

## Impact of Low Dose Aspirin in Prevention of Preeclampsia in Low Risk Nulliparous Primigravida Women

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### ARTICLE INFO

*Article Type:*  
Original Article

*Keywords:*  
Nulliparous  
Hypertension  
Obesity  
Primigravida  
Preeclampsia

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*Received on:* March 26, 2024

*Revised on:* April 20, 2024

*Accepted on:* April 23, 2024

### ABSTRACT

*Background:* Preeclampsia remains one of the most important challenges in obstetrics. Antiplatelet agents, such as aspirin (acetylsalicylic acid), are among the most promising candidates for prevention of preeclampsia.

*Objective:* To determine efficacy of low dose aspirin in prevention of preeclampsia in low risk primigravida women.

*Methods:* This descriptive Case Series Study was done at Gynecology and Obstetrics Department, MCH Unit 1 PIMS Hospital, Islamabad. Patients presenting at MCH Unit 1 were recruited. Women were given 75 mg of aspirin daily and followed according to the usual schedule typically every 4 weeks until 26 to 28 weeks of gestation every 2 to 3 weeks until delivery. At each visit women's blood pressure, weight and urinary protein excretion was measured. Urinary protein was measured with dipstick in a fresh mid-stream urine sample. Data was entered and analyzed in SPSS.

*Results:* A total of 175 pregnant women with primigravida were successfully followed till delivery in this study. Mean age of women remained to be  $27.51 \pm 4.74$  years with age range of 20 to 40 years. Frequency of obesity, family histories of hypertension and preeclampsia were also noted and found to be 32.0%, 100.0% and 19.4% respectively. Mean blood pressure with respect to weeks of pregnancy revealed a linear upward trend. Urinary protein by dipstick method was observed at every prescribed visit of pregnant women. Preeclampsia was diagnosed in 31(17.7%) of low risk group females. Higher age, family history of preeclampsia with first degree relative have been found to be significantly associated (p-value <0.05) with occurrence of preeclampsia among nulliparous women.

*Conclusion:* A higher number of nulliparous women with hypertension and/or preeclampsia amongst first degree relative are predicted to suffer from preeclampsia after 20 weeks of gestation. Further higher nulliparous age is also found a significant risk factor in this study. Obesity is also a risk factor of preeclampsia but not remained significant in this study.

## Introduction

Pre-eclampsia stands as a significant obstetric challenge, impacting 3-5% of pregnancies.<sup>1</sup> Characterized by new-onset or worsening hypertension and proteinuria after the 20th week of gestation, it poses risks to both maternal and fetal health.<sup>2</sup> With approximately 63,000 maternal deaths annually worldwide, accounting for 12% of all maternal deaths<sup>3</sup>, the disorder underscores an urgent need for predictive and preventive measures.

Identifying high-risk women for preterm pre-eclampsia early in pregnancy and implementing interventions to reduce its prevalence are primary concerns in contemporary obstetrics.<sup>4</sup> Over the past two decades, numerous trials have explored the efficacy of low-dose aspirin (50 to 150 mg per day) in preventing pre-eclampsia. A meta-analysis involving data from 32,217 women across 31 randomized trials revealed consistent, albeit moderate, reductions in relative risk associated with antiplatelet agent use during pregnancy, particularly concerning birth before 34 weeks and serious outcomes.<sup>5</sup>

Among potential preventive agents, antiplatelet agents like aspirin show promise due to their ability to modulate the prostacyclin-thromboxane balance, pivotal in pre-eclampsia pathogenesis.<sup>6</sup> Violla et al. reported an 86.9% prevention rate of pre-eclampsia with low-dose aspirin, affirming its potential efficacy.<sup>7</sup>

Despite the ongoing challenge of identifying the exact cause of preeclampsia, various hypotheses and scientific discoveries over time have significantly influenced our understanding of its pathophysiology. These contributions have left a mark on contemporary management strategies and classification criteria. This paper aims to shed light on how past hypotheses and scientific insights continue to shape current practices in managing preeclampsia. Through a historical journey spanning from ancient times to the present day, this paper will offer an overview of the evolution of knowledge surrounding preeclampsia and eclampsia. While not exhaustive in its historical analysis of primary sources, the focus is directed towards outlining theories on disease causation, treatment approaches, and disease

classifications drawn from credible primary and secondary sources.<sup>8</sup>

Aspirin plays a crucial role in preventing preeclampsia, as evidenced by a recent randomized controlled trial conducted in Shanghai, China, which investigated the effects of low-dose aspirin on preeclampsia prevention and pregnancy outcomes. The trial yielded several key findings including a) the study assessed the efficacy of low-dose aspirin in preventing preeclampsia, b) it confirmed the preventive effects of aspirin on preeclampsia, with efficacy varying based on dosage, c) the mechanism of action of aspirin and its impact on pregnancy outcomes were elucidated and d) the trial identified the most suitable population for preeclampsia prevention through aspirin intervention.<sup>9</sup>

Furthermore, the results indicated a significant reduction in the incidence of both preeclampsia and early-onset preeclampsia with low-dose aspirin administration. Additionally, there was a clear dose-dependent relationship observed in preeclampsia prevention, as evidenced by the Mantel-Haenszel trend test demonstrating a linear correlation between aspirin dosage and the incidence of preeclampsia and early-onset preeclampsia ( $P < 0.05$ ). Pearson's correlation analysis further supported this, revealing a negative correlation between aspirin dosage and the incidence of preeclampsia and early-onset preeclampsia.<sup>9</sup>

This research aims to investigate the preventive effects of aspirin initiated before 20 weeks of gestation on pre-eclampsia in nulliparous women. By establishing correlations between aspirin usage and pre-eclampsia risk in low-risk primigravida women, the study seeks to inform targeted preventive strategies, thereby enhancing patient quality of life and perinatal outcomes.

## Methods

This descriptive case series study was conducted at the Gynecology and Obstetrics Department, MCH Unit 1 of PIMS Hospital in Islamabad from December 1, 2020, to May 31, 2021. A sample size of 175 patients diagnosed with preeclampsia was determined using statistical calculations, and non-probability consecutive sampling was employed for data collection. Inclusion criteria encompassed

primigravida patients aged 20 to 40 years, with a gestational age of 11+6 weeks or more, carrying singleton pregnancies, and having first-degree family relatives with a history of chronic hypertension or preeclampsia. Exclusion criteria included patients with allergies to aspirin, tobacco smoking during pregnancy, history of asthma, peptic ulcer, inflammatory bowel diseases, hemophilia, or thrombophilia.

Institutional ethics committee approval was obtained before the commencement of the study.

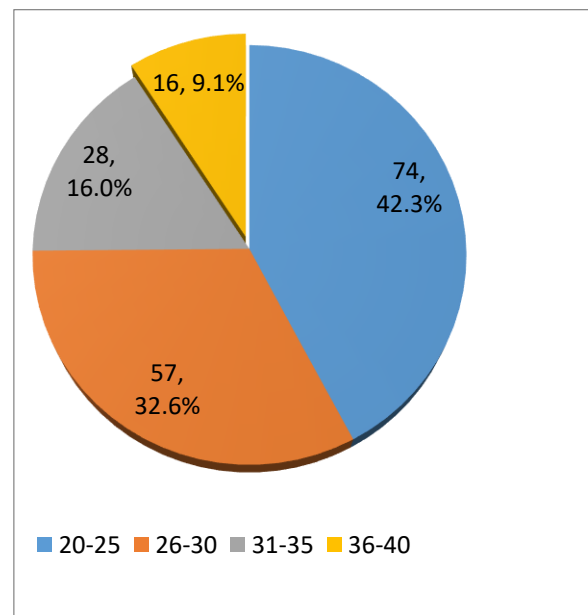
Eligible patients presenting at MCH Unit 1 provided informed verbal consent before enrollment. Enrolled patients underwent detailed obstetric and menstrual history assessments, followed by general, systemic, and obstetrical examinations, along with routine investigations. Women were administered 75 mg of aspirin daily before bedtime from 11+6 weeks after confirming fetal cardiac activity until delivery. Follow-up visits were scheduled according to standard protocols, typically every 4 weeks until 26 to 28 weeks of gestation, and then every 2 to 3 weeks until delivery. During each visit, blood pressure, weight, and urinary protein excretion were monitored. Urinary protein levels were assessed using dipstick analysis on fresh mid-stream urine samples. Compliance with treatment was evaluated by inquiring about tablet intake and continuing tablets. Data were recorded on a specially designed Performa by the researcher to ensure data continuity and quality.

Statistical analysis was performed using SPSS version 23.0, calculating descriptive statistics for both qualitative and quantitative variables. Mean and standard deviations were computed for quantitative variables such as age and gestational age, while frequencies and percentages were determined for qualitative variables including onset of preeclampsia, family history of hypertension, family history of preeclampsia, obesity, and residential status.

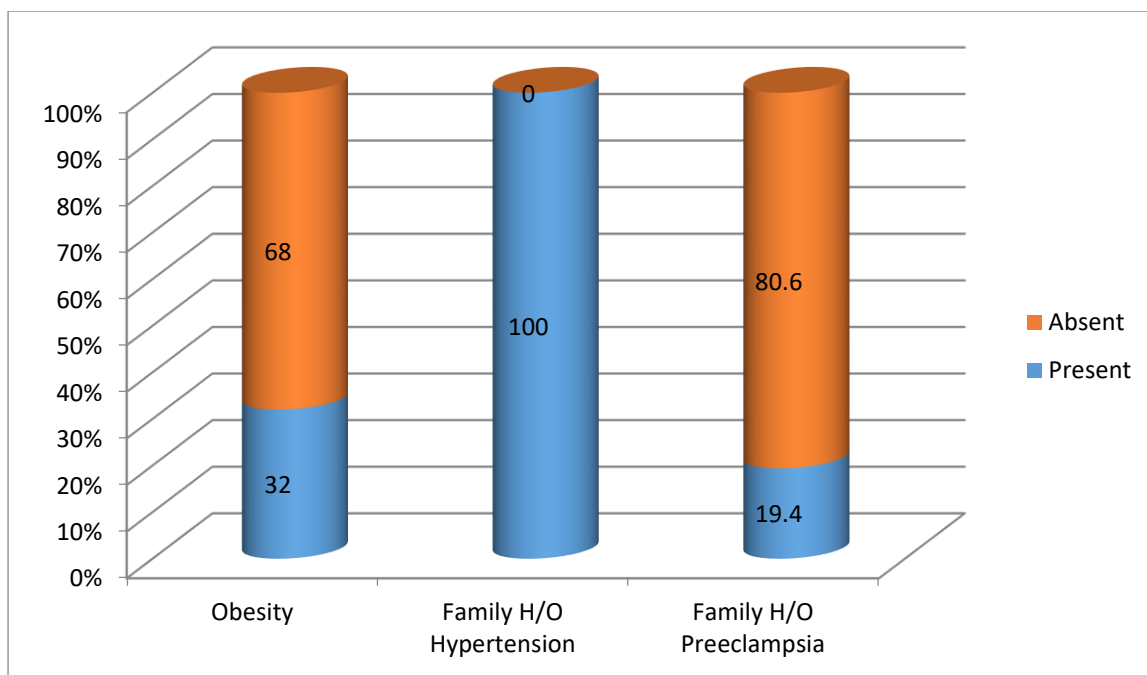
Effect modifiers such as age, family history of hypertension, family history of preeclampsia, obesity, and residential status were stratified, and post-stratification chi-square tests were applied, considering a P value <0.05 as significant.

#### Results

A total of 175 pregnant women with primigravida were successfully followed till delivery in this study. Mean age of women remained to be 27.51±4.74 years with age range of 20 to 40 years. Segregation of various age ranges is shown in figure 1. Most of (75%) women were in age range of 20-30 in present study.



**Figure 1: Age Ranges of Pregnant Women**  
Baseline gestational age of study subjects were remained to be 19.66±1.88 weeks whereas weight and height were remained to 64.21±4.31Kg and 153.38±4.37 cm respectively. Mean body mass index (BMI) of patients remained to be 27.27±1.15 kg/m<sup>2</sup> at higher side as criteria of BMI for obesity in Asians is ≥27.5 kg/m<sup>2</sup> as. Frequency of obesity, family histories of hypertension and preeclampsia were also noted and found to be 32.0%, 100.0% and 19.4% respectively as shown in Figure 2.



**Figure 2: Proportions of Obesity Hypertension and Preeclampsia**

**Table 1: Mean blood pressure with respect to weeks of pregnancy**

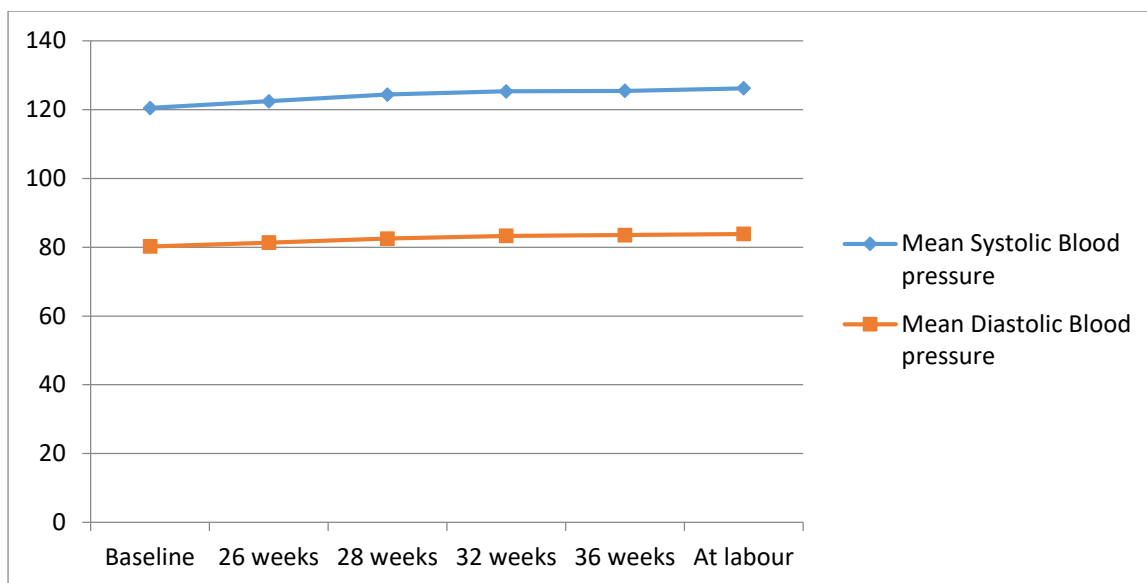
Type and time of Blood Pressure	Mean	SD
Baseline Systolic	120.46	2.09
Baseline Diastolic	80.23	1.05
Systolic at 26 weeks	122.40	7.03
Diastolic at 26 weeks	81.34	4.12
Systolic at 28 weeks	124.34	8.94
Diastolic at 28 weeks	82.51	5.52
Systolic at 32 weeks	125.29	10.46
Diastolic at 32 weeks	83.26	6.69
Systolic at 36 weeks	125.40	10.67
Diastolic at 36 weeks	83.51	7.08
Systolic at labor	126.17	11.73
Diastolic at labor	83.83	7.44

Mean blood pressure with respect to weeks of pregnancy revealed a linear upward trend and increase in mean blood pressure is directly

proportion to the higher number of weeks as presented in table 1 and figure 3.

Urinary protein by dipstick method was observed at every prescribed visit of pregnant women and there were no urinary proteins observed at baseline however 10.9% cases had 1+ urinary protein at 26<sup>th</sup> week of gestation. Similarly 17.7% had 1+ protein at 28<sup>th</sup> and 32<sup>nd</sup> week of gestation while at 36<sup>th</sup> week 14.9% had 1+ and 2.9% had 2+ urinary protein. Preeclampsia was diagnosed in 31(17.7%) of low risk group females while rest of 144(82.3%) had normal delivery in present study. A strong association of occurrence of preeclampsia with higher age of primigravida has been found in this study with p-value <0.05 as shown in Table 2.

Likewise family history of preeclampsia with first degree relative has also been found to be significantly associated (p-value <0.05) with occurrence of preeclampsia among nulliparous women in this study while obesity is not found to be associated with an remained insignificant (p-value >0.05) with occurrence of preeclampsia as shown in Table 3.



**Figure 3: Trend of Mean Blood Pressure with Gestational Age**

**Table 2: Association of Preeclampsia with age Range**

Age Range	Preeclampsia Diagnosed				Total	
	Yes (n=31)		No (n=144)		n	%
	n	%	N	%		
20-25	0	0.0	74	51.4	74	42.3
26-30	18	58.1	39	27.1	57	32.6
31-35	8	25.8	20	13.9	28	16.0
36-40	5	16.1	11	7.6	16	9.1

p-value = 0.0001

Chi. Square = 27.723

**Table 3: Association of Preeclampsia with Family History and Obesity**

Variable		Preeclampsia Diagnosed				p-value
		Yes		No		
		n	%	n	%	
Family History of Preeclampsia	Yes	14	45.2	20	13.9	0.0001
	No	17	54.8	124	86.1	
Obesity	Yes	10	32.3	46	31.9	0.564
	No	21	67.7	98	68.1	

Amongst total 31 patients 19(61.3%) diagnosed with preeclampsia at or before 26<sup>th</sup> week of gestation while others 12(38.7%) diagnosed at

or before 28<sup>th</sup> week of gestation. No any new case of preeclampsia was diagnosed after 28 weeks of gestation in this study.

## Discussion

Currently, preeclampsia was identified in 31 (17.7%) of females classified as low risk, while the remaining 144 (82.3%) experienced normal deliveries. An earlier systematic review examining the prevention of preeclampsia with low-dose aspirin during randomized controlled trials revealed a low incidence. This meta-analysis categorized trials based on the risk status of the participants into two groups: those at low risk for preeclampsia and those at high risk. The analysis assessed the incidence of preeclampsia among women receiving either placebo or aspirin, calculating relative risks and 95% confidence intervals for both groups. A total of 33,598 women were included, comprising 5 trials with 16,700 low-risk women and 17 trials with 16,898 high-risk women. The incidence of preeclampsia was 3.75% (626/17,700) in the low-risk group, 9.01% (1,524/16,898) in the high-risk group, and 6.40% (2,150/33,598) overall. While low-dose aspirin did not significantly affect the incidence of preeclampsia in the low-risk group (RR = 0.95, 95% CI = 0.81-1.11), it showed a slight beneficial effect in the high-risk group (RR = 0.87, 95% CI = 0.79-0.96). Thus, low-dose aspirin appears to offer mild benefits in reducing preeclampsia incidence among high-risk women.<sup>10</sup> However, the results of this study differ from the present study, which observed a low incidence of preeclampsia among low-risk pregnant women.<sup>11</sup> This disparity may be attributed to larger study group sizes and the inclusion of randomized trial controls in the former analysis, while the present study utilized a non-probability convenient sampling technique, potentially contributing to the higher incidence observed.

Furthermore, a recent nested case-control study conducted across five different centers in Brazil aimed to determine the incidence and risk factors for preeclampsia and associated maternal and perinatal outcomes among nulliparous healthy pregnant women. Clinical data were prospectively collected and compared between preeclampsia cases and controls using risk ratio (RR) (95% CI) and multivariate analysis. Among 1,165 participants, the incidence of preeclampsia was 7.5%. Factors such as body mass index at the

first medical visit and diastolic blood pressure exceeding 75 mmHg at 20 weeks of gestation were independently associated with preeclampsia. Preeclamptic women experienced higher rates of adverse maternal and perinatal outcomes, including cesarean section, preterm birth, low birth weight, and neonatal complications. These findings underscore the importance of identifying and managing risk factors for preeclampsia to improve maternal and neonatal health outcomes.<sup>12</sup>

In contrast, the results of the present study show an upward trend in systolic and diastolic blood pressures with increasing gestational age, although no significant fluctuations were observed. However, the present data lacks information on preterm delivery and cesarean section rates due to several limitations. Another recent cohort study focused on clinical risk assessment for preeclampsia in early pregnancy among nulliparous women. Of the 2,773 nulliparous women assessed, 4.4% developed preeclampsia. The pre-specified variables model demonstrated superior predictive ability compared to other models, particularly for predicting preeclampsia with deliveries before 34 and 37 weeks of gestation.<sup>11</sup> Notably, certain risk factors such as higher maternal age, family history of preeclampsia, and obesity were identified in the present study, with age and family history showing significant associations with preeclampsia.

Additionally, previous research has highlighted the role of nutritional factors<sup>13</sup> and obesity in predisposing women to preeclampsia, emphasizing the importance of weight management and dietary interventions in reducing risk.<sup>14</sup> While the evidence suggests a link between obesity and increased risk of preeclampsia and cardiovascular disease, the impact of weight reduction before pregnancy or during pregnancy remains uncertain. Nevertheless, promoting healthy lifestyles, including weight management and adequate nutrition, may help mitigate the risk of preeclampsia and improve overall maternal and neonatal outcomes.<sup>15,16</sup>

**Conclusion:** A higher number of nulliparous women with hypertension and/or preeclampsia amongst first degree relative are predicted to

suffer from preeclampsia after 20 weeks of gestation. Further higher nulliparous age is also found a significant risk factor in this study whereas most number of cases were found to be in age group of 26-30 years of age. Obesity is also a risk factor of preeclampsia but not remained significant in this study.

**Conflict of Interest:** The authors have no competing interests.

**Funding Source:** No funding was received from any agency for this study.

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