

# Use of Prophylactic Aspirin in patients with previous history of Pre-eclampsia

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## ABSTRACT

**Background:** Aspirin is considered a safe and secure prophylactic or preventative agent for the treatment of preeclampsia patients. Pre-eclampsia is developed in pregnant women which cause complications in their pregnancy due to high blood pressure and damage to other body organs. The incidence of Pre-eclampsia is 2-8% of pregnancies, but has a higher risk of about 10% in those females suffering from hypertension or autoimmune diseases.

**Aim:** To know how effectively aspirin is used in preventing the pre-eclampsia in pregnant women who have had the previous history of preeclampsia.

**Methodology:** A randomized controlled trial of aspirin and placebo was conducted. The women enrolled in this study have a gestational period of 6 to 32 weeks. All the women were administrated with 80 mg of placebo or aspirin daily. All the continuous and categorial variables were analyzed statistically and the results were presented as mean±S.D. and frequency(%) for these variables, respectively.

**Results:** All the data was gathered from 260 women who were enrolled in this study. It showed that the occurrence of pre-eclampsia was higher in the placebo group as compared to aspirin group (4.1% vs. 1.6%, p=0004). However, in every risk group, the effects of placebo and aspirin were the same for women with hypertension, the incidence was 13.4% in aspirin and 15.7% in placebo and for women with diabetes, the incidence was 6.7% in aspirin and 6.6% in placebo; but for women with previous history of pre-eclampsia, the incidence was 1.6% in aspirin and 4.1% in placebo which was significantly different. Further, the incidence of pre-eclampsia with primary and secondary outcomes in aspirin and placebo were the same.

**Conclusion:** Our research finding reveals that a low dose of aspirin had a considerable therapeutic effect in preventing pre-eclampsia in high-risk pregnant women.

**Keywords:** Pre-eclampsia, aspirin, preventive agent

## INTRODUCTION

Prophylactic Aspirin is used for primary prevention of heart attack and stroke in patients with 40 to 65 years of age<sup>1,2</sup> several studies show that aspirin is used by the patients who possess risk factors such as hypertension, smoking and diabetes. Some studies reveal that prophylactic aspirin is recommended to reduce preeclampsia, a condition which is developed in pregnant women with constricted intravascular volume, high peripheral vascular resistance(PVR)<sup>7-10</sup>, It can cause long-term cardiovascular diseases in mothers as well as in infants<sup>11</sup>. It is also known to increase the mortality rate in pregnant women and affects 2-8% of pregnancies. This disease is responsible for 1/6<sup>th</sup> of all premature birth all over pregnancies<sup>2,12,13,14</sup>.

It has been reported that each year pre-eclampsia is responsible for more than 70,000 death of pregnant women<sup>2,7,15</sup> The low dose of aspirin can cause the reduction in the production of platelet thromboxane without inhibiting vascular prostacyclin<sup>7,16,17</sup>. Although, the production of prostacyclin is believed to reduce pre-eclampsia by regulating utero-placental hemodynamics. Data on the small trial of aspirin suggested that it can reduce the chances of pre-eclampsia in pregnant women<sup>1,18</sup>. Women who had a previous history of pre-eclampsia before their 32 weeks of pregnancy have a have up to 15% risk of incidence of pre-eclampsia<sup>2,17,19,20</sup>.

Several other large trials have also been conducted to check the effect of prophylactic aspirin on preeclampsia, all data suggested that aspirin did not have significant effects on pre-eclampsia<sup>8,15,21</sup>. This difference may arise due to the screening test of the large population, due to the inclusion of pregnant women who are at lower risk of pre-eclampsia<sup>2,8,22</sup>. Moreover, it may be because of under reporting of other smaller negative trials<sup>22</sup>. In our study, we did a randomized controlled trial to check the effect of prophylactic aspirin and placebo in pregnant women who are at higher risk of developing pre-eclampsia.

## METHODOLOGY

**Study Design:** The present study was a non-randomized double-blinded clinical trial, and the data was collected through non-probability consecutive sampling. A total of about 350 pregnant women have screened at university of Lahore teaching hospital from Nov 2019 to Nov 2021. Among all of them, 260 pregnant women qualified for entry. The women were randomized to receive either aspirin or placebo. The records of their medications were obtained. All the women had screened for urinary protein and also the women who were diagnosed with proteinuria. Women with multiple health issues were not enrolled in the study. The protocol was approved by prior authorities and Ethical Review Committee a written consent was taken from all the women.

### Inclusion Criteria

- Age of the women is above or equal to 18 and less than 40 years
- Gestational age of about 6-32 weeks
- Patients who are risk for Pre-eclampsia
- At least one risk factor like hypertension or diabetes
- Ready for written consent
- Singleton pregnancy

### Exclusion Criteria

- Age less than 18 years
- Fetal abnormalities
- Miscarriages
- Allergic to Aspirin
- Autoimmune diseases
- In vivo fertilization
- Cardiovascular issues

**Treatment Regimen:** The women enrolled in the study were between the 6th and 32th weeks of pregnancy. Afterwards, the women were assigned randomly to receive 80mg of Aspirin or placebo resembling aspirin one time per day until delivery. All the women were observed, and the records were kept. Prenatal care was also recorded. The routine visits were also ensured after 2 weeks until the 36th week of pregnancy. Weight of the patient, and blood pressure were measured at each visit and the urine protein level detection test was performed regularly.

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**Data Collection and Outcome Variables:** Data was collected at regular visits of the subjects. Pre-eclampsia was primary outcome in women with no hypertension or proteinuria at baseline at the onset of study. Women with normal blood pressure, proteinuria, thrombocytopenia, and hypertension with Epi-gastric pain were evaluated for diagnosis of preeclampsia. The records of all women were made with other disorders independently. Secondary outcomes were preterm birth, abruption placentae, small for gestational age and other complications.

**Statistical analysis:** To analyse statistically, different tests were performed such as chi-square test and Fisher's exact test to evaluate the two groups that were given aspirin and placebo. Continuous and categorical variables were presented as mean±S.D and percentages, respectively. All the risk factors were estimated by stratification according to risk groups. Data were analyzed to compare the primary and secondary outcomes of both risk groups.

## RESULTS

About 260 women were enrolled at University of Lahore teaching hospital between November 2019 and November 2021. 240 completed the trial till the end. 20(7.7%) women were lost to follow up, among which 11 were from aspirin group and 9 were from placebo group. 119 women were administered with aspirin and 121 subjects were administered with placebo. Baseline characteristics have been given in Table 1.

Table 1. Baseline Characteristics of all the Study Participants

Characteristics	Aspirin (n = 119)	Placebo (n = 121)	p-value
Age	27.3±5.2	29± 4.6	0.13
Gestation age at enrollment	6.6±3.4	6.8 ± 3.3	0.56
Systolic BP	125±17.9	126 ± 19.1	0.58
Diastolic BP	81±17	80 ± 15	0.76

The effects of pre-eclampsia on the risk groups have been given in Table 2. It has been seen that the effects of placebo and aspirin were the same with each risk group. No significant difference has been observed in each risk group. The effect of aspirin and placebo has shown a distinct benefit in those patients who also received other treatments or drugs. Aspirin showed a significant reduction of preeclampsia as compared to placebo. There was no significant effect of aspirin shown in primary and secondary outcomes of pregnant women (Table 3).

Table 2. Effects of Pre-eclampsia on the Risk Groups

Risk Group	Incidence of Pre-eclampsia		p value
	Aspirin (n=119)	Placebo (n=121)	
Patient with pre-eclampsia	2(1.6 %)	5 (4.1%)	0.004
Patient with pre-existing hypertension	16(13.4%)	19 (15.7%)	0.57
Patient with diabetes	8(6.7%)	8 (6.6%)	0.97

Table 3: Secondary Outcomes of Aspirin and Placebo

Secondary Outcomes	Aspirin (n = 119)	Placebo (n = 121)	p - value
Placental abruption	1 (0.8 %)	3 (2.4 %)	0.51
Preterm delivery	21 (17.6%)	31 (25.6) %	0.92
Perinatal death	2 (1.6%)	5 (4.1 %)	0.73
Small for gestational age infants	1 (0.8%)	2 (1.6 %)	1.11
Postpartum haemorrhage	6 (5%)	6 (4.9 %)	1.24

## DISCUSSION

Due to demographical changes pre-eclampsia increase the maternal morbidity and mortality in pregnant women. Research has been made to know the preventive interventions for pre-eclampsia. It has been proposed that prophylactic aspirin due to its anti-platelet properties has been used to decrease the risk for pre-eclampsia. Data gathered from several studies indicates that use

of prophylactic aspirin used to decrease the risk of pre-eclampsia by 10% and other studies indicates that aspirin has its major effects on reducing the preterm preeclampsia in pregnant women<sup>7,16-17</sup>. It has also been observed in some other previous studies that the low dose of aspirin did not help in reducing pre-eclampsia in pregnant women who were at high risk with hypertension and diabetes than other women<sup>10,20,23</sup>.

In our research we analyse the patients by randomly assigning them into the treatment (aspirin) group and the placebo group. Women who had risk of developing pre-eclampsia, i.e., diabetic women, hypertensive women, and the women with the history of pre-eclampsia during the previous pregnancies were enrolled for the study. Pre-eclampsia was observed in 4.1% of women who were administered with a placebo and in 1.6% of the women who received aspirin, significantly lower number of patients with a p-value of 0.004. Aspirin was observed to significantly prevent pre-eclampsia in all the women with higher risk of developing it. Our data demonstrated that prophylactic aspirin do not affect the incidence of Abruption of placenta, Preterm Delivery, and Perinatal death.

This study and several other trials of prevention of pre-eclampsia depict the impact of antiplatelet therapy on the occurrence of pre-eclampsia, perinatal death, and preterm birth in a large number of women<sup>24-28</sup>. These trials clearly witness the discrepancy among the large trails (>200 sample size) and the small trails (< 200 sample size). Overall, the small trials show the decrease in the risk of pre-eclampsia by 80% approximately whereas, the large trails show that it reduced by only 9%. This huge difference between the large and small trials might be due to the publication bias, may be the small trials that deduced positive results are likely to be carried out more frequently and published as compared to the small trails that deduce negative results<sup>29</sup>. Same possibility tends to occur for our study and other large trails. The incidence rate of pre-eclampsia is reduced by approximately 13% when the results of large and small trails are taken in combination. This reduction rate is significant, but its clinical importance is still questionable because for the prevention of pre-eclampsia in a single patient.

Different analysis about the use of aspirin demonstrated that significant effect of prophylactic aspirin in pregnant women is conditional for the prevention of pre-eclampsia. In our research Women were assigned randomly to receive aspirin and placebo only one time a day until their delivery. Significant difference is seen in patients using other medication with aspirin and placebo. So, our study reveals that aspirin also in combination with other drugs show considerable results for the treatment of pre-eclampsia. Moreover, on the even brighter side, aspirin did not show any fatal side effects in pregnant women.

## CONCLUSION

Our study concluded that prophylactic aspirin is effective and beneficial to treat women with preeclampsia. So, aspirin should be necessarily administered to pregnant women suffering from diabetes, hypertension, and previous history of pre-eclampsia.

**Conflict of interest:** Nil

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