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Predictors of Preeclampsia in High-Risk Pregnant Women Prescribed Low-Dose Aspirin in a Resource-Limited Setting

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Abstract

Background: Preeclampsia is typically prevented by using low-dose aspirin in women with high-risk factors. Data on pregnant women who use low-dose aspirin to avoid preeclampsia are scarce in Ethiopia. This study aims to determine the prevalence and predictors of preeclampsia in women taking low-dose aspirin at a tertiary care hospital.

Methods: An observational study was conducted retrospectively on pregnant women who were at high risk for preeclampsia and who were given low-dose aspirin for the prevention of preeclampsia at Saint Paul's Hospital and Millennium Medical College, Addis Ababa, Ethiopia, from June 1st, 2018 to May 31st, 2022. Kobo Toolbox was used to extract the data and SPSS version 26 was utilized for data analysis. The preeclampsia syndrome predictors were found using a binary logistic regression model. Variables that had a p-value of 0.05 or lower were taken into consideration.

Result: Data were extracted from the cards of 392 participants with a mean age of 29.7 years (SD ± 5.33) and included in the final analysis. The prevalence of preeclampsia syndrome was 19.4% (95% CI; 15-24%). Variables like: Older maternal age (≥ 35) (AOR=3.25, 95% CI (1.18-8.97)), nulliparity (AOR=11.59, 95% CI (2.81-27.70)), history of preeclampsia (AOR=4.11, 95% CI (1.289-8.74), late initiation of low-dose aspirin (AOR=2.2 95% CI (1.60–4.21)), pregestational diabetes (AOR=2.88, 95% CI (1.07-77)), chronic hypertension (AOR=13.2, 95% CI (5.11-17.2)), two or more preexisting medical conditions (AOR=15.1; 95% CI (6.32-22.28)) were significantly associated with preeclampsia syndrome.

Conclusion: Despite taking aspirin as a preventive strategy, preeclampsia struck a significant proportion of pregnant women. Older women, nulliparity, history of preeclampsia, chronic hypertension, late initiation of low-dose aspirin, pregestational diabetes, and two or more concomitant medical disorders were found to be predictors. Principally, nulliparity, chronic hypertension, and two or more medical disorders considerably amplify the risk. Priority should be given to pre-conceptional optimization of pre-existing medical conditions, early and routine prenatal care monitoring, and appropriate counseling of modifiable risk factors. Future researchers ought to concentrate on doing multicenter, larger cohort, more robust, more compliance-oriented studies.

Keywords: Predictors; Preeclampsia; High-risk pregnant women; Low-dose aspirin; Ethiopia

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Abbreviations

ANC: Antenatal Care; AOR: Adjusted Odds Ratio; ASPRE: Combined Multi-Marker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention; BMI: Body Mass Index; BP: Blood Pressure; dBP: Diastolic Blood Pressure; IQR: Interquartile Range; CHTN: Chronic Hypertension; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; sBP: Systolic Blood Pressure; SD: Standard Deviation; SPSS: Statistical Package for Social Sciences

Introduction

Preeclampsia still plays a significant role in the morbidity and mortality of pregnant women,

their fetuses, and their newborns. Prevalence rates of preeclampsia vary by country and are between 2% and 10% worldwide [1,2].

Women with preeclampsia were more likely than the general population to develop future cardiovascular and cerebrovascular disorders [3,4]. Preeclampsia-related prematurity and fetal growth retardation have long-term effects that are principally responsible for cerebral palsy and delayed neurodevelopment [5,6].

Women at high risk for preeclampsia are defined as having one or more risk factors, such as pregestational diabetes, history of preeclampsia in a previous pregnancy, chronic hypertension, pregnancy after assisted reproductive technology, multiple pregnancies, autoimmune disease, renal disease, or nulliparity. A high risk for preeclampsia was also considered if more than one of the following moderate risk factors were BMI >30 kg/m^2, family history of preeclampsia, or maternal age >35 years [7-11]. The US Preventive Services Task Force's updated evidence report and systematic review found that the incidence of preeclampsia among trial participants with these important risk factors ranged from 8% to 30% [2].

Aspirin is a platelet- and inflammation-fighting angiogenesis inhibitor [12,13]. To prevent or delay early preeclampsia, low-dose aspirin has been administered during pregnancy. For mothers who have those high preeclampsia risk factors, many organizations now advise taking low-dose aspirin. One of the most researched non-steroidal anti-inflammatory medications for the prevention of preeclampsia, low-dose aspirin is only modestly effective. The effective low-dose aspirin ranges from 60 mg/d to 162 mg/d for preventing preeclampsia [14,15]. Women at high risk of preeclampsia should take low-dose aspirin (81 mg/day), according to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine. Beginning between 12 and 28 weeks of pregnancy (ideally before 16 weeks), it should be taken every day until birth [2,16-18]. Low-dose aspirin prophylaxis decreases preeclampsia by 10% to 24% in people at high risk for preeclampsia, according to many large-group meta-analyses and randomized controlled trials [7,19,20]. There was a 28% decrease in the incidence of preeclampsia in a recent ASPRE trial using 150 mg/day of aspirin [21]. Studies found that between 2.4% and 18% of those using low-dose aspirin also had preeclampsia [16,22].

The rate of preeclampsia and its predictors among high-risk pregnant women taking low-dose aspirin to prevent preeclampsia is not yet known in Ethiopia. The findings of this study will show an illustrative picture of women at high risk for preeclampsia who are taking low-dose aspirin in our setting, and act as a springboard for upcoming prospective cohort studies and trials.

Therefore, this study was carried out over four years to present the occurrence of preeclampsia and potential preeclampsia predictors in high-risk pregnant women receiving low-dose aspirin for preeclampsia prevention at St. Paul's Hospital and Millennium Medical College.

Methods and Materials

Study setting, design, and participants

A four-year hospital-based retrospective observational study was conducted from June 1st, 2018 to May 31st, 2022 at Saint Paul's Hospital and Millennium Medical College, Addis Ababa, the capital city of Ethiopia. Saint Paul's Hospital is one of the tertiary referral hospitals directly under the federal ministry of Health. It is also a teaching hospital for the Millennium Medical College. The hospital serves more than 200,000 people referred from all over the country each year. A fellowship program is available in fetomaternal medicine. Eight fetomaternal specialists at the college provide care for pregnant women with high-risk ANC. Pregnant women with one or more high-risk factors, such as pregestational diabetes (type 1 or type 2 DM), history of preeclampsia in a previous pregnancy, chronic hypertension, autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematous), chronic kidney disease, or more than one moderate risk factors such as nulliparity, BMI greater than 30 kg/m^2, a preeclampsia family history, and maternal age greater than 35.

Beginning low-dose aspirin at or after 12 weeks of pregnancy and before 28 weeks, it was stopped at delivery or when preeclampsia first appeared. In our setting, only low-dose 81 mg aspirin tablets are available, and 81 mg or 162 mg are prescribed. Most pregnant women at high-for preeclampsia were given 81 mg tablets. A dose of 162 mg was administered to some high-risk pregnant women with late-onset ANC contact and multiple high-risk factors. All mothers who received low-dose aspirin for prophylaxis of preeclampsia after 12 weeks of gestation and before 28 weeks of gestation, were fully documented, and did not lose follow-up during the study period were the study population.

Using a single population formula, the sample size was calculated under the assumption that pregnant women with high risk factors would have a maximum prevalence of preeclampsia of 30% (2). Despite the lack of regional statistics, it made reasonable to use the highest prevalence in another region.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2}$$

$$= \frac{(1.96)^2 (0.3)(1-0.3)}{(0.05)^2} = 323$$

Where:

- n=the required sample size
- P= the maximum proportion of preeclampsia in the previous study.
- Zα/2=the critical value at 95% confidence level of certainty (1.96)
- d=the margin of error between the sample and the population, 5%.

The overall number of study population throughout the course of 4 years was 413. Using the final population correction calculation, we arrived at the final sample size of 182, to which we added 10% to account for loss to follow-up and incomplete documentation, yielding a final sample size of 200. But it was plausible to include all 413 of the population. There were 392 cards total after 21 cards (8 incomplete cards and 13 lost follow-up cards) were excluded. Consecutive sampling was used to choose study participants overall. Data were collected from 1st to 30th June 2022.

Study variables

Dependent variable: Included preeclampsia syndrome development (developed or not developed).

Independent Variables: Included socio-demographic variables such as age and place of residence; moreover, obstetric variables such as parity, mode of conception, interpregnancy interval, previous pregnancy outcomes, history of preeclampsia, number of gestations, gestational age at initiation of low-dose aspirin, number of antenatal

care contacts, and preexisting medical conditions.

Operational definitions

Antiphospholipid syndrome: It was diagnosed by the existence of unfavorable obstetric outcomes (fetal death after 10 weeks of gestation, preterm birth due to severe preeclampsia or placental insufficiency, multiple embryo losses before 10 weeks of gestation), as well as persistent antiphospholipid antibody laboratory findings.

Chronic hypertension: The patient's report at or before the 12-week visit or a blood pressure reading of 140/90 mmHg taken upon admission up to 20 weeks of gestation were used to make the diagnosis.

Chronic kidney disease: No matter the etiology, it is characterized by renal impairment or decreased renal function before pregnancy that has lasted three months or more and has been identified and recorded at the time of booking by a nephrologist or internist.

Early initiation of low-dose aspirin: Starting earlier than 16 weeks of pregnancy

Late initiation of low-dose aspirin: Beginning after the 16th week of pregnancy

Preeclampsia without severe features: According to the International Society for the Study of Hypertension in Pregnancy, it was specified as a previously normotensive woman who had BP 140/90 mmHg, 24-h urine protein 300 mg, or urine protein 1+) does not fulfill criteria for severe preeclampsia.

Preeclampsia with severe features: If they have at least one of the following features in addition to meeting the criteria for preeclampsia without severe features: sBP >160 mmHg or/and dBP >110 mmHg, oliguria, thrombocytopenia, pulmonary edema, epigastric or right upper quadrant pain, decreased liver function, cerebral or visual abnormalities.

Preeclampsia syndrome/preeclampsia: Encompasses preeclampsia without severe features, preeclampsia with severe features, superimposed preeclampsia with and without severe features, and eclampsia.

Superimposed preeclampsia: Significant proteinuria should start to appear after 20 weeks of pregnancy and should be identified and documented by a fetal maternal specialist if chronic hypertension or chronic renal disease is identified in conjunction with symptoms or signs of preeclampsia.

Data collection tools, data quality assurance, and statistical analysis

A structured data-extracting checklist was developed from different kinds of literature [2,4,8,9,22]. Data were extracted by a General Practitioner (GP) and a nurse who had prior relevant experience. Data collectors were given training about the goal of the research and data collection procedures. The primary investigator oversaw the training and on-site monitoring. Each day after data collection, the quality of the data was evaluated. Exclusion criteria were considered. The extracted data coded and cleaned were entered into Kobo Toolbox. Then, it was exported and analyzed with SPSS version 26. The data were described with descriptive statistics like frequency, percentage, mean, median, and interquartile range. For categorical variables, frequencies and percentages were reported; for continuous variables with normally distributed data, mean; and for data with a non-normal distribution, median and interquartile range. The Chi-square and Fisher's exact tests were used to show an association between categorical variables. Variables whose p-value <0.25 in the univariable analysis were included in the multivariate binary logistic regression model. Backward stepwise variable selection was employed. Model fitness was checked by the Hosmer-Lemeshow test. P value <0.05 was used for statistical significance in the final model to identify predictors of preeclampsia. Finally, the results were displayed using statistical tables.

Results

Sociodemographic characteristics and clinical characteristics

Three hundred ninety-two client charts were reviewed and analyzed. Participants in the study ranged in age from 19 to 43, with a mean age of 29.7 years and a standard deviation of 5.33. Most mothers were multiparous and had uneventful previous pregnancy outcomes. Ninety-three (23.7% of total) mothers had a history of preeclampsia. The majority of patients were in the age category 21 to 34. The median interval between pregnancies was 20.5 months (range: 3-192) (Table 1).

Obstetric characteristics in the index pregnancy and preexisting medical conditions

Nearly 96% of high-risk pregnant women received low-dose aspirin 81 mg tablets, the rest 162 mg. Of the total number of women prescribed low-dose aspirin, 97.4% became pregnant naturally. Most mothers had singleton pregnancies and 1 triplet, started low-dose aspirin early, and had 8 or more ANC contacts. The mean number of contacts in ANC was 12 ± 6 (range: 3-18). The median gestational age at the start of aspirin was 15 weeks (interquartile range: 12-25). The mean gestational age of onset of preeclampsia was 35 ± 8 weeks (minimum 22 weeks and maximum 41 weeks). The mean gestational age at delivery was 36 ± 4 weeks. In nearly 40% of patients, preeclampsia was complicated, and forced to give birth before 37 weeks of gestation. More than half (63.2%) of the women with preeclampsia in the study were delivered by cesarean section. Most women with preeclampsia had babies weighing more than 2.5

Table 1: Sociodemographic characteristics and some clinical characteristics (N=392).

Variables	Category	n	%
Age category	<20	14	3.6
	21-34	290	74
	≥ 35	88	22.4
Residence	Addis Ababa	271	69.1
	Out of Addis Ababa	121	30.9
Parity	Nulliparous	130	33.2
	Multiparous	262	66.8
Previous pregnancy outcomes	Uneventful	337	86
	Abortion	35	8.9
	Stillbirth	20	5.1
History of preeclampsia (n=272)	Yes	93	34.2
	No	179	65.8
Interpregnancy interval (months) (n=290)	<6	36	9.2
	6-23	114	29.1
	24-59	104	26.5
	≥ 60	36	9.2

Table 2: Obstetric characteristics in the index pregnancy.

Variables	Category	N	%
Mode of conception	Natural	382	97.4
	Assisted	10	2.6
Number of gestations	Singleton	380	96.9
	Multiple gestations	12	3.1
Frequency of ANC contacts	<8	100	25.5
	≥ 8	292	74.5
Gestational age at low-dose aspirin initiation	<16 weeks	305	77.8
	≥ 16weeks	87	22.2
Preeclampsia has developed	Yes	76	19.4
	No	316	80.6
Gestational age for preeclampsia	<28 weeks	13	17.1
	28-34 weeks	20	26.3
	34-37 weeks	27	35.5
	>37 weeks	16	21.1
Complicated preeclampsia compelling current delivery before 37 weeks	Yes	30	39.5
	No	46	60.5
Gestational age at birth in women with preeclampsia	<34	23	30.3
	≥ 34	53	69.7
Mode of delivery in preeclampsia women	Vaginal delivery	28	36.8
	Cesarean delivery	48	63.2
Birth outcomes in women with preeclampsia	Abortion	13	17.1
	Live birth	53	69.7
	Stillbirth	10	13.2
Birth weight in women with preeclampsia (n=89) in kg	<1	15	16.9
	1-1.5	11	12.4
	1.5-2.5	30	33.7
	≥ 2.5	33	37.1

kg at birth. The stillbirth rate in preeclampsia women was 13.2%. The majority of patients (78.3%) had pre-existing medical conditions, of which 25.7% had two or more diseases. The most frequent preexisting medical conditions were chronic hypertension (52.8%) and pre-gestational diabetes (30%) or both (14%). Of the total study participants, 211 (53.8%) had chronic hypertension alone or chronic hypertension with other diseases. Additionally, 136 (34.7%) of the study participants had pregestational diabetes or other medical conditions. Four patients had antiphospholipid syndrome (Table 2, 3).

Prevalence of preeclampsia syndrome in mothers prescribed low-dose aspirin

A total of 392 mothers were prescribed low-dose aspirin for the prevention of preeclampsia, of which 76 (19.4%) (95% CI; 15-24%) patients developed preeclampsia syndrome. Of the mothers diagnosed with preeclampsia, 43 (56.6%) were diagnosed after 34 weeks of gestation. on the severity of preeclampsia; thirty-two (42.1%) mothers had preeclampsia with severe features, 25 (32.9%) preeclampsia without severe features, and 10 (13.2%) superimposed preeclampsia with severe features and 9 (11.8%) superimposed preeclampsia without severe features. Eclampsia was not described in the review.

Table 3: Preexisting medical conditions.

	N	%
Medical Conditions		
Yes	307	78.3
No	85	21.7
Number of medical conditions		
One	258	84
Two or more	49	16
Chronic hypertension	162	52.8
Pregestational diabetes	92	30
Chronic kidney disease	2	0.7
Antiphospholipid syndrome	2	0.7
CHTN+DM	43	14
CHTN+CKD	3	1
CHTN+Antiphospholipid syndrome	2	0.7
CHTN+DM+CKD	1	0.3

Identification of predictors of preeclampsia

Twelve variables: Maternal age, parity, history of preeclampsia, interpregnancy interval, mode of conception, number of gestations, gestational age at initiation of low-dose aspirin, previous pregnancy outcomes, frequency of ANC visits, chronic hypertension, pregestational diabetes, and concomitant medical disorders were entered into univariable binary logistic regression analysis model. Except for the interpregnancy interval, the remaining 11 variables were candidates for multivariable binary logistic regression models with a p-value <0.25. Multivariable binary logistic regression analysis was fitted with a stepwise backward elimination variable selection technique. Seven variables: Older maternal age, nulliparity, history of preeclampsia, late initiation of low-dose aspirin, chronic hypertension, pregestational diabetes, and concomitant medical disorders were significant at a p-value of <0.05 in the final model.

Older mothers (aged 35 years or older) were three times more likely to develop preeclampsia than those younger than 34 years old (AOR=3.25, 95% CI (1.18-8.97). Nulliparity increased the chance of developing preeclampsia by nearly 12 times (AOR=11.59, 95% CI (2.81-27.70)). The odds of recurrent preeclampsia in mothers with preeclampsia in a previous pregnancy were four times higher than in mothers without a history of preeclampsia (AOR=4.11, 95% CI (1.289-8.74). Regarding the timing of initiation of low-dose aspirin, mothers who started low-dose aspirin after 16 weeks of gestational age were almost twice as likely to develop preeclampsia (AOR=2.2 (1.60-4.21) as compared to mothers who started low-dose aspirin) before 16 weeks of gestation. Women with chronic hypertension were almost 13 times more likely to develop Preeclampsia (PE) (AOR=13.2, 95% CI (5.11-17.2)) than those without chronic HTN. Pregestational diabetes also tripled the chance of developing preeclampsia (AOR=2.88 (1.07-7.77)). The likelihood of developing Preeclampsia (PE) in those who had two or more medical disorders was nearly fifteen times (AOR=15.1; 95% CI (6.32-22.28)) higher than those having one medical disorder (Table 4).

Discussion

To determine the prevalence of preeclampsia syndrome and to pinpoint its predictors in women who were at high risk of preeclampsia, and were taking low-dose aspirin, a retrospective observational study

Table 4: Results of multivariable binary logistic regression analysis for mothers prescribed low-dose aspirin to prevent preeclampsia (n=392) at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia from June 1st, 2018 to May 31st, 2022.

Variables		Preeclampsia has developed		95% CI OR	P-values
		Yes n (%)	No n (%)		
Age	<20	7 (0.5)	7 (0.5)	1.9 (1.18-8.97)	0.200
	21-34	9 (3.1)	281 (96.9)	1	
	≥ 35	60 (68.2)	28 (31.8)	3.25 (1.18-8.97)	0.023
Parity	Nulliparous	54 (41.5)	76 (58.5)	11.59 (2.81-27.70)	0.001
	Parous	22 (84)	240 (91.6)	1	
Mode of	Natural	71 (18.6)	311 (81.4)	1	
conception	Assisted	5 (0.5)	5 (0.5)	3 (2.1-9.2)	0.450
Number	Singleton	70 (18.4)	310 (81.6)	1	
Gestation	Multiple	6 (0.5)	6 (0.5)	3.70 (.085-16.032)	0.800
Previous pregnancy outcomes	Uneventful	46 (13.6)	291 (86.4)	1	
	Abortion	20 (57.1)	15 (42.9)	0.59 (0.162-2.18)	0.433
	Stillbirth	10 (0.5)	10 (0.5)	3.74 (1.144-12.284)	0.090
History	Yes	60 (64.5)	33 (35.5)	4.11 (1.289-8.743)	0.013
of preeclampsia	No	16 (8.9)	163 (91.1)	1	
Timing of low-dose aspirin in weeks	<16	60 (19.7)	245 (80.3)	1	
	≥ 16	16 (18.4)	71 (81.6)	2.2 (1.60-4.21)	0.023
Frequency of ANC contacts	< 8	20 (0.2)	80 (0.8)	2.1 (1.5-5.4)	
	≥ 8	56 (19.2)	236 (80.8)	1	
Chronic HTN	Yes	56 (26.5)	155 (73.5)	13.2 (5.11-17.2)	<0.001
	No	20 (11)	161 (89)	1	
Pregestational DM	Yes	57 (41.9)	79 (58.1)	2.88 (1.07-7.77)	0.036
	No	19 (7.4)	237 (92.6)	1	
Concomitant medical disorders	One	51 (19.8)	207 (80.2)	1	
	Two	25 (51)	24 (49)	15.1 (6.32-22.28)	<0.001
	or more				

1: Reference category

was carried out at St. Paul's Hospital and Millennium Medical College. This is the first study to use a retrospective observational study in the hospital and throughout the nation in preeclampsia-risk women on low-dose aspirin. To the best of our knowledge, trials have comprised the majority of studies on this subject. The findings of this study will aid in identifying the problems with preeclampsia prevention and care. As a result, both at the institutional and national levels, the grave consequences of preeclampsia will be lessened.

The current study found that the prevalence of preeclampsia syndrome in women at high risk of preeclampsia after receiving low-dose aspirin was 19.4%. This finding was found to be higher as compared with the studies conducted in different areas where it was found to be 2.4% in a trial involving 11,976 women [23], 6.9% involving a total of 28,237 [10], and 8.2% in a trial involving 798 patients [16]. The differences could be attributed to the different study designs, as they are control trials, settings, socioeconomic position, and the level of low-dose aspirin adherence. This finding is almost comparable to the magnitude (18%) of preeclampsia found in a study involving 1,254 patients [24].

In this study, 7 variables were established to be predictors of preeclampsia syndrome. Maternal age was an important predictor specifically patients whose age was greater than or equal to 35 were high likely to develop preeclampsia than those who are less than 34 years of age. This is consistent with studies in Germany [25] and Pakistan [26]. This may be reinforced by the gradual deterioration of the cardiovascular system with advancing age. As we age, poor eating habits and reduced exercise, as well as impaired body's ability to process salt, lead to vascular disease [27]. Another reason may be that older patients tend to have additional risk factors such as obesity, diabetes, and chronic hypertension that make them more susceptible to preeclampsia.

Nulliparity was also significantly associated with a 12-fold increased risk of preeclampsia. In contrast to a systematic review and meta-analysis including 23,162 and 3,294 nulliparous women, which found no significant difference in the risk of preeclampsia among women receiving aspirin [28,29], in our study patients, who had no previous pregnancies were highly likely to develop preeclampsia than those who have previous pregnancies. The discrepancy may be because participants in both studies were healthy and had no risk factors. However, as with our findings, systematic reviews and meta-analyses consistently found that the most common predisposing factor for preeclampsia was nulliparity [30]. This conclusion may be supported by a possible explanation for immune maladaptation during pregnancy [31].

Late initiation of low-dose aspirin was significantly associated with a higher risk of preeclampsia than early initiation. A meta-analysis of 34 double-blind, randomized trials confirmed our findings, which showed significant benefits, especially when starting aspirin early [32]. This may be explained by the fact that aspirin can promote early implantation of the placenta [33].

Additionally, women who had pregestational diabetes had an increased risk of developing preeclampsia. Our conclusions are consistent with a study of 471 and 462 women with pre-gestational diabetes [34,35]. This association is biologically credible, as elevated blood glucose levels may increase the risk of preeclampsia by causing epithelial dysfunction and vasoconstriction [36,37].

Preeclampsia history increased the likelihood of developing the condition, which is in keeping with the findings of the majority of research [30,37,38]. Despite the onset of preeclampsia, the overall recurrence rate of preeclampsia was 64.5%. The highest rates of recurrent preeclampsia were found to be between 65% and 50% in another research, which is why this number is very consistent with them [39,40]. Although other studies found early onset second-trimester preeclampsia as a substantial risk factor, our study did not stratify each risk in each trimester of pregnancy, making the comparison somewhat challenging.

Consistent with many preceding studies, chronic hypertension was identified as a crucial predictor and the odds ratio was higher for preeclampsia [30,37,41,42]. It is generally known that decreased placental perfusion played a role in the development of preeclampsia, even if the exact pathophysiology of chronic hypertension in pregnant women is unclear. The preeclampsia rate in those with chronic hypertension was 26.5%. This finding was resembling the previous findings [41,43]. But it was much higher than the finding of the meta-analysis, 16% [30]. The contrast originated from the study design resulting in pooled results. In our study, it was problematic to discern the beneficial effect of low-dose aspirin contrary to the ASPRE trial [41]. As found in the ASPRE study, preeclampsia cannot be largely prevented because endothelial dysfunction and inflammation can occur in chronic hypertension even before pregnancy in the absence of severe placental dysfunction. The most important change is that our study used a similar cohort of women treated with low-dose aspirin.

Preeclampsia rates rose in tandem with the number of concurrent prior medical conditions (20% *vs.* 51%). The likelihood of developing preeclampsia in those who had two or more medical disorders was nearly fifteen times higher than in those having one medical disorder, and similar findings were witnessed in previous studies [30,43-45]. Concerning antiphospholipid antibody syndrome and chronic renal disease, there were too few cases and preeclampsia incidents for logistic regression, but they were incorporated into concomitant medical disorders.

Similar to a systematic review and meta-analysis of 92 cohort studies that considered the use of several effect sizes [30], our review showed antiphospholipid syndrome had the highest rate of preeclampsia (4/4, 100%), followed by age >35 (68.2%), history of preeclampsia (64.5%), two or more medical disorders (51%), pregestational diabetes (41.9%), nulliparity (41.5%), and chronic hypertension (26.5%).

Contrary to the literature currently available [11,37,41], assisted reproductive technology, previous bad obstetric outcomes (stillbirth), and multiple gestations were not significantly associated with preeclampsia in our cohorts controlling other confounders. The very small populations examined for each factor may have shown differences, which is the likely explanation. Age under 20 years old was not significantly linked to preeclampsia. Studies [46,47] on adolescence have produced contradictory findings. In our study, the sample size in this age range was limited in addition to the inconsistent outcomes.

Our careful review of records is a strength. The study showed novel results in a resource-limited setting like Ethiopia. To determine the level of resistance to low-dose aspirin, the review attempted to describe parallels between one medical disorder and many concomitant medical disorders. Regarding the limitations, this is a retrospective study. Numerous significant confounding variables, including treatment compliance, BMI, calcium supplements, aspirin dose variations, the length of pregestational diabetes and chronic hypertension, knowledge and attitudes concerning preeclampsia, and low-dose aspirin, could not be evaluated. Based on the onset of preeclampsia in previous pregnancies, we were unable to determine the risk of developing the condition. Variability in criteria for high risk of preeclampsia has been noted. A causal link between the independent and dependent variables could not be established because the study was cross-sectional. It is difficult to generalize from the study because it was restricted to one institution and used a small sample size. Last but not least, it was challenging to discover comparable studies both domestically and abroad, making comparisons with other studies challenging.

Conclusion and Recommendations

After using low-dose aspirin, preeclampsia syndrome was far more common in women at high risk for preeclampsia than in practically all clinical studies. Older maternal age nulliparity, history of preeclampsia, late initiation of low-dose aspirin, pregestational diabetes, chronic hypertension, and two or more preexisting medical conditions were found to be predictors of preeclampsia syndrome. The determinants of nulliparity, chronic hypertension, and the presence of two or more concurrent diseases greatly amplify the chance of preeclampsia. It is crucial to think about calcium supplements, at least for women who have several high-risk factors. Pre-conceptional optimization of pre-existing medical illnesses, early and routine prenatal care monitoring, and appropriate counseling of modifiable risk factors should all receive priority attention. Future researchers should focus on multicenter, large cohort, more robust, compliance-oriented comparative studies to determine the beneficial effects of low-dose aspirin.

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