The effect of aspirin on preeclampsia, intrauterine growth restriction and preterm delivery among healthy pregnancies with a history of preeclampsia

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Abstract

Background: Due to the significance of preeclampsia (PE) and its adverse outcomes in the health of both mother and newborn, the present study was carried out to investigate the effect of aspirin on preventing the occurrence of PE, intrauterine growth restriction (IUGR), and preterm delivery in women with a previous history of PE.

Methods: The present clinical trial was conducted on 90 pregnant women with a previous history of PE referred to the Khalij Fars Hospital in Bandar Abbas, Hormozgan Province Iran from April 2017 to August 2018. The subjects of the study were randomly assigned into two groups of intervention and control to receive either 80 mg of aspirin or placebo daily during the pregnancy. Patients' information was obtained and recorded upon entering the study, follow-up visits, and childbirth.

Results: Among participants who entered the clinical trial, 86 patients (95.6%) completed the study. During the pregnancy, systolic blood pressure increased by 8.25 ± 14.83 and 19.06 ± 18.33 mmHg in aspirin and placebo groups, respectively ($p = 0.001$). Also, the same happened with diastolic blood pressure (6.12 ± 11.46 vs 13.48 ± 13.95 mmHg, $p = 0.010$). The rate of PE was equal to 27 (62.8%) and 38 (88.4%) in the aspirin and placebo groups, respectively (aOR = 0.23, $p = 0.013$). In the aspirin group, the rate of IUGR was equal to 27.9% compared with 25.6% of newborns in the control group (aOR = 1.18, $p = 0.750$). Similarly, there was no significant difference in the rate of preterm delivery between the two groups ($p = 0.061$).

Conclusion: The findings of the present study conducted exclusively on women with previous documented PE revealed that taking aspirin may have a preventive effect on PE in the current pregnancy.

Keywords: Aspirin; Intrauterine growth restriction; Preeclampsia; Preterm delivery

1. INTRODUCTION

Preeclampsia (PE), as one of the main causes of maternal and perinatal morbidity and mortality, complicates about 2% to 8% of all pregnancies worldwide.[1] PE is a unique systemic disorder of pregnancy that is characterized by elevated blood pressure and proteinuria or its equivalents after 20 weeks of gestation.[2]

PE alters the placental blood flow and triggers vascular disorders in different organs of the mother's and fetus's body.[3,4] Several explanations have been proposed for development of PE including vascular spasm, vascular endothelial cell damage, raised platelet activity, and increased coagulation system activity in small blood vessels.[5,6] However, despite extensive research efforts, the exact pathophysiology of PE is still unknown.[7]

Delivering the placenta is the only definitive treatment of PE; but on the other hand, preterm delivery itself can lead to increased neonatal morbidity and mortality.[8] In the past, medical treatment of PE has been limited to symptomatic relief, prevention of seizure, and prescription of antihypertensive drugs and agents used for termination of pregnancy.[3,9] However, in recent years, identifying safe and cost-effective interventions for prevention of various health problems has been the major challenge in the field of medicine. The use of aspirin for prevention of PE is among these interventions.[10,11] There are contradictory results in the literature regarding the efficacy of aspirin taken by high-risk pregnant women. Also, it is hypothesized that intrauterine growth restriction (IUGR) and PE share similar pathophysiology such as abnormal trophoblastic invasion.[12,13] In this regard, a number of studies have reported that taking aspirin may prevent IUGR as well as PE;[13,14] while others did not report a significant change in IUGR rate after taking aspirin.[15]

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 852-857.

Received August 5, 2019; accepted May 12, 2020.

doi: 10.1097/JCMA.0000000000000400.

Previous studies on the effect of aspirin for prevention of PE included pregnant women who were at high risk for PE, but the exact definition of high risk for PE was different for each study leading to bias and loss of precision. In some of the previous studies, chronic medical conditions such as chronic hypertension,[16,17] diabetes mellitus,[16,17] abnormal uterine artery Doppler,[15,18] or abnormal serum biomarkers[18] in combination with previous history of PE were used as inclusion criteria for recruiting the participants to achieve a higher sample size.

While, the novelty and originality of the current research are that our target population was healthy pregnant women with a previous history of PE, and the patients with any history of chronic medical conditions or abnormal Doppler or laboratory findings in the first trimester of pregnancy were excluded from the study.

Accordingly, the current study was performed to investigate the effect of aspirin on preventing the PE, IUGR, and preterm delivery in pregnant women with a previous history of PE.

2. METHODS

The present randomized clinical trial was conducted on 86 patients referred to the Khalij Fars Hospital in Bandar Abbas, Hormozgan Province, Iran from April 2017 to August 2018 to receive their prenatal care. The inclusion criteria were pregnant women with gestational age of 12 to 15 weeks and a history of PE in previous pregnancies (at least one previous pregnancy). The exclusion criteria were multiple gestations, gestational diabetes mellitus, chronic medical diseases (eg, hypertension or diabetes mellitus), smoking, coagulation disorders, abnormal uterine artery Doppler at ultrasound screening,[19] abnormal serum level of pregnancy-associated plasma protein A (PAPP-A) at the first-trimester screening,[20] allergy to aspirin, and unwillingness to participate in the research.

The study protocol was discussed and approved by the Medical Ethics Committee of Hormozgan University of Medical Sciences (HUMS.REC.1396.89), and informed consent was obtained from each participant after explaining the objectives of our study. This research was also registered at the Iranian Registry of Clinical Trials (code: IRCT20181218042033N1). The patients were randomly divided into two groups according to the output table of the Random Allocation software: (1) intervention group including pregnant women who were at the gestational age of 12 to 15 weeks and were treated with 80 mg of aspirin orally daily, and (2) control group including those who received the placebo for the same period of time. In both groups, the treatment continued until the 36th week of pregnancy or discontinued earlier as necessary in cases of preterm delivery. At the first visit, demographic characteristics such as maternal age, gestational age, and obstetrical history were obtained from the participants. At each follow-up visit, patients were evaluated for development of PE by measuring blood pressure and urine dipsticks. Also, all the participants underwent ultrasound examination in the third trimester of pregnancy for the assessment of fetal growth. Finally, birth weight, type of delivery (cesarean section [C/S] or normal vaginal delivery [NVD]), and newborn's Apgar scores at the first and fifth minutes were recorded.

The data were analyzed using SPSS software version18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were reported as frequency (percentage) and mean (±SD), respectively. A comparison was done between the intervention and control groups using Chi-Square or Mann-Whitney U test and Student's *t* test for categorical and continuous variables, respectively. A multivariate logistic regression analysis was used to identify (1) the associations between PAPP-A values measured at late first trimester and occurrence of PE after adjusting for potential confounders and (2) to test the difference in the incidence of PE, IUGR, and preterm delivery between the aspirin and placebo groups. Furthermore, Kaplan-Meier survival analysis was used to estimate the PE, IUGR, and preterm delivery rates during the pregnancy. A p value of <0.05 was considered as statistically significant.

3. RESULTS

Among the 100 pregnant women assessed for eligibility, 90 patients were randomly assigned to the aspirin (n = 45) or placebo groups (n = 45), respectively. Ten participants were excluded before entering the trial due to previous chronic medical disease (n = 4), abnormal PAPP-A values (n = 3), abnormal uterine artery Doppler at the first trimester (n = 1), and history of allergic reaction to aspirin (n = 2). Two patients from the aspirin group and one patient from the placebo group were lost to follow-up and one patient from the placebo group discontinued the intervention due to intrauterine fetal demise (Fig. 1). Table 1 presents a summary of the maternal demographic and obstetrical characteristics. Mean age of the patients in the intervention group was equal to 29.5 ± 5.5 years old, and in the placebo group, it was equal to 31.1 ± 6.4 years old, which was not statistically significant (p = 0.21).

Also, there were no significant differences in the gravidity, parity, abortion, and dead fetus rate between the study groups (p > 0.05). At the beginning of the study, mean gestational age was equal to 13.7 ± 1.3 weeks in the intervention group vs 14.2 ± 1.7 weeks in the placebo group (p = 0.13). The rates of NVD and C/S delivery were similar between the intervention and placebo groups (p = 0.13).

Mean serum level of PAPP-A multiple of the median (MoM) in the first trimester was significantly lower in women who developed PE later in pregnancy compared to those who did not develop PE (1.14 ± 0.43 vs 1.51 ± 0.45, p value = 0.003). Table 2 shows the results of multivariate logistic regression. As depicted in Table 2, adjusted odds ratios (aORs) are given for PAPP-A MoM values and other maternal risk factors to predict the PE. Results of the final model of logistic regression (Table 2) showed that the PAPP-A MoM in the first trimester is significantly associated with the occurrence of PE later in pregnancy (aOR = 15.48, p value = 0.003).

As illustrated in Table 3, the two study groups were compared in terms of systolic and diastolic blood pressures and heart rate at the onset and end of the clinical trial. Mean systolic and diastolic blood pressure at the first visit was similar between the aspirin and placebo groups (p = 0.261 and p = 0.204). The systolic blood pressure significantly increased during the study in the placebo group compared to the aspirin group (19.06 ± 18.33 vs 8.25 ± 14.83, p = 0.001). Also, an elevation in diastolic blood pressure at the end of the trial was significantly greater in the placebo group than aspirin group (13.48 ± 13.95 vs 6.12 ± 11.46, p = 0.10). The two study groups showed no significant differences in the heart rate at the baseline and end of the study (p = 0.70 and p = 0.95).

The study groups were compared in terms of gestational age at delivery, birth weight and Apgar scores at first and fifth minutes and the results revealed no statistically significant differences between aspirin and placebo groups (p > 0.05) (Table 4).

Table 5 shows the prevalence of PE, IUGR, and preterm delivery either in isolated form or in combination. PE was the most common complication that occurred in both study groups so that, the prevalence of isolated form of PE was equal to 39.9% and 60.5% in the aspirin and placebo groups, respectively.

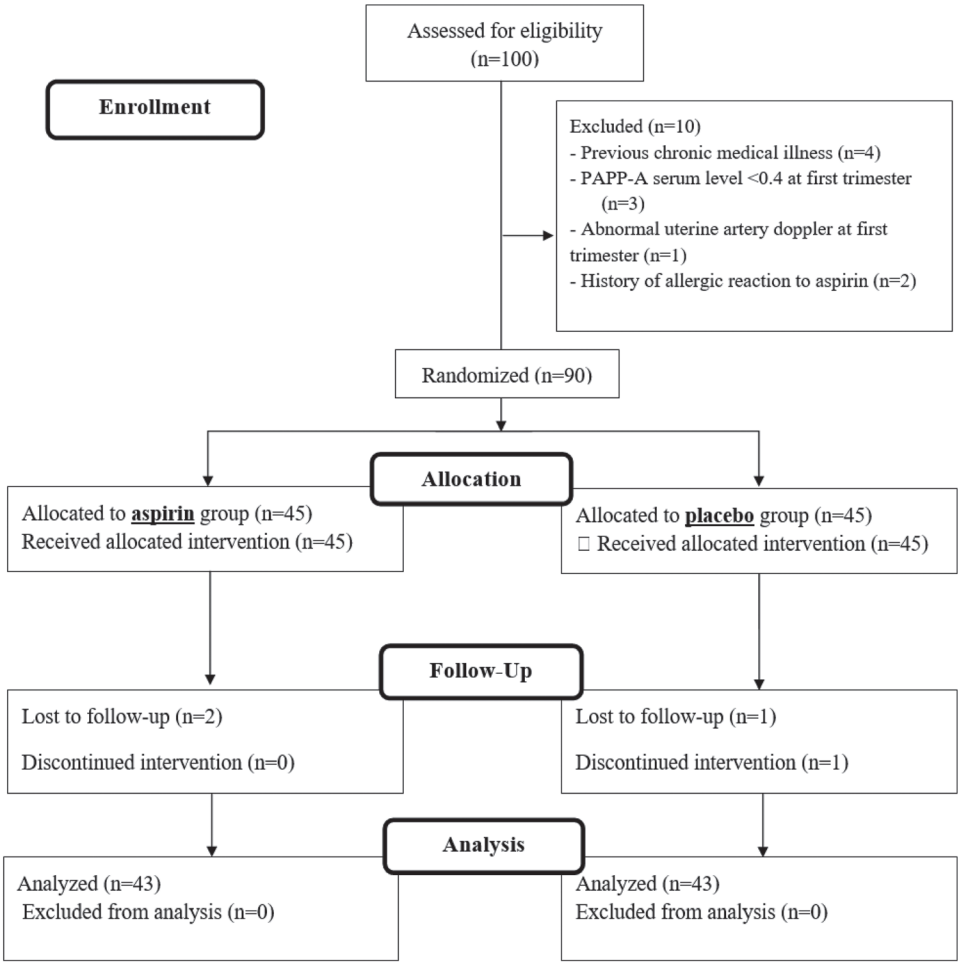

Fig. 1 CONSORT flowchart of this randomized clinical trial.

Table 1

Baseline characteristics of study groups

Variables	Study groups		*p*
	Aspirin (n = 43)	Placebo (n = 43)	
Maternal age, years (mean ± SD)	29.5 ± 5.5	31.1 ± 6.4	0.21
Obstetrical history			
Gravidity (mean ± SD)	2.8 ± 1.1	3.0 ± 1.2	0.46
Parity (mean ± SD)	1.3 ± 0.8	1.7 ± 1.1	0.06
Abortion (mean ± SD)	0.5 ± 0.7	0.4 ± 0.6	0.15
Dead fetus (mean ± SD)	0.2 ± 0.3	0.1 ± 0.2	0.09
Gestational age at the onset of study, weeks (mean ± SD)	13.7 ± 1.3	14.2 ± 1.7	0.13
Number of previous pregnancies complicated by PE (mean ± SD)	1.1 ± 0.4	1.2 ± 0.5	0.55
Type of delivery			
NVD, n (%)	19 (44.2%)	13 (30.2%)	0.13
C/S, n (%)	24 (55.8%)	30 (69.8%)	

C/S = cesarean section, NVD = normal vaginal delivery.

Table 2

Results of multivariate logistic regression for association between pregnancy-associated plasma protein A and preeclampsia after adjustment for maternal risk factors

Variables	aOR	95% CI	*P*
Maternal age	0.97	(0.85-1.12)	0.701
Parity	1.26	(0.44-3.59)	0.662
SBP	0.96	(0.88-1.05)	0.358
DBP	0.99	(0.86-1.14)	0.872
Previous pregnancies with PE	0.16	(0.01-1.82)	0.139
Receiving aspirin	0.08	(0.02-0.44)	0.004
PAPP-A	15.48	(2.47-96.87)	0.003

aOR = adjusted odds ratio, DBP = diastolic blood pressure, PAPP-A = pregnancy-associated plasma protein A, PE = preeclampsia, SBP = systolic blood pressure.

Additionally, overall prevalence of PE (either in isolated form or in combination with other complications) was equal to 62.8% and 88.4% in aspirin and placebo groups, respectively.

After adjusting for maternal variables and clinically relevant factors, including age, parity, and number of previous pregnancies complicated by PE, a statistically significant reduction was observed in PE rate in the aspirin group compared to the placebo group (aOR = 0.23, p value = 0.013). However, the results of logistic regression analysis showed no significant difference in rates of IUGR and preterm delivery between the aspirin and placebo groups (p = 0.750 and p = 0.061) (Table 6).

Figure 2 shows the results of Kaplan-Meier analysis for PE, IUGR, and preterm delivery. Results of the analysis indicated that 37.2% of the patients receiving aspirin were not

Table 3

Study groups compared in terms of vital signs in follow-up and visit to hospital for childbirth

	Research group				
	Aspirin (n = 43)		Placebo (n = 43)		
Variable	Mean	SD	Mean	SD	*p*
SBP at onset of study, mmHg	132.09	15.04	129.88	12.27	0.261
SBP at delivery, mmHg	141.00	18.78	148.95	20.39	0.061
SBP difference during the study period, mmHg	8.25	14.83	19.06	18.33	0.001
DBP at onset of study, mmHg	83.48	9.22	81.39	8.33	0.204
DBP at delivery, mmHg	90.12	13.61	94.88	12.79	0.088
DBP difference during the study period, mmHg	6.12	11.46	13.48	13.95	0.010
Heart rate at onset of study	83.69	3.43	84.04	3.29	0.700
Heart rate at delivery	84.97	3.38	85.03	3.64	0.950

DBP = diastolic blood pressure, mmHg = millimeters of mercury, SBP = systolic blood pressure.

Table 4

Study groups compared in terms of gestational age, birth weight and Apgar of first and fifth minutes

	Research group		
Variable	Aspirin (n = 43)	Placebo (n = 43)	*p*
Gestational age (weeks), (mean ± SD)	36.79 ± 2.63	36.30 ± 3.30	0.670
Birth weight (g), (mean ± SD)	2778.60 ± 754.66	2729.06 ± 721.66	0.628
First-minute Apgar, (mean ± SD)	8.60 ± 0.82	8.25 ± 1.57	0.202
Fifth-minute Apgar, (mean ± SD)	9.60 ± 0.76	9.25 ± 1.70	0.357

Table 5

Frequency of complications of pregnancy among aspirin and placebo groups

	Aspirin (n = 43)		Placebo (n = 43)	
Complication	Frequency	%	Frequency	%
Uncomplicated	11	25.6	5	11.6
Preterm delivery	3	7	0	0
IUGR	1	2.3	0	0
PE	15	39.9	26	60.5
IUGR and PE	10	23.3	11	25.6
Preterm delivery and PE	2	4.7	1	2.3
Preterm delivery and IUGR	1	2.3	0	0

IUGR = intrauterine growth restriction; PE = preeclampsia.

Table 6

Rates of preeclampsia, intrauterine growth restriction, and preterm delivery in women treated with aspirin vs placebo

Variables	Aspirin (n = 43)	Placebo (n = 43)	aOR (95% CI)	*p*
PE	27 (62.8%)	38 (88.4%)	0.23 (0.07–0.73)	0.013
IUGR	12 (27.9%)	11 (25.6%)	1.18 (0.44–3.17)	0.750
Preterm delivery	6 (14%)	1 (2.3%)	9.78 (0.90–105.89)	0.061

Data presented as number (percentage%). Adjusted odds ratio was adjusted for maternal age, parity, and number of previous pregnancies complicated by PE.
IUGR = intrauterine growth restriction, PE = preeclampsia.

affected with PE during the pregnancy compared to 11.6% of the patients receiving placebo (p = 0.011). However, no significant efficacy was observed for aspirin in terms of reducing the risks of IUGR (p = 0.838) and preterm delivery (p = 0.131).

4. DISCUSSION

Delivering the baby and placenta as soon as possible is the only definitive treatment of PE,[8] which can be associated with an increased risk of preterm birth and its related side effects such as a greater need for neonatal intensive care unit admissions, higher mortality rate of newborns, etc.[21] Review of the literature shows that IUGR, as fetal growth below the 10th percentile appropriate for gestational age often occurs in association with PE; however, this finding is maybe due to similar pathologies influencing the placental blood circulation.[22] Concomitant occurrence of PE and IUGR is associated with a worse pregnancy outcome compared to either PE or IUGR alone.[23]

Thus, various treatments have been suggested to prevent the occurrence of IUGR and PE simultaneously including taking aspirin for those who are at a greater risk especially for PE. The history of PE in previous pregnancies is among the major risk factors for the development of PE in the current pregnancy, so it is considered a useful key for predicting the occurrence of later cases of PE. Preventive treatment with aspirin has been suggested recently in previous studies.[13]

In the present study, mean systolic and diastolic blood pressure was not significantly different at the onset of the study. Therefore, alteration in blood pressure was measured and averaged to make a between-group comparison in order to evaluate the effect of intervention on systolic and diastolic blood pressure. A significant increase was found in the mean systolic and diastolic blood pressure in both study groups. However, the amount of increase in the blood pressure was significantly lower in the intervention group than the control group. So, it could be concluded that aspirin compared to the placebo has a preventive effect on the elevation of blood pressure during pregnancy. On the other hand, it seems that aspirin is not effective enough in preventing IUGR and preterm delivery. The occurrence rate of IUGR was found to be 27.9% and 25.6% in the intervention and placebo groups, respectively. Also, the incidence of preterm delivery was equal to 14% and 2.3% in the study groups, respectively. On the other hand, the prevalence of PE

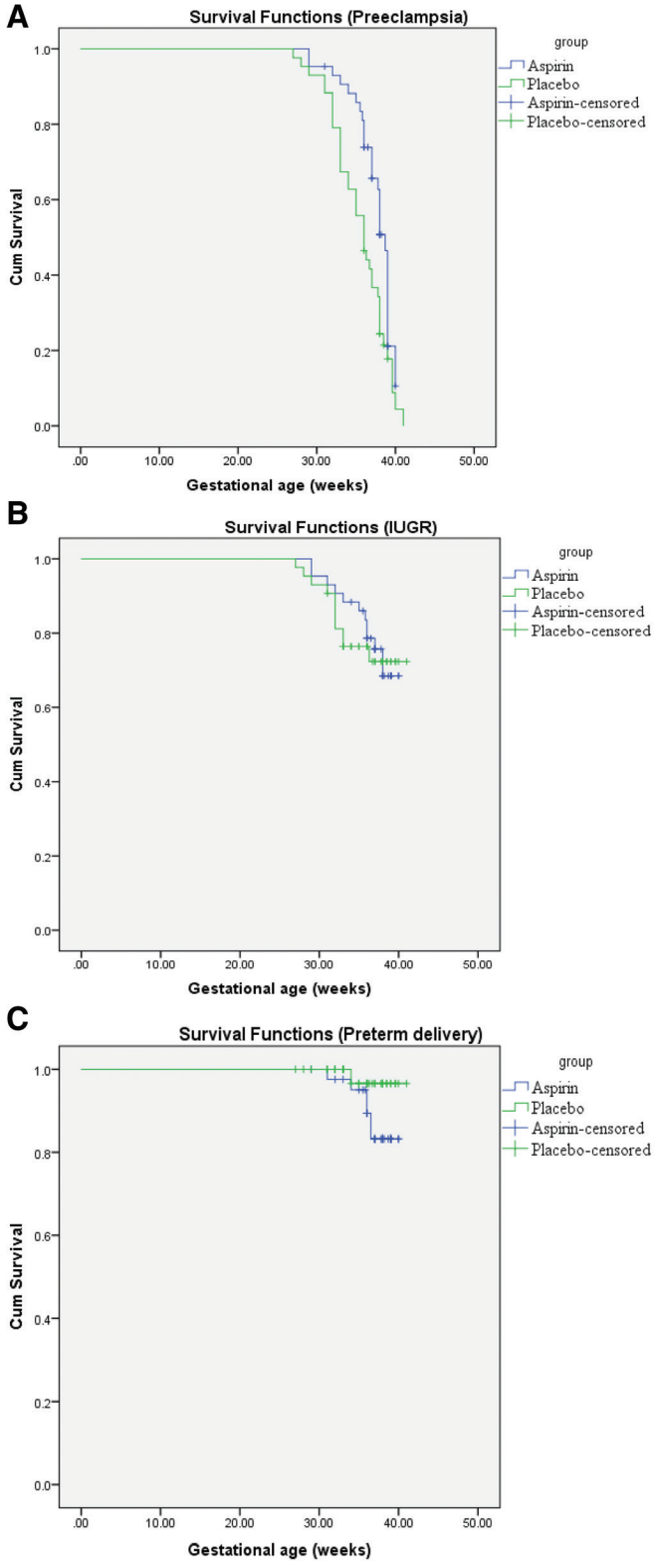

Fig. 2 Results of survival analysis (Kaplan-Meier curve) for three different complications. A, PE; B, IUGR; and C, preterm delivery. PE = preeclampsia; IUGR = intrauterine growth restriction.

was estimated to be 62.8% and 88.4% in aspirin and placebo groups, respectively, so, it can be suggested that the intervention has a preventive effect on the occurrence of PE.

Rolink et al,[18] showed that the preterm PE rate was equal to 1.6% and 4.3% in aspirin and placebo groups, respectively. The difference between the two research groups was statistically significant (p = 0.004). In their later study, the total number of women afflicted with PE at ≥37 weeks of gestation was 53 patients (6.6%) in the intervention group while it was 5 patients (7.2%) in the placebo group. However, there are certain differences between their study and the present research including the use of higher doses of aspirin (150 vs 80 mg/day in the present study) and selection of the patients for the study (so that, in the clinical trial by Rolink et al, 68.5% of the subjects in the aspirin group and 10.2% of those in the placebo group had a history of PE in previous pregnancies while in the present study, all the subjects in both groups had a history of PE in their prior pregnancies), but the conclusion regarding the efficacy of aspirin in prevention of PE was the same in both studies.

In a meta-analysis by Roberge et al,[14] the rate of PE, especially severe PE significantly decreased among the patients who had consumed aspirin before 16 weeks of gestation. Also, the rate of IUGR significantly reduced in the patients who took aspirin than those taking a placebo. An increase in the dosage of aspirin was shown to be associated with more favorable outcomes. However, in the above-mentioned meta-analysis, there was no information regarding previous history of PE in majority of the patients and the selection criteria of the patients were not clear enough in most of the studies included in the review.

In contrast to our study, Odibo et al.[8] reported no supporting data in their clinical trial regarding the effectiveness of aspirin for preventing PE. A small sample size (n = 30) was among the limitations of their study as well as a high proportion of participants who were primigravid with no history of PE.[8] However, despite similarities (such as dosage and onset of aspirin therapy) between the two studies, our finding regarding the effectiveness of aspirin was not in line with their study.

Ayala et al.[13] and Ebrashy et al.[15] found that the rate of PE differs significantly between aspirin and placebo groups, but their results regarding the IUGR and preterm delivery rates were inconsistent. However, in contrast with our clinical trial, the study participants in most of previous trials were pregnant women diagnosed with an abnormal Doppler screening of uterine artery or women with other risk factors for development of PE (not only previous history of PE).

The small sample size and lack of specification of the intensity of PE in the current pregnancy were among the limitations of the present study. Herein, the efficacy of aspirin was evaluated exclusively on the patients with a previous history of PE, which is the strength of our study while there was no previous study in which all the participants had a prior history of PE. However, future studies are required with larger sample sizes to further evaluate the efficacy of aspirin in women with a previous history of PE.

In conclusion, in the light of the present findings, it could be concluded that taking aspirin is a preventive intervention for the treatment of PE in pregnant women with at least a history of one pregnancy afflicted with PE. However, in our study, the rate of IUGR and preterm delivery did not change significantly after taking aspirin.

ACKNOWLEDGMENTS

The present authors wish to be grateful to all who participated in this research especially the esteemed professors and staff of the maternity wards of Khalij Fars Hospital in Bandar Abbas. The gratitude is extended to the research deputy of Hormozgan University of Medical Sciences.

REFERENCES

1. Duley L. Pre-eclampsia and the hypertensive disorders of pregnancy. *Br Med Bull* 2003;**67**:161–76.
2. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011;**25**:391–403.
3. Cunningham G HJ, Leveno K, Bloom S, Gilstrap L. *Williams Obstetrics*. Golban; 2009.
4. Wagner SJ, Barac S, Garovic VD. Hypertensive pregnancy disorders: current concepts. *J Clin Hypertens* 2007;**9**:560–6.
5. Dolea C, AbouZahr C. *Global burden of hypertensive disorders of pregnancy in the year 2000. GBD 2000 Working Paper*, World Health Organization, Geneva. Available at https://www.who.int/healthinfo/statistics/bod_hypertensivedisordersofpregnancy.pdf; 2003.
6. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *Am J Hypertens* 2008;**21**:521–6.
7. Onyegbule AO, Onah CC, Iheukwumere BC, Udo JN, Atuegbu CC, Nosakhare NO. Serum copper and zinc levels in preeclamptic Nigerian women. *Niger Med J* 2016;**57**:182–4.
8. Odibo AO, Goetzinger KR, Odibo L, Tuuli MG. Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2015;**46**:414–8.
9. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;**354**:810–6.
10. 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. *J Am Coll Cardiol* 2005;**46**:975–83.
11. Hermida RC, Ayala DE, Iglesias M. Administration time-dependent influence of aspirin on blood pressure in pregnant women. *Hypertension* 2003;**41**(3 Pt 2):651–6.
12. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* 2014;**10**:466–80.
13. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2013;**30**:260–79.
14. 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. *Am J Obstet Gynecol* 2017;**216**:110–20.e6.
15. 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. *Croat Med J* 2005;**46**:826–31.
16. Hauspurg A, Sutton EF, Catov JM, Caritis SN. Aspirin effect on adverse pregnancy outcomes associated with stage 1 hypertension in a high-risk cohort. *Hypertension* 2018;**72**:202–7.
17. Moore GS, Allshouse AA, Post AL, Galan HL, Heyborne KD. Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk Aspirin Study. *J Perinatol* 2015;**35**:328–31.
18. 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. *N Engl J Med* 2017;**377**:613–22.
19. Khong SL, Kane SC, Brennecke SP, da Silva Costa F. First-trimester uterine artery Doppler analysis in the prediction of later pregnancy complications. *Dis Markers* 2015;**2015**:679730.
20. Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks. *Prenat Diagn* 2010;**30**:216–23.
21. Habli M, Levine RJ, Qian C, Sibai B. Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation. *Am J Obstet Gynecol* 2007;**197**:406. e1–e7.
22. Roberge S, Odibo AO, Bujold E. Aspirin for the prevention of preeclampsia and intrauterine growth restriction. *Clin Lab Med* 2016;**36**:319–29.
23. Srinivas SK, Edlow AG, Neff PM, Sammel MD, Andrela CM, Elovitz MA. Rethinking IUGR in preeclampsia: dependent or independent of maternal hypertension? *J Perinatol* 2009;**29**:680–4.