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Research Article

Prevention of Early Onset Preeclampsia with Aspirin 150mg

Savita Namdev Kamble[1], Yuga Mohan Jamdade[2], Karthik K.M[3]
[1]Associate professor, Department of OBGY, B J Government Medical College, Pune, Maharashtra, India.
[2]Assistant Professor, Department of OBGY, B J Government Medical College, Pune, Maharashtra, India.
[3]Assistant Professor. Department of OBGY, Siddaganga Medical College & hospital, Tumakuru, Karnataka, India.
Corresponding Author: Dr Karthik K.M, S/O Mahesh K.P, Agrahara badavane, Banavara, Arsikere (taluk) Hassan (dist), Karnataka, PIN: 573112, India.
Email: kmkarthik25.1994@gmail.com
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ABSTRACT
Background: Objectives: To study efficacy of aspirin 150 mg for prevention of early onset preeclampsia and to study maternal and fetal outcome. **Methods:** Hospital based interventional, case-control and prospective study. Study was carried out in tertiary health care center. Pregnant women between 12 to 20 weeks gestation with high risk for preeclampsia were included in the study. **Results:** Low dose aspirin reduces the incidence of early onset preeclampsia and its severity. Total 34% reduction was seen in the study. The treatment did not hamper the onset of spontaneous labour. Aspirin therapy reduced the incidence of caesarean section by better utero placental blood-flow and reduced IUGR. **Conclusion:** Aspirin acts as a prophylactic by preventing preterm preeclampsia and severe forms of preeclampsia. The maternal outcome is improved because the risk of severe preeclampsia, APH, PPH and caesarean section is reduced. The fetal outcome is improved in terms of birth weight, reduction in preterm deliveries & IUGR.

Keywords: Preeclampsia, aspirin 150 mg, maternal mortality and morbidity, prophylactic, drug therapy.

INTRODUCTION

Hypertensive disorders affect as many as 10% of all pregnancies worldwide.[1] This heterogeneous group of disorders includes chronic hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension. These disorders account for a significant proportion of perinatal morbidity and mortality. Hypertensive disorders feature among the top 6 causes of maternal mortality in the United States and are responsible for nearly 10% of all maternal deaths.[2] The incidence of preeclampsia has risen dramatically over the past few decades.[3,4] The incidence of early-onset preeclampsia, which accounts for a disproportionate degree of maternal and neonatal morbidity and mortality, has increased by greater than 140%.[5] Given the substantial health burden of hypertensive disorders in pregnancy, there is increasing interest in optimizing management of these conditions.

Preeclampsia is defined as new-onset hypertension after 20 weeks of gestation and proteinuria and/or evidence of end-organ compromise, including CNS symptoms (headache and/or visual changes), pulmonary edema, thrombocytopenia, renal insufficiency, or liver dysfunction.[1] HELLP syndrome is a variant of preeclampsia, with severe features, and is not specifically characterized as a separate entity by the American College of Obstetrics and Gynecologists (ACOG).[1] Preeclampsia complicates 2% to 8% of pregnancies worldwide.[6] There has been a marked increase in hypertensive disorders of pregnancy over the last several years, with a 143% increase in incidence of early-onset disease from 1990 to 2010.[5]

Gestational hypertension is defined as new-onset elevated BPs after 20 weeks' gestation without proteinuria or other signs of preeclampsia.[7] The alternate diagnosis of chronic hypertension should be made if BPs do not normalize in the postpartum period. Gestational hypertension complicates 2% to 3% of pregnancies in the United States.[4,8] Approximately half of women initially diagnosed with gestational hypertension before term eventually develop preeclampsia[9]; therefore, close surveillance for worsening disease is warranted.

Normal pregnancy is associated with elevated levels of coagulation factors and increased

platelet activation. In Preeclampsia, the balance between the production of thromboxane A2 (TxA2) from platelets and prostacyclin from endothelial cells is altered. This imbalance is present from 13 weeks of gestation in patients at high risk[10]. Aspirin (acetylsalicylic acid) selectively inhibits TxA2[11] formation at low dosages (≤160 mg daily) and thus changes the balance between thromboxane and prostacyclin in a favour of vasodilating prostacyclin, which may improve the utero-placental circulation.

In hypoxic conditions[12], aspirin inhibits the expression of sFlt-1 in human trophoblasts, and thus shows proangiogenic activity. sFlt-1 is the soluble form of VEGF receptor & is present in high levels in circulation of patients with preeclampsia and is responsible for the angiogenic imbalance seen in preeclampsia pathogenesis.

The efficacy of aspirin seems to be subject to a chronobiological effect[13], since a randomized trial in Spain showed a beneficial effect on diurnal blood pressure regulation and a reduction in obstetrical effects if aspirin was taken in evening or bedtime, compared with the morning intake [hazard ratio 0.19, 95% confidence interval is (CI) 0.10–0.39]. Aspirin should be administered once a day in the evening at low doses ranging from 75 to 150 mg.

In a randomized trial, Bonten *et al.*[14] found that COX-1-dependent platelet activity was significantly reduced upon awakening after low-dose aspirin taken the previous evening or on retiring.

First-trimester use of aspirin is not associated with the increased risk of fetal abnormalities and there is no evidence of any increase in maternal bleeding from any site or placental abruption[15]. There is no association between low-dose aspirin during the third trimester and antenatal closure of ductus arteriosus, neonatal haemorrhage or intraventricular haemorrhage[16].

As per the recent study[17] it is observed that nulliparous women who had taken aspirin regularly in pregnancy would less likely to have preeclampsia than women who have not taken. In more than 50 trials have been carried out all over the world and metaanalysis among these studies reported that administration of low-dose aspirin in high risk pregnancies is associated with a decrease in the rate of preeclampsia by 10%[18].

Majority of these studies have used lower doses of the drug (75–100 mg) and only few trials have actually used 150 mg since there could be a possibility of nonresponders[19,20]. There is paucity of the data for Indian population regarding the response to different dosages of aspirin. To our knowledge, there are limited trials with dosage of 150 mg.

Hence the present study was planned for prevention of early onset preeclampsia and the fetomaternal outcome with the use of 150 mg aspirin.

METHODOLOGY

This hospital based interventional, case-control and prospective study was carried in government tertiary hospital in western Maharashtra. Antenatal out-patient department (OPD) and antenatal ward from December 2019 to December 2021, over a period of 2 years. Pregnant women fulfilling the inclusion criteria (BMI>30kg/m^2, elderly primigravida, chronic hypertension, previous h/o preeclampsia, eclampsia) were selected. An informed consent was taken. History was obtained in detail & thorough clinical examination was carried out. History of bleeding disorders, any allergies to aspirin was taken into consideration. All women were subjected to blood tests for complete blood cell count, bleeding time, clotting time, KFT, LFT, HBsAg, HIV, urine albumin, Coagulation tests (PT, APTT, FDP and fibrinogen).

A total of 250 women were included. They were randomly allotted to two groups;

Group 1 (cases): Aspirin 150mg was started between 12 to 20 weeks. This therapy was continued till 34 weeks of gestation and patients were followed up till delivery.

Group 2 (control): Aspirin was not given, routine antenatal care was given and followed up till delivery.

A total of 125 women received 150 mg of aspirin per day as a single evening dose with dinner. Of these 125 women 20 were lost to follow up as the study was carried out in covid pandemic; in 22 cases the data collected was inadequate. Thus 83 cases were taken up for the final analysis.

Out of the 250 women; 125 women in the control group received no aspirin but continued to receive their routine antenatal medication. In this group 20 were lost to follow up and in 20 the data collected was incomplete. This left 85 women for the final analysis, in control group.

Throughout pregnancy the patients were monitored for development preeclampsia (hypertension, edema, RFT, LFT and proteinuria); IUGR (clinical and USG

examination) and altered coagulation profile (BT, CT, CRT, Platelet Count, and PT).
Aspirin was stopped at 34 weeks of gestation and at the time of delivery patients were watched for
APH, mode of delivery, PPH, need for augmentation / induction and alteration of coagulation profile. On delivery the baby was assessed for birth weight, IUGR and maturity. A close watch was maintained on bleeding disorders in the immediate neonatal period. Teratogenic effects and perinatal morbidity and mortality were also studied.
The available data was tabulated and analysed using appropriate statistical methods. The ACOG (2020) definition and classification was used. The grading suggested by Fernando Arias (5th edition) was used to grade severity.

Statistical Analysis
The tests used for statistical calculations are:
1. Chi-Square Test was used for the analysis of the difference between two proportions.
2. T-test to test the significance of the difference between two proportions or percentages.

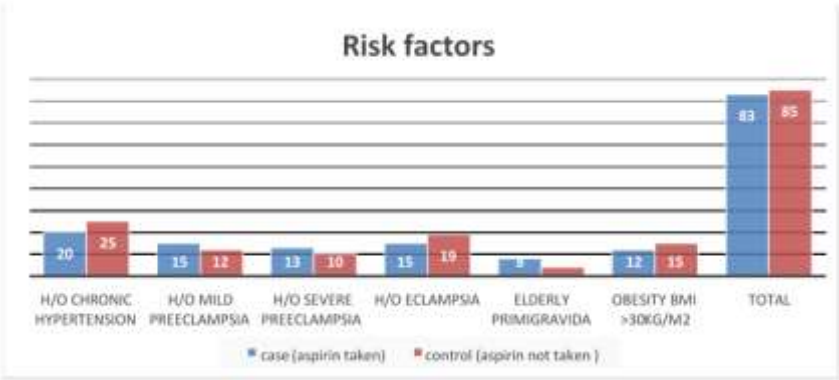
For the parameters age, BMI, gestational age, hospital stay and haemoglobin an average value was obtained and a calculation of standard deviation done. A p value less than 0.05 considered to be statistically significant.

RESULTS
In the present study the age of the mothers ranged from 18 to 39 years, in both cases and control groups the majority of the women were in the age group of 26 to 30 yrs.
With regard to obstetric history, among cases majority were of 2nd gravida with 46.9% and in control majority were also in 2nd gravida with 44.7%. Considering previous risk factors (Table no.1) among the case and control, in cases , 24% of the women were having chronic hypertension, 18% had mild preeclampsia in previous pregnancy, 15.6% were had severe preeclampsia, 18% of the women had eclampsia, obesity was seen in 14.5% (BMI>30kgm2). Based on gestational age when the preeclampsia was detected (Table no.2), total 21 % of women in control group developed preeclampsia before 34 weeks of gestation where as in cases only 4.8% developed preeclampsia before 34 weeks. Thus there is a significant reduction in incidence of preeclampsia before 34 weeks. p=0.001(<0.05) significant.
According to severity of preeclampsia (Table no.3), in the women who have taken aspirin only 6 % developed severe preeclampsia and 3.6% developed eclampsia where as 20 % of the women who have not taken aspirin developed severe preeclampsia and 9.4% developed eclamspia.
As per route of delivery and time of delivery (Table no.4), women who have not taken aspirin, 24% of them delivered preterm and only 6% of women who took aspirin delivered preterm. The incidence for need of induction among cases is 20% and among control group is 49.5%. P value is 0.029, df=1, chi square value is 4.718, p value is significant.
Regarding gestational age at the time of delivery (Table no.5), only 1 woman who have taken aspirin delivered before 34 weeks of gestation and 6 woman who have not taken aspirin delivered before 34 weeks of gestation. Hence after treating with aspirin one can overcome from early onset preeclampsia and thus avoiding preterm deliveries and associated neonatal morbidity and mortality.
Intrauterine growth restriction (Table no.7) as a complication of preeclampsia, it was present in 13 females (15.7%) who have taken aspirin and 25 females (29.4%) who have not taken aspirin, with significant reduction in incidence of IUGR after giving aspirin. df=1 p value is 0.03 (<0.05 is significant). There was no teratogenicity in both cases and control groups.
Need of NICU admission (Table no.8) for neonates born to preeclamptic mother, only 12 neonates who are born to mothers who have taken aspirin were required NICU admission and 23 neonates among mothers who have not taken aspirin were admitted in NICU mainly due to prematurity. df=1 p<0.05(significant).

Table 01: Distribution of Cases and Controls according to Risk Factors

Risk factors	Case (83) (Aspirin Taken)		Control (85) (Aspirin not taken)	
Chronic Hypertension	20	24.1%	25	29.4%
H/O Mild Preeclampsia	15	18%	12	14.1%
H/O Severe Preeclampsia	13	15.6%	10	11.7%

H/O Eclampsia	15	18.1%	19	22.4%
Elderly Primigravida	8	9.6%	4	4.7%
Obesity BMI > 30kg/m^2	12	14.5%	15	17.6%
Total	83	100%	85	100%



Bar diagram (for table no.1): showing Risk factors in the study group.

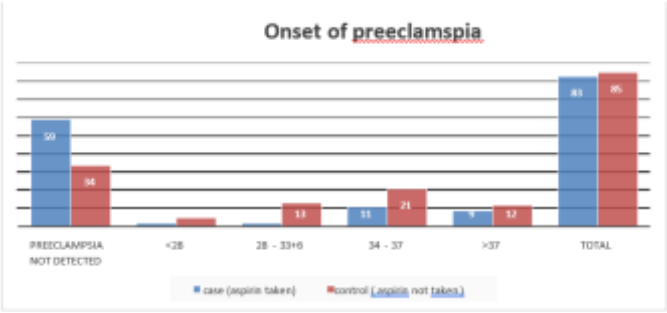
Table 02: Gestation age at which preeclampsia was detected.

Time of onset	Case (83) (Aspirin Taken)		Control (85) (Aspirin not taken)		P value
Preeclampsia not detected	59	71.1%	34	40%	0.001
<28	2	2.4%	5	5.9%	
28-33+6	2	2.4%	13	15.3%	
34-37	11	13.3%	21	24.7%	
>37	9	10.8%	12	14.1%	
Total	83	100%	85	100%	

χ^2=19.605 df=4 p<0.05(significant)

Table 02(a): Distribution of cases and control according to early onset preeclampsia and late onset preeclampsia.

Onset of preeclampsia	Case (83) Aspirin taken		Control (85) Aspirin not taken	
Preeclampsia not detected	59	71%	34	40%
early onset (before 34 weeks of gestation)	04	4.8%	18	21%
late onset (after 34 weeks of gestation)	20	24%	33	38.8%

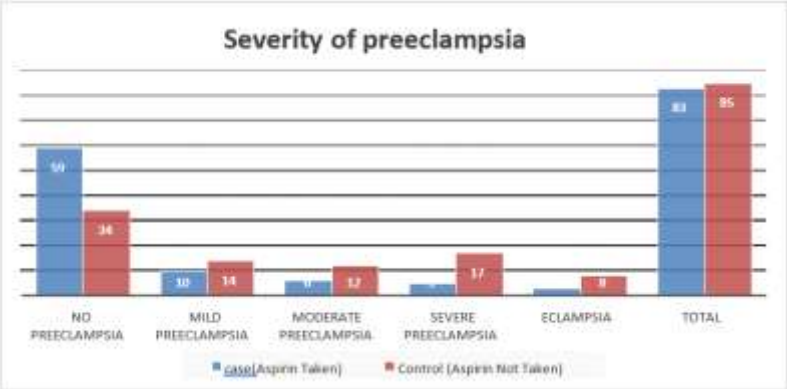


Bar diagram (for table no.2.a) showing gestational age when preeclampsia was detected in the study group.

Table 3: Distribution of Cases and Controls according to severity of preeclampsia.

Severity of preeclampsia	Case(83) (Aspirin Taken)		Control(85) (Aspirin not taken)		P value
No preeclampsia	59	71.1%	34	40%	0.0001
Mild preeclampsia	10	12%	14	16.5%	
Moderate Preeclampsia	6	7.3%	12	14.1%	
Severe Preeclampsia	5	6%	17	20%	
Eclampsia	3	3.6%	8	9.4%	
Total	83	100%	85	100%	

χ^2=17.898 df=4 p<0.05(significant)



Bar diagram (for table no.3) showing the severity of preeclampsia in the study group

Table 4: Distribution between route of delivery and time of delivery

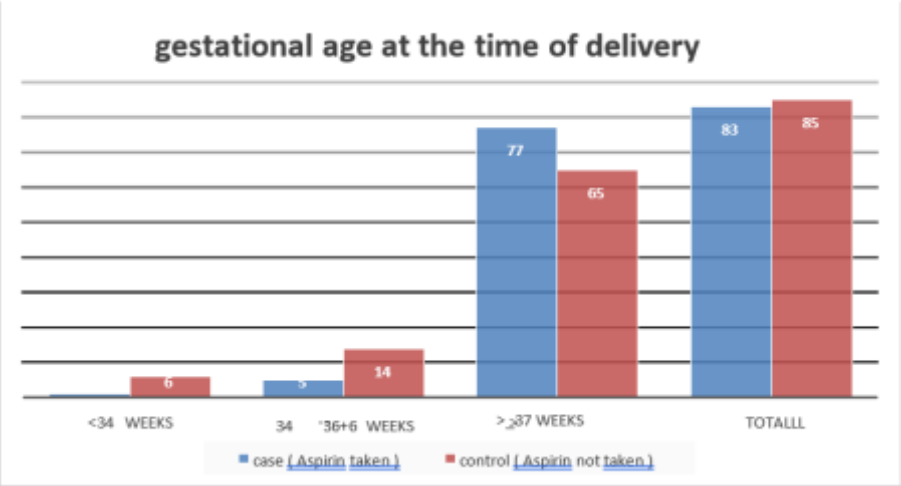
type of delivery total cases 83 total control 85	Cases (83)		Control (85)	
	preterm	Full term	Preterm	Full term
VD	4	65	15	50
LSCS	2	12	05	15
Total	6(7.2%)	77(92%)	20(24%)	65(76%)

P value is 0.029, df=1, chi square value is 4.718, p value is significant.

Table 05: Distribution of Cases and Controls according to Time of delivery

Time of delivery	Case(83) (Aspirin Taken)		Control(85) (Aspirin not taken)		P value
<34 weeks	1	1.2%	6	7%	0.008
34 - 36+6 weeks	5	6%	14	16.4%	
≥37 weeks	77	92.7%	65	76.4%	
Total	83	100%	85	100%	

P value <0.05 (significant)



Bar diagram (for table no.10) showing gestational age at the of delivery in the study group.

Table 06: Distribution of Cases and Controls according to fetal outcome

Fetal outcome	Case(83) (Aspirin Taken)		Control(85) (Aspirin not taken)	
Live Birth	80	96.4%	75	88.2%
IUD	3	3.6%	10	11.7%
Total	83	100%	85	100%

Table 07: Distribution of Cases and Controls according to IUGR

IUGR	Case(83) (Aspirin Taken)		Control(85) (Aspirin not taken)	
No	70	84.3%	60	70.6%
Yes	13	15.7%	25	29.4%
Total	83	100%	85	100%

χ^2=4.536 df=1 p value is 0.03 (<0.05 is significant)

Table 08: Distribution of Cases and Controls according to NICU admission.

NICU	Case(83) (Aspirin Taken)		Control(85) (Aspirin not taken)	
No	71	85.5%	62	72.9%
Yes	12	14.5%	23	27.1%
Total	83	100%	85	100%

χ^2=4.043 df=1 p<0.05(significant)

Table 09: table showing average birth weight in the two groups

	Cases (83) (Aspirin taken)	Control (85) (Aspirin not taken)	P value
Average birth weight	2675gms	2013gms	<0.05

DISCUSSION

Overall 50.4% of the women had history of preeclampsia & eclampsia, with recurrence rate is 28%. BM Sibai *et al.*[21] with aspirin 60mg also found the recurrence rate of 25%.

If preeclampsia were to occur in those treated with aspirin it occurred late. It occurred later than 34 weeks in 20 (24%) of 83 women treated with aspirin and 4 (4.8%) developed it earlier than this. Where as 18 (21%) women

had preeclampsia before 34weeks & 33 (38.8%) developed it later than this. Statistical tests bear out these comments as the difference under both the heads is significant.

Hence aspirin prevents the incidence of early onset preeclampsia. In the present study we found reduction in onset of preeclampsia before 34 weeks. Wright D *et al.*[22] double blind trial of aspirin with Aspirin 150 mg/day found reduction in preterm preeclampsia.

In the route of delivery 83% of cases delivered vaginally and 16.8% underwent caesarean while 76% of control delivered vaginally and 23.5% underwent caesarean. The most common indication among cases group was fetal distress (5 cases), where as in control group (9 cases- fetal distress and 6 cases - abruption).

45% of the caesarean sections in the control group are for fetal distress. Apart from other factors this is a testimony to the fact that aspirin improves utero-placental circulation. Babies in the control group were clearly jeopardised and could not stand the stress of labour. This view is further supported on comparing the incidence of IUGR in the two groups (vide infra). The incidence for need of induction among cases is 20% and among the control group is 49.5%. Inductions were done mainly due to severe preeclampsia, abruption, IUGR

Elizabeth M Coviello et al[23] the rate of successful vaginal delivery increases with gestational age. Successful induction has the benefit of preventing maternal and fetal comorbidities associated with previous caesarean deliveries in subsequent pregnancies.

Term deliveries occurred in 92.7% of cases as against 76.4% of controls. The difference between the two is significant. Early Preterm deliveries i.e before 34 weeks is only 1 among cases with over all preterm deliveries 6(7.5%) as against 6 deliveries before 34 weeks with overall pre term deliveries of 20(23.6%) among control, which shows a significant reduction in early preterm deliveries. There by reducing neonatal mortality and morbidity by giving aspirin. There were only 3 still births in the treated group mainly because of abruptio placenta, while 10 babies were IUFD in the control group because of abruptio placenta, severe IUGR, very preterm and extremely preterm deliveries. The difference is significant.

In the treated group 70(84.3%) of the neonates were spared of IUGR that means only 13(15.7%) were suffered of it. In the control group only 25 (29.4%) were spared while (70.6%) suffered from IUGR. The difference between these values is significant.

Beaufils *et al.*[15] in their pioneering study showed that aspirin significantly reduced IUGR. Bujold *et al.*[17] in a metaanalysis showed that aspirin reduced the chance of IUGR by 40% in the present study the chance of IUGR was reduced by 46.5%.The overall picture does suggest that aspirin has a role to play in preventing IUGR.

There is reduction in NICU admission of neonate in treated group (14.5%) as compared to control group (27%). This is mainly due to reduction in preterm deliveries and IUGR.

The average birth weight in the treated group was 2675 grams. While in the control group it was 2013 grams.

CONCLUSION

1. Aspirin acts as a prophylactic by preventing preterm preeclampsia and severe forms of preeclampsia.
2. The maternal outcome is improved because the risk of severe preeclampsia, APH, PPH and caesarean section is reduced.
3. The fetal outcome is improved in terms of birth weight, reduction in preterm deliveries & IUGR, rate of NICU admission. While teratogenicity remains unaltered.

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