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Low-dose aspirin for the prevention of preeclampsia in nulliparous pregnant women -a prospective study at a tertiary care hospital

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ABSTARCT

Background: Preeclampsia is a hypertensive disorder specific to pregnancy that remains a significant cause of maternal and neonatal morbidity and mortality. Low dose aspirin has been reported to reduce the incidence of preeclampsia.
Aims and Objectives: To determine whether treatment with aspirin reduces the incidence of preeclampsia among nulliparous pregnant women.
Materials and Methods: Our prospective study included 100 nulliparous, 13 to 25 weeks pregnant women. The total sample (n=100) was divided randomly in to two groups: Group A (n=50) received aspirin (60 mg plus starch) and Group B (n=50) received placebo (lactose plus starch). Measured variables were hypertension, preeclampsia, intrauterine fetal growth retardation and abruptio placentae. The observed data was tabulated and analyzed statistically.
Results: We found almost similar demographic and clinical characteristics of the women in the two groups, except that more women in the Group P had a systolic blood pressure of 120 to 134 mm Hg when compared to Group A (P = 0.01). We also found a significant difference in weight of women among different groups (P=0.0007). We found the incidence of preeclampsia as 4% and 6% in group A and B respectively. We found almost similar rates of incidence of outcomes like oligohydramnios, premature rupture of the membranes, preterm and post-term delivery, rate of caesarean delivery, average gestational age, birth weight, length at delivery and the number of infants admitted to the neonatal intensive care unit.
Conclusion: The incidence of preeclampsia may be reduced by aspirin use among healthy nulliparous pregnant women.

Key Words: Aspirin, caesarean delivery, Hypertension, Nulliparous, Preeclampsia, Pregnancy

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INTRODUCTION

Preeclampsia refers to a syndrome characterized by the new onset of hypertension plus proteinuria, end-organ dysfunction, or both after 20 weeks of gestation in a previously normotensive woman. It is a common risk factor for maternal and perinatal morbidity and mortality worldwide, especially in developing countries and nulliparous pregnant women are the group at highest risk for this disorder.[1]

Early diagnosis followed by appropriate management, including delivery, may prevent some of the serious sequelae of the disease, such as eclamptic seizures and multiorgan failure. Since there is no curative treatment other than delivery, an intervention that could prevent preeclampsia would have a significant impact on maternal and infant health worldwide.[2, 3]

Hallmarks of preeclampsia include placental ischemia, maternal immune activation, increased arterial resistance, decreased production of vasodilators, and maternal endothelial dysfunction. This causes decreased blood flow to major organs. These factors, combined with the maternal hypertension, often result in intrauterine fetal growth restriction (IUGR) and small-for-gestational-age infants.[4, 5]

Aspirin is currently the most widely prescribed treatment in the prevention of cardiovascular complications. At low doses (60 to 100 mg per day), aspirin is also widely used to prevent pregnancy-related vascular disorders, such as preeclampsia and intrauterine growth restriction, and maternal disorders like antiphospholipid syndrome. The indications for the use of aspirin during pregnancy are, however, the subject of much controversy.[6, 7]

In 2014, the U.S. Preventive Services Task Force (USPSTF) issued an update recommending the use of low-dose aspirin to prevent preeclampsia among women who are at risk of developing the disease.[8]

Aspirin has anticoagulant and anti-inflammatory properties that contribute to the mechanism of action in preventing preeclampsia. When given at the beginning of the second trimester.[9, 10]

In preeclampsia, platelet TXA2 increases significantly, whereas prostacyclin drops sharply. This imbalance is present from 13 weeks of gestation in patients at high risk. TXA2/PGI2 imbalance can be reversed by 2 weeks of treatment with low-dose aspirin, which inhibits TXA2 secretion, and thus platelet aggregation, without altering secretion of endothelial prostacyclin (PGI2), thereby favoring systemic vasodilatation.[11, 12]

Although the use of nonsteroidal anti-inflammatory drugs such as aspirin has been associated with increased maternal and neonatal bleeding risk and antenatal closure of the fetal ductus arteriosus, those adverse effects have not been observed in large, clinical trials of low-dose aspirin and pregnancy, and the risk of overall harm is small. Aspirin is excreted in breast milk, but low-dose aspirin is discontinued at childbirth, and women who have taken low-dose aspirin during pregnancy have no restrictions on initiation of breastfeeding.[8]

One reason may be the lower dose that is used for the prevention of preeclampsia. There is also no link between low-dose aspirin and fetal anomalies, and lowdose aspirin is typically initiated at the end of the first trimester, when organogenesis is complete.[9]

We carried a double-blind, placebo-controlled study to establish whether treatment with aspirin reduces the incidence of preeclampsia among nulliparous pregnant women.

MATERIALS AND METHODS

Our prospective study included 100 nulliparous, 13 to 25 weeks pregnant women. We carried our study after obtaining institutional ethical committee approval and informed consent from patients. The study was carried out at Chalmeda Anand Rao Institute of Medical Sciences (CAIMS), Karimnagar, from January 1st 2017 to December 31st 2017.

Inclusion Criteria:

1. Nulliparous women
2. 13 to 25 weeks pregnant women
3. Blood pressure below 135/85 mm Hg
4. Absence of proteinuria

Exclusion Criteria:

1. Women with chronic hypertension,
2. Women with renal disease,
3. Women with diabetes mellitus and other medical illnesses.

The total sample (n=100) was divided randomly in to two groups:

Group A (n=50): Received aspirin (60 mg plus starch)

Group B (n=50): Received placebo (lactose plus starch).

All the women were instructed to take one tablet daily until the onset of labor, asked to avoid taking any products containing aspirin, and given a supply of acetaminophen for headache or other pain (if needed).

The subjects were followed every 4 weeks until 26 to 28 weeks of gestation, every 2 to 3 weeks until 36 weeks of gestation, and then weekly until delivery or the onset of preeclampsia. At each visit, the women's blood pressure, weight, and urinary protein excretion were measured.

Urinary protein was measured with a dipstick in a fresh, clean, midstream urine sample and categorized as follows.

1. **Negative-** A value of zero to trace
2. **1+ value -** Equivalent to 30 mg per deciliter,
3. **2+ value -**Equivalent to 100 mg per deciliter.

Measured variables were

1. **Hypertension**- systolic blood pressure of ≥ 140 mm Hg or a diastolic blood pressure of ≥ 90 mm Hg
2. **Severe Hypertension** - if two or more systolic values obtained four or more hours apart were ≥ 160 mm Hg or if two or more diastolic values were ≥ 110 mm Hg, or if there was one diastolic value ≥ 110 mm Hg and an antihypertensive drug was subsequently given.
3. **Gestational hypertension** - hypertension without proteinuria after week 20 of gestation or during the postpartum period. If hypertension occurred only during labor, a serum uric acid concentration ≥ 6 mg per deciliter (357 mmol per liter) was required for the diagnosis of gestational hypertension.
4. **Preeclampsia** - hypertension plus proteinuria (either ≥ 300 mg per 24 hours or 2+ or more by dipstick on two or more occasions 4 hours apart) in the absence of a urinary tract infection.
5. **Severe preeclampsia** - severe hypertension and proteinuria; urinary protein excretion ≥ 5 g per day with any degree of hypertension; hypertension complicated by pulmonary edema or a low platelet count (<100,000 per cubic milliliter); or hemolysis, an elevated serum aspartate aminotransferase concentration (>70 U per liter), and a low platelet count (the HELLP syndrome).
6. **Intrauterine fetal growth retardation** - a birth weight below the 10th percentile according to the growth tables of **Brenner et al**.[13]
7. **Abruptio placentae** was diagnosed according to clinical findings (vaginal bleeding and uterine tenderness) or placental examination.

The observed data was tabulated and analyzed using SPSS (Statistical Package for Social Science) version 16.0. Comparisons between the groups were performed with the chi-square test, Fisher's exact test, the Wilcoxon rank-sum test, or the Mantel-Haenszel test. $P < 0.05$ was considered as significant.

RESULTS

We found almost similar demographic and clinical characteristics of the women in the two groups, except that more women in the Group P had a systolic blood pressure of 120 to 134 mm Hg when compared to Group A (P = 0.01). We also found a significant difference in weight of women among different groups (P=0.0007). However the mean systolic blood pressures in the groups was similar **(Table 1 and Graph 1)**. We recorded all the hypertensive related complications **(Table 2 and Graph 2)**. We found the incidence of preeclampsia as 4% and 6% in group A and B respectively. We did not find any significant differences between the groups in the incidence of gestational hypertension (6 and 7 % respectively).

Other Outcomes: We found almost similar rates of incidence of outcomes like oligohydramnios, premature rupture of the membranes, preterm and post-term delivery, rate of cesarean delivery, average gestational age, birth weight, length at delivery and the number of infants admitted to the neonatal intensive care unit. One fetal death in each group was observed and was related to severe preeclampsia or eclampsia **(Tables 3 and 4)**.

Abruptio placentae was seen in one and two women in group P and A respectively (P=0.5597). The incidence of excessive blood loss, postpartum hemorrhage, change in the hematocrit, or need for transfusions was almost similar in both the groups **(Table 5)**.

Maternal and Fetal Complications of Therapy: In neonates, there was no significant difference in the incidence of cephalohematoma, cerebral hemorrhage, petechiae, purpura, excessive bleeding at the time of circumcision, any bleeding disorder, or the need for transfusion **(Table 6)**.

Table 1: Comparison of Demographic Characteristics in both groups at the time of Enrolment

Characteristic	Group A	Group P	P value
Age in years	21±6	22±5	0.3675
Height in cm	160±5	162±8	0.0732
Weight in Kg	62±4	58±7	0.0007*
Gestation week < 20 weeks	40%	50%	0.3173
Systolic BP >140	14%	22%	0.3002
Diastolic BP>90	8%	12%	0.5071
Primagravida	78%	74%	0.6413
Previous Abortion	22%	26%	0.6413

Graph 1: Comparison of Demographic Characteristics in both groups at the time of Enrolment

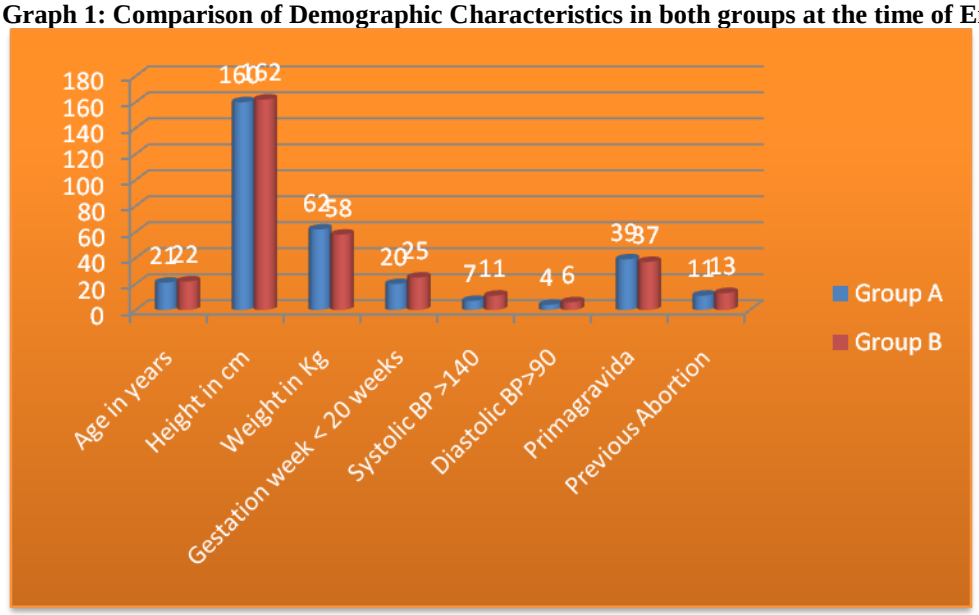

Table 2: Incidence of Hypertensive Complications in both the groups

Disorder		Group A (n=50)		Group P (n=50)		Relative Risk (95% CI)	P value
		No.	%	No.	%		
Gestational Hypertension		6	12	7	14	0.8571 (0.3098 to 2.3712)	0.7665
Preeclampsia	Total	4	8	6	12	1.5000 (0.4505 to 4.9947)	0.5088
	Mild	3	6	3	6	1.000 (0.2119 to 4.7189)	1.000
	Severe	1	2	3	6	0.3333 (0.0359 to 3.0969)	0.3340
Total		10	20	13	26	0.7692 (0.3725 to 1.5887)	0.4783

Graph 2: Incidence of Hypertensive Complications in both the groups

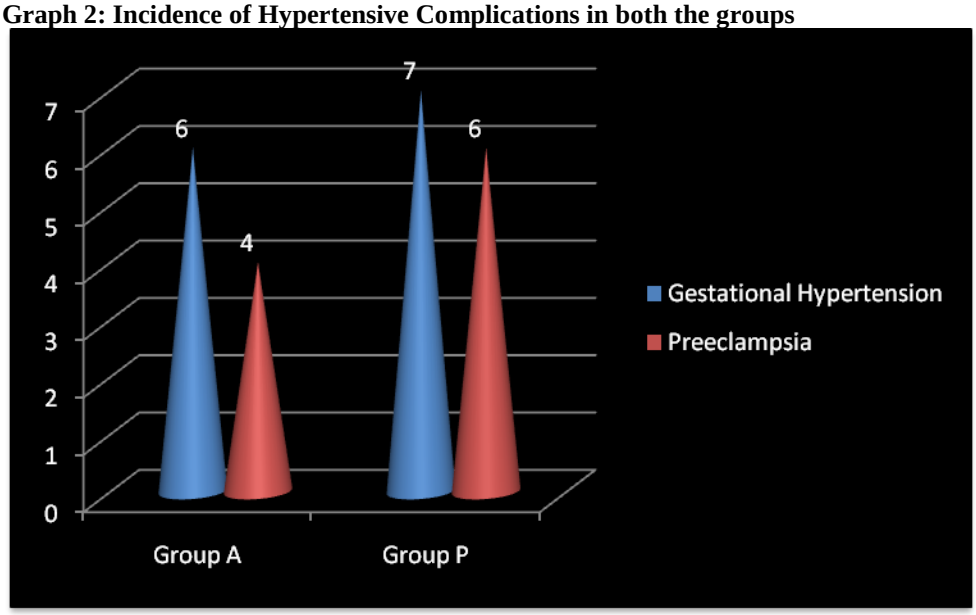

Table 3. Obstetrical Complications in both the groups

Complication		Group A		Group P		P value
		No.	%	No.	%	
Post-term Delivery (≥42 weeks)		3	6	4	8	0.6966
Pre-term Delivery	< 37 weeks	6	12	5	10	0.7505
	< 34 weeks	2	4	1	2	0.5597
Oligohydramnios		2	4	3	6	0.6480
Premature rupture of membranes		1	2	2	4	0.5597
Induction of labour		8	16	8	16	1.0000
Caesarean sections		8	16	9	18	0.7911

Table 4. Perinatal Outcomes in both the groups

Outcome	Group A	Group P	P value
Week of gestation	38.1±4.2	38.4±3.9	0.7121
Birth weight in grams	3064±624	3112±628	0.7023
Birth length in cm	49.1±3.4	48.9±3.5	0.7726
Apgar score at 1 minute	7.8±1.7	7.9±1.6	0.7626
Apgar score at 5 minutes	8.9± 1.0	9.0 ±1.1	0.6354
Admission to neonatal ICU [No. (%)]	8 (16)	10 (20)	0.6045
Neonatal Deaths [No. (%)]	1 (2)	1 (2)	1.0000

Table 5.Maternal Complications in both the groups

Maternal Complications		Group A	Group P	P value
Abruptio Placenta [No. (%)]		2 (4)	1 (2)	0.5597
Postpartum haemorrhage [No. (%)]		3 (6)	2 (4)	0.6480
Blood transfusion required [No. (%)]		1 (2)	1 (2)	1.0000
Excessive blood loss [No. (%)]		3 (6)	4 (8)	0.6966
Estimated Blood loss	Vaginal	410±205	405±150	0.8896
	Caesarean	865±310	845±255	0.7254
% Change in Hematocrit from admission to discharge	Vaginal	4.5±3.90	4.4±3.90	0.8982
	Caesarean	6.2±4.1	5.9±3.9	0.7086

Table 6. Neonatal Bleeding Complications in both the groups

Neonatal Bleeding Complications	Group A	Group B	P value
Cephalohematoma [No. (%)]	10 (5)	6 (3)	0.6116
Petechiae or Purpura [No. (%)]	4 (2)	4 (2)	1.0000
Any bleeding disorder [No. (%)]	14 (7)	12 (6)	0.8401
Cerebral Haemorrhage [No. (%)]	2(1)	2(1)	1.0000
Required Transfusion [No. (%)]	2(1)	2(1)	1.0000

DISCUSSION

Preeclampsia is characterized by a functional imbalance between vascular prostacyclin and thromboxane A2 production. Based on this hypothesis, few studies were carried out to correct this pathologic condition by pharmacologic manipulation with low-dose aspirin. The current literature suggests that low-dose aspirin is effective in reducing the incidence of preeclampsia and/or fetal growth retardation. Hence we carried out our study to find out the effectiveness of low dose aspirin in reducing preeclampsia in nulliparous pregnant women, who are supposed to be at a higher risk for developing preeclampsia disorder.[2, 14]

Our study showed a 33.33% reduction in the incidence of preeclampsia, which was confined mainly to women with an initial systolic blood pressure of 120 to 134 mm Hg, but no reduction in the overall rate of hypertension. **Dekker GA and Sibai BM (1993)** found the incidence of preeclampsia among those treated with aspirin averaged 2.2 percent (range, 0 to 5), a rate substantially lower than that in women given placebo (average, 15 percent; range, 9 to 35). **Hauth et al (1993)** carried a similar study on women at low risk and found a 70 percent reduction in the incidence of preeclampsia among women who received aspirin.[14, 15] However, regarding perinatal morbidity, aspirin group was associated with an increased incidence of abruptio placentae.

We also found that apart from a small reduction in the incidence of preeclampsia among the women who received aspirin, but the women in this group in whom preeclampsia did develop were more likely to deliver their infants earlier. The other benefits that have been ascribed to aspirin include a lower incidence of intrauterine growth retardation and of preterm delivery and higher birth weight, as found in our study and in similar studies might be due in part to the prevention of early preeclampsia.[14, 16]

Studies by **Wallenburg HC et al (1987)** and **Trudinger et al (1988)** found that women treated with aspirin in whom preeclampsia did not develop had longer pregnancies, and their infants had higher birth weights. We did not find such benefits in our trial. This might be due to the more heterogeneous groups of women studied by others.[17, 18]

O'Brien et al (1993) found that ingestion of acetaminophen in doses of 15 mg per kilogram of body weight was associated with a significant inhibition of prostacyclin production during the third trimester. But we have no data on the use of acetaminophen by these women, but we think it unlikely that its use differed in the two groups.[19]

However it was found that aspirin has been implicated in a number of adverse actions affecting the mother, fetus, or neonate.[14, 16] The maternal risks include increased antepartum and postpartum hemorrhage; the fetal risks include oligohydramnios; and the neonatal risks are persistent pulmonary hypertension and a variety of bleeding problems.[14] We found no increase in the frequency of adverse effects among the women in the aspirin group, as was reported in studies by **Uzan et al (1991)** and **McParland et al (1990)**.[20, 21]

The incidence of abruptio placentae in both women at high risk and those at low risk was similar in the aspirin and the placebo groups.[15, 20, 21]However **Uzan et al (1991)** found that women taking 150 mg of aspirin per day had a lower incidence of abruptio placentae and fetal loss (2 percent) than those in a placebo-treated group (12 percent).[20]

The effect of reduction of preeclampsia in aspirin group was small in our study, but aspirin had a greater benefit among women with higher initial systolic blood pressure.

CONCLUSION

Preeclampsia is a significant cause of maternal and neonatal morbidity and mortality, and identification of women who are most at risk for developing the disease is imprecise. Our results suggest that the incidence of preeclampsia may be reduced by aspirin use among healthy nulliparous pregnant women. For women at risk, daily low-dose aspirin can reduce the incidence of preeclampsia and, therefore, decrease the risk for fetal Intrauterine

Growth Restriction and for medically necessary preterm birth.

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