ORIGINAL ARTICLE

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

Khadijeh Abdali[1], Msc; Rozita Taghizadeh[2], Msc; Sedigheh Amoei[3], MD; Seyed Hamid Reza Tabatabai[4], MSc

[1]Department of Midwifery, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Department of Midwifery, Obstetrics ward, Zainabie Hospital, Shiraz University of Medical Sciences, Shiraz, Iran;
[3]Department of Obstetrics and Gynecology, School Of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;
[4]Department of Statistic, Faculty of Health, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding author:
Khadijeh Abdali, MSc; Department of Midwifery, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 711 6474250; **Fax:** +98 711 6474252; **Email:** abdali_kh@yahoo.com

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Abstract

Background

Gestational hypertension is one of the three common causes of maternal death. This study was designed to compare the effects of aspirin and placebo on 24 hour blood pressure mean in women at risk of preeclampsia in two different diurnal times to prevent preeclampsia.

Methods

Sixty four women who were at risk of gestational hypertension were recruited to be included in the study using convenience sampling method and divided into 4 groups by random allocation. Control groups one and two received placebo tablet. Experimental groups one and two received aspirin tablets (100 mg) in the morning and at night, respectively , one tablet a day every day starting at the time of recruitment and continued till 32nd week of gestation, by double blind method. The patients' blood pressure was monitored at the end of each month for 24 consecutive hours from 12 to16 weeks until delivery. Data were analyzed using repeated measures design and along with multiple comparative tests in SPSS software (version 8.0).

Results

In Aspirin and control group 1, systolic and diastolic BP mean variations were similar, (P=0.835 and P=0.705 for systole and diastole, respectively). In Aspirin and control group 2, systolic and diastolic BP mean variations were statistically significant. (for systole and diastole P<0.001). Mean reduction for systole was 14.12 mmHg in 32nd week and 12.12 mmHg in 40th week and for diastole it was 11.69 mmHg in 32nd week and 9.04 mmHg in 40th week.

Conclusion

Taking aspirin at night is more effective on 24-hour blood pressure mean reduction in women at preeclampsia risk compared with that in the morning.

Trial Registration Number: IRCT138803211548N5

Keywords: Aspirin; Ambulatory blood pressure monitoring; Gestational hypertension; Preeclampsia

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Introduction

The most common causes of maternal death are gestational hypertension, infection, bleeding and ectopic pregnancy. Preeclampsia complicates the patients' condition resulting in hypertension, uteroplacental insufficiency, placenta abruption, intrauterine fetal death, preterm delivery, low birth weight, irreversible damage to vital organs of mother and maternal mortality.[1]

In the United States, 15% of maternal deaths are due to preeclampsia. Daily, 1600 women in the world lose their life because of pregnancy or childbirth complications, (600,000 cases annually).[2] Currently, several clinical trials are going on about reducing thromboxane A2 products (vasoconstrictor) and increasing prostacyclin (vasodilator) so that hypertension decreases and placental perfusion increases.[3]

Several studies showed the effects of aspirin on blood pressure in pregnant women. Starting at 28th to 32nd weeks of gestation is too late, but starting before 17 weeks of gestation significantly decreases the incidence of preeclampsia.[4] The differences of blood pressure pattern in healthy individuals and those who later affected gestational hypertension in early pregnancy is the reason for taking aspirin before the 17th week of gestation.[5] Taking aspirin at night has more efficacy on blood pressure than other times in a day. In these studies, less attention has been paid to taking drug more than 80 mg. Previous studies have shown that taking a dose of less than 80 mg of aspirin has no effect on the placenta thromboxan.[6] The above-mentioned points are probably the causes of controversy in studies.

The results of some research indicated that consumption of low-dose aspirin (50 to150 mg) at night, compared with other times of the day, is effective on the reduction of circadian blood pressure mean variation in pregnant women,[7] patients with mild hypertension,[8] untreated blood pressure,[9] and pregnant women at preeclampsia risk.[10] Starting treatment with 100 mg aspirin at night at 12 to 16 weeks of gestation has a remarkable effect on the circadian blood pressure mean reduction of patients and decreases the rate of preeclampsia. 14 studies compared the effect of aspirin with 80,100 and 150 mg dose and placebo on the 12,416 high-risk pregnancies. It was revealed that aspirin decreases the risk of preterm delivery(21%), preeclampsia (14%), spontaneous abortions (14%) and increases the birth weight to the rate of half-pound. However, several studies conducted on samples of more than 13000 women at risk of preeclampsia have shown that prevalence of preeclampsia, intrauterine growth retardation, premature birth and pregnancy complications has not decreased.[11] Women at high risk of preeclampsia who were identified with ABPM (ambulatory blood pressure monitoring) evaluation at the first trimester of pregnancy, might benefit most from the cost-effective preventive intervention with timed low-dose ASA(aspirin),[12] and it is true about abnormal placentation diagnosed by uterine artery Doppler studies.[13] Aspirin therapy in women who were found high-risk using Uterine artery Doppler resulted in a significant reduction in preeclampsia.[14] Chronotherapy constitutes a cost-effective strategy for enhancing BP control and monitoring patients with resistant hypertension.[15,16] All studies have shown aspirin reduces the incidence of preeclampsia and IUGR (intrauterine growth retardation) in women at moderate or higher risk for preeclampsia.[17] Bedtime administration of some drugs was more effective as compared to morning administration in hypertensive patients,[18] dipper and non-dipper hypertensive,[19] and prehypertensive patients.[20] However, previous studies in because such research has not been done on Iranian race, this study was conducted to compare the effectiveness of aspirin administration in two different times a day. It is hoped that the results of this study could effectively take steps in prevention of gestational hypertension and preeclampsia in women at risk.

Materials and Methods

This study which was conducted during

2011-2012 is a randomized double blind clinical trial in pregnancy clinics of Shiraz University of Medical Sciences and approved by ethics committee of this university. 100 Middle Eastern pregnant women participated in this study. They had all the criteria for inclusion in this study. These women, compared with other women, were at higher risk of gestational hypertension and preeclampsia. These risks include personal or family history of hypertension, gestational hypertension and preeclampsia, personal history of spontaneous abortion, obesity, middle age and young age (fewer than 18 and above 35 years). Exclusion criteria in this study included any need to steroidal, non-steroidal and anti-hypertensive drugs, multiple pregnancy, cardiovascular disease, chronic gastrointestinal disease, asthma, bleeding disease, diabetes or any endocrine disorder such as hyperthyroidism or intolerance to the circadian blood pressure monitoring device.

Of all 100 patients who participated in this study, 36 were excluded from this study due to different reasons: 6 cases because of spontaneous abortion, 8 cases due to intolerance to the monitoring device after the first meeting, 4 cases because of forgetting to take more than 6 aspirin tablets per month and 5 cases because of having less than 4 hypertension mean profiles, 7 cases because of gestational hypertension, and 6 cases because of preeclampsia. The design and protocol of the study is shown in figure 1.

Sixty four women who were at risk of gestational hypertension were recruited using convenience sampling method and randomized into 4 groups by table of random numbers (n=16 in each group). Control groups one and two received placebo tablet; experimental groups one and two received aspirin tablets (100 mg) in the morning and at night respectively , one tablet a day every day starting at the time of recruitment and continued till 32nd week of gestation.

All volunteers signed a consent form before the study and then to evaluate the initial blood pressure of the patients before entering the study a reading device 24-hour monitoring (IEM made in Germany) was tied to the patients' non-dominant arm which was less efficient. The place of the device will not restrain the patientsfrom performing daily activities. The device is a light which does not hurt the patients and they were able to sleep during the measurements. Recording blood pressure was based on the time that the device was installed to the software program of a computer. The patients' blood pressure was recorded each quarter per day and every half hour per night,[21] (approximately 50 to 70 times in 24 hours). 24 hour blood pressure assessments were studied with the rest-activity cycle of the patient (Their activities should be as usual and they must not sleep less than 6 hours and more than 12 hours at night). Patients whose blood pressure was not recorded for more than 3 hours and also patients who received any drugs during the research process were excluded from the study. If they felt any pain in different parts of their body, they could take acetaminophen. After 24 hours, registered information was printed as multiple charts. If the mean of 24-hour blood pressure of patients during the study was more than 135/85 mmHg, the mean of daily blood pressure was more than 140/90 mm Hg, or the mean of blood pressure at night was more than 120/75 mmHg, it was considered as hypertension and the patient was excluded from the study.[22] Patients with hypertension, abortion, intolerance to the monitoring device, gastrointestinal problem at any time of the study were excluded. (Ethical Considerations)

The patients were referred to a person who was not aware of type of the drug, but was aware of consumption time with counting pills and checking of the time and the records(double blind method). At first, each sample could receive approximately 30 tablets for one month (all tablets were the same color) along with the instruction for the consumption of drugs (1 tablet per day, morning or night). Intervention started at the time of recruitment and continued till the 32nd week of gestation. After 24-hour blood pressure monitoring, the next package of the drug was delivered by

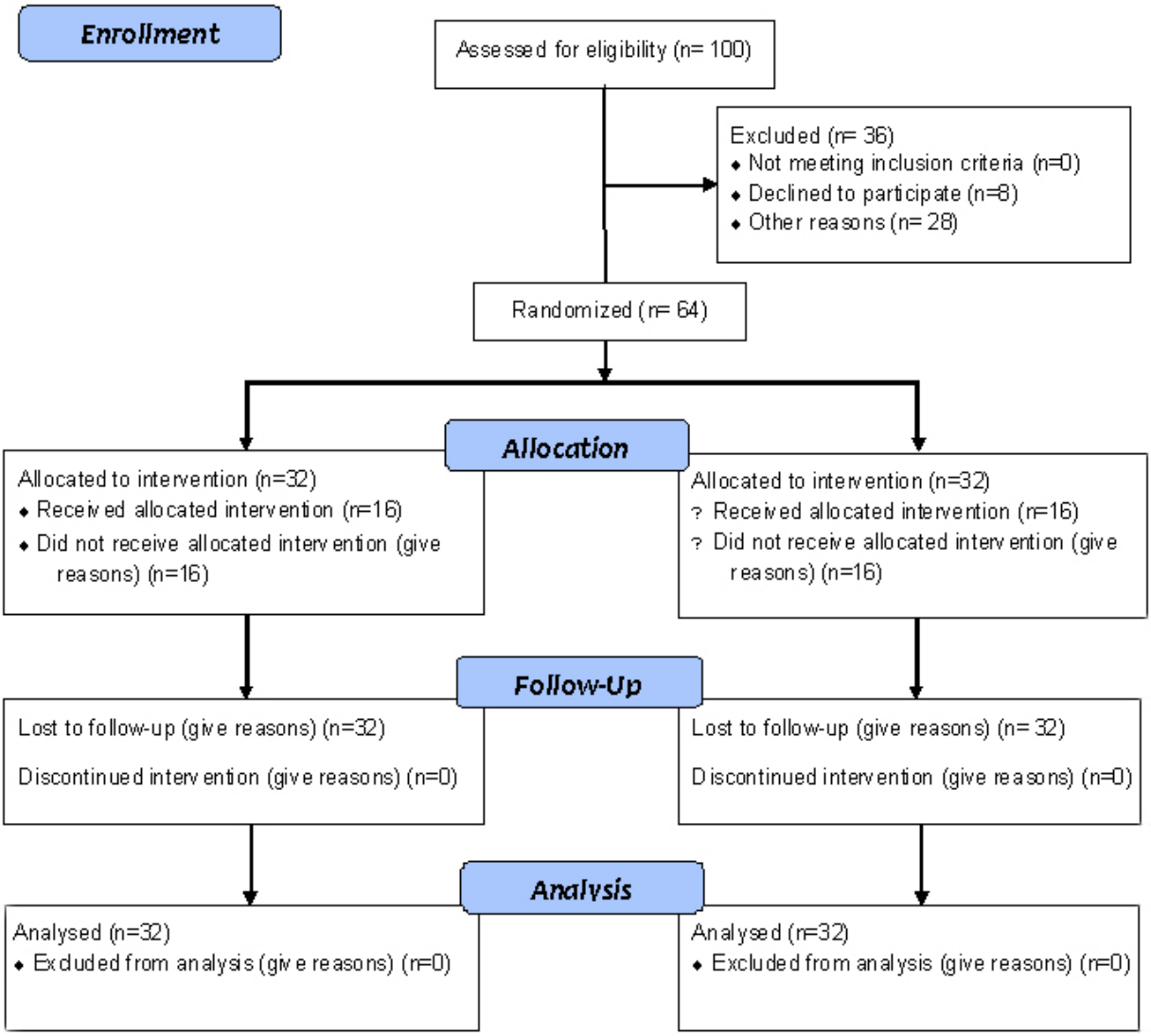

Figure 1: The flowchart of design and protocol of the study.

the previous person . This trend continued to the end of each month up till the 32nd week of gestation. If any patient lost more than 6 tablets every month, she was excluded from the study. The minimum drug required for each patient was 120 and maximum 150 numbers (considering the time of entry into the study).

This intervention started from 12 to 16 weeks and ended up to 32 weeks. The blood pressure registrar device was recording the patient's blood pressure for 24 hours consecutively at the end of each month until delivery. Each patient was monitored 7 times during pregnancy (from 12th-16th week to 40th week). Primary data related to blood pressure records in each group were corrected in order to throw out outlier values and measurement errors according to statistical methods. Mean and standard deviation of the collected data were analyzed in SPSS software (version 8.0) using repeated measures design and multiple comparative tests.

Results

In this study, out of 100 eligible women registered for the study, only 64 people entered the study. The sample's demographic information showed that the age of participants was between 17-42 years (mean 28.7, SD 5.8), weight between 49-85 kg, (65.7 average, SD of 8.5), height 150-178 cm (161.1 average, SD of 6.1), BMI 18.7-38.3(kg/m^2) (average 25.3, SD of 3.3), systolic blood pressure 97.4-120.3 mmHg (106.2 average, SD 4.9,

figure 2) and diastolic blood pressure was 53.0-73.4 mmHg (61.9 average, SD 5/3, figure 3).

Of all 64 samples, 23 were primipara and 41 multipara(P=862/0 messured with multiple comparative tests). In the experimental group 1and control group 1, systolic and diastolic blood pressure mean variations were similar; it was increased during pregnancy and they were not statistically significant at any time during pregnancy, (P=0.8 and P=0.7 for systole and diastole, respectively).

The difference between systolic blood pressure mean in the experimental group 2 and control group 2 was statistically significant after the second month of treatment. (P<0.001 for systole) (table 1). The mean reduction of systolic blood pressure in the experimental group 2 was 14.1 mmHg in 32nd week and 12.1 mmHg in the 40th week, (P=0.001 at 40th week).

The difference between diastolic blood pressure mean in the experimental group 2 and control group 2 was statistically significant after the 28th week of gestation. The reduction of systolic blood pressure mean in the 32nd week of gestation was 11.69 mmHg and in the 40th week of gestation it was 9.04 mmHg (P<0.001 for diastole) (table 2).

Systolic blood pressures in the experimental group 1 and control groups1 and 2 were similar and increased during pregnancy (figure 2). Diastolic blood pressure in the experimental group 1 and control groups1 and 2 were similar and increased during pregnancy (figure 2).

Cesarean delivery method between groups was not statistically significant (P=0.9). The

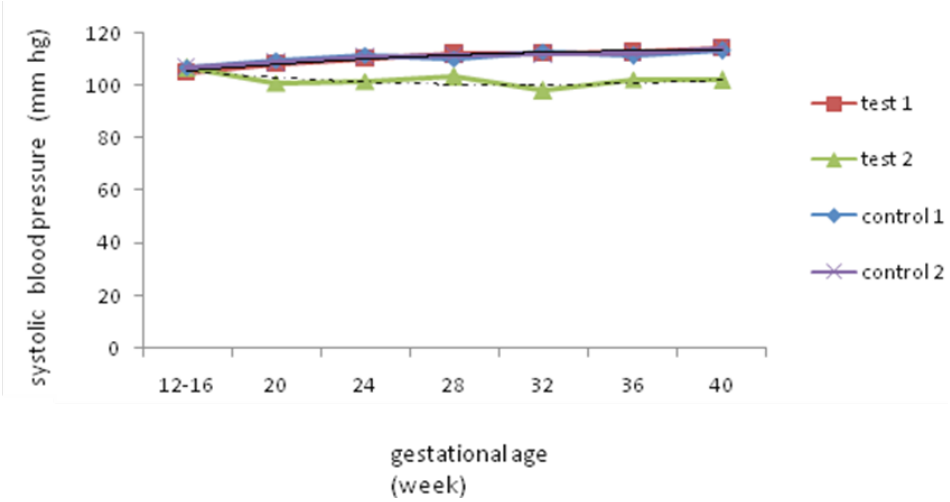

Figure 2: Comparison of 24 hour systolic blood pressure mean before and after treatment in two different diurnal times in the four groups.

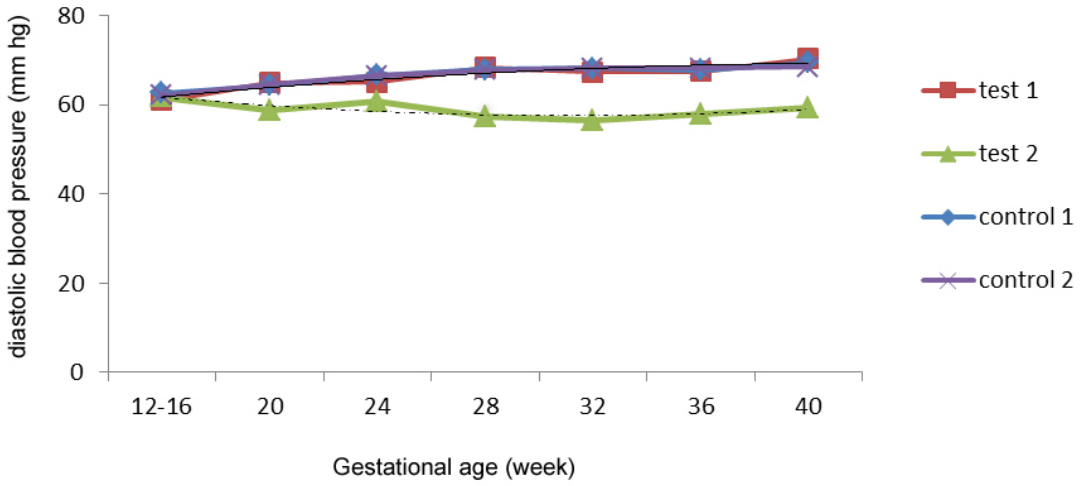

Figure 3: Comparison of 24 hour diastolic blood pressure mean before and after treatment in two different diurnal times in the four groups.

Table 1: Comparison of 24 hour systolic blood pressure before and after treatment in two different diurnal times in the four groups

Group		Test 1 (n=16)	Control 1 (n=16)	Test 2 (n=16)	Control 2 (n=16)	P value
	GA	mean±SD	mean±SD	mean±SD	mean±SD	
24 hour blood pressure mean (mm Hg)						
Pretreatment (12-16week)		104.95±3.833 A	106.74±3.860 A	106.44±7.006 A	106.69±4.619 A	0.710
after treatment (12–32 week)	20	108.09±6.217 A	109.27±7.426 A	101.09±5.336 B	108.56±5.257 A	0.001
	24	110.25±6.862 A	111.32±6.436 A	101.53±4.725 B	112.12±4.926 A	0.001
	28	111.84±4.676 A	110.26±5.704 A	103.28±9.025 B	111.3±4.379 A	0.001
	32	112.13±5.435 A	112.62±6.212 A	97.95±11.648 B	111.09±7.502 A	0.001
After discontinuation treatment (33 weeks until delivery)	36	112.39±3.683 A	111.04±5.249 A	102.26±5.008 B	112.08±2.488 A	0.001
	40	113.99±3.390 A	113.26±6.124 A	101.92±5.336 B	114.04±3.226 A	0.001

P values equal or lower than P=0.001 are considered as significant; A, B: The same letters show no significant difference between the results; GA: Gestational age

Table 2: Comparison of 24 hour diastolic blood pressure mean before and after treatment in two different diurnal times in the four groups

Groups		Test 1 (n=16)	Control 1 (n=16)	Test 2 (n=16)	Control 2 (n=16)	P value
	GA	mean±SD	mean±SD	mean±SD	mean±SD	
24 hour mean blood pressure(mmHg)						
Pretreatment (12-16week)		61.045±3.977 A	62.68±6.890 A	61.80±5.643 A	62.10±4.96 A	0.861
After treatment (12th–32nd week)	20	64.98±5.420 A	64.40±5.809 A	58.74±10.20 A	64.50±6.322 A	0.054
	24	65.14±5.068 A	66.71±9.735 A	60.68±8.399 A	66.54±6.698 A	0.103
	28	68.41±7.600 A	68.03±4.520 A	57.48±9.048 B	67.84±7.938 A	0.001
	32	67.42±6.967 A	68.21±8.107 A	56.62±8.154 B	68.31±6.660 A	0.001
After discontinuing treatment (33rd week until delivery)	36	67.60±5.439 A	67.83±7.860 A	57.86±5.632 B	68.29±4.116 A	0.001
	40	70.319±3.208 A	69.46±6.477 A	59.45±4.615 B	68.49±3.745 A	0.001

P values equal or lower than P=0.001 are considered as significant; A, B: The same letters show no significant difference between the results; GA: Gestational age

mean of birth weight at delivery time was 3167 with SD 7.4. The heart rate showed no difference between groups during pregnancy.

Intrauterine growth retardation in the control and experimental groups was respectively 4 versus 2 patients, preterm delivery 4 versus 3 patients, blood pressure during pregnancy 5 versus 2 patients and preeclampsia 4 versus 2patients. The amount of bleeding was similar before and after delivery in groups.

Discussion

Systolic and diastolic blood pressure mean in groups who received aspirin and placebo in the morning was similar during pregnancy. So taking aspirin in the morning had no effects on systolic and diastolic blood pressure mean in pregnant women at preeclampsia risk compared with the control group at the same time.

To compare systolic and diastolic blood pressure mean in groups who received aspirin and placebo at bedtime, the systolic and diastolic blood pressures were significantly decreased during pregnancy and unlike the morning, taking aspirin at night had a significant effect on systolic and diastolic blood pressure mean in pregnant women at preeclampsia risk. In this study, the comparison between systolic and diastolic blood pressure in the groups taking placebo in the morning and at bedtime showed that taking aspirin and placebo in the morning and placebo at bedtime had no effects on systolic and diastolic blood pressure. Previous studies also indicated that when receiving aspirin in the morning, daily blood pressure had no change, but blood pressure reduced at night.[18]

The important point is that unlike other groups, in group taking aspirin at bedtime, after 32 weeks of gestation (discontinuation of treatment) blood pressure reduction remained low and did not increased. This study indicated a long term effect of aspirin therapy after stopping treatment with aspirin.

Investigations into preventing preeclampsia have not led to conclusive results. For a long time, researchers focused on aspirin with its anti-platelet effects and in this field contradictory results were obtained, requiring more investigation. Causes of contradictions in these studies were related to the time of initiation of aspirin therapy, being very late (after the 17 weeks of gestation). Taking aspirin at night was more effective on blood pressure than taking it in the morning (probably due to the increase of platelet activity at night and peak effect of aspirin on the decrease of plasma renin activity).[23] Another reason is that in studies less attention has been paid to taking drug dosage less than 80 mg. The researcher's aim had been taking aspirin to prevent preeclampsia but not to reduce hypertension.[17]

Although medications may be useful in controlling blood pressure during pregnancy, childbirth educators should educate pregnant women, who are at risk of pregnancy hypertension, to avoid smoking, maintain a healthy weight, exercise regularly and eat a healthy diet. It is recommended that all women who are at risk of preeclampsia or hypertension in pregnancy have regular blood pressure check and regular assessment of other cardiovascular risk factors including serum lipids and blood glucose.

Research has shown that low dose aspirin therapy is not a contraindication to perform caesarean section with regional anesthesia in the absence of bleeding.[24] However, birth attendants and birth educators need to inform pregnant women of the risk of bleeding during the use of aspirin and educate them about any consequences. Pregnant women should know that if they use aspirin and they experience vaginal bleeding, it may indicate a problem. In such cases, the women must contact their health care provider immediately. In this study, more data and a large number of cases could help to determine better result with any changes in preeclampsia risk. We could also assess blood pressure for 48 consecutive hours. In other studies, aspirin is recommended to be used at 3 different times a day (morning, afternoon and evening) on a high risk pregnant women. Evaluating 48-hour blood pressure

mean variation is recommended to confirm the results of this study. Comparison of lower and higher doses (80-50 mg) of aspirin (150-100 mg) and also treatment till delivery time and in postpartum with aspirin may provide useful information on the effective dose of aspirin in reducing blood pressure and preventing preeclampsia.

Conclusion

Results of this study indicated that aspirin taken in the early hours of day as compared to placebo was not effective on 24-hour blood pressure mean reduction in women at risk for preeclampsia, whereas aspirin taken at bedtime compared with placebo was effective on the mean of 24-hour blood pressure reduction in women at preeclampsia risk. The impact of taking aspirin at bedtime compared with taking it in early hours of the day is different and more effective on 24-hour blood pressure mean in women at preeclampsia risk.

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Conflict of Interest: None declared

Reference

1 Koonin LM, MacKay AP, Berg CJ, et al. Pregnancy-related mortality surveillance--United States, 1987-1990. Morb Mortal Wkly Rep CDC Surveill Summ. 1997;46:17-36.
2 Lowdermilk DL, Perry SE. Maternity & Women's Health Care. 8th ed. St. Louis: Mosby; 2004. p. 7-840.
3 Gerard N, Thomas P. Medical complication during pregnancy. 5th ed. Philadelphia: Elsevier w.b. Saunders; 2004. p. 53-79.
4 Hermida RC, Ayala DE, Iglesias M, et al. Time-dependent effects of low-dose aspirin administration on blood pressure in pregnant women. Hypertension. 199;30:589-95.
5 Hermida RC, Ayala DE, Mojón A, et al. Blood pressure patterns in normal pregnancy, gestational hypertension and preeclampsia. Hypertension. 2000; 36:149-58.
6 Walsh S, Wang Y. Maternal perfusion with low-dose aspirin preferentially inhibits placental thromboxane while sparing prostacyclin. Hypertension Pregnancy. 1998;17:203-21.
7 Hermida RC, Ayala DE, Iglesias M. Administration time–dependent influence of aspirin on blood pressure in pregnant women. Hypertension. 2003;41:651-6.
8 Hermida RC, Ayala DE, Calvo C, et al. 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.
9 Hermida RC, Ayala DE, Calvo C, et al. Administration time-dependent influence of aspirin on blood pressure in previously untreated hypertensive patients. Am J Hypertension. 2002;15:109-10.
10 Hermida RC, Ayala DE, Fernández JR, et al. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. Hypertension. 1999;34:1016-23.
11 Gerard N, Thomas P. Medical complication during pregnancy. 6th ed. Philadelphia: Elsevier Saunders; 2004. p. 53-4.
12 Ayala DE, Ucieda R, Hermida RC. Chronotherapy With Low-Dose Aspirin for Prevention of Complications in Pregnancy. Chronobiol Int. 2012;30:260-79
13 Bujold E, Morency AM, Roberge S, et al. 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. J Obstet Gynaecol Can. 2009;31:818-26.
14 Coomarasamy A, Papaioannou S, Gee H, et al. Aspirin for the prevention of preeclampsia in women with abnormal

uterine artery Doppler: a meta-analysis. Obstet Gynecol. 2001;98:861-6.
15 Hermida RC, Ríos MT, Crespo JJ, et al. Treatment-Time Regimen of Hypertension Medications Significantly Affects Ambulatory Blood Pressure and Clinical Characteristics of Patients With Resistant Hypertension. Chronobiol Int. 2013;30:192-206.
16 Smolensky MH, Hermida RC, Ayala DE, et al. Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press Monit. 2010; 15:173-80.
17 Bujold E, Roberge S, Lacasse Y, et al. Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy a meta-analysis. Obstet Gynecol. 2010; 116:402-14.
18 Hermida RC, Calvo C, Ayala DE, et al. Dose- and administration time-dependent effects of nifedipine gits on ambulatory blood pressure in hypertensive subjects. Chronobiol Int. 2007;24:471-93.
19 Hermida RC, Ayala DE, Calvo C, et al. Differing administration time-dependent effects of aspirin on blood pressure in dipper and non-dipper hypertensives. Hypertension. 2005;46:1060-8.
20 Hermida RC, Ayala DE, Mojón A, et al. Ambulatory blood pressure control with bedtime aspirin administration in subjects with prehypertension. Am J Hypertens. 2009;22:896-903.
21 Alister M, Straus S . Evidence based treatment of hypertension Measurement of blood presssure: an evidence based review. BMJ. 2001;322:908-1.
22 Geoffrey A, Karen A Duggan, et al. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure. BMJ. 2010;340:c1104.
23 Snoep JD, Hovens MM, Pasha SM, et al. Time-dependent effects of low-dose aspirin on plasma renin activity, aldosterone, cortisol, and catecholamines. Hypertension. 2009;54:1136-42.
24 Young P, Johanson R. Haemodynamic, invasive and echocardiographic monitoring in the hypertensive parturient. Best Practice & Research Clinical Obstetrics & Gynaecology. 2001;15:605-22.