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ORIGINAL ARTICLE

Role of Aspirin in High Pulsatility Index of Uterine Artery: A Consort Study

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Abstract

Background Preeclampsia is a heterogeneous disorder prevalent in 3–10% of pregnant women globally. The etiology is multifactorial. There is a initial stage of endothelial dysfunction and placental ischemia (Stage 1); this leads to maternal syndrome of hypertension, edema, and proteinuria (Stage 2). Drugs acting on immunomodulatory, anti-inflammatory, antioxidant and proresolving pathways can minimize the complications of preeclampsia. The therapeutic effect of aspirin is based on acetyl group and salicylate group. Both components have independent therapeutic effects on anti-inflammatory pathway and proresolving pathway.

Aims and Objectives This study was designed to assess the effectiveness and safety of aspirin in prevention and treatment of symptoms and complications of preeclampsia in women at high risk of preeclampsia.

Methods This is a prospective experimental study to evaluate the effectiveness of aspirin versus placebo in the prevention of maternal syndrome of preeclampsia in women with high risk of preeclampsia (G1 = 97, G2 = 92). Patients with age ≥ 34, chronic hypertension, multiple pregnancies, gestational diabetes, and high pulsatility index of uterine artery were enrolled between 12 and 20 weeks of gestation and prescribed 75 mg aspirin daily till 34 weeks of gestation. Control group was not prescribed aspirin.

Observations and Results There was a reduction in relative risk of preeclampsia in aspirin group as compared with control group. There was no significant increase in the number of cases of abruption placenta, preterm delivery, neonatal intraventricular hemorrhage, patent ductus arteriosus, and postpartum hemorrhage following aspirin therapy.

Conclusion In patients with high mean pulsatility index of uterine arteries, low dose aspirin can be a useful intervention. Uterine artery Doppler is a simple and noninvasive test which can be used safely for the prediction of preeclampsia. Aspirin is safe, economical, and easily available commercially.

Keywords Acetylsalicylic acid · Preeclampsia · Uterine artery · Doppler · Ultrasound

Introduction

Preeclampsia has multiple system involvements defined by persistent hypertension associated with proteinuria, thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, and cerebral edema [1, 2]. The basic pathology in Stage 1 is placental ischemia leading to release of release of sFLT and sENG, which bind VEGF, PLGF and endoglin. Deprived of these angiogenic factors there is, hypoxia, reperfusion injury, and generation of reactive oxygen species, which gradually lead to release of cytokines, lipid peroxidases, and syncitiotrophoblast microfragments from placenta into maternal circulation [3]. Finally, there is Stage 2 of inflammation, oxidative stress, endothelial dysfunction, endoplasmic reticulum stress, atherosis, and blood vessels deterioration [4]. In preeclampsia, there is placental ischemia and endothelial dysfunction with a decreased ratio of Prostaglandin I2/Thromboxane. Various compensatory mechanisms are activated.

Aspirin-triggered lipoxins promote resolution of inflammation through activation of the proresolving pathway [5]. Aspirin blocks the generation of reactive oxygen species in the endothelial cell [6]. It inhibits leukocyte–endothelial interaction and cell chemotaxis of neutrophils [7]. It promotes monocyte chemotaxis and nonphlogistic phagocytosis of apoptotic neutrophils by macrophages [8]. Aspirin is the only NSAID to promote the release of Nitric oxide the most potent vasodilator [9].

Preeclampsia is a heterogeneous disorder. Raised uterine artery impedance is found in a subset of preeclampsia patients where the preclinical stage is marked by increased downstream resistance in the spiral arteries supplying the fetal tertiary stem villi floating in the placental sinuses [10]. Raised uterine artery pulsatility index is also associated with early onset preeclampsia (< 32 weeks) [11]. Early onset preeclampsia is more severe and has worse fetal outcomes because of added problems of prematurity [12]. Raised uterine artery pulsatility index is also associated with increased aortic pulse wave velocity and augmentation index in the first trimester of pregnancy [13]. Increased aortic pulse wave velocity and augmentation index are also a marker of future cardiovascular risk [14]. The role of aspirin is well documented in the proresolving phase of various cardiovascular disorders through release of Aspirin-Triggered Lipoxins [15]. Aspirin is also the only known NSAID to induce NO in a dose-dependent manner. Hence, we have attempted to study the role of aspirin in pregnant women who might benefit maximum from it.

The uterine artery high pulsatility index is not a specific parameter to predict preeclampsia because preeclampsia is a two-stage heterogeneous disorder with multiple etiologies leading to maternal syndrome of edema, hypertension, and proteinuria. The patients with high uterine artery PI form a subset of patients whose cardiovascular system fails the hemodynamic stress imposed by pregnancy (increased plasma volume of 40% over the prepregnant state). Uterine artery pulsatility index is associated with subgroup of early-onset preeclampsia.

Ultrasound indices were used to study the blood flow in the uterine arteries. This requires a high-resolution gray scale 2D image, superimposed color flow map, and Doppler spectral analysis. In normal pregnancy in the second trimester, the uterine artery is wider with reduced elastic recoil. In PIH, uterine artery maintains its diameter and elasticity due to lack of remodeling. In a normal pregnancy, the uterine waveform has increased diastolic flow and no early diastolic notching. In PIH, the uterine artery waveform has low diastolic velocity and early diastolic notching. Pulsatility index is an objective assessment of the Doppler waveform (Peak systolic flow velocity–End diastolic velocity/Mean velocity). The protodiastolic notch is a marker of vessel recoil and elasticity (low flow in early diastole). During pregnancy, the pulsatility index decreases and protodiastolic notch disappears latest by 24 weeks. This is because of increase in diastolic flow. Most studies use a pulsatility index of > 1.6 in the second trimester for prediction of preeclampsia [16].

Most studies use subjective criteria for the definition of a diastolic notch, but a drop of at least 50 cm/s from the maximum diastolic velocity is a reasonable criterion after 20 weeks [17]. Hence, with uterine artery Doppler, we aim to identify a subset of early onset preeclampsia patients, who might benefit from low dose aspirin (1 mg/kg/day).

Materials and Methods

This clinical trial was performed on pregnant women attending prenatal clinic at Saveetha Medical College and hospital, Chennai, India between April 1, 2015, and December 31, 2016, after getting written informed consent from participants in local language. The sample size was calculated to achieve a power of 80% and confidence limits of 95% (two-sided type 1 error of 0.05 and 80% power). Pregnant women at high risk of preeclampsia were divided into two groups. The study group of 97 pregnant women were treated with 75 mg of aspirin, and control group of 92 pregnant women did not receive any specific medication. The division of cases and controls was based on simple computerized random number allocation. Figure 1 outlines the consort flow diagram of the case and control group (Fig. 1).

Doppler ultrasound examination of uterine arteries was done at 12–20 weeks gestation pregnant women attending a routine target scan. This study was approved by the ethical and research board. All women with no major fetal anomaly were offered the option of uterine artery Doppler evaluation. Written consent was obtained in all cases. A first-trimester scan was done to measure crown-rump length to date pregnancy in all cases.

Inclusion Criteria

The inclusion criteria of study were pregnant women with 12–20 weeks of gestation who were at high risk for pregnancy-induced hypertension. The high risk criteria for this study were age above 34 years, chronic hypertension, twins, gestational diabetes, previous preeclampsia and those with high pulsatility index of uterine artery.

Exclusion Criteria

In our study, pregnant women with fetal anomalies, sensitivity to aspirin, history of active peptic ulcer disease, liver disease, chronic renal failure, congenital heart disease, systemic lupus, and bleeding disorders were excluded from our study after performing an ultrasound study of abdomen and pelvis.

Patients, Treatment, and Evaluation

Pregnant women were enrolled based on inclusion and exclusion criteria. Objectives and implementation of study were explained, and written consent was obtained.

Detailed maternal factors like age, gestational age, parity, prepregnancy body mass index, previous low birth weight, hemoglobin levels, chronic hypertension, gestational diabetes, and previous preeclampsia were recorded. Gestational age was based on LMP and first-trimester ultrasound. Placental problems like infarcts, retroplacental calcifications, small placenta, and premature separation were noted. The ultrasound machines used for the study were PHILIPS HD11XE (Acuson, Mountain View, CA,

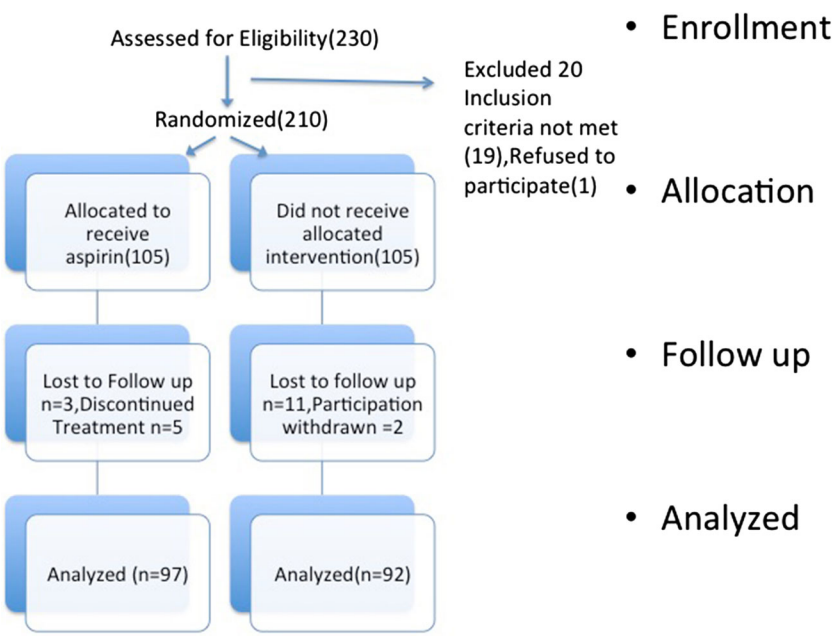

Fig. 1 Consort flow diagram of the study

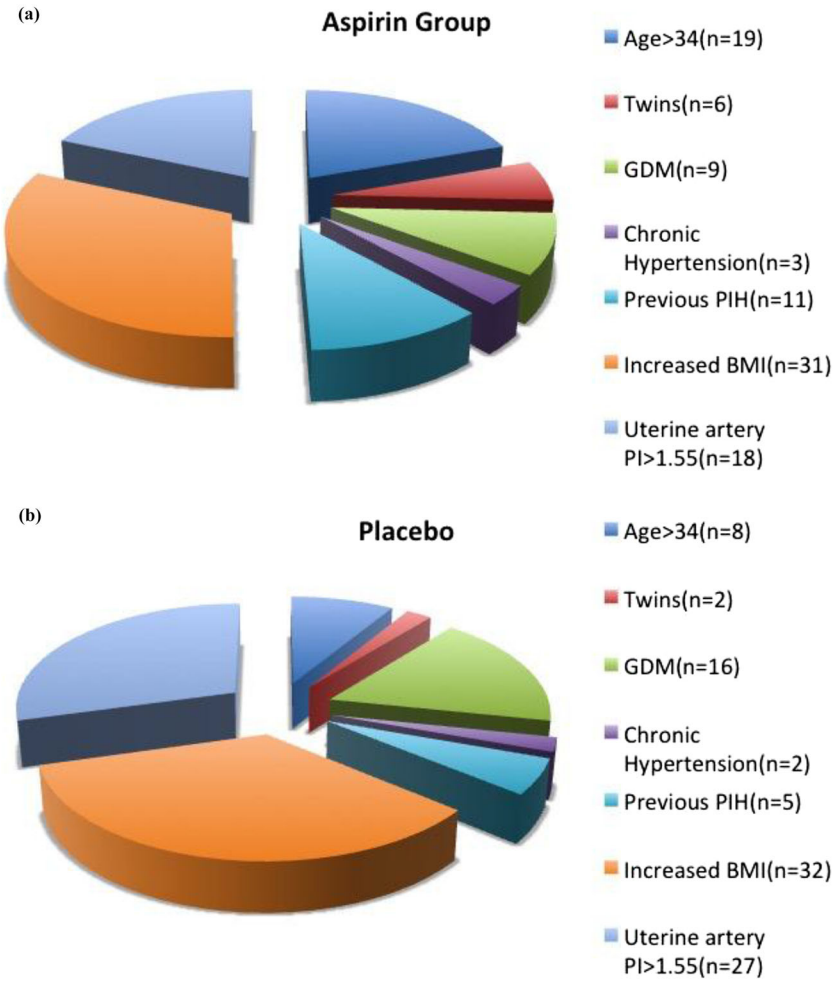

Fig. 2 **a** Case group (G1): base line characteristics of pregnant women at high risk started on aspirin. **b** Control group (G2): base line characteristics of pregnant women at high risk not started on aspirin

Table 1 Effect of aspirin on the incidence of preeclampsia in high-risk women according to risk factor

Variable	Incidence of preeclampsia aspirin (%)	Incidence of preeclampsia placebo (%)	Relative risk (95% confidence limits)
Risk group			
Age > 34 ($n = 27$)	10.5	12.5	0.84 (0.08, 8.02)
Chronic hypertension ($n = 5$)	33.33	50	0.67 (0.08, 5.53)
Multiple gestation ($n = 8$)	16.67	50	0.33 (0.035, 3.20)
Gestational diabetes mellitus ($n = 25$)	22.22	25	0.88 (0.20, 3.93)
Previous preeclampsia ($n = 16$)	36.36	40	0.91 (0.24, 3.43)
Increased BMI ($n = 63$)	22.58	31.25	0.72 (0.31, 1.65)
Uterine artery pulsatility index > 1.55 ($n = 45$)	44.44	70.37	0.63 (0.35, 1.11)
Any high risk ($n = 189$)	25.77	41.30	0.62 (0.41, 0.94)

USA); GE LOGICS7 Expert; Siemens Sonoline Acuson X150 (Siemens).

The uterine artery was identified in longitudinal scan lateral to the uterus. Pulsed wave Doppler was used to obtain three similar consecutive waveforms. The same was repeated for the contralateral uterine artery, and the mean pulsatility index (Maximum–Minimum velocity/Mean velocity) of the two vessels was calculated. Presence or absence of an early diastolic notch was recorded. Pulsatility index was preferred over resistivity index because it takes the area under the curve into consideration. The curved transducer (3.5-or 5-MHz) had spatial peak temporal average intensities < 100 mW/cm^2. Recordings for measurements were obtained in the absence of fetal breathing

Table 2 Maternal and perinatal outcomes in the aspirin and control group

Outcome	Aspirin ($n = 97$)	Placebo ($n = 92$)	Relative risk (confidence interval)
Postpartum hemorrhage	4	5	0.75 (0.21, 2.73)
Abruption placentae	1	2	0.47 (0.04, 5.14)
Preterm delivery	31	34	0.86 (0.58, 1.28)
Intrauterine growth retardation	9	10	0.85 (0.36, 2.00)

movements and fetal heart rate between 120 and 160 bpm. The angle between the ultrasound beam and the direction of blood flow was always less than 50°. Mean pulsatility index > 1.55 was taken as a high risk factor for preeclampsia.

Women fulfilling the inclusion criteria were enrolled and allocated to case group or control group according to computer-generated random numbers. Figure 2a summaries the high risk factors in the patients started on aspirin. Figure 2b depicts the high risk factors in patients in the control group. Case group was given 75 mg of aspirin once daily at bedtime from 12 weeks till 34 weeks of gestation. Compliance was assessed by taking detailed history and counting the pills. Routine ultrasound was done at each subsequent antenatal visit for fetal growth.

Preeclampsia is defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy.

This requires two recordings of diastolic blood pressure of ≥ 90 mmHg at least 4 h apart in previously normotensive women, and proteinuria of 300 mg or more in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection is available.

Statistical Analysis

Comparisons of the aspirin and control group were performed with the use of chi-square tests, Fischer's exact tests, Wilcoxon rank sum test, or Mantel–Haenszel tests. Overall relative risk estimates were calculated with stratification according to risk group. Fischer exact test was used to analyze maternal history variables. Differences were considered significant when $p < 0.05$. Logistic regression was used to obtain the Odd's ratio (OR) and 95% CI. Statistical analysis was done using MEDCALC.

Results

A total of 210 pregnant women were enrolled in the study. During the study period, follow-up was available for a total of 97 pregnancies in the study group and 92 pregnancies in the control group. The baseline characteristics of women and the distribution according to the risk group in cases and controls is shown in Fig. 2 a, b. Within each risk group, there was no significant difference between the aspirin and control group. All the patients with chronic hypertension were given labetalol 100 mg twice daily for blood pressure control in both the aspirin group and control group. Patients with gestational diabetes were prescribed insulin titrated according to blood sugars.

The effect of aspirin on the incidence of preeclampsia according to the risk category is shown in Table 1. A total of 63 (33.33%) pregnancies resulted in pregnancy-induced hypertension out of total 189 pregnancies. The incidence of preeclampsia was lower in aspirin group as compared to control group both within each risk group and in aggregate (25.77 vs. 41.33%). In all the subgroups, aspirin significantly reduced the incidence of preeclampsia as compared to controls. Regardless of the gestation age at entry, the incidence of preeclampsia was lower in aspirin group as compared to control group. The median number of tablets taken was 100 in the aspirin group, and only two women reported taking other NSAIDs in the aspirin group. In the control group, no women took other NSAIDs.

Aspirin was effective in preventing preeclampsia in all the high-risk groups regardless of parity, race, baseline blood pressure, and gestational age at baseline. Aspirin reduced the incidence of preeclampsia by 15.56% (25.77 vs. 41.33%). In the high-risk group (incidence of preeclampsia 41.33%), six women were treated to prevent one case of preeclampsia (NNT benefit 6.439).

There was no significant difference in the incidence of postpartum hemorrhage, abruption placenta, preterm delivery, infant small for gestation age and neonatal intraventricular hemorrhage in the aspirin and control groups. Table 2 brings up the association of aspirin treatment with postpartum hemorrhage, abruption placenta, and preterm delivery (Table 2).

Discussion

Aspirin is the trade name of acetylsalicylic acid coined by the Bayer laboratories [18]. Aspirin inhibits cyclooxygenase 1 and 2. This inhibits the inflammatory pathway of metabolism of Arachidonic acid. The production of

prostanoids prostacyclin, prostaglandins, and thromboxane is also inhibited [19].

In proresolving pathway, aspirin acetylates the active site of cyclooxygenase 2. This redirects its activity for production of 15R-HETE from Arachidonic acid. 15 R-HETE is then rapidly converted to lipoxin by 5-lipoxygenase in leukocytes [20]. Eicosapentenoic acid is transformed into 18 R-HEPE by aspirin acetylated COX 2. 18 R-HETE is converted to Resolvin E1 by action of 5 lipoxygenase in leukocytes [20]. These aspirin-triggered Lipoxins and Resolvins resolve inflammation and act as an immunomodulator and antioxidant [21, 22].

Different conflicting studies have been done on effects of aspirin in prevention of preeclampsia [23]. Earlier, some studies had suggested that aspirin was effective only if started before 16 weeks of gestation, but this was later clarified that aspirin has a role even if it is started in late second and third trimester [24, 25]. Even if aspirin was shown in smaller trials to be more effective before 16 weeks, the rationale for use was its effect on deep placentation [26, 27]. But it has been clearly shown that the first wave of trophoblast migration happens at 10–14 weeks, and the second wave of trophoblastic migration in deep myometrium happens by 18–20 weeks and gets completed only by 22–24 weeks. The rationale use of aspirin and results of large trials clearly suggest that aspirin is as efficacious in second as in the first trimester. Use of funnel plots in meta-analysis, small sample size and publication bias of positive findings have been implicated in recent literature [28–30]. The role of aspirin in prevention of eclampsia has been observed in our study in the second trimester. This is in accord with the rational use of aspirin and results of large studies.

In the subanalysis, the high-risk group that benefitted most from aspirin therapy is high uterine artery pulsatility index, increased maternal age, chronic hypertension, and multiple gestations. Our study is in line with previous research conducted on high-risk patients [31–34].

Our results didn't reveal significant differences between the two groups in incidence of abruption placenta, postpartum hemorrhage, neonatal intraventricular hemorrhage, and low birth weight. The findings of this study also indicate that there was no significant difference between the case and control group with regard to the average birth weight and gestational age at delivery. Also, aspirin did not reduce the incidence of preterm in the high-risk group. Contraindications to aspirin prescription are documented allergy to aspirin, asthma, bleeding disorders, and gastritis. G6PD enzyme deficiency is a relative contraindication though long-term low-dose aspirin has been found to be safe.

Limitation of our study is that though aspirin has shown to be beneficial in subgroups of increased age, chronic hypertension, and mutifetal gestation, the sample size is small. Further research with randomized placebo-controlled trials on a large cohort of these pregnant women may establish the role of aspirin in these subsets of pregnant women. Low dose aspirin and a diet rich in omega-3 fatty acids may have an additive benefit in triggering the pathways of proresolution in early subclinical stage of preeclampsia. The subset of pregnant women for whom this intervention might prove to beneficial remains to be studied.

Conclusion

Preeclampsia screening in our study was performed in maternity ultrasound clinics providing routine antenatal care rather than specialized researchers in fetal medicine units. This pragmatic approach shows that maternal history and Doppler ultrasound assessment of uterine arteries can detect a subgroup of patients with nonresilient cardiovascular system in the preclinical stage and timely intervention with aspirin can improve outcome. Thus, implementation of uterine artery-screening program in routine antenatal care would help to identify pregnancies that would benefit from low-dose aspirin and further intense surveillance. Uterine artery Doppler can be safely performed at the time of routine target anomaly scan in second trimester. It is simple, economical, feasible with good detection rates. Aspirin is useful in the subset of preeclampsia patients with high uterine artery pulsatility index.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest. We do not have any commercial association that might pose a conflict of interest in connection with the manuscript. We certify that neither this manuscript nor one with substantially similar content under our authorship has been published or is being considered for publication elsewhere.

Ethical Clearance Ethical Committee approval was obtained from the Institutional Research Board.

Informed Consent The research participants were informed about the study in local language and informed written consent was taken after explaining the nature of ultrasound Doppler scan in pregnancy. We have obtained the patient's consent for participation in research. Ethical committee clearance and research board clearance was obtained for this study according to the Principle of Helsinki.

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