

ORIGINAL ARTICLE

PREVENTION OF PREECLAMPSIA WITH LOW-DOSE ASPIRIN OR CALCIUM SUPPLEMENTATION

Ali-Akbar Taherian MD*, Ali Taherian, Amin Shirvani

*Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences,
Isfahan, Iran*

Background– Preeclampsia is a common and serious complication of pregnancy that affects both mother and newborn. This study was designed to evaluate the effects of low-dose aspirin or calcium supplements, taken during pregnancy, on the incidence of preeclampsia.

Methods– The study was a randomized clinical trial on 990 healthy nulliparous women performed at the Isfahan Health Center between April 1998 and March 2001. The women, in their first half of pregnancy, were randomly assigned to one of three groups (group 1 received 75 mg aspirin each day; group 2 were treated with 500 mg oral calcium daily; and group 3 was designated as the control group, receiving no medication). Data were recorded using a standardized questionnaire. Statistical analyses was performed using Chi-square, ANOVA and Duncan tests.

Results– Preeclampsia occurred in 15 women in the aspirin group (15/330, 4.6%), 13 women in the calcium group (13/330, 4%), and 33 women in the control group (33/330, 10.1%). There were significant differences between the aspirin and control groups ($p < 0.05$), and between the calcium and control groups ($p < 0.05$). There was no significant difference between the aspirin and calcium groups ($p = 0.7$).

Conclusion– Our results suggest that prescription of low-dose aspirin or calcium-D during pregnancy in healthy nulliparous women is effective in reducing the occurrence of preeclampsia.

Keywords • calcium • clinical trial • low-dose aspirin • preeclampsia

Introduction

Hypertensive disorders of pregnancy remain the second most common cause of maternal mortality in the United States, accounting for 15% of all maternal deaths.¹ Preeclampsia is a major cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries.²

Most cases of preeclampsia occur in nulliparous women.^{3,4} This disease is a multisystem disorder of unknown etiology, and placental ischemia is considered to have a major role in the pathogenesis of these complications.^{5,6}

Preeclampsia is associated with reduced

intravascular production of prostacyclin and excessive production of thromboxane A₂.^{7,8}

During the past two decades, numerous clinical trials were conducted to evaluate the effectiveness of various methods to prevent or reduce the incidence of preeclampsia.²

The results of several clinical trials and meta-analyses have suggested that calcium supplementation^{9,10} or low-dose aspirin^{11,12} reduces the incidence of preeclampsia. Other trials also have shown the beneficial effects of these compounds in reducing the occurrence of preeclampsia.^{13,14}

Our study was conducted to evaluate the effect of low-dose aspirin or calcium supplements, taken during pregnancy, on the incidence of preeclampsia in nulliparous healthy women in Isfahan, Iran.

*Correspondence: A.A. Taherian MD, Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences, Al-Zahra Hospital, Isfahan, Iran. P.O. Box: 907, E-mail: taherian@med.mui.ac.ir.

Patients and Methods

Nulliparous women attending antenatal outpatient clinics of Isfahan Health Centers between April 1998 and March 2001 were asked to participate in this randomized, controlled study. The sampling method was nonprobability convenience and the sample size was calculated based on the comparison of two relative frequencies formula with an estimated α and β errors as 20% and 80%, respectively.

The inclusion criteria were; nulliparity, single gestation, first prenatal visit before 20 weeks of gestation, systolic/diastolic blood pressure (BP) lower than 130/80 mmHg, and no proteinuria detectable by a dipstick. Subjects were excluded if they had a history of cardiovascular, renal or endocrinologic problems, medical or obstetric complications and those with known hazardous condition (multifetal gestation, hydatidi-form mole).

The 990 healthy nulliparous women were randomly allocated to three equivalent groups. We used a table of random number to assign each case independently to one of three groups (aspirin, calcium and control groups). Group 1 received 75 mg aspirin each day; group 2 were treated with 500 mg oral calcium-D daily (calcium-D = 500 mg calcium carbonate + 200 IU vitamin D); and the control group 3 received no medication at all. The study commenced at the 20th week of gestation and continued until delivery. Each subject was informed regarding the details of the study and all of them gave a written consent before engaging in the trial.

All cases received prenatal care according to the approved model.¹⁵ BP, bodyweight and maternal height were measured at an initial prenatal visit; at each subsequent prenatal visit, BP, body weight and urine protein measurements were taken. The women were examined by trained staff every 4 weeks through the 28 weeks of gestation, and every 2 weeks through the 36th week and weekly thereafter.

BP was measured with the subject in the sitting position by a certified examiner using a standard mercury sphygmomanometer (Riester, Germany). According to a published protocol,¹⁶ systolic BP was recorded with the appearance of the first Korotkoff sound, and diastolic BP with disappearance of the fifth Korotkoff sound. Maternal height and weight were measured

according to routine, standard methods. Patients were considered to have mild preeclampsia if they demonstrated an increase of 30 mmHg in systolic or 15 mmHg in diastolic BP above the standard pressure. In addition, they should have demonstrated equal or greater than 300 mg/24 hours in urine collection, or in two random urine specimens obtained 4 hours apart and containing at least 1+ protein by the dipstick method. Severe preeclampsia was defined as BP equal or greater than 160/110 mmHg and 4+ protein by dipstick on two occasions 4 hours apart, according to the American College of Obstetricians and Gynecologists' Bulletin.¹⁷ After rupture of the membranes, the urine specimens were collected by catheter.

Newborns were weighed with a beam balance-scale, within half an hour after birth. All the staff were carefully instructed at the beginning of the study on the methodology and several physicians supervised their performance. Ethical permission was obtained from the Deputy of Health Affairs of Isfahan University of Medical Sciences (IUMS).

Data were collected using a standardized questionnaire and included demographic, medical and obstetrical histories. Prenatal care records and hospital charts were also recorded. The newborn chart included the neonatal weight at birth, the presence of respiratory distress syndrome, sepsis, jaundice and intrauterine growth retardation (IUGR), according to Divon et al.¹⁸ Fetal or neonatal death was also included if required.

Data analysis was performed with SPSS 9 (SPSS Inc, Chicago, IL, USA) statistical software. Chi-square analysis was used for the incidence of preeclampsia, IUGR, preterm delivery, fetal and newborn morbidity, mortality, education and employment status. Analysis of variance (ANOVA) was used for age, height, weight, body mass index (BMI) and duration of gestation. For maternal weight gain, Duncan test was used following ANOVA. Descriptive parameters (mean \pm SE, frequency and percentage for categoric data) and confidence interval (95%) were used for data presentation.

Results

The mean \pm SE of age in aspirin, calcium and control groups was 21.5 \pm 0.21, 21.9 \pm 0.28 and 21.2 \pm 0.19 years, respectively. Three groups of

Table 1. Comparison of demographic characteristics, employment and education status in the three study groups.

Variable	Aspirin (n = 330) Mean (95% CI)	Calcium (n = 330) Mean (95% CI)	Control (n = 330) Mean (95% CI)	p Value
Age (yr)	21.5 (21.11, 21.89)	21.9 (21.61, 22.39)	21.2 (20.81, 21.59)	0.39
Height (cm)	160.6 (160.11, 161.09)	159.8 (159.23, 160.37)	159.4 (158.81, 159.99)	0.0042
Weight (kg)				
At initial visit	57.6 (56.80, 58.40)	57.7 (56.86, 58.57)	57.3 (56.34, 58.26)	0.83
At birth	68.4 (67.52, 69.28)	68 (67.08, 68.92)	67.2 (66.10, 68.30)	0.18
Maternal weight gain	10.7 (10.31, 11.09)	10.6 (10.25, 10.95)	9.9 (9.51, 10.29)	0.003**
Body mass index (kg/m ²)				
At initial visit	22.3 (22.01, 22.59)	22.5 (22.17, 22.83)	22.6 (22.21, 22.99)	0.52
At delivery	26.5 (26.17, 26.83)	26.6 (26.25, 26.95)	26.6 (26.21, 26.99)	0.79
Weeks of gestation	39.0 (38.86, 39.14)	38.7 (38.52, 38.88)	39.0 (38.86, 39.14)	0.0001
Employed (%)	21.5%	14.0%	15.5 %	0.01
Education				0.3
Not educated	3.8%	4.5%	2.6%	
Preliminary	27.0%	45.1%	41.9%	
High school	45.0%	38.9%	40.1%	
University graduate	15.4	11.5	14.2	

* NS = not significant ($p > 0.05$); **Duncan test showed significant differences between the aspirin and control groups, and between the calcium and control groups.

women were similar in age, body weight, BMI, and degree of education (Table 1).

Of the 990 healthy nulliparous women observed, 61 (6.2 %) developed preeclampsia. The frequency of preeclampsia occurrence in the group 1 (aspirin), group 2 (calcium) and control group 3 was 4.6%, 4% and 10.1%, respectively. There was a statistically significant difference between the aspirin and control groups ($p = 0.007$), and between the calcium and control groups ($p = 0.005$). In contrast, no significant difference between the aspirin and calcium groups was detected ($p = 0.7$) (Table 2).

The mean weight gain (\pm SE) during pregnancy in the aspirin, calcium and control groups was 10.7 ± 0.19 , 10.6 ± 0.18 and 9.9 ± 0.19 kg, respectively. ANOVA followed by Duncan test showed a significant difference in weight gain during pregnancy between the aspirin and control ($p < 0.05$) groups, and between the

calcium and control groups ($p < 0.05$).

The mean duration of pregnancy (\pm SE) in the aspirin, calcium and control groups was 39 ± 0.07 , 38.6 ± 0.09 and 39 ± 0.07 weeks, respectively ($p < 0.001$). The rate of preterm delivery, defined as birth before 37 weeks of gestation, in the aspirin, calcium and control groups was 11.8%, 13.7 % and 8.9 % (not significant, $p = 0.16$).

The mean weight at birth (\pm SE) was $3,120 \pm 24$ g in cases treated with aspirin, $3,035 \pm 23$ g in those under calcium-D therapy, and $2,910 \pm 22$ g in the control group. ANOVA followed by Duncan test showed that these values were statistically different in the aspirin and control ($p = 0.001$), aspirin and calcium ($p = 0.001$), and calcium and control groups ($p = 0.003$). The incidence of IUGR in the aspirin, calcium and control groups was 7.1 %, 10.7 % and 11.9 %, respectively. Finally, fetal and newborn morbidity and mortality were similar in three groups (Table 2).

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Table 2. Pregnancy outcomes: frequency of preeclampsia, birth weight, intrauterine growth retardation (IUGR), preterm delivery and newborn morbidity.

Variable	Aspirin (n = 330)	Calcium (n = 330)	Control (n = 330)	p Value
Preeclampsia incidence (n)				
Mild (%)	11 (3.4)	10 (3.1)	27 (8.3)	0.0025
Severe (%)	4 (1.2)	3 (0.9)	6 (1.8)	0.58
M+S* (%)	15 (4.6)	13 (4)	33 (10.1)	0.0017
Blood pressure (mmHg)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Systolic**	95.27 (94.21,96.33)	97.79 (96.61, 98.97)	96.70 (95.74, 97.66)	< 0.0001
Diastolic**	56.97 (56.07,57.87)	58.25 (57.37, 59.13)	57.50 (56.68, 8.32)	< 0.0001
Systolic†	110.1 (108.67, 111.53)	108.15 (106.72, 109.58)	110.5 (108.78,112.22)	0.086
Diastolic†	66.84 (65.66, 68.02)	66.75 (65.59, 67.91)	68.01 (66.72,69.30)	0.27
Birth weight (g)	3121 (3073.96, 3168.04)	3027 (2981.92, 3072.08)	2909 (2865.88, 2952.12)	< 0.0001
IUGR (%)	7.1%	10.7%	11.9%	0.093
Preterm delivery (≤ 37 wk)	11.8%	13.7%	8.9%	0.16
Fetal & newborn morbidity				
Anomaly (%)	0.3%	0.9%	1.3%***	—
RDS %	2.4%	2.4%	0.6%	0.13
Sepsis %	0.3%	0.6%	0.6%	—
Jaundice %	6.7%	6.4%	4.9%	0.56
Death %	0.3%	—	0.6%	—

*Sum = (mild + severe) preeclampsia; NS = not statistically significant; $p < 0.05$ = statistically significant; **Blood pressure at initial visit † Blood pressure at delivery; IUGR = intrauterine growth retardation; RDS = respiratory distress syndrome; ***Chi-square assumptions were not met.

Discussion

Preeclampsia complicates 6% to 8% of all pregnancies with the majority of cases (75%) occurring during a mother's first pregnancy.^{1,3} Preeclampsia is a multisystem disorder of unknown etiology. During the past several years, numerous clinical trials described the use of various methods to prevent or reduce the

incidence of preeclampsia.² The results of the present study, which was performed on 990 healthy nulliparous women in Isfahan, Iran, showed that the use of low-dose aspirin or calcium-D daily reduced the frequency of preeclampsia. There were statistically significant differences in preeclampsia between the aspirin and control groups ($p = 0.007$) and between the calcium and control groups ($p = 0.005$). These

results are supported by several randomized trials that suggested the effectiveness of low-dose aspirin^{10,12} or calcium supplementation^{13,19} in reducing the incidence of preeclampsia; however, findings of other clinical trials are not in agreement with our results.^{3,14,20}

The evaluation of literature focused on studies related to the causes of preeclampsia, especially marked vasoconstriction and its pathogenesis. Some hypotheses consider a primary role involving endothelial cell dysfunction, aberrations in prostaglandin synthesis, fatty acid and antioxidant metabolism and the renin-angiotensin system. Trials with aspirin or calcium supplementation based on these theories were appraised.²¹ Some reports suggest a role for nitric oxide in the hemodynamic adaptation during normal pregnancy and decreased production or action of nitric oxide in preeclampsia. These reports suggest that calcium supplementation prevents preeclampsia by increasing the production of vascular nitric oxide.^{21,22}

There is strong evidence to suggest the use of calcium supplementation and prophylactic low-dose aspirin in preventing or delaying the onset of preeclampsia. However, this evidence is only available in small randomized, placebo-controlled trials; the results of large, multicenter trials are generally disappointing. The controversies may in part be explained by lack of strict inclusion criteria, late starting of treatment, use of ill-defined endpoints and different timing of aspirin ingestion.^{23,24} In the current study, no significant difference was detected in the rate of IUGR between the three groups. The mean fetal birth weight was significantly higher in the aspirin group than among subjects in the calcium and control groups (Table 2).

Fetal growth may be provoked by using low-dose aspirin, which reduces thromboxane A₂ synthesis and therefore increases the ratio of prostacyclin to thromboxane, leading to improvement in uteroplacental circulation.⁸ Perinatal and newborn morbidity and mortality rates were similar among the three groups. We believe that the similarities might be due to improvements in antepartum surveillance, assessments of fetal well-being and newborn care.

We suggest that low-dose aspirin or calcium-D can be used as an effective and inexpensive preventive measure to reduce the risk of preeclampsia in healthy nulliparous pregnant women. This supplementation also had a

desirable effect on newborn birth weight.

We recommend conducting further studies on the correction of prostacyclin deficiency. Prostacyclin plays a major role in abnormal vasoconstrictor-vasodilator ratio in preeclampsia.

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