ARTICLE

A 5-year review of preeclampsia screening in a tertiary private hospital in the Philippines: A retrospective cohort study

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ABSTRACT

Preeclampsia remains a significant cause of maternal and perinatal morbidity and mortality worldwide, contributing to about 76,000 maternal deaths and 150,000 perinatal deaths annually. Despite numerous studies on predictive factors and screening tests for preeclampsia, local consensus on the optimal strategy remains elusive. This study aimed to assess the predictive accuracy and detection rate of preeclampsia screening in a tertiary private hospital. A retrospective descriptive cohort study was conducted on pregnant patients who underwent preeclampsia screening from 2018 to 2022. Data analysis involved quantitative methods, assessing predictive accuracy and detection rates for preeclampsia onset at < 34, < 37, and < 40 weeks of gestation. Of the 156 subjects, 8.3% developed preeclampsia, with most cases exhibiting severe features (3.8%). Based on the onset, 3.8% were late-onset, 3.2% early-onset, and 1.2% postpartum. Chronic hypertension emerged as a significant risk factor. Predictive accuracy was highest for early-onset preeclampsia (<34 weeks), reaching 94.23%, while overall predictive accuracy across all gestational ages was 83.12%. Detection rate was also highest for early-onset preeclampsia (100%) but was noted to decrease in later onset specifically 75% and 25% for <37 weeks and <40 weeks, respectively. Aspirin prophylaxis was administered to screen-positive patients, resulting in a 75% reduction in preeclampsia development. This local study underscores the importance of preeclampsia screening, showcasing its strengths in detecting early-onset cases but also its limitations, particularly in identifying term preeclampsia. Compared to traditional tests relying on maternal factors, it demonstrated superior accuracy and higher detection rates, maximizing the benefits of aspirin prophylaxis.

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INTRODUCTION

Preeclampsia, a condition affecting pregnant women, is characterized by high blood pressure and proteinuria that may lead to organ dysfunction, such as renal insufficiency, liver involvement, neurological or hematological complications. This condition often leads to premature birth and is associated with substantial morbidity and mortality. Globally, preeclampsia affects approximately 2–8% of all pregnancies, resulting in about 76,000 maternal deaths. To address these challenges, there has been growing interest in utilizing screening methods to identify individuals at increased risk of developing preeclampsia. Several studies have contributed to preeclampsia screening and prediction, emphasizing the importance of early detection to initiate prevention and appropriate management (Chappell et al. 2021, Duley 2009, Mol et al. 2016, Townsend et al. 2019).

In order to achieve this, its pathophysiology should be understood. Mol et al. (2016) emphasized the role of placental

KEYWORDS

Preeclampsia, Preeclampsia screening, Predictive accuracy, Aspirin prophylaxis

dysfunction and abnormalities in maternal vascular adaptation. The review provided insights into the underlying mechanisms and potential targets for intervention. Numerous studies have also mentioned that a combination of clinical factors, serum biomarkers, and ultrasound Doppler can aid in the prediction of preeclampsia. However, its clinical significance in our local setting is yet to be evaluated in properly designed intervention studies, wherein independent and external validation of prediction models are rare.

English et al. (2015) explored the risk factors and effective management strategies for preeclampsia. They discussed the role of factors such as maternal age, obesity, and previous history of preeclampsia, and highlighted the importance of individualized care for high-risk women. However, the clinical assessment of the risk of preeclampsia which relies primarily on maternal history such as screening proposed by the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE), exhibits limited predictive ability. Evidence showed that preeclampsia screening based on NICE achieves detection rates of 41% for preterm and 34% for term preeclampsia, with a 10% false positive rate. Likewise, screening based on ACOG has detection rates of 5% for preterm and 2% for term preeclampsia, with a 0.2% false positive rate. Therefore, both showed suboptimal performance. Whereas, a combination of markers (clinical characteristics, serum biomarkers, ultrasound Doppler and mean arterial pressure), as proposed by The Fetal Medicine Foundation (FMF), displayed higher predictive accuracy and detection rate as shown by validation tests. This is also called the FMF triple test, the algorithm of which has already been adapted clinically in various countries, such as in this research study. The FMF triple test has a detection rate of 90% for early-onset preeclampsia and 75% for preterm preeclampsia, with a 10% false positive rate. This screening test is therefore superior to the traditional approach based solely on maternal risk factors. Various first-trimester prediction models have been developed, but most have not undergone or have failed external validation. The FMF triple test prediction model, on the other hand, has successfully undergone both internal and external validation (Chaemsaithong et al. 2022).

Despite a thorough examination of literature from various international sources, local studies exploring the predictive accuracy of this screening test in pregnant patients are few. In the country, only two institutions provide preeclampsia screening using the FMF algorithm. This screening test is also more costly compared to its traditional counterpart. Thus, this research seeks to fill this gap and contribute to the body of knowledge in maternal and fetal health within the local context. The ultimate aim is to enhance prenatal care practices and optimize outcomes for both mothers and infants.

The main objective of this study was to investigate the predictive accuracy of preeclampsia screening in the local setting. Its specific aims were to first describe the demographic and clinical characteristics of the study population; second, to determine the prevalence of preeclampsia in the study population; third, to determine the predictive accuracy of preeclampsia screening in patients developing preeclampsia < 34 weeks, < 37 weeks, and < 40 weeks of gestation in terms of sensitivity, specificity, positive predictive value and negative predictive value, and likelihood ratio; and fourth, to determine the detection rate of preeclampsia screening.

MATERIALS AND METHODS

Study Population

This is a retrospective, descriptive cohort study that included all pregnant patients between 11 and 13 6/7 weeks of gestation who underwent preeclampsia screening between 2018 to 2022 at a tertiary private hospital in the Philippines. Exclusion criteria were as follows: patients with incomplete medical records and charts, patients who transferred to another medical facility, and patients who were minors. A total of 275 patients underwent preeclampsia screening. Among these, 156 fit the study criteria and were included for analysis.

Study setting, clinical assessment, laboratory and ultrasound parameters

Preeclampsia screening was offered to all pregnant patients between 11 and 13 6/7 weeks of gestation seen at the Women's Health Care Unit at a tertiary private hospital in the Philippines.

The subjects were interviewed regarding their medical, obstetric, and social history, and other clinical characteristics pertinent to the development of preeclampsia. Height, weight, and body mass index (BMI) were recorded. Proper blood pressure (BP) measurement was done as per standardized protocol - sitting posture with their back resting against the seat, their arms supported at the level of the heart, and legs uncrossed (English et al. 2015). The Mean Arterial Pressure (MAP) was then calculated by dividing the sum of the systolic and twice the diastolic blood pressure by three. Maternal serum concentrations of Pregnancy-associated Plasma Protein A (PAPP-A) and Placental Growth Factor (PlGF) were taken in the institution's laboratory using an automated immunoanalyzer - BRAHMS KRYPTOR Analyzer (Thermo Fisher Scientific). Ultrasound measurements, including Doppler studies of the Uterine Artery Pulsatility Index (UtA-PI), were performed by perinatologists adhering to standardized protocols. All of these data were then entered into a risk calculation software that integrates the FMF triple test, called the BRAHMS Fast Screen Pre I Plus Software Version 3.0.0.6. In this software, measured values of MAP, UtA-PI, PAPP-A and PlGF were automatically converted to multiples of the median (MoM) in order to adjust for those characteristics found to provide a substantive contribution to the log10 transformed value (Shen et al. 2021). The risk is subsequently calculated; the cut-off varies per individual. Results would show high risk (screen positive) or low risk (screen negative) per onset of preeclampsia at < 34 weeks, < 37 weeks, and < 40 weeks of gestation.

The presence or absence of preeclampsia was subsequently determined as well as the onset. ACOG (2019) defined Preeclampsia as having systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg on at least two occasions 4 hours apart after 20 weeks of gestation in a previously normotensive woman, and proteinuria: urinary albumin ≥300 mg/24 hours urine collection, spot urine protein creatinine ratio ≥0.3, or dipstick reading 1+. Preeclampsia was also divided into with and without severe features. Severe features include: SBP ≥160 mm Hg, or DBP ≥110 mmHg on two occasions at least 4 hours apart, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache unresponsive to medication and visual disturbances. Diagnosis may also be done even in the absence of proteinuria, but with the presence of severe features. For women with chronic hypertension, superimposed preeclampsia was a significant increase in BP compared with baseline (30 mmHg systolic, 15 mmHg diastolic) in association with new-onset proteinuria. Preeclampsia is also classified into early-onset and late-onset, contingent upon the

gestational age at the point of diagnosis. Early preeclampsia manifests prior to 34 weeks of gestation, while late preeclampsia is diagnosed at or beyond 34 weeks of gestation. Postpartum preeclampsia is defined as preeclampsia occurring within 48 hours of childbirth, but can also develop up to 6 weeks or later. Aspirin intake and details of delivery such as gestational age at delivery, birth weight, APGAR scores, and mode of delivery, were gathered.

Outcome measurements

The following outcomes were determined: demographic and clinical characteristics of the study population, prevalence of preeclampsia in the study population, predictive accuracy of the preeclampsia screening based on the onset, and its detection rate.

Statistical Analysis

Frequency and Distribution Percentage, and Mean and Standard Deviation. Descriptive statistics were performed. Continuous data were presented as mean (standard deviation, SD). Categorical data were presented as number(%). Comparisons between the groups were performed using either unpaired t-test or Chi square test. Statistical significance was set at $p<0.05$.

Sensitivity and Specificity, Positive and Negative Predictive Values, and Likelihood Ratios. These tests were used to quantify the predictive accuracy of preeclampsia screening in developing preeclampsia at < 34 weeks, < 37 weeks, and < 40 weeks of gestation.

Detection Rate. Detection rate was equivalent to the sensitivity. This was then adjusted to take account for the effect of aspirin. There was a 30% increase in the true positives, considering that low dose aspirin reduces risk of preeclampsia by 30% as shown in other studies (Wang et al. 2022).

Ethical Considerations

The research protocol underwent both technical and ethics review within the department. After which, this was approved by the Institutional Ethics Review Committee (IERC) and Institutional Scientific Review Committee (ISRC) of the institution. The study was implemented only after the approval of the protocol. The study involved chart review thus no patient contact was made. Strict observance of the confidentiality of patients' records was done. All identifying information was removed. Each patient was assigned a control number. Only the data pertinent to the objectives of the study were extracted from the medical records of the qualified patients and recorded on the patient data collection form.

RESULTS

A total of 275 pregnant patients underwent preeclampsia screening from 2018-2022 at a tertiary private hospital. Following the application of inclusion and exclusion criteria, 156 subjects were eligible and included in this study.

The baseline demographics and clinical characteristics of the study population were shown in Table 1.1. The mean maternal age was 34.5 years with standard deviation (SD) of 4.0 years. This suggests that the study population consisted of pregnant patients who were, on average, in their mid-thirties, with relatively low variability in age. All participants belonged to the Asian race, indicating a homogeneous racial composition. The mean maternal weight and height were 63.5 kg and 158.2 cm, respectively. Based on the Asia-Pacific classification, the distribution of BMI categories showed a significant proportion classified as obese (44.2%), followed by normal weight (34%), overweight (17.3%), and underweight (4.5%). The mean gestational age at screening was 12 5/7 weeks. Majority of pregnancies occurred spontaneously (96.2%), with a small percentage utilizing assisted reproductive technologies specifically in vitro fertilization (IVF) (3.8%). Roughly equal proportions of participants were nulliparous (52.6%) and multiparous (47.4%). The vast majority of pregnancies involved a single fetus (98.7%), with a small percentage involving multiple fetuses (1.3%). None of the participants reported a history of smoking, and the majority had no history of previous preeclampsia (95.5%). Fifty subjects (32.1%) reported aspirin intake during pregnancy.

Table 1.1: Baseline demographic and clinical characteristics of study population *(n=156)*.

VARIABLE	MEAN (SD) OR N (%)
Maternal Age in years	34.5 (4.0)
Racial origin - Asian	156 (100%)
Maternal Weight in kg	63.5 (13.6)
Maternal Height in cm	158.2 (5.9)
Body Mass Index based on Asia-Pacific Classification in kg/m^2	
Underweight	7 (4.5%)
Normal	53 (34%)
Overweight	27 (17.3%)
Obese	69 (44.2%)
Gestation age at screening (weeks)	12 weeks 5 days (0.8)
Conception	
Spontaneous	150 (96.2%)
Assisted (IVF)	6 (3.8%)
Obstetric History	
Nulliparous	82 (52.6%)
Multiparous	74 (47.4%)
Number of fetus	
Singleton	154 (98.7%)
Multifetal	2 (1.3%)
Smoking history	
Yes	0
No	156 (100%)
History of previous preeclampsia	
None	149 (95.5%)
Yes	7 (4.5%)

Medical History	
Hypertension	15 (9.6%)
a. Chronic	11 (73.3%)
b. Gestational	4 (26.7%)
Diabetes Mellitus	47 (30.1%)
a. Pre-gestational	0
b. Gestational	44 (93.6%)
c. Overt	3 (6.4%)
Renal disease	1 (0.6%)
Autoimmune disease	22 (14.1%)
a. SLE	1 (4.5%)
b. APAS	19 (86.4%)
c. Others	13 (59.1%)
Advanced maternal age	40 (25.6%)
Thyroid disease	15 (9.6%)
a. Hyperthyroidism	3 (20%)
b. Hypothyroidism	12 (80%)
Heart disease	2 (1.3%)
Liver disease	2 (1.3%)
Bronchial asthma	9 (5.8%)
Infertility	8 (5.1%)
a. Primary	5 (62.5%)
b. Secondary	3 (37.5%)
Vitamin D Deficiency	5 (3.2%)
Recurrent Pregnancy Loss	5 (3.2%)
Aspirin intake during pregnancy	50 (32.1%)
Age of gestation delivered in weeks	38 weeks (2.2)
Term	135 (86.5%)
Preterm	21 (13.5%)
5 minute APGAR Score	
Reassuring (7-10)	155 (99.4%)
Low (</= 6)	1 (0.6%)
Birth weight in grams	2965 (615.4)
Size for gestational age	
AGA	139 (89.1%)
SGA	4 (2.6%)
LGA	13 (8.3%)
Mode of delivery	
CS	103 (66%)
NSD	44 (28.2%)
Vacuum	8 (5.1%)
VBAC	1 (0.6%)
Components of Preeclampsia screening	
PAPP-A (MoM)	1.12 (0.7)
PlGF (MoM)	1.02 (0.4)
UtA-PI (MoM)	1.68 (6.8)
MAP (mmHg)	85.64 (15.1)
Screen Positive (High risk)	29 (18.6%)
Screen Negative (Low risk)	127 (81.4%)

Forty seven patients (30.1%) had Diabetes Mellitus, with the majority having gestational diabetes (93.6%) and a small percentage having overt diabetes (6.4%). Fifteen patients (9.6%) had hypertension, with the majority having chronic hypertension (73.3%), compared to gestational hypertension (26.7%). Autoimmune diseases, including systemic lupus erythematosus (SLE), anti-phospholipid antibody syndrome (APAS), and other reproductive immune disorders, were seen in 14.1% of participants. Thyroid disease was noted in 9.6% of participants, with hyperthyroidism and hypothyroidism present in 20% and 80% of cases, respectively. The remaining medical conditions identified were: bronchial asthma (5.8%), infertility (5.1%), vitamin D deficiency (3.2%), recurrent pregnancy loss (3.2%), heart disease (1.3%), liver disease (1.3%), and renal disease (0.6%).

The average age of gestation at delivery was 38 weeks with 86.5% resulting in term births and 13.5% in preterm births. All newborns had reassuring 5-minute APGAR Scores (APGAR score 7-10), except for 1 newborn (0.6%) who had a low score (≤ 6). The average birth weight was 2965 grams. Most newborns (89.1%) were appropriate for gestational age (AGA), while 13 (8.3%) were large for gestational age (LGA) and 4 (2.6%) were small for gestational age (SGA). Cesarean section (CS) was the most common mode of delivery, accounting for 66% (103) of births, followed by Normal Spontaneous Delivery (NSD) at 28.2% (44), vacuum extraction at 5.1% (8), and Vaginal Birth after Cesarean Section (VBAC) at 0.6% (1).

The mean values of the components of preeclampsia screening were as follows: PAPP-A: 1.12 MoM (SD = 0.7), PlGF: 1.02 MoM (SD = 0.4), UtA-PI: 1.68 MoM (SD = 6.8), and MAP: 85.64 mmHg (SD = 15.1). The results of screening showed that there were 29 (18.6%) classified as screen positive (high risk), while 127 (81.4%) were screen negative (low risk).

In the comparison between the demographic and clinical characteristics of those with preeclampsia and without preeclampsia, there was no significant difference between the two groups in most of the clinical characteristics including age,

BMI, mode of conception, parity, history of previous preeclampsia, and other medical conditions, except for the history of hypertension, specifically chronic hypertension (Table 1.2). Chronic hypertension was noted to be associated with the development of preeclampsia (30.8% vs 7.7%, p=0.024). In terms of delivery outcome, preterm delivery was more likely among women with preeclampsia (p=0.009), and birth weight was also significantly lower (2490g vs 3008.2g, p=0.004). Likewise, there was a higher percentage of newborns that were SGA as compared to those without preeclampsia (23.1% vs 0.7%, p= 0.004). Both groups had the highest percentage of CS as mode of delivery. Among the components of preeclampsia screening, the serum marker PlGF was noted to be significantly lower in the preeclampsia group (mean 0.74, p=0.015). However, there was no significant difference in the values of PAPP-A, UtA-PI, and MAP between the two groups.

Table 1.2: Baseline demographic and clinical characteristics by Preeclampsia status

VARIABLE	MEAN (SD) OR N (%)		P value
	WITHOUT PREECLAMPSIA *(n=143)*	WITH PREECLAMPSIA *(n=13)*	
Maternal Age in years	34.5 (4.1)	34.6 (3.2)	0.910*
Racial origin - Asian	143 (100%)	13 (100%)	*Cannot test association one variable is constant*
Maternal Weight in kg	63.7 (13.6)	61.5 (13.3)	0.585*
Maternal Height in cm	158.1 (5.8)	159.2 (7.4)	0.517*
Body Mass Index based on Asia-Pacific Classification in kg/m^2			
Underweight	5 (3.5%)	2 (15.4%)	0.220 †
Normal	49 (34.3%)	4 (30.8%)	
Overweight	24 (16.8%)	3 (23.1%)	
Obese	65 (45.5%)	4 (30.8%)	
Gestation age at screening (weeks)	12 weeks 5 days (0.8)	12 weeks 4 days (0.7)	0.297*
Conception			
Spontaneous	138 (96.5%)	12 (92.3%)	0.412 †
Assisted (IVF)	5 (3.5%)	1 (7.7%)	
Obstetric History			
Nulliparous	73 (51.0%)	9 (69.2%)	0.209 †
Multiparous	70 (49.0%)	4 (30.8%)	
Number of fetus			
Singleton	142 (99.3%)	12 (92.3%)	0.160 †
Multifetal	1 (0.7%)	1 (7.7%)	
Smoking history			
Yes	0	0	*Cannot compute association since 1 variable is constant*
No	143 (100%)	13 (100%)	
History of previous preeclampsia			
None	138 (96.5%)	11 (84.6%)	0.106 †
Yes	5 (3.5%)	2 (15.4%)	
Medical History			
Hypertension	11 (7.7%)	4 (30.8%)	
a. Chronic	7 (63.6%)	4 (100%)	**0.024 †**
b. Gestational	4 (36.4%)	0 (0%)	
Diabetes Mellitus	44 (30.8%)	3 (23.1%)	0.410 †
a. Pre-gestational	0	0	
b. Gestational	41 (93.2%)	3 (100%)	
c. Overt	3 (6.8%)	0	
Renal disease	1 (0.7%)	0	0.917 †
Autoimmune disease	22 (15.4%)	0	0.127 †
a. SLE	1 (4.5%)	0	
b. APAS	19 (86.4%)	0	
c. Others	13 (59.1%)	0	
Advanced maternal age	34 (23.8%)	6 (46.2%)	0.080 †
Thyroid disease	15 (10.5%)	0	0.254 †
a. Hyperthyroidism	3 (20%)	0	
b. Hypothyroidism	12 (80%)	0	
Heart disease	2 (1.4%)	0	0.840 †
Liver disease	2 (1.4%)	0	0.840 †
Bronchial asthma	9 (6.3%)	0	0.447 †
Infertility	7 (4.9%)	1 (7.7%)	0.510 †
a. Primary	4 (57.1%)	1 (100%)	
b. Secondary	3 (42.9%)	0	
Vitamin D Deficiency	5 (3.5%)	0	0.643 †
Recurrent Pregnancy Loss	5 (3.5%)	0	0.643 †
Aspirin intake during pregnancy	43 (30.1%)	7 (53.8%)	0.77 †

Age of gestation delivered in weeks	38 weeks 1 day (2.1)	36 weeks 4 days (2.4)	**0.009***
Term	126 (88.1%)	9 (69.2%)	0.056 †
Preterm	17 (11.9%)	4 (30.8%)	
5 minute APGAR Score			
Reassuring (7-10)	142 (99.3%)	13 (100.0%)	0.917 †
Low (</= 6)	1 (0.7%)	0	
Birth weight in grams	3008.2 (572.4)	2490 (865.5)	**0.004***
Size for gestational age			
AGA	130 (90.9%)	9 (69.2%)	**0.004 †**
SGA	1 (0.7%)	3 (23.1%)	
LGA	12 (8.4%)	1 (7.7%)	
Mode of delivery			
CS	92 (64.3%)	11 (84.6%)	0.293 †
NSD	43 (30.1%)	1 (7.7%)	
Vacuum	7 (4.9%)	1 (7.7%)	
VBAC	1 (0.7%)	0	
Components of Preeclampsia screening			
PAPP-A (MoM)	1.14 (0.7)	0.94 (0.6)	0.293*
PlGF (MoM)	1.05 (0.4)	0.74 (0.3)	**0.015***
UtA-PI (MoM)	1.73 (7.1)	1.09 (0.2)	0.745*
MAP (mmHg)	85.7 (13.6)	85.3 (27.4)	0.958*

*Statistical tests used: * - unpaired T test, † - chi square test*
Bold text – significant at p < 0.05

The prevalence of preeclampsia in the study population was 8.3%, with different classifications reflecting the severity and complexity of the condition (Table 2). Preeclampsia with severe features remained the most prevalent (3.8%), followed by chronic hypertension with superimposed preeclampsia (2.6%) and preeclampsia without severe features (1.9%). Based on the onset, the majority (3.8%) were late onset (≥ 34 weeks) and 3.2% were early onset (< 34 weeks), while 1.3% occurred in the postpartum period.

Table 2: Prevalence of Preeclampsia in the study population *(n=156)*.

	Prevalence
All Preeclampsia	13 (8.3%)
Preeclampsia without severe features	3 (1.9%)
Preeclampsia with severe features	6 (3.8%)
Chronic hypertension with superimposed preeclampsia	4 (2.6%)
Based on the onset	
Early-onset (<34 weeks of gestation)	5 (3.2%)
Late-onset (>/=34 weeks of gestation)	6 (3.8%)
Postpartum	2 (1.3%)

The screening performance of the test was shown in Table 3. The highest sensitivity was recorded at 100% for preeclampsia with onset < 34 weeks of gestation. The sensitivity was noted to decrease as gestational age advanced with values 66.67% and 0% for < 37 weeks, and < 40 weeks of gestation, respectively. The specificity and negative predictive value (NPV) were consistently high across all gestational ages. On the other hand, there was a decreasing trend in positive predictive values (PPV) as gestational age progressed, similar to the trend in sensitivity. The predictive accuracy was high for all gestational cutoffs, with values 94.23% for < 34 weeks, 84.77% for < 37 weeks, and 89.86% for < 40 weeks of gestation. This indicated that the predictive accuracy of the screening test was highest for early-onset preeclampsia as compared to those with late-onset. Overall, the predictive accuracy across all gestational ages was 83.12%.

In this analysis, the detection rate was equivalent to sensitivity, which is the proportion of affected individuals with a screen positive (high risk) result. For early-onset preeclampsia, the detection rate was remarkably high at 100%. This rate decreased for later onset cases (66.67% for those occurring before 37 weeks), and 0% for term preeclampsia. Considering the effect of aspirin, a recomputation of detection rates was done. This resulted in an increase in the detection rates - 100%, 75%, and 25% for < 34 weeks, < 37 weeks, and <40 weeks of gestation, respectively. In terms of preterm versus term preeclampsia, the detection rates were 90.91% and 25%, respectively, with a false positive rate of 16.08%.

Adjusting the true positive rate to account for the effect of aspirin prophylaxis may provide a more accurate reflection of the performance of the screening test in the presence of this intervention. This adjustment ensures that the detection rate accounts for both the natural occurrence of preeclampsia and any preventive measures, such as aspirin prophylaxis, that may affect its incidence. Especially in this study, wherein most of the screen positive patients (96.6%) were prescribed aspirin, except for one patient with a known allergy to the drug. Among the screen positive group with aspirin intake, 75% did not develop preeclampsia which was significantly higher than those who did (25%) (Table 5). A total of 50 subjects took aspirin, and among these, 21 belonged to the screen negative (low risk) group. Reasons for aspirin intake despite the low-risk result were as follows: history of APAS and/or other reproductive immune disorders, history of chronic hypertension, and history of previous preeclampsia. The dosage of aspirin used varied from 80-160mg per day.

DISCUSSION

Preeclampsia is a multifaceted condition that affects various organ systems during pregnancy, manifesting after the 20th week of gestation. It is characterized by the sudden onset of high blood pressure accompanied by significant proteinuria. Globally, the prevalence of preeclampsia ranges from 2% to 8%, contributing significantly to maternal and perinatal morbidity and mortality. Annually, an alarming number of mothers, approximately 76,000, and a substantial number of infants, around 500,000, face mortality due to this condition. It also accounts for 15% of all premature deliveries (Duley 2009, English et al. 2015). In this study, the prevalence of preeclampsia was higher at 8.3%, with the majority of cases having severe features. This emphasizes the importance of detecting and preventing preeclampsia due to its deleterious effects on both mother and fetus.

The pathophysiology of preeclampsia involves elevated blood pressure and organ dysfunction, with manifestations such as hypertension, proteinuria, liver dysfunction, renal insufficiency, and coagulation abnormalities. If left untreated, preeclampsia can progress to eclampsia, a life-threatening condition marked by seizures. Although the exact cause of preeclampsia remains unclear, it is believed to stem from abnormal placental development and function from impaired spiral arteriole remodeling, resulting in systemic inflammation and vascular dysfunction. Some suggest that this might be triggered by an altered maternal immune response or a defective development of maternal tolerance to the allogenic fetus. Endothelial damage leads to widespread organ dysfunction and systemic effects, contributing to the clinical features of the disorder. Insufficient uteroplacental perfusion can then result in fetal growth restriction (FGR) or placental abruption, potentially leading to preterm delivery or stillbirth. Offspring born to mothers with preeclampsia are also vulnerable to medium- and long-term consequences, including neurodevelopmental impairment, insulin resistance, diabetes mellitus, coronary heart disease, and hypertension (Chappell et al. 2021, Mayrink et al. 2018). Indeed, the results of this study showed that patients diagnosed with preeclampsia were more likely to deliver preterm compared to those without preeclampsia. A higher percentage of SGA newborns was also seen. This only reiterates the fetal effects of preeclampsia on patients due to placental insufficiency.

Table 3: Predictive accuracy of Preeclampsia screening in pregnant patients developing preeclampsia <34 weeks, <37 weeks, and <40 weeks of gestation

Statistic	<34 weeks	<37 weeks	<40 weeks	Overall
Sensitivity	100.00%	66.67%	0.00%	72.73%
Specificity	94.04%	85.14%	91.72%	83.92%
PPV	35.71%	8.33%	0.00%	25.81%
NPV	100.00%	99.21%	97.79%	97.56%
Accuracy	94.23%	84.77%	89.86%	83.12%
LR+	16.78	4.48	0.00	4.52
LR-	0.00	0.39	1.09	0.32
Disease prevalence	3.21%	1.99%	2.03%	7.14%

LR+, Positive Likelihood Ratio; LR-, Negative Likelihood Ratio; PPV, Positive Predictive Value; NPV, Negative Predictive Value

Table 4.1: Detection rate of preeclampsia screening based on onset (<34 weeks, <37 weeks, and <40 weeks of gestation)

Preeclampsia Screening	Detection rate (%)		False positive rate
	Initial	Adjustment for effect of Aspirin	
< 34 weeks	100%	100%	6%
< 37 weeks	66.67%	75%	14.86%
< 40 weeks	0%	25%	8.28%
Overall detection rate	72.73%	78.57%	16.08%

Table 4.2: Detection rate of preeclampsia screening based on onset (early vs late)

Preeclampsia Screening	Detection rate (%)		False positive rate
	Initial	Adjustment for effect of Aspirin	
Early-onset preeclampsia	100%	100%	6%
Late-onset preeclampsia	33.33%	42.86%	11.60%
Overall detection rate	72.73%	78.57%	16.08%

Table 4.3: Detection rate of preeclampsia screening based on onset (preterm vs term)

Preeclampsia Screening	Detection rate (%)		False positive rate
	Initial	Adjustment for effect of Aspirin	
Preterm preeclampsia	87.5%	90.91%	10.37%
Term preeclampsia	0%	25%	8.28%
Overall detection rate	72.73%	78.57%	16.08%

Table 5: Development of Preeclampsia in patients with Aspirin intake

Aspirin Intake	Without preeclampsia	With preeclampsia	P value
Total (n=50)	43 (86%)	7 (14%)	**0.003***
Screen Positive (n=28)	21 (75%)	7 (25%)	
Screen Negative (n=22)	22 (100%)	0	

*Chi square test, significant at $p < 0.05$

The early identification of women at high risk for preeclampsia is crucial for timely intervention and management. With reliable risk prediction for preeclampsia, interventions to prevent preeclampsia become more important. Aspirin is the drug of choice for the prevention of preeclampsia, based on the findings of a meta-analysis that showed a moderate benefit of aspirin. The mechanism by which aspirin prevents preeclampsia remains unclear. Proposed theories suggest that it may enhance placental implantation and protect the maternal vasculature by reducing platelet reactivity, lowering thromboxane concentrations, and augmenting prostacyclin production (Mol et al. 2016, Chappell et al. 2021). In a study by Rolnik et al. (2017), low dose aspirin at 150 mg daily administered to high risk women from < 16 weeks until 36 weeks' gestation has been shown to reduce the rate of preterm preeclampsia by 62%. In another systematic review and meta-analysis by Wang et al. (2022), aspirin reduced the incidence of preeclampsia by 30% in the general population. In this study, aspirin was noted to reduce preeclampsia by 75% among the screen positive group. This is higher than the reduction rates in previous research studies. There is no

consensus on the dose of aspirin prophylaxis, with no randomized trials comparing different aspirin doses. However, different bodies have recommended the following dosages: ACOG - 81mg initiated between 12 and 28 weeks of gestation, ideally before 16 weeks; NICE - 75–150mg from 12 weeks; and the International Federation of Obstetrics and Gynecology (FIGO) - 150mg at night initiated between 11 and 14 weeks (+6 days) gestation (Chappell et al. 2021).

Several organizations, such as the ACOG and the NICE, have advocated for preeclampsia screening based on maternal risk factors. As per NICE guidelines, women should be considered high-risk if they have any one high-risk factor or any two moderate-risk factors. High risk factors include previous preeclampsia or hypertension in pregnancy, chronic kidney disease, hypertension, diabetes (type 1 or type 2), and autoimmune disorders, including SLE or APAS. Moderate risk factors are first pregnancy, age 40 years or more, a pregnancy interval greater than 10 years, BMI 35 kg/m² or more, polycystic ovarian syndrome, family history of preeclampsia, and multiple pregnancy. In 2013, the ACOG recommended aspirin for women with a history of early-onset preeclampsia and preterm delivery at less than 34 weeks of gestation, or for women with more than one prior pregnancy complicated by preeclampsia (Mol et al. 2016, Chappell et al. 2021). However, evidence indicated that preeclampsia screening based on NICE and ACOG guidelines exhibited suboptimal performance. Specifically, the NICE recommendation yielded detection rates of only 41% and 34%, with a 10% false-positive rate (FPR), for preterm and term preeclampsia, respectively. While the ACOG screening demonstrated detection rates of merely 5% and 2% for preterm and term preeclampsia, respectively, with a 0.2% FPR (Chaemsaithong et al. 2022).

On the other hand, the FMF developed first trimester screening test utilized a combination of clinical factors and measurements of MAP, ultrasound markers such as UtA-PI, and serum biochemical markers such as PlGF and PAPP-A. The FMF triple test had detection rates of 90%, 75% and 41% for early, preterm and term preeclampsia, respectively, with a 10% FPR. Using the same screening method and risk cut-off among women of Afro-Caribbean descent, the detection rates for early, preterm, and term preeclampsia were at 100%, 92%, and 75%, respectively (Tan et al. 2018). Consequently, Poon and Nicolaides (2014) published a research using the FMF logistic regression model wherein the detection rate was 95% for early onset preeclampsia with a 10% FPR. This combined screening test is the only model with successful external validation, and was found to be more superior to traditional methods based on maternal risk factors alone (Townsend et al. 2019, Chaemsaithong et al. 2022).

In our local setting, a study from another tertiary private hospital compared the diagnostic accuracy of early screening for preeclampsia by NICE guidelines, ACOG guidelines, and comprehensive first trimester screening which showed accuracies of 76.73%, 43.07%, and 89.6%, respectively. The comprehensive first trimester screening, which integrated the FMF triple test, was superior to both the methods advocated by ACOG and NICE. The software used for risk calculation was LifeCycle software from PerkinElmer Life and Analytical Sciences. Screening was further divided into early-onset and late-onset preeclampsia which showed accuracy of 97.52% and 85.15% respectively (Gonzaga and Javier 2018).

Identification of effective biochemical markers for preeclampsia relies on the etiopathogenic factors discussed earlier. PAPP-A and PlGF are proteins both produced by trophoblasts. PAPP-A is a syncytiotrophoblast-derived, insulin-like growth factor binding protein protease believed to play an important role in placental growth and development. PlGF is a member of the vascular endothelial growth factor (VEGF) family and is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries. Research indicates that analyzing both PAPP-A and PlGF levels can offer useful predictive insights into the likelihood of developing preeclampsia, wherein decreased levels likely indicate compromised placental function (Park et al. 2015, Antwi et al. 2018). Chappell et al. (2013) noted that PlGF at a threshold of 100 pg/mL has a sensitivity of 96% for a diagnosis of preeclampsia within 14 days. In the ASPRE trial by Shen et al. (2021), low PlGF concentration < 0.712 MoM, compared to PlGF ≥ 0.712 MoM, is associated with development of preterm preeclampsia with delivery at < 37 weeks' gestation despite aspirin prophylaxis. Likewise, in this research study, the PlGF in the preeclampsia group was significantly lower (mean = 0.74 MoM) as compared to those without preeclampsia (mean = 1.05 MoM). This supported the assertion that low-circulating PlGF in pregnancy is an effective biomarker for poor placental function.

Another serum biomarker implicated is the soluble fms-like tyrosine kinase-1 (sFlt-1) which is an anti-angiogenic factor that binds to the functional receptor binding domain of VEGF; increased concentrations are thought to increase preeclampsia risk. However, studies showed that sFlt-1 levels at 11-13 weeks were not significantly different between women who subsequently developed preeclampsia and women who did not develop preeclampsia (Chaiyasit et al. 2022). This may be more useful in preeclampsia screening in the second and third trimesters, as seen in the study of Zeisler et al. (2016) wherein sFlt-1 to PlGF ratio of 38 or lower in pregnant patients between 24 to 36 6/7 weeks of gestation had an 80.0% sensitivity and NPV of 99.3% for detecting preeclampsia in the subsequent 7 days.

Women who later developed preeclampsia exhibited elevated SBP and MAP prior to the clinical manifestation of symptoms. A meta-analysis conducted in 2008, encompassing over 60,000 women with 3300 cases of preeclampsia, demonstrated that MAP proved to be a more reliable predictor of preeclampsia among low-risk women during the first or second trimester compared to either systolic or diastolic readings alone (Cnossen et al. 2008). UtA-PI is a Doppler ultrasound measurement that assesses the blood flow resistance in the uterine arteries. Abnormal UtA-PI values have been associated with an increased risk of preeclampsia (Pedroso et al. 2018). This increased resistance likely reflects high downstream resistance due to defective differentiation of trophoblasts with resulting defective invasion of spiral arteries and failure of these vessels to transform into low-resistance vessels. Although the use of UtA-PI solely has high specificity, it has low sensitivity in predicting early-onset preeclampsia. This only suggests that the predictive value of the markers if used alone is low, and that the combination of these as seen in the FMF triple test is more superior (Townsend et al. 2019).

From the results of this study, the only risk factor noted to be associated with preeclampsia was chronic hypertension. Other variables such as age, BMI, parity, previous history of preeclampsia, and medical conditions like diabetes and autoimmune diseases, showed no significant difference in those with and without preeclampsia. It was also noted that PlGF in those with preeclampsia was significantly lower than those who did not develop the condition. On the other hand, there was no significant difference in the values of PAPP-A, UtA-PI and MAP. However, comparing the variables between the two groups might not be significant since external variables such as aspirin intake, which can reduce the risk of preeclampsia, were not controlled.

The primary goal of most screening tests is to decrease morbidity or mortality within the screened population by detecting diseases early, in this case, enabling a prompt initiation of aspirin prophylaxis. Thus, having a high detection rate is important. It was determined based on this study that the predictive accuracy of preeclampsia screening using FMF triple test was notably high, reaching 94.23% for < 34 weeks, 84.77% for < 37 weeks, and 89.86% for < 40 weeks of gestation. The detection rate was excellent at 100% for early-onset preeclampsia, however, was noted to decline with later onset (75% in < 37 weeks, and 25% in < 40 weeks). The false positive rate was also lowest for early-onset (6%). The specificity and NPV were high across all gestational ages, which indicated that the screening test was effective at correctly identifying individuals who were not likely to develop preeclampsia. However, the PPV results were quite low, which means that there may be a significant risk of false positives. Overall, compared to other screening methods available such as ACOG and NICE guidelines, preeclampsia screening through FMF triple test still had a higher accuracy and higher detection rate, most especially in early-onset preeclampsia which was associated with higher maternal and fetal complications. Despite both types of preeclampsia potentially impacting maternal health, early-onset preeclampsia was associated with an increased risk of maternal morbidity, neonatal morbidity, and perinatal mortality in comparison to late-onset preeclampsia. Furthermore, early-onset preeclampsia is more likely to result in premature birth, underscoring the urgency of its diagnosis and management (Chaemsaithong et al. 2022).

An increasing amount of evidence indicates distinctions between early-onset and late-onset preeclampsia regarding their pathophysiological features. Some studies proposed that early-onset preeclampsia is predominantly linked to intrinsic placental factors involving incomplete spiral artery remodeling due to immune maladaptation, whereas, late-onset preeclampsia is more closely associated with maternal predisposing factors rather than significant placental involvement (Li et al. 2016). A mixed placental–maternal disease may still be a feature in late-onset disease, but with a smaller placental component (Staff et al. 2013). In a review by Burton et al. (2019), the authors stated that early-onset preeclampsia arises owing to defective placentation, while late-onset preeclampsia may center around interactions between normal senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease (metabolic syndrome). In late-onset preeclampsia, the main drivers seem to be increased maternal body mass index (BMI), increased gestational weight gain (GWG), and other clinical characteristics composed of metabolic syndrome and maternal age (Robillard et al. 2022). It is also thought that in late onset cases, placental growth reaches its limits at term resulting in diminishing villous pore size impeding intervillous perfusion and increasing oxidative stress (English et al. 2015). This could explain the profound difference in the detection rates of early-onset and late-onset preeclampsia as seen in this study. Nonetheless, studies that compare clinical parameters or laboratory biomarkers between early-onset and late-onset preeclampsia are still limited.

CONCLUSION

This study provided a comprehensive overview of the predictive accuracy of preeclampsia screening, including its strengths (high detection rate for early-onset preeclampsia) and limitations (low detection rate for late-onset preeclampsia especially at term). These results are comparable with other studies that investigate the predictive accuracy and detection rates of the FMF triple test. Certainly, the prediction algorithm for early-onset preeclampsia demonstrates strong performance, effectively identifying a significant portion of women at risk of developing the condition. However, it appears ineffective in screening for late-onset preeclampsia, prompting speculation about potential differences in their underlying pathophysiology. Despite being considered as the less severe condition, late-onset preeclampsia accounts for the majority of cases, and thus, exerts a substantial burden on the healthcare system. This raises concerns about its clinical utility as to who may benefit from early intervention or monitoring, hence, further evaluation and potentially refining the screening test for improved performance, particularly in cases of late-onset preeclampsia, is warranted. Another limitation of the screening test is that it does not include the risk of postpartum preeclampsia. In this study, there were two cases which were both screen negative but eventually developed postpartum preeclampsia. Including the risk of postpartum preeclampsia in the screening test can also be beneficial.

Despite numerous published studies on predictive factors and screening tests for preeclampsia, local consensus on the optimal strategy has yet to be reached and applied in routine clinical practice. Hence, further research such as test validation in different populations, is encouraged to continue improving the accuracy of these predictive models.

Further studies on effective aspirin dosage are also recommended. At present, the most cost-effective method for identifying individuals who should receive aspirin remains undetermined; moreover, the actual recommeded dosage lacks clarity, necessitating clinical trials to compare different aspirin doses.

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

SR and CV were responsible for formulating the research topic. SR performed the literature search, data collection and interpretation of results. CV aided in the presentation of the data. SR drafted the manuscript. CV reviewed the manuscript and provided insights on how to improve the paper.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Review Committee (IERC) and Institutional Scientific Review Committee (ISRC) of the St. Luke's Medical Center – Global City.

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