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# Effect of early administration of low dose Aspirin to Prevent Preeclampsia in Women at High Risk

Authors
**Varnica Psyche, Shashibala Prasad, Jatin Soni**
DMCH Darbhanga

**Abstract**

**Background:** *The role of aspirin in preventing preeclampsia is a topic of debate since long time. Till now its recommended only for high risk cases with wide range of variations in protocol from country to country.*

**Methods:** *We conducted a double-blind, randomized, placebo-controlled trial in four groups of pregnant women at high risk for preeclampsia, including 471 women with pregestational insulin-treated diabetes mellitus, 774 women with chronic hypertension, 688 women with multifetal gestations, and 606 women who had had preeclampsia during a previous pregnancy. The women were enrolled between gestational weeks 13 and 26 and received either 75 mg of aspirin or placebo daily.*

**Results:** *Outcome data were obtained on all but 36 of the 2600 women who entered the study. The incidence of preeclampsia was similar in the 1300 women in the aspirin group and the 1300 women in the placebo group (aspirin, 18 percent; placebo, 20 percent; P = 0.23). The incidences in the aspirin and placebo groups for each of the four high-risk categories were also similar: for women with pregestational diabetes mellitus, the incidence was 20 percent in the aspirin group and 21 percent in the placebo group (P = 0.38); for women with chronic hypertension, 24 percent and 26 percent (P = 0.66); for those with multifetal gestations, 15 percent and 17 percent (P = 0.10); and for those with preeclampsia during a previous pregnancy, 18 percent and 18 percent (P = 0.47). In addition, the incidences of perinatal death, preterm birth, and infants small for gestational age were similar in the aspirin and placebo groups.*

**Conclusions:** *In our study, low-dose aspirin did not reduce the incidence of preeclampsia significantly or improve perinatal outcomes in pregnant women at high risk for preeclampsia.*

## Introduction

Prophylaxis with low-dose aspirin (75mg od) has been recommended to prevent preeclampsia (ACOG 2013), the rationale being underlying pathology i.e. an imbalance between vasodilating and vasoconstricting prostaglandins which is responsible for hypertension and abnormalities of coagulation. Low-dose aspirin therapy protect against vasoconstriction and pathologic blood coagulation in the placenta by inhibiting thromboxane production more than prostacyclin production. Several single-center trials, have demonstrated a substantial reduction in the risk of proteinuric hypertension as well as reductions in the incidences of preterm birth, infants small for gestational age, and perinatal death mostly among women at increased risk for preeclampsia,. Based on these reports ACOG in 2013 suggested use of prophylactic aspirin to prevent preeclampsia. Discrepancy in results seen with several larger

trials revealing no beneficial effects of aspirin. The underlying cause for it being the inclusion of women at low risk for preeclampsia.

## Methods

### Study Subjects

We screened all the pregnant women at DMCH Darbhanga and affiliated PHC and CHC's for entry into the study from 1st September 2016 till 31stjuly 2017. We selected women with one of four high-risk groups: women with pregestational, insulin-treated diabetes mellitus, women with chronic hypertension, women with multifetal gestations, and women who had had preeclampsia in a previous pregnancy and we identified around 2600 women who qualified for same. The diagnosis of chronic hypertension required documentation of antihypertensive-drug therapy by medical records or a blood pressure while sitting of 140/90 mm Hg or higher taken on two occasions at least four hours apart, either before pregnancy or during pregnancy but before entry into the study. Multifetal gestation was documented by ultrasound examination before enrolment. Previous preeclampsia was defined as new-onset proteinuric hypertension as determined by medical records or, in the absence of a record, an oral history of preeclampsia that resulted in delivery before the 37th gestational week. At the screening visit, all the women underwent urinary-protein testing by dipstick. If the test was 1+ or greater, a 24-hour urine sample was collected; women with values of >300 mg of protein per 24 hours were considered to have proteinuria. Women with multifetal gestations were ineligible for the study if they also had diabetes mellitus, chronic hypertension, or proteinuria as defined above, as were women with a history of preeclampsia and current proteinuria. Women with both diabetes and hypertension were included in the diabetes group. The protocol was approved by the institutional review board of our medical college, and all the women gave written informed consent.

### Protocol

Eligible women were enrolled between the 13th and 24th week of pregnancy. All the women were randomly assigned according to risk group to receive 75 mg of aspirin or a lactose-containing placebo tablet identical in appearance to the aspirin tablet, once daily. The method used for randomisation is a computer-generated permuted-block randomization sequence stratified according to risk group. The packets of aspirin and placebo were distributed among patients in such a way that each woman receiving the next labelled packet.

Both aspirin and placebo were to continue until delivery and to discontinue the medication if preeclampsia develops. They were instructed to avoid all aspirin-containing products and to use acetaminophen if they needed an analgesic drug. The follow up prenatal visits were as dictated by the standard schedule i.e. every 4 weeks until the 28th week of pregnancy, every 2 weeks from then until the 36th week, and then weekly until delivery. Weight, qualitative urinary protein excretion (measured by dipstick), and blood pressure were measured at each visit. Blood pressure was measured with the woman seated quietly; the fifth Korotkoff sound was used to determine diastolic blood pressure. If the result of a qualitative protein test was 2+ or more, a 24-hour urine sample was usually collected to measure protein excretion. Compliance was determined by direct questioning and by tablet counts.

### Outcome Variables

The primary outcome variable was preeclampsia, defined in the women who did not have hypertension plus proteinuria at base line as the development of hypertension plus one of the following: renal insufficiency, thrombocytopenia, Liver involvement, cerebral symptoms or pulmonary edema. Hypertension was defined as either a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg on two occasions at least four hours apart. Proteinuria was defined as excretion of 300 mg of protein in a

24-hour urine collection, or two dipstick-test results of >2+(>100 mg per deciliter), the values recorded at least 4 hours apart, with no evidence of urinary tract infection. Thrombocytopenia was defined as a platelet count of less than 100,000 per cubic millimeter. Renal insufficiency was defined as creatinine>1.1 or doubling of baseline. Liver involvement defined as serum transaminase level twice normal. Cerebral symptoms as headache, visual disturbance, convulsions

In women who had normal blood pressure but proteinuria at base line, the diagnosis of preeclampsia required the presence of thrombocytopenia, a serum aspartate aminotransferase concentration of >70 U per liter, or hypertension accompanied by either severe headaches, epigastric pain, or a sudden increase in proteinuria (either five times the base-line value or twice base line if the base-line value exceeded 5 g per 24 hours). In the women who had hypertension but no proteinuria at base line, a diagnosis of preeclampsia required the development of proteinuria or thrombocytopenia. In the women who had both hypertension and proteinuria at base line, the diagnosis of preeclampsia required any one of the following: thrombocytopenia, an elevated serum concentration of aspartate aminotransferase (>70 U per liter), or worsening hypertension (as shown by two diastolic readings >110 mm Hg taken four hours apart in the week before delivery) combined with either exacerbation of proteinuria (see above), severe headaches, or epigastric pain.

A woman was deemed to have preeclampsia if she had an eclamptic convulsion or the HELLP syndrome, defined as hemolysis (serum total bilirubin concentration, >1.2 mg per deciliter [20 μmol per liter], a serum lactate dehydrogenase concentration of >600 U per liter, or hemolyticanemia as determined by peripheral smear), elevated serum concentration of aspartate aminotransferase (>70 U per liter), and thrombocytopenia.

To ensure consistency in the diagnosis of preeclampsia, the records of all the women with apparent preeclampsia, worsening hypertension, new-onset proteinuria, or proteinuria at base line of 1+ or more were reviewed independently by three physicians unaware of the treatment-group assignments. They had to agree unanimously on the validity of the designated outcomes. Forty-three percent (1089) of the women's charts were reviewed in this way.

Secondary outcome variables included abruptio placentae, preterm birth, infants small for gestational age, neonatal intraventricular hemorrhage, postpartum hemorrhage, and neonatal bleeding. An infant was considered small for gestational age if its weight was below the 10th percentile of normative birth weights for singletons[13] and twins.[14] Preterm birth was defined as delivery before the completion of 37 weeks' gestation. Intraventricularhemorrhage was defined according to ultrasound criteria[15]; all films that suggested intraventricular hemorrhage as well as an equal number of films considered normal were reviewed in a blinded fashion by two radiologists. Abruptio placentae was diagnosed according to clinical criteria (vaginal bleeding and uterine tenderness) and examination of the placenta. The medical records of all the women with suspected abruption were reviewed by two physician members of the protocol committee who had no knowledge of the treatment assignments.

**Statistical Analysis**

Comparisons of the aspirin and placebo groups were performed with the use of chi-square tests, Fisher's exact tests, Wilcoxon rank-sum tests, or Mantel–Haenszel tests. Overall relative-risk estimates were calculated with stratification according to risk group.

An overall sample size of 50 was chosen to allow us to detect a reduction of 50 percent in the incidence of preeclampsia within each of the four risk groups separately, with a type I error of 0.05, two-sided, and 80 percent power.

**Results**

Of the 2600 women enrolled in the study between 1st September 2016 till 31stjuly 2017, 1273 were assigned to the aspirin group and 1266 to the placebo group. Outcome data could not be obtained on 19 women in the aspirin group and on 17 in the placebo group. All the women with outcome data were included in the treatment group to which they were assigned.

The base-line characteristics of the women and the distribution according to risk group are shown in Table 1

**Table 01**

| Characteristic | Women with Diabetes (N=470) | Women with Chronic Hypertension (N=780) | Women with Multifetal gestation (N=728) | Women with previous preeclampsia (N=622) |
|---|---|---|---|---|
| Mean Age (year) | 26±6 | 30±6 | 25±6 | 25±5 |
| Mean week of gestation at entry (wk) | 19±4 | 21±4 | 21±4 | 21±4 |
| Primigravida (%) | 32 | 12 | 24 | - |
| Blood Pressure (mm Hg) | | | | |
| SYSTOLIC | 116±16 | 130±14 | 114±12 | 118±16 |
| DIASTOLIC | 82±10 | 88±14 | 68±10 | 66±12 |
| Body mass index | 26±4 | 28±7 | 27±5 | 26±3 |
| Smoked during pregnancy (%) | 21 | 17 | 15 | 14 |

Base-Line Characteristics of the Women at High Risk for Preeclampsia. Within each risk group, there were no significant differences between the aspirin and placebo groups. Thirteen percent of the women with diabetes had vascular disease, and 79 percent of the women with chronic hypertension were taking antihypertensive drugs at base line.

The effect of aspirin on the incidence of preeclampsia according to the risk category and status at the time of entry is shown in Table 2

**Table 02**

| Variable | Incidence of Preeclampsia | | Relative risk (95% confidence interval) |
|---|---|---|---|
| | Aspirin (%) | Placebo (%) | |
| **Risk Groups** | | | |
| Pregestational DM (n=470) | 20 | 21 | 0.9 (0.6, 1.2) |
| Hypertension (n=780) | 24 | 26 | 0.9 (0.8, 1.4) |
| Multifetal gestation (n=728) | 15 | 17 | 0.8 (0.5, 1.1) |
| Previous eclampsia (n=622) | 18 | 18 | 1.0 (0.8, 1.1) |
| All groups (n=2600) | 18 | **22** | 0.9 (0.8, 1.1) |
| **Entry Status** | | | |
| No proteinuria, no hypertension(n=1697) | 16 | 19 | 0.8 (0.7, 1.0) |
| Proteinuria, hypertension (n=123) | 32 | 24 | 1.4 (0.8, 2.6) |
| Proteinuria, no hypertension (n=51) | 26 | 31 | 0.8 (0.3, 1.8) |
| No proteinuria, hypertension (n=729) | 24 | 24 | 1.0 (0.8, 1.3) |

Effect of Aspirin on the Incidence of Preeclampsia in High-Risk Women According to Risk Group and Entry Status.. The incidence of preeclampsia was similar in the aspirin and placebo groups, both within each risk group and in the aggregate. This absence of a difference between the aspirin and placebo groups, within each risk group and in the aggregate, persisted even when the criterion for proteinuria was changed from 300 to 500 mg of protein per 24 hours.

The effects of aspirin on the incidence of preeclampsia according to the characteristics at base line, specifically the absence or presence of hypertension, proteinuria, or both, are also shown in Table 2. Regardless of status at entry, the incidence of preeclampsia was similar in the aspirin and placebo groups. The effect of aspirin and placebo in several subgroups of women in whom antiplatelet treatment either has been reported to have a distinct benefit or might conceivably have a benefit is shown in Table 3

**Table 03**

| Risk factor | Incidence of preeclampsia (%) | | Relative risk (95% confidence interval) |
|---|---|---|---|
| | Aspirin | Placebo | |
| *Week of gestation at entry* | | | |
| <20 (n=1327) | 20 | 22 | 0.9 (0.8, 1.2) |
| ≥20 (n=1273) | 18 | 19 | 0.9 (0.7, 1.1) |
| | | | |
| *Week of gestation at delivery* | | | |
| <32 (n=229) | 27 | 19 | 1.4 (0.9, 2.2) |
| ≥32 (n=2371) | 16 | 19 | 0.9 (0.7, 1.0) |
| | | | |
| *Systolic blood pressure at entry* | | | |
| <120 mm Hg (n=1200) | 12 | 15 | 0.8 (0.6, 1.1) |
| 120-134 mm Hg (n=1400) | 24 | 26 | 0.8, (0.6, 1.2) |
| | | | |
| *Parity* | | | |
| Nullipara (n=668) | 26 | 27 | 0.9 (0.7, 1.2) |
| Para (n=1932) | 13 | 15 | 0.9 (0.7, 1.1) |

Effect of Aspirin on the Incidence of Preeclampsia in High-Risk Women According to Risk Factor..7,8 In none of these subgroups did aspirin significantly reduce the incidence of preeclampsia as compared with placebo. This conclusion pertains to the individual risk groups as well as to the aggregate group. There was also no significant effect of aspirin on the frequency of certain maternal and perinatal outcomes Table 4

**Table 04**

| Outcome | Incidence (%) | | Relative risk (95% confidence interval) |
|---|---|---|---|
| | Aspirin | Placebo | |
| Postpartum haemorrhage | 8 | 8 | 0.9 (0.7, 1.3) |
| Abruptio Placentae | 2 | 3 | 0.7 (0.4,1.3) |
| Preterm delivery | 30 | 33 | 0.9 (0.9, 1.0) |
| Infant small for gestational age | 10 | 10 | 1.0 (0.9, 1.5) |
| Perinatal Death | 3 | 4 | 0.8 (0.5, 1.1) |
| Neonatal intraventricular haemorrhage | 1 | 1 | 1.0 (0.8, 2.8) |

(Maternal and Perinatal Outcomes in the Aspirin and Placebo Groups.)

The median numbers of tablets taken were 100 in the aspirin group and 99 in the placebo group, and only 2 percent of the women reported having taken other aspirin-containing medications. Compliance, measured on the basis of tablet counts and interviews, was high; 93 percent of the women in both groups took half or more of their pills, and 79 percent took at least 80 percent of the tablets. The incidence of preeclampsia did not differ significantly between the groups regardless of the percentage of tablets taken.

**Discussion**

Results from our study showed that low-dose aspirin did not prevent preeclampsia in pregnant women at risk for the disease. Our study was limited to women whose risk of preeclampsia was known to be higher than that of the general population i.e., women with pregestational insulin treated diabetes mellitus, chronic hypertension, multifetal gestations, or preeclampsia during a previous pregnancy. Preeclampsia developed in 22percent of the women in the placebo group, which justifies our approach. Aspirin was ineffective in preventing preeclampsia in all four risk groups, regardless of parity, base-line blood pressure, gestational age at base line or delivery, or degree of compliance. No effect on the incidence of preterm birth, infants small for gestational age, or perinatal death seen after aspirin prophylaxis. Aspirin prophylaxis was not associated with adverse consequences to either the

mothers or the neonates, there being no evidence of any increase in abruptio placentae, postpartum hemorrhage, or neonatal intraventricular hemorrhage. A small aspirin effect leading to a reduced incidence of preeclampsia is seen in a small subset of large population studied. Similarly, we cannot exclude the possibility of some small adverse effect of aspirin.

A disparity between the small trials (less than 200 women) and the large trials (200 or more women) is evident.

| OUTCOME | INCIDENCE | | RELATIVE RISK (95% confidence interval) |
|---|---|---|---|
| | ASPIRIN | PLACEBO | |
| Preeclampsia | | | |
| Small trials | 10/319 | 50/284 | 0.2 (0.1, 0.4) |
| Large trials | 949/13,928 | 1032/13765 | 0.9 (0.8, 1.0) |
| Total | 959/14247 (6.7%) | 1082/14049 (7.7%) | 0.9 (0.8, 1.0) |
| Preterm delivery | 2404/13279 (17.5) | 2450/13645 (18.6) | 0.9 (0.9, 1.0) |
| Perinatal death | 418/14407 (2.9) | 450/14253 (3.2) | 0.9 (0.8, 1.0) |

Data for smaller trials is from Viinikka et al and Collins

For larger trials data si from Estudo colaborativo para prevencao da preeclampsia com aspirin. Rotchell et al Goldings and collins

Antiplatelet therapy was associated with a reduction of 82 percent (from 17.6 to 3.1 percent) in the risk of preeclampsia in the small trials but with a reduction of only 9 percent (from 7.5 to 6.8 percent) in the large trials. What might account for these differences? One possibility is publication bias, because small trials with positive findings are more likely to be submitted and published than are small trials with ambiguous or negative findings.18 The results of this and other large trials tend to support this possibility. When the large and small trials are combined, aspirin is found to have reduced the incidence of preeclampsia by 13 percent (6.7 percent vs. 7.7 percent), a difference that is statistically significant but of questionable clinical importance, because 100 women would have to be treated to prevent one case of preeclampsia. Even in the high-prevalence groups we studied (incidence of preeclampsia, 20.3 percent), 38 women would have to be treated to prevent one case of preeclampsia — a benefit that we believe is too small to justify routine use of aspirin prophylaxis. The cumulative results indicate that antiplatelet therapy also does not reduce the incidence of perinatal death, but it is associated with a reduction in the incidence of preterm birth (from 18.6 to 17.5 percent). Although statistically significant, the clinical importance of this reduction is also debatable.

In summary, low-dose aspirin did not reduce the incidence of preeclampsia in women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestations, or a history of preeclampsia. It also did not significantly reduce the incidence of perinatal death, preterm birth, or small-for-gestational-age infants. However, aspirin did not affect the mothers or neonates adversely. We conclude that aspirin should not be given to prevent preeclampsia in women with pregestational insulin-treated diabetes, chronic hypertension, multifetal gestation, or preeclampsia in a previous pregnancy.

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