ORIGINAL ARTICLE

Evaluation the effect of low-dose aspirin on endothelial dysfunction in preeclamptic patients

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Background: Preeclampsia complicates up to 3% of pregnancies in developing countries. Endothelial dysfunction plays an important role in pathogenesis of preeclampsia. In this study, we aim to evaluate the effect of low-dose aspirin on endothelial dysfunction in preeclamptic patients. **Materials and Methods:** in this triple-blind randomized clinical trial, enrolled patients were divided randomly into two groups. Acetylsalicylic acid (ASA) 80 mg or placebo will be taken daily by oral administration from the initiation of diagnosis until 2 months after delivery. Every patient's flow-mediated dilation (FMD) were evaluated at the beginning of study and 2 months after delivery with the same experienced operator at a same period of the time (3–5 pm) by high-resolution B-mode ultrasonographic. *T*-test or Mann–Whitney test was used in the comparison of means between the intervention and placebo groups. To compare FMD in each group, before and after the intervention, paired *t*-test was used. **Results:** Mean value of FMD in intervention (9.61 ± 5.58) and control group (9.40 ± 4.33) have no significant differences before drug consumption (P = 0.089). FMD in intervention group significantly increased after ASA consumption ([9.61 ± 5.58 vs. 13.65 ± 7.91] [P = 0.044]). **Conclusion:** Increase mean of FMD in intervention group shows that this supplement can improve endothelial function.

Key words: Acetylsalicylic acid, endothelial dysfunction, preeclampsia

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INTRODUCTION

Endothelial dysfunction causes different disorders in human body including preeclampsia during pregnancy. The pathogenesis may be due to inflammatory responses that trigger pregnancy-induced hypertension consequently. This condition increases burden of disease in developed and developing countries. Preeclampsia complicates up to 5–10 and 3% of pregnancies in developed and developing countries, respectively.[1-3] The prevalence of preeclampsia is 3% in Iran. In addition, eclampsia happens in 0.1% of pregnancies in Iran.[4] It plays an important role in occurring prenatal and perinatal events including premature delivery, severe hypertension, increasing the risk of stroke, maternal death. Mothers with the medical history of preeclampsia are predisposed to for cardiovascular diseases due to endothelial dysfunction may be persistent after delivery.

Several studies reported the role of endothelial cells in endothelial-dependent diseases including preeclampsia and it is recently proved that endothelial dysfunction plays an important role in pathogenesis of preeclampsia. The endothelial function should be evaluated by measuring brachial artery flow-mediated dilation (FMD) by high-resolution B-mode ultrasonography after triggering shear stress. Bujold *et al*. reported that low-dose aspirin, as an antiplatelet, in early pregnancy decrease the risk of preeclampsia and intrauterine growth retardation (IUGR).[5] Another study represented that low-dose aspirin decreases the risk of preeclampsia in healthy nulipar pregnant women but has no impact on prenatal morbidity.[6] Although there are lots of surveys on preeclampsia, a few studies evaluate the effect of

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ASA in preeclamptic patients. The aim of this study is to evaluate the effect of low-dose acetylsalicylic acid (ASA) on endothelial dysfunction in preeclamptic patients.

MATERIALS AND METHODS

Patient setting

This trial has been registered at http://www.irct.ir/ Registration with ID number IRCT2016040527135N2 and has been approved by the Isfahan University of Medical Sciences Ethical Board. In this randomized clinical trial, pregnant women with documented preeclampsia on the basis of National High Blood Pressure Education Program working group on high blood pressure in pregnancy, 2000, who visited in St-Zahra Hospital, Isfahan, Iran, were included in the study. Patients with any clinical evidences of diabetes mellitus, pernicious anemia, aplastic anemia, megaloblastic anemia, known cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, renal failure, thyroid disease, history of pregnancy-induced hypertension, malignancy, liver dysfunction, infectious disease, migraine, and stroke did not include in this study. In addition, patients with the history of twin pregnancy, smoking cigarette, alcohol consumption, and drug abuse did not include in the study. Women who sensitize to the drug (vertigo, insomnia, rash, severe cough, angioedema, purities and bronchospasm, and drug consumption), poor compliance to use prescribed drug and hygiene advice and who use drugs <2 months during pregnancy excluded from the study.

Intervention

Enrolled patients were divided randomly (allocation ratio equal to 1:1) into two groups by random allocation service (www.saghaei.net/ra/). ASA80 mg (Osveh, Tehran, Iran)[6] or placebo was taken daily by oral administration from the initiation of diagnosis until 2 months after delivery by the trial participant. Intervention was applied by a cardiologist. This trial is triple-blinded (patient, operator, and statistician).

Assessment

Confounding variables included maternal age were assessed. Every patient's FMD were evaluated at the beginning and 2 months after delivery with the same experienced operator at a same period of the time (3–5 pm) by high-resolution B-mode ultrasonographic (SonoAce, Deutschland). FMD estimated by the following formula:

$$FMD\ (\%) = ([POD - BBD]/BBD) \times 100$$

Basal brachial diameter (BBD) is measured in resting position, and postocclusion diameter (POD) is measured 30 s before and 90 s after cuff evacuation (cuff pressure is increased up to 300 mmHg for 5 min before evacuation).

Statistical analyses

Potential confounding variables included in the independent samples *t*-test were maternal age, parity, prepregnancy body mass index (BMI), and abortion. *T*-test or Mann–Whitney test will be used in the comparison of means of birth weight and gestational age, between the intervention and placebo groups. To compare FMD in each group, before and after the intervention, paired *t*-test was used by SPSS software, Version 21, Chicago, IL, USA ($P < 0.05$ was decided significant).

RESULTS

Eighty-two preeclamptic pregnant patients were enrolled in this study between February 2015 and February 2016. Patient enrollment is described in Figure 1.

The mean of patients' ages was 31.03 ± 4.21 years (with a range of 21–41 years). The details of patients' demographic data are summarized in Table 1. As shown in Table 1, patients have no significant differences in age, BMI, level of serum triglycerides, low-density lipoprotein, high-density lipoprotein, fasting blood sugar, and hemoglobin.

The mean value of FMD in intervention (9.61 ± 5.58) and control group (9.40 ± 4.33) have no significant differences before consumption of drugs ($P = 0.089$). As demonstrated in Table 2, FMD increased significantly in intervention group after daily consumption of 80 mg of ASA. In control group, in contrast, FMD has shown no significant differences before and after daily consumption of placebo.

Meanwhile, FMD in intervention group significantly increases after daily consumption of 80 mg ASA in comparison with control group after daily consumption of placebo.

DISCUSSION

In this clinical trial on pregnant women suffering from preeclampsia visited in St-Zahra Hospital, Isfahan, Iran, 82 enrolled patients were divided randomly into two groups who received ASA 80 mg or placebo daily by oral administration from initiation of diagnosis until 2 months after delivery. Endothelial function assessed by FMD. Our results showed that daily oral administration of low-dose ASA increase FMD significantly which means it can improve endothelial function.

Several experimental studies approved the effect of ASA on platelet function as a potent antioxidant. These surveys showed ASA can affect endothelial function through oxidative stress pathway in vascular inflammation process.[7,8] Shechter *et al*. reported that Platelet activation

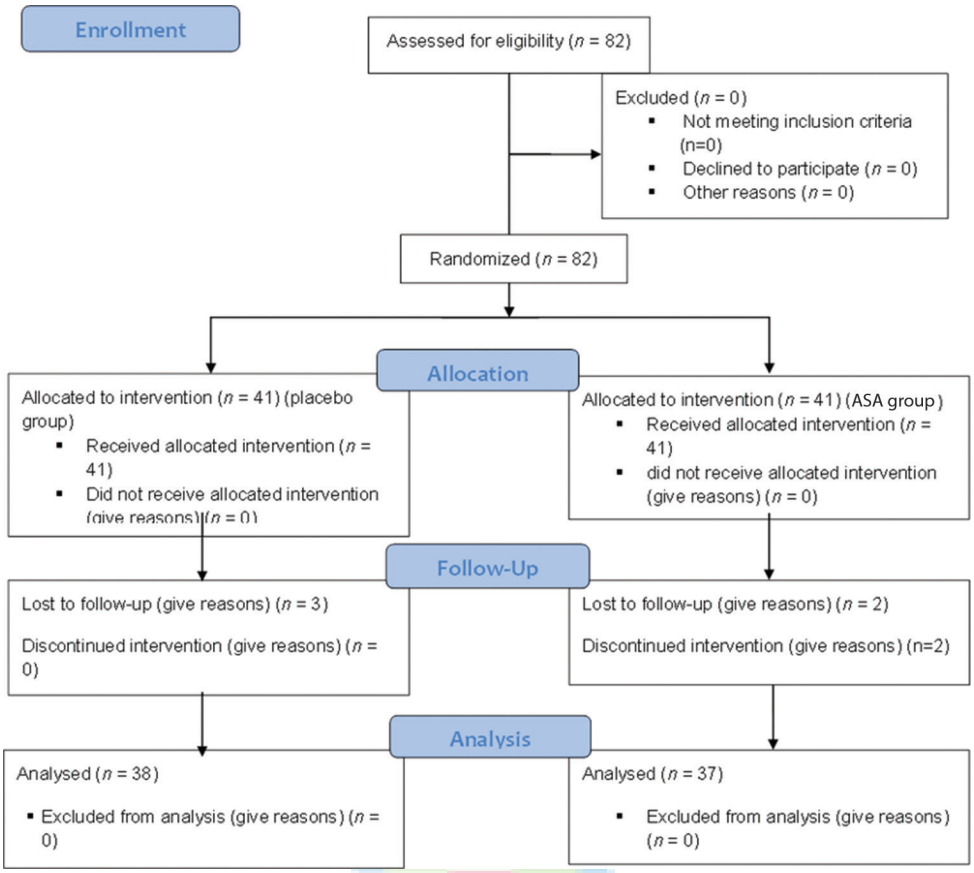

Figure 1: Patient enrollment

Table 1: Demographic and baseline characters of patients

Paired *t*-test	Mean±SD		*P*
	Control group (38)	Intervention group (37)	
Age	31.24±4.40	30.81±4.07	0.713
BMI	24.61±2.76	23.46±2.53	0.528
TG	115.78±18.34	110.63±16.95	0.525
LDL	98.03±13.78	92.92±17.19	0.203
HDL	48.92±7.15	50.71±7.91	0.392
FBS	90.62±8.65	90.95±7.27	0.304
Hemoglobin	12.28±0.94	12.67±0.94	0.194

BMI = Body mass index; TG = Triglycerides; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; FBS = Fasting blood sugar; SD = Standard deviation

Table 2: Flow-mediated dilation in each group before and after consumption of drug/placebo

	Before consumption FMD	After consumption FMD	*P*
Intervention group	9.61±5.58	13.65±7.91	0.044
Control group	9.40±4.33	9.23±4.74	0.201
P	0.089	0.001	

FMD = Flow-mediated dilation

occurs in an endothelium-dependent FMD impairment environment. FMD is inversely correlated to platelet reactivity in both controls and acute myocardial infarction patients. This study showed that platelet adhesion and aggregation in inflammation state lead to endothelial dysfunction and platelet reactivation decrease endothelial dilation.[9] In support of this study, Raghavan *et al*. also reported that antiplatelet treatment can reduce vascular dysfunction.[10] Magen *et al*. in a study at 2005 showed that addition of low-dose aspirin to antihypertensive treatment and statins in hypertensive and hypercholesterolemic patient can reduce systolic and diastolic blood pressure through improved NO-mediated endothelial function.[11,12] Similar effects of low-dose aspirin on blood pressure and reduce risk of preeclampsia were seen in a study on pregnant women in Houston, and suggest that aspirin administration in pregnancy are useful for high-risk mothers and are safe for fetus.[13]

Endothelial dysfunction due to inflammation process and imbalance between vasoconstrictor and vasodilator modulates are known pathophysiology of preeclampsia. In endothelial disorders, such as preeclampsia, poor placental perfusion leads to activation of platelets and the clotting cascade, resulting in an imbalance among prostacyclin (vasoactive modulates in blood flow and inhibit aggregation) with thromboxane A2 (acting as a vasoconstrictor and promoting platelet aggregation). Increased thromboxane and reduced prostacyclin levels are associated with infarction and thrombotic vasculopathy, which caused preeclampsia and its adverse features

outcomes.[14,15] Schramm *et al*. in a study on aspirin effect for the prevention of preeclamsia in lupus pregnant patient reported that low-dose aspirin (60–80 mg/day) may prevent preeclampsia by modulating the thromboxane A2/prostacyclin ratio to optimize placental blood flow and prevent placental thrombosis. While aspirin will not eliminate all cases of preeclampsia, it is currently the best and safest available drug for influencing the pathogenesis and clinical presentation of preeclampsia. In this study, aspirin treatment had a risk reduction of up to 20% for preeclampsia development in lupus patient.[14] Furuno *et al*. in a survey about the effects of various doses of aspirin on platelet activity and endothelial function indicate that aspirin at any daily dose over 81 mg suppressed platelet activity, and the optimal dose of endothelial function was 162 mg/day. However, 660 mg/day of aspirin worsened endothelial function. This study explains aspirin plays an important role in the primary and secondary prevention of cardiovascular events and it has remained the most cost-effective clinical drug for over three decades. Higher doses of aspirin can cause bleeding complication and also impair endothelial function. A high dose of aspirin achieves both platelet inhibition and vasodilation, whereas a low dose spares endothelial cyclooxygenase activity and vasodilatation.[16]

Park *et al*. in a study at 2015 on high-risk pregnant women reported prescription of aspirin (60–150 mg/day) to this group, appears to be effective in reducing the prevalence of early PE. Aspirin also can reduce the risk of preterm delivery, IUGR, and prenatal death.[17] Roberge *et al*. study showed similar effects and suggested that low-dose aspirin initiated at ≤16 weeks of gestation is associated with a greater reduction of perinatal death and other adverse perinatal outcomes than when initiated at >16 weeks.[18]

Study limitations

First and most important limitation of our study is small sample size due to difficulties to diagnosis pure preeclamptic patients who met inclusion criteria. In addition, cultural difficulties limited our study. The last but not least was an unequal period of drug administration by participants due to emergency indications for cesarean section which some of the participants did meet.

CONCLUSION

This study demonstrated an association between low-dose aspirin and increase flow-mediated vasodilation in the brachial artery in preeclamptic patient. Increase mean of FMD in groups who took regular daily oral 80 mg aspirin starting right at the initiation of diagnosis until 2 months after delivery shows that this drug through biological pathway can improve endothelial function and can be significantly affected maternal blood pressure during pregnancy and some endothelium-dependent disease such as preeclampsia and its associated adverse outcomes.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

FB contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MH contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. EZ contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. KH contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SB contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

REFERENCES

1. Schroeder BM; American College of Obstetricians and Gynecologists. ACOG practice bulletin on diagnosing and managing preeclampsia and eclampsia. American College of Obstetricians and Gynecologists. Am Fam Physician 2002;66:330-1.
2. Roberts JM, Lain KY. Recent Insights into the pathogenesis of pre-eclampsia. Placenta 2002;23:359-72.
3. Wen SW, Champagne J, Rennicks White R, Coyle D, Fraser W, Smith G, *et al.* Effect of folic acid supplementation in pregnancy on preeclampsia: The folic acid clinical trial study. J Pregnancy 2013;2013:294312.
4. Piri SH, Kiani A, Faghih Zadeh S. A survey on the prevalency and effect of demographic factor in preeclampsia and eclampsia. Daneshvar J 2001;32:35-42.
5. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, *et al.* Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: A meta-analysis. Obstet Gynecol 2010;116(2 Pt 1):402-14.
6. Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenat Diagn 2014;34:642-8.
7. Ou HC, Lee WJ, Wu CM, Chen JF, Sheu WH. Aspirin prevents resistin-induced endothelial dysfunction by modulating AMPK, ROS, and Akt/eNOS signaling. J Vasc Surg 2012;55:1104-15.
8. Raghavan RP, Laight DW, Cummings MH. Aspirin in type 2 diabetes, a randomised controlled study: Effect of different doses on inflammation, oxidative stress, insulin resistance and

endothelial function. Int J Clin Pract 2014;68:271-7.
9. Shechter M, Shechter A, Hod H, Fefer P, Shenkman B, Koren-Morag N, *et al.* Brachial artery endothelial function predicts platelet function in control subjects and in patients with acute myocardial infarction. Platelets 2012;23:202-10.
10. Rao GH. Management of type-2 diabetes with anti-platelet therapies: Special reference to aspirin. Front Biosci (Schol Ed) 2011;3:1-15.
11. Magen E, Viskoper JR, Mishal J, Priluk R, London D, Yosefy C. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. J Hum Hypertens 2005;19:667-73.
12. Monobe H, Yamanari H, Nakamura K, Ohe T. Effects of low-dose aspirin on endothelial function in hypertensive patients. Clin Cardiol 2001;24:705-9.
13. Walsh SW. Low-dose aspirin: Treatment for the imbalance of increased thromboxane and decreased prostacyclin in preeclampsia. Am J Perinatol 1989;6:124-32.
14. Schramm AM, Clowse ME. Aspirin for prevention of preeclampsia in lupus pregnancy. Autoimmune Dis 2014;2014:920467.
15. Saleh AA, Bottoms SF, Mammen EF. Low-dose-aspirin: Treatment of the imbalance of increased thromboxane and decreased prostacyclin in preeclampsia. Am J Perinatol 1992;9:311-3.
16. Furuno T, Yamasaki F, Yokoyama T, Sato K, Sato T, Doi Y, *et al.* Effects of various doses of aspirin on platelet activity and endothelial function. Heart Vessels 2011;26:267-73.
17. Park F, Russo K, Williams P, Pelosi M, Puddephatt R, Walter M, *et al.* Prediction and prevention of early-onset pre-eclampsia: Impact of aspirin after first-trimester screening. Ultrasound Obstet Gynecol 2015;46:419-23.
18. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: A meta-analysis. Ultrasound Obstet Gynecol 2013;41:491-9.