patients with abnormal uterine artery blood flow. Iranian Red Crescent Medical Journal. 2014;16(8): e17175.

9. Ebrashy A, Ibrahim M, Marzook A, Yousef D. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14-16 weeks pregnancy: randomized controlled clinical trial. Croatian medical journal. 2005;46(5): 826-31.

10. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. New England Journal of Medicine. 2017;377(7):613-22.

11. Âtarod Z, Rahmanpour H, Hossein zadeh M, Khalilian AR. Evaluation of the effect of low doses aspirin in prevention of pre-eclampsia and primipara. Journal of Mazandaran University of Medical Sciences. 2003;13(39):36-40.

12. Ghazanfarpour M, Latifnejad Roudsari R, Treglia G, Sadeghi R. Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: A systematic review of randomised controlled trials. Journal of obstetrics and gynaecology. 2015;35(8):783-7.

13. Asemi Z, Samimi M, Heidarzadeh Z, Khorrammian H, Tabassi Z. A randomized controlled clinical trial investigating the effect of calcium supplement plus low-dose aspirin on hs-CRP, oxidative stress and insulin resistance in pregnant women at risk for pre-eclampsia. Pakistan Journal of Biological Sciences. 2012;15(10):469.

14. Taherian A, Taherian A, Shirvani A. Comparison of the Effect of Aspirin and Calcium on Prevention of Preeclampsia in Healthy First Abdominal Women in Isfahan. Monthly Journal Of Research In Medical Sciences. 2002;7(2):136-40.

15. Movahed F, Lalooha F, Moinodin R, Dabbaghi Ghale T, Rezaee Majd Z, Yazdi Z. The Effect of Aspirin in the Prevention of Preeclampsia in Women with Abnormal Uterine Artery Doppler Ultrasonography Findings. Journal of Zanjan University of Medical Sciences. 2017;25(108):11-9.

16. Hermida RC, Ayala DE, Calvo C, López JE. Aspirin administered at bedtime, but not on awakening, has an effect on ambulatory blood pressure in hypertensive patients. Journal of the American College of Cardiology. 2005;46(6):975-83.

17. Mesdaghinia E, Talari H, Abedzadeh-Kalahroudi M. Effect of aspirin for prevention of preeclampsia in women with abnormal ultrasonic findings in uterine artery. Feyz Journal of Kashan University of Medical Sciences. 2011;15(2): 98-104.

18. Yu C, Papageorghiou A, Parra M, Palma Dias R, Nicolaides K, Group FMFSTS. Randomized controlled trial using low- dose aspirin in the prevention of pre- eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. Ultrasound in obstetrics & gynecology. 2003;22(3):233-9.

19. Grab D, Paulus W, Erdmann M, Terinde R, Oberhoffer R, Lang D, et al. Effects of low- dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo- controlled, double- blind trial. Ultrasound in Obstetrics and Gynecology. 2000;15(1):19-27.

20. Bujold E, Morency A-M, Roberge S, Lacasse Y, Forest J-C, Giguère Y. Acetylsalicylic acid for the prevention of preeclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis. Journal of Obstetrics and Gynaecology Canada. 2009;31(9):818-26.

Table-1: General Carecteristics of included studies.

Author, Year, Ref	N	City	Mean Age, year	Duration, week	Groups		Intervention	Baseline comparability	Treatment Blinding	Randomization technique	Main findings	P- value
					Intervention	Control						
Abdali et al., 2013, (1)	64	Shiraz	28.71± 5.87	16	1. 100 mg at night 2.100 mg at morning	1. Placebo tablet at night 2. Placebo tablet at morning	Monitored at the end of each month for 24 consecutive hours	Yes	Yes	Yes	Aspirin at night is more effective	<0.001
Talari et al., 2014,(8)	80	Kashan	Intervention: 27.8± 4.5 Control: 27.0±5.9	End pregnancy period	80 mg per day after lunch	Placebo through the same routine	Abnormal findings on doppler ultrasonography	Yes	Yes	Yes	ASA prophylaxis can be used for prevention of preeclampsia	0.007
Asemi et al., 2012, (13)	42	Kashan	Intervention: 26.5± 5.5 Control: 24.4±3.7	9	500 mg Calcium supplement plus 80 mg Aspirin per day after	Placebo	Fasting blood sample	Yes	Yes	Yes	Significant differences between two groups (TAC, GSH, CRP) and No Significant differences between two groups FPG, HOMA-IR	TAC: p=0.04, GSH: p=0.07, CRP: p=0.01
Taherian et al., 2002, (14)	990	Isfahan	Intervention (gropuasprin): 21.5± 0.21, (gropu Calcium): 21.9±0.28 Control: 21.2±0.19	End pregnancy period	Group1: 75 mg Aspirin per day Group2: 500 mg Calcium D per day	Without drug	Blood pressure measurement in routine pregnancy care	Yes	Yes	Yes	Significant decrease in preeclampsia in the aspirin and calcium groups compared to the control group	Group 1 (p=0.007) Group 2: (p=0.003)
Atarod et al., 2003, (11)	489	Mazandaran	---	-	3/4 100 mg Aspirin per day	3/4 Placebo tablet	Every routine visit to the perinatal clinic to check blood pressure, proteinuria, edema	No	Yes	Yes	There was no statistically significant difference between the two groups.	p>0.05
Movahed et al., 2017, (15)	100	Qazvin	Intervention: 25.7± 4.7 Control: 24.04±4.3	End pregnancy period	80 mg Aspirin per day	One unit Placebo tablet	Every routine visit to the perinatal clinic to check blood pressure	Yes	Yes	Yes	There was no statistically significant difference between the two groups.	p>0.05

N: Number, TAC: Total Antioxidant Capacity, CRP: C-Reactive Protein, GSH: Total Glutathione, FPG: Fasting Plasma Glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.