

# Optimising Preeclampsia First-Trimester Screening Using Three Parameters

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## ABSTRACT

**Objective:** To evaluate the performance of first-trimester preeclampsia-screening algorithm in predicting preeclampsia (PE).

**Study Design:** Observational study.

**Place and Duration of the Study:** Department of Obstetrics and Gynaecology, Combined Military Hospitals (CMH) Lahore, Pakistan, between 1<sup>st</sup> January and 31<sup>st</sup> August 2022.

**Methodology:** Data of 100 women of any parity aged 18-35 years at gestational age < 13 weeks based on the last menstrual period (LMP), was analysed. First trimester Fetal Medicine Foundation (FMF) screening algorithm for preeclampsia was used entering maternal characteristics, mean arterial pressure and uterine pulsatility index only, for risk calculation. Patients were followed up till delivery for the development of preeclampsia and fetomaternal outcomes. Clinical characteristics of women with and without preeclampsia were compared using the Chi-square and independent samples t-test.

**Results:** The mean age of patients was 29.29±4.56 years and 60% were nullipara. Seventy-eight patients were placed in the low-risk category and 22 patients were in the high-risk category according to the FMF algorithm. Preeclampsia developed in 13 patients. For a risk cut-off of 1 in 100, the FMF algorithm showed a detection rate of 38% with diagnostic accuracy of 75% and a false positive rate (FPR) of 20%.

**Conclusion:** Although the performance of adapted FMF algorithm to predict preeclampsia gestational was low, it was found superior to prediction by maternal risk factors alone. Adjustment for additional factors or ethnicity-specific values may help in further improvement of detection rate.

**Key Words:** Blood pressure, Biomarkers, Biological markers, Preeclampsia, Risk assessment.

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## INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are important causes of fetomaternal morbidity and mortality affecting 2-8% women globally.<sup>1</sup> Preeclampsia is the most serious HDP, with multi system involvement. It is diagnosed when a pregnant woman has high blood pressure with either proteinuria or evidence of end-organ damage. Maternal mortality due to preeclampsia reported by the developed countries is around 5%.<sup>2</sup>

The risk factors associated with HDP include maternal age, obesity, HDP in previous pregnancy, family history of hypertension, diabetes mellitus, and anti-phospholipid syndrome.<sup>3,4</sup> The international guidelines based on ASPIRE trial (*Aspirin to Prevent Recurrent Venous Thromboembolism*) recommend use of low dose aspirin in women with these risk factors to decrease the risk of PE.<sup>5,6</sup>

In Pakistan, risk determination is done at the first antenatal visit utilising maternal characteristics and medical history similar to NICE guidelines. The International Federation of Obstetrics and Gynaecology recommends using FMF first-trimester screening-algorithm, based on maternal risk factors, mean arterial pressure (MAP), serum placental growth factor or pregnancy-associated plasma protein A (PAPP-A) / placental growth factor (PIGF), and uterine artery pulsatility index (UtPI) calculating patient specific risk.<sup>6</sup> A facility for measuring biomarkers - PAPP-A and PIGF is not available in this setup. However, UtPI can be determined in many setups globally, as well as in Pakistan, at the recommended gestation of 11 to 13 weeks.<sup>1,7,8</sup>

Multiple studies have shown fairly good accuracy in predicting PE using these parameters. In Caucasians (risk cut-off of 1 in 100), screen positive rate of 10% was seen with prediction of early onset PE (DR 90%), preterm PE (DR 75%), and term PE (DR 47%).<sup>9</sup> Tan revealed that the detection rate by FMF algorithm is better than the detection using NICE guidelines (DR 30%).<sup>10</sup> However, it needs further validation in populations before it can be fully implemented.

The purpose of this study was to identify high risk pregnant women likely to develop preeclampsia by adapted FMF first-trimester PE-screening algorithm using three parameters - maternal characteristics, MAP and UtPI in a group of Pakistani population. The

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result of this study may help in identifying at-risk women within limited resources and thereby improving feto-maternal outcomes with timely management.

## METHODOLOGY

This cohort observational study was carried out in the Department of Obstetrics and Gynaecology, CMH Lahore, from 1<sup>st</sup> January to 31<sup>st</sup> August 2022. The study was started after an approval from Ethical Review Board (Ref No 663/ER-C/CMH/LMC). A sample size of 102 was calculated on OpenEpi Version 3, open source sample size calculator keeping confidence interval 95% with power of 80% and prevalence rate of 5%.<sup>2</sup> However, a total of 120 patients were recruited for the study. Non-probability convenience sampling technique was followed. Women of any parity aged 18-35 years at gestational age <13 weeks based on LMP (last menstrual period) were included in the study, while pregnancies terminating before 24 weeks gestation and patients who refused to consent were excluded from the study. Preeclampsia was defined when systolic blood pressure (BP) was  $\geq 140$  mmHg, diastolic BP was  $\geq 90$  mmHg on two separate occasions four hours apart; and proteinuria was  $\geq 300$  mg/24 hours by laboratory or evidence of and organ involvement after 20 weeks gestational age on LMP. MAP was calculated with the formula:  $MAP = DP + 1/3(SP - DP)$ , where DP represented diastolic BP and SP represented systolic BP.

Informed written consents were taken. The basic demographics like age, parity, gestational age, past obstetric history and BMI were recorded. The maternal characteristics required by adapted FMF algorithm including conception method, smoking in pregnancy, history of diabetes, chronic hypertension, Antiphospholipid syndrome (APLS), Systemic Lupus Erythematosus (SLE) were recorded. APLS was considered positive if patient had a record of positive cardiolipin antibodies, lupus anticoagulant, and beta 2 glycoprotein antibodies, or had history of one or more unexplained late miscarriages at or after 10 weeks of pregnancy, 1 or more premature births at or before 34 weeks of pregnancy complicated with PE with morphologically normal fetus, or 1 or more confirmed incidents of thromboembolism. SLE was considered positive if patient had a record of positive antinuclear antibodies. The Primary outcome measure was the development of PE requiring delivery and, the secondary outcome measures were adverse maternal and neonatal outcomes.

Women were seated and allowed to rest for 3-5 minutes, normal (22 to 32 cm) adult cuffs were fitted. BP was recorded with automated blood pressure device which was regularly calibrated during the study, and MAP was calculated. UtPI was measured through trans-abdominal Doppler ultrasound carried out in the radiology department by a consultant radiologist, free of cost for all patients. Sagittal section of uterus was obtained, and cervical internal os was identified. Transducer was then gently tilted from side to side, and colour flow mapping was used to identify each uterine artery along the side of the cervix and

uterus, and measure PI.<sup>11</sup> The mean value (mUtPI) was calculated by adding the right and left pulsatility index together, divided by two.<sup>12,13</sup>

Maternal factors, MAP and UtPI were entered into first trimester adapted FMF screening algorithm for PE and the risk was calculated taking cut-off of 1 in 100 as high risk for PE.<sup>14</sup> Patients were informed about the findings and were required to follow-up till delivery. Data of biophysical markers, risk and PE status, delivery, and neonatal details were recorded on specially designed proforma. Two groups were then formed based on the results, those who developed PE (n=13) and those who did not develop PE (n=87).

Data were analysed with SPSS-16. The mean and standard deviation were presented for quantitative variables like age, parity, and gestational age. Frequency and percentages were computed for qualitative variables and Chi-square test was used for the comparison, while Independent samples t-test was used to compare the outcome of the two groups of women with and without PE, taking p-value < 0.05 as significant. Sensitivity, specificity, and diagnostic accuracy were calculated with the help of 2X2 table.

## RESULTS

A total of 120 patients were recruited in the study. Out of these, 11 (9.1%) patients did not return for a follow-up after the first trimester. Pregnancy outcome details could not be collected in 9 (7.5%) patients. Therefore, a complete data of 100 patients was used for the analysis of performance of FMF algorithm (Figure 1).

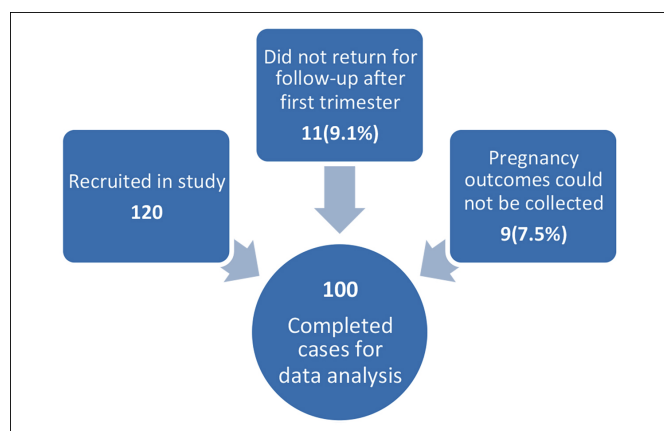


Figure 1: Induction of participants for the study.

The mean age of patients was  $29.29 \pm 4.56$  years while mean BMI was  $26.4 \pm 3.97$  kg/m<sup>2</sup>. A majority of the patients (71, 71%) were less than 30 years of age. All patients (100, 100%) were of Asian ethnicity and were non-smokers (Table I).

A majority of the patients were nullipara (60, 60%). Of the multipara (40, 40%), only 5% gave a previous history of PE. An assisted conception was reported in a minority 8 (8%) of the (8, 8%) patients. The mean inter-pregnancy interval was found to be  $25.61 \pm 23.79$  months, while range was 10-192 months.

**Table I: Baseline characteristics of participants.**

Characteristic	Total study population n=100	With preeclampsia n= 13	Without preeclampsia n= 87	p-value
Age, years (Mean±SD)	29.29±4.56	29.92±4.64	29.19±4.57	0.593 <sup>a</sup>
Body Mass Index, kg/m <sup>2</sup> (Mean±SD)	26.4±3.97	25.75±3.43	26.49±4.05	0.533 <sup>a</sup>
Asian (n/%)	110(100)	40(100)	70(100)	NA
Smoking (n/%)	0(0)	0(0)	0(0)	NA
Diabetes (n/%)	19(19)	3(23.1)	16(18.4)	0.688 <sup>b</sup>
Chronic kidney disease (n/%)	1(1)	0(0)	1(1)	0.698 <sup>b</sup>
Chronic hypertension (n/%)	11(11)	2(15.4)	7(8.04)	0.388 <sup>b</sup>
Family h/o hypertension (n/%)	19(19)	2(15.4)	17(19.5)	0.722 <sup>b</sup>
Systemic lupus erythematosus (n/%)	0(0)	0(0)	0(0)	NA
Antiphospholipid syndrome (n/%)	0(0)	0(0)	0(0)	NA
Pregnancy details				
Nulliparous (n/%)	60(60)	10(76.9)	50(57.5)	0.001 <sup>b*</sup>
Multiparous	40(40)	3(23.1)	37(42.5)	
Parous with prior pre-eclampsia (n/%)	5(5)	3(23.1)	2(2.3)	
Parous without pre-eclampsia (n/%)	35(90)	0(0)	35(40.2)	
Conception				
Spontaneous (n/%)	92(92)	10(76.9)	82(94.2)	0.032 <sup>b*</sup>
Assisted (n/%)	8(8)	3(23.1)	5(5.7)	
Gestational age, weeks (Mean ± SD)	12.11±1.03	12.22±0.96	12.01±0.79	0.475 <sup>a</sup>
Mean arterial pressure, mm Hg (Mean ± SD)	94.34±5.71	95.53±5.45	94.16±5.76	0.423 <sup>a</sup>
Crown rump length, mm (Mean ± SD)	57.87±10.60	61.69±12.01	57.30±10.33	0.167 <sup>a</sup>
Uterine artery PI (Mean ± SD)	1.48±0.39	1.65±0.47	1.45±0.37	0.094 <sup>a</sup>

a: Independent samples t-test; b: Chi-square test; \*Statistically significant.

**Table II: Association of calculated risk with the development of pre-eclampsia.**

Risk stratification <sup>a</sup>	Study population	Developed preeclampsia		p-value
		Yes (n, %)	No (n, %)	
High-risk	22	5(38)	17(20)	0.125 <sup>a</sup>
Low-risk	78	8(62)	70(80)	
Total	100	13(13)	87(87)	

a: Chi-square test; \*Risk cut-off is 1 in 100

In multipara, the mean birth weight of neonate in previous pregnancy was found to be 2.7±0.73 kg. No case of APLS or SLE was reported. The mean gestational age at screening was found to be 12.11±1.03 (IQR 11-13.6) weeks with mean crown rump length of 57.87±10.60 mm. The mean MAP was 94.34±5.71 mm Hg, while mean UtPI was found to be 1.48±0.39 overall. The mean MAP was 95.53±5.45 mm Hg and mean UtPI was 1.65±0.47 in the group of patients who developed PE (Table I).

There was preponderance of the low-risk patients (78, 78%) as compared to the high-risk ones (22, 22%) as seen in Table II. No statistically significant association (p = 0.125) was found between adapted FMF algorithm calculated risk and development of PE. For a risk cut-off of 1 in 100, the adapted FMF algorithm showed sensitivity and specificity of 38% and 80%, respectively with diagnostic accuracy of 75% at a FPR of 20% (Table II). A positive predictive value (PPV) of 23% was seen while the negative predictive value (NPV) of 22% was obtained. A total of 13 patients (13%) developed PE in which 22.7% (n=5) belonged to the high-risk group as compared to 10.3% (n=8) patients from the low-

risk group. Only 1 patient developed PE before 34 weeks gestation.

Among the maternal characteristics, a statistically significant difference was found with reference to parity and conception method only. A statistically significant number of cases developing PE were nullipara (p=0.001). The p-value of 0.032 was found in conception method where 23.1% (n=3) of patients developing PE had assisted conception as compared to only 5.7% (n=5) of those not developing PE (Table I).

The fetomaternal outcomes showed statistically significant differences in terms of prophylactic aspirin intake, gestational age at delivery, mode of delivery, birth weight, Apgar score and NICU admission (Table III). Aspirin was advised to 73 patients, out of which 4(5.5%) were advised a dose of 75 mg and 69 (94.5%) patients were advised 150 mg of aspirin (Table III).

## DISCUSSION

The FMF algorithm has been used for prediction of preeclampsia worldwide.<sup>9,15</sup> It is based on assumption that maternal characteristics and biomarker cut-offs would be same for all populations. A majority of patients in the current study were nullipara (71%) which is comparable to a recent study in the Netherlands in which 83.4% of patients were nullipara.<sup>16</sup> None of the patients in the current study were smokers as compared to 6.1% smokers reported in the aforementioned study.<sup>16</sup> A high majority (19,19%) of patients with diabetes during pregnancy found in the current study was higher than 1.9% of patients found to be diabetic in the study carried out by Zwertbroek, none of whom had developed PE.<sup>1</sup>

**Table III: Maternal and fetal outcomes.**

Characteristic	Total study population n=100	With preeclampsia n=13	Without preeclampsia n=87	p-value
Developed preeclampsia (n, %)				
Yes	13(13)			
No	87(87)			
Aspirin advised (n, %)				
Yes	81(81)	13(100)	60(69)	0.001 <sup>a*</sup>
No	19(19)	0(0)	27(31)	
Gestational age at delivery (Mean±SD)	37.63±1.44	36.66±1.45	37.78±1.39	0.008 <sup>b*</sup>
Mode of delivery (n, %)				
Spontaneous vaginal	65(65)	5(38.4)	62(71.3)	0.019 <sup>a*</sup>
Cesarean section	35(35)	8(61.6)	25(28.7)	
Birth weight, kg (Mean ± SD)	2.88±0.43	2.47±0.36	2.94±0.41	0.001 <sup>b*</sup>
Apgar score at 10 mins (n, %)				
<7	6(6)	3(23.1)	4(4.59)	0.01 <sup>a*</sup>
>7	94(94)	10(76.9)	83(96.9)	
NICU admission (n, %)				
Yes	7(7)	5(38.4)	2(2.3)	0.001 <sup>a*</sup>
No	93(93)	8(61.5)	85(97.7)	

a: Chi-square test; b: Independent samples t-test; \*Statistically significant.

A high number of diabetic cases was seen in this study which may be due to the fact that the hospital is a tertiary care referral centre dealing with high risk cases. This is also reflected in a higher number of cases reported with chronic hypertension (11, 11%) and those with a family history of hypertension (19, 19%) as compared to the other studies.

A detection rate (DR) of 90% for early PE, 75% for preterm PE, and 41% for term PE, at a FPR of 10% was reported by Tan *et al.* in 2017.<sup>10</sup>

Another study carried out in Netherlands reported a DR of 80% for preterm and 83% for term PE,<sup>16</sup> but the study included high-risk patients only in contrast to the present study which was not restricted to high-risk patients.

A recent regional study carried out by Prasad *et al.* in 2021 revealed a DR of 52.5 to 80% with FPR of 10%.<sup>17</sup> Prasad *et al.* argued that such algorithm is unlikely to be effective for screening in South Asian population. Park *et al.* also reported a lower DR in his study in 2013.<sup>18</sup> This argument is also reflected in the current study. For risk cut-off of 1 in 100, the FMF algorithm reported a DR of 38% for prediction of PE at any gestational age for FPR of 20%. The algorithm resulted in PPV and NPV of 23% and 22%, while PPV and NPV obtained in the recent Caucasian study are 7.7 and 98.9%, respectively.<sup>16</sup> Chaemsaitong *et al.* also reported statistically significant lower values of biomarkers in Asian population as compared to Caucasians.<sup>19</sup> This could be due to anthropometric measurement differences in the two populations. However, a recent multi-centre study carried out to predict preterm PE in Asian population found a DR of 64% which is comparable to FMF algorithm performance in Caucasians.<sup>20</sup> Wright *et al.* reported a DR of 50% for prediction of PE at any gestational age in their study.<sup>21</sup>

Another study by Wright found that maternal factors, MAP and UtPI are sufficient for prediction of PE in 60-70% of the

cases.<sup>22</sup> Aspirin was advised to 81 patients in the study and PE developed in 16% of these patients. Low dose aspirin has been shown to reduce the risk of preterm PE by 62% in a study by Chaemsaitong *et al.*<sup>23</sup> The mean gestational age at delivery in the current study was found to be 36.6 weeks and 37.7 weeks in groups with and without PE, respectively. These findings are comparable to the findings of Prasad *et al.* who reported mean gestational ages of 36.4 and 37.6 weeks in two groups.<sup>17</sup> The mean birth weights in both groups in the study (2.47 kg with PE, 2.94 kg without PE) are also comparable to the same study on South Asian women (2.46 kg with PE, 2.93 kg without PE).<sup>1</sup> The results of Apgar score <7 in 6% cases and NICU admission in 7% of cases of the current study were comparable to those obtained by Zwertbroek where Apgar score <7 and NICU admission were seen in 2.6% and 6% cases, respectively.<sup>16</sup>

To the authors' knowledge, this is the first study assessing the performance of adapted FMF algorithm in Pakistan. Although a high rate of follow-up was seen (83%), it was carried out in a single centre with a limited sample size in a military hospital, hence the results need further corroborative evidence in order to be generalised. Another limitation is that, although sonologists performed the Doppler scan and measured UtPI according to FMF standards, they were not FMF certified for this measurement. The algorithm may not be implemented in all hospitals due to the uterine artery pulsatility index measurement requiring a specialist and hence, not being performed routinely in most of the setups. Furthermore, studies based on multi-centres with larger sample size from public and private sectors, equipped with FMF certified sonologists are needed to generate robust evidence.

## CONCLUSION

Despite the sub-optimal results achieved with a DR of 38%, the study showed that FMF algorithm using maternal factors and biophysical markers can be implemented in a setup with



better DR of PE than with maternal factors alone. Adjustments may be needed for indigenous population and large scale studies are required to assess cost-effectiveness and feasibility of screening. This may help in timely management of patients with improved fetomaternal outcomes in low resource settings.

#### ETHICAL APPROVAL:

An ethical approval was obtained from the Ethical Review Committee of CMH, Lahore Medical College via Ref. No. 663/ERC/CMH/LMC.

#### PATIENT'S CONSENT:

Written informed consents were obtained from the patients regarding the collection of data and publication of results prior to the start of the study.

#### COMPETING INTEREST:

The authors declared no competing interests.

#### AUTHOR'S CONTRIBUTION:

SB: Conception of work and design, analysis, interpretation, drafting of the final document, and reviewing of the content critically.

ST: Contributed to conception and design of work, analysis, drafting and reviewing the content critically.

AW: Contributed to critical review and interpretation of the content and final drafting of the document.

QH: Contributed to data collection, analysis, and drafting of the manuscript.

All authors approved the final version of the manuscript for publication and took complete responsibility and accountability for all aspects of the work.

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