

Original Research Article

Effect of low dose aspirin on fetal outcome in women at risk for developing pregnancy induced hypertension

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ABSTRACT

Background: Though pregnancy induced hypertension is a worldwide problem, it is more prevalent in developing countries particularly south east Asian and African countries. It contributes to 20% of perinatal death and 40-50% of low birth weight babies in India. Fetal salvage is also an important consideration in providing quality care. Low dose aspirin given between 12 weeks to 28 weeks of gestational age in high-risk women at Developing Pregnancy Induced Hypertension (PIH) is anticipated to prevent the development of PIH and complications that arises especially those regarding maternal and fetal mortality due to PIH.

Methods: This prospective randomized controlled trial was conducted in the dept of O and G, SCB MC and Hospital, Cuttack during November 2018 to October 2019. Pregnant women between the gestational age of 13 to 28 week were screened for risk factors and included in this study. Low dose aspirin of 60 mg daily till delivery was given to pregnant women who consented to be a part of study randomly with the other group taking placebo.

Results: Incidence of IUGR babies in low dose aspirin treated mothers was as low as 1%. Incidence of LBW babies is lower in low dose aspirin treated mothers than with those who were not treated. Mean birth weight in cases was 2780 gm±352 gm vs control 2592 gm±483 gm. There is increased incidence of still birth in high risk group not treated with aspirin. No significant difference in reducing incidence premature deliveries between case and control.

Conclusions: Low dose aspirin has a definite role in the prevention of PIH in high risk pregnancy and its complication like IUGR and low birth weight. Low dose aspirin reduces the incidence of PIH. Low dose aspirin can be considered a safe drug without any deleterious side effect for mother and the fetus. Benefits of prevention of PIH, justifies its administration in women at high risk.

Keywords: Aspirin, Fetus, LBW, Pre-eclampsia

INTRODUCTION

Hypertension in pregnancy is a predominant cause of intrauterine growth retardation, intrauterine asphyxia, neonatal and maternal morbidity and mortality. In spite of all the advances made in medical science, Pregnancy Induced Hypertension (PIH) continues to be responsible for a high proportion of hospital admission, labor induction, maternal and fetal morbidity and mortality.

Pre-eclampsia causes the flow of blood through the placenta to be reduced, restricting the flow of oxygen and nutrients to the fetus which could restrict growth. A family history of the condition, obesity, diabetes, high blood pressure or kidney disease increases the probability of developing the condition. Severe pre-eclampsia can develop in around 2 per cent of pregnancies, with mild pre-eclampsia in up to 6 per cent of women.¹

The risk of complications is considerably higher when the disease is severe and develops early on in the pregnancy. It can lead to premature birth and, in extreme cases, death of both mother and baby. It can also cause Intra uterine growth retardation, still birth and neonatal death due to complication of pre-maturity.

Aspirin is a cyclooxygenase inhibitor with anti-inflammatory and antiplatelet properties. Low-dose aspirin has been used during pregnancy most commonly to prevent or delay the onset of preeclampsia. Other suggested indications for low-dose aspirin have included prevention of stillbirth, fetal growth restriction, preterm birth, and early pregnancy loss. Recent systematic reviews of low-dose aspirin use during pregnancy have improved our understanding of the role of low-dose aspirin in each of these clinical situations.²

Thromboxane A₂ (TXA₂) secreted by platelet increases, and prostacyclin (PGI₂) decreases, which finally leads to a change of hemodynamic and hypertension in pre-eclampsia. Aspirin can interrupt the transformation from arachidonic acid to TXA₂ by inhibiting the activity of cyclooxygenase, thus, to reduce platelet accumulation and thrombosis.³

Administering low-dose aspirin (150 mg) led to a 62% reduction in the rate of pre-term preeclampsia, resulting in delivery before 37 weeks. The study, published in the New England Journal of Medicine, found an 82% reduction in the rate of early preeclampsia, resulting in delivery before 34 weeks.⁴

On the basis of this, it is conjectured theoretically that aspirin could prevent pregnancy-induced hypertension syndrome and its complication. It was recommended that all gravid with one middle or a high-risk factor for pre-eclampsia should orally intake small dose of aspirin (60 mg- 150mg) every day from 12 weeks pregnancy to labor.⁵

METHODS

The present study was conducted on 240 pregnant women visiting the antenatal clinic of dept of O and G, of S.C.B. Medical College and Hospital, Cuttack between November 2018-October 2019. Amongst the 240 only 203 patients could be followed up till delivery. This was a prospective randomized control trial, which was single blinded. Study was conducted after the approval of Institutional Ethical Committee. Pregnant women between 13 to 28 weeks of gestation were screened for risk factors for development of PIH were included.

Inclusion criteria

- Aged ≥ 18 and < 55 years
- Live foetus at gestational age 12-20 weeks
- Be at high risk of developing pre-eclampsia based on clinical risk factors such as the following:

At least one high-risk factor, namely history of preeclampsia, diabetes mellitus (type 1 or 2) or chronic hypertension.

At least two intermediate-risk factors, including obesity (≥ 28 kg/m²), young primigravida (< 20 years) advanced maternal age (≥ 35 years), family history of pre-eclampsia (mother and/or sister) or nulliparity

- Able to provide written informed consent

Exclusion criteria

- Allergic to aspirin
- Asthma
- Peptic ulcers
- Severe heart, liver or renal disease
- Those not consented to be part of study
- Previous or present h/o bleeding diathesis

These women were divided into 4 groups

Group A- women with low platelet count (1 lakh-1.5 lakh/mm³) treated with aspirin 60 mg daily from date of enrolment till deliver.

Group B- women with low platelet count without aspirin on placebo.

Group C- women with risk factors treated with aspirin 60 mg daily from date of enrolment till delivery.

Group D- without with risk factor without aspirin therapy on placebo.

These patients were followed up at 4 weeks interval up to 28 weeks, at 2 weeks interval up to 36 weeks and thereafter at weekly interval till delivery. At each visit weight gain, pedal oedema and blood pressure Urine albumin and total platelet count was done at the time of enrolment. Urine albumin was repeated at 28-32 weeks, 32-36 weeks and 36-40 weeks, or when features of pre-eclampsia developed. At delivery gestational age, fetal maturity, fetal birth weight, fetal and neonatal mortality and morbidity and fetal congenital abnormalities were recorded. Any neonatal bleeding or maternal adverse effects like abruptio and post-partum hemorrhage was also noted. The result was subjected to statistical analysis using SPSS 23.0 version. To describe about the data, descriptive statistics, frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and S.D were used. To find the significant difference between the bivariate samples in independent groups, the independent t test was used. To find the significance in categorical data, Chi-Square test was used. In all the above statistical tools, the probability value of < 0.05 was considered as significant level.

Randomization

Randomization was performed using a computerized central randomization system in a 1:1 allocation ratio.

The website randomly assigns a randomization code to each participant. Eligible women will be randomized to one of the two groups. Knowledge of the treatment allocation is open to the investigators and the participants. Those with low platelet count are separated into a separate group.

RESULTS

In this present study 240 cases were registered. Out of which 200 belong to high risk group, 40 cases were having platelet count between 1-1.5 lakh/mm³. Out of the 240 cases registered only 203 cases (84.6%) could be followed up till delivery (Figure 1 and 2).

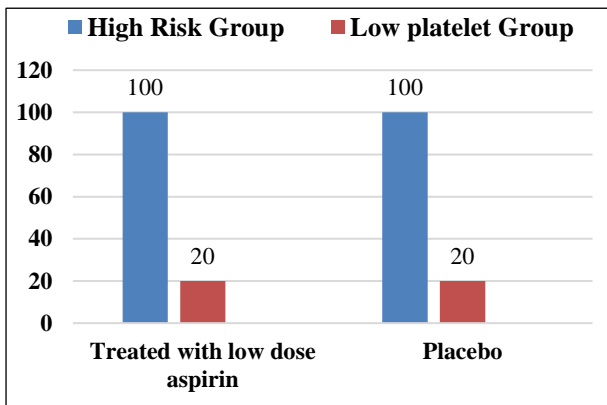


Figure 1: Distribution of cases as per entry characteristics.

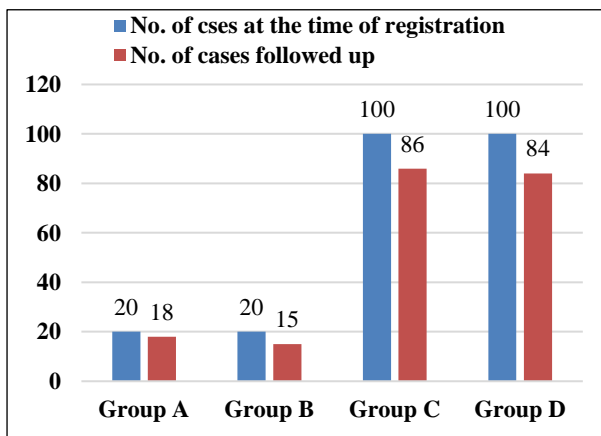


Figure 2: Distribution of followed up cases.

If authors look into the distribution of risk factors in the study population 16.6% had low platelet count i.e. between 1-1.5 lakh/mm³. This group was studied separately in this study. 7.5% were young primigravidae, 3.8% were elderly primigravida, 3.4% were diagnosed with Diabetes at the time of enrolment in this study. History of previous pregnancy complicated by pre-eclampsia were 22.9% which formed the majority of the study population. 12.1% were multiple pregnancy, 5.8% were having maternal obesity with BMI >=28 kg/m², 5% had Rh incompatibility and 19.2% had previous still birth

or abortions in previous pregnancy. 3.7% had chronic hypertension (Figure 3).

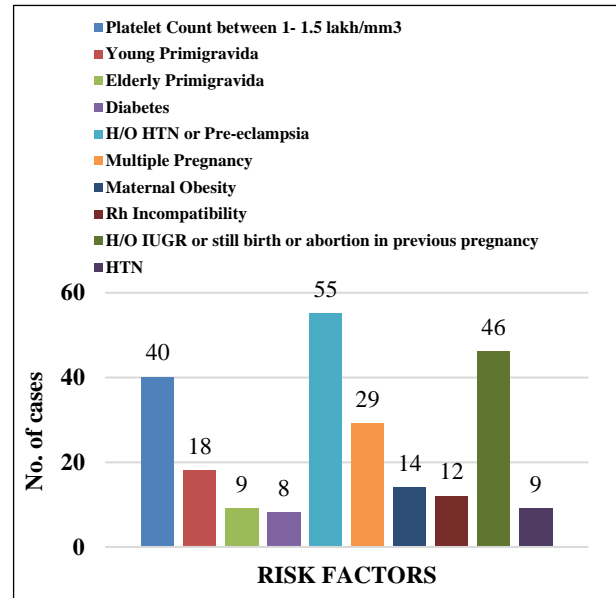


Figure 3: Distribution of cases as per risk factors.

In this study when we compared the characteristics of two groups that is the aspirin and the placebo group at the time of registration there was no significant difference in regard to maternal age, weight, blood pressure, platelet count and presence of urine albumin. Hence the above two groups can be statistically comparable to each other (Table 1).

Table 1: Clinical characteristics of different cases at initial visit.

Clinical characters	Aspirin		Placebo	
	Mean	SD	Mean	SD
Age in years	26.12	4.93	25.28	4.66
Weight in Kg	48.42	7.66	48.20	7.94
Diastolic BP in mm Hg	74.92	5.58	75.3	7.86
Systolic BP in mm Hg	114.5	9.20	117.25	12.98
Total platelet count (lakhs/mm ³)	High risk (other than low platelet)			
	2.22	0.24	2.21	0.3
Low platelet count case				
	1.31	0.08	1.36	0.05
Urine Albumin	Absent		Absent	
Pedal Oedema	Absent		Absent	

In this study we found that out of 203 cases that were followed up till the incidence of IUGR babies in group A and Group C, which were treated with low dose aspirin, was around 1% only. Whereas the incidence of IUGR in Placebo treated groups (Group B and D) was higher than groups with treated with aspirin. They were 13.3% in Group B and 7.14% in Group D (Figure 4).

In this study authors found that the incidence of low birth weight babies among the high-risk groups treated with low dose aspirin was 8.8% and incidence of low birth weight among the high-risk groups not treated with aspirin was 19.8%. the difference observed was statistically significant with p value of <0.005 (Table 2).

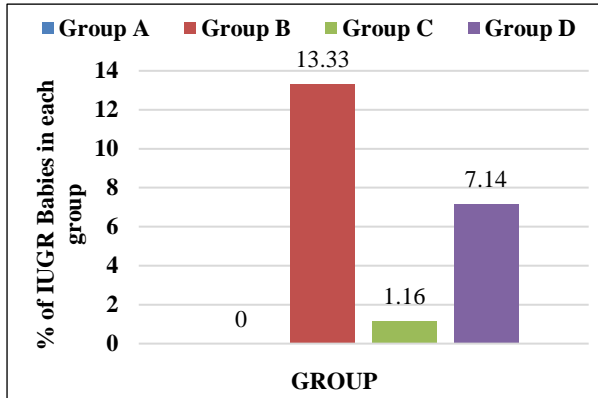


Figure 4: Events of IUGR in different studied groups.

Authors also analysed the birth weight of all the babies and compared the mean birth weight between low dose aspirin treated groups. It was found that the mean birth weight in low dose aspirin treated group was 2780 gm±352 gm, whereas in the placebo treated group the mean birth weight was 2592 gm ± 483 gm (Table 2).

Table 2: Low birth weight and low dose aspirin.

Birth weight at term	Group C	Group D	Total
<2.5 kg	9	18	27
≥ 2.5 kg	93	73	166
Total no. of live births	102	91	193
Incidence of low birth weight in group C = 9/102*100 = 8.8%			
Incidence of low birth weight in group D = 18/91*100 = 19.8%			
Mean birth weight in low dose aspirin treated group = 2780 gm±352 gm			
Mean birth weight in placebo group= 2592 gm±483 gm			

Table 3: Consider the comparison of study groups with regard to other neonatal outcome.

Characteristics	Group A	Group B	Group C	Group D
Still Births	0	1	1	4
Living Births	18	14	85	80
NICU Admission	Nil	2	4	7
Other neonatal bleeding	Nil	Nil	Nil	Nil
Congenital abnormalities	Nil	Nil	Nil	Nil
Birth asphyxia	Nil	Nil	Nil	Nil

In this study when authors analysed the fetal outcomes there is increased incidence of still birth in high risk group not treated with aspirin. There are no adverse neonatal outcomes such as congenital malformations and bleeding in Aspirin treated group (Table 3).

When compared the incidence of preterm deliveries in each group, in this study we found that incidence of preterm in group A was 5.55% in Group B was 13.33%, in Group C was 9.3% and in Group D was 15.47%. however, these observations were not statistically significant with p-value >0.005 (Table 4).

Table 4: Distribution of preterm deliveries in this study.

GA at delivery	Group A	Group B	Group C	Group D
≤36 weeks	1	2	8	13
≥37 weeks	17	13	78	71
Total	18	15	86	84

DISCUSSION

The present study was conducted in the Dept of O and G, SCB medical college and hospital, Cuttack, being a prospective RCT. In the present study, 240 cases were taken among the pregnant women visiting the ANC of Department of Obstetrics between the gestation of 13 to 28 weeks. Out of these 40 cases had low platelet (1-1.5 lakh/mm³), whereas 200 had normal platelet count. Women with previous history of bleeding disorders were excluded from the study. These women were randomly divided into groups receiving aspirin n=104, and not receiving aspirin n=99. 37 patients could not be followed up to delivery in this study figure 1 and figure 2.

Figure 3 indicates the distribution of cases as per risk factors. Maximum number of women were having history of hypertension or pre-eclampsia- eclampsia in previous pregnancy.⁶ Hernandez et al also showed similar such results. Whereas, in general, primigravida are amongst the highest of the risk factors.⁷ Table 1 describes the baseline characteristics of the women studied. There is no difference between the treated and the controlled group with

regard to maternal age, weight, blood pressure, total platelet count and urine albumin.

Fetal growth retardation occurred in 7% of the controlled pregnancies, when compared, only 1% of the pregnancy treated with low dose pregnancy with high risk factors had fetal growth restriction. Similar results were obtained by Wallenberg et al.⁸ Whereas CLASP collaboration study did not find any significant difference in the case and control group (Figure 4).⁴

In Table 2 when authors analyse the incidence of low birth weight, it is lower in low-dose aspirin treated group (8.8%), whereas it was higher in control group (19.8%). The difference observed was statistically significant p -value <0.005. In studies done by CLASP collaboration, Kozer et al and Chiaffarino et al, the mean birth weight was greater in the treated group than in the control group.⁹⁻¹¹

Table 3 in this study analyses the neonatal outcome among the 203 case which were followed till delivery among the control group the incidence of still birth was more than when compared with the group on low dose aspirin. This finding was similar to studies which are collaborated and described by Henderson et al, there was no increase in risk of neonatal bleeding or congenital malformation in low dose aspirin treated groups which was similar to findings described by Volcamonico et al.^{12,13}

In table 4 in this study authors found that incidence of preterm in group A was 5.55% in Group B was 13.33%, in Group C was 9.3% and in Group D was 15.47%. However, these observations were not statistically significant with p-value >0.005. Similar such statistically not significant results were obtained by Sibai BM et al, Souza et al, and also advocated by recent ACOG recommendation.¹⁴⁻¹⁶

CONCLUSION

The present shows that low dose aspirin even as low as 60 mg daily has a definite role in prevention of PIH in high risk women and fetal outcomes. It is evident that in this study the incidence of IUGR babies in low dose aspirin treated mothers was as low as 1%. Incidence of LBW babies is lower in Aspirin treated mothers than with those who were not treated. Mean birth weight in cases was 2780 gm±352 gm vs control 2592 gm±483 gm. There is increased incidence of still birth in high risk group not treated with aspirin. No significant difference in reducing incidence premature deliveries between case and control.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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