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Original Research Article

Assessment of effectiveness of fetal medicine foundation calculator in predicting risk for preterm preeclampsia using first trimester mean uterine artery pulsatility index and maternal factors in Indian population

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ABSTRACT

Background: Preeclampsia (PE) is a hypertensive disorder of pregnancy associated with significant maternal morbidity and mortality. The outcome of the disease depends to a large extent on risk factors, maternal vascular responsiveness, screening performance and prevention effectiveness. Fetal medicine foundation has developed an online calculator that predicts the risk for PE in pregnant woman in first trimester using MUAPI (mean uterine artery pulsatility index) and maternal factors.
Methods: Diagnostic test evaluation of FMF (fetal medicine foundation) calculator done using data collected from consenting 316 women with singleton pregnancy between the gestational age 11 weeks to 14 weeks+1 day who fulfilled inclusion and exclusion criteria. All cases were followed up and results were analyzed statistically.
Results: FMF calculator predicted a high-risk population of 12 pregnant women. On follow up of 316 subjects 13 pregnant women developed preterm preeclampsia with an incidence of 4.1%. Among high-risk population 9 subjects developed preterm PE and among the 304 cases in low-risk group 4 patient developed preterm PE. In this study sensitivity of FMF calculator was 69.2% and specificity was 99% with a PPV of 75, NPV of 98.6, positive likelihood ratio of 69.9 and diagnostic odds ratio of 225. The area under ROC was 0.841 with 95% CI (0.711-0.972) was high indicating that the algorithm was able to differentiate between pregnant women at high or low risk for preterm PE.
Conclusions: This study concludes that the algorithm used in FMF calculator in first trimester is highly specific and have high sensitivity for predicting preterm PE and can be used in routine clinical practice to identify women at high risk.

Keywords: Mean uterine artery pulsatility index, Preeclampsia, FMF calculator, Preterm preeclampsia

INTRODUCTION

PE is a hypertensive disorder of pregnancy which affects around 8 to 10% of pregnant women in India, compared to the pooled global incidence of 3%.[1] As per WHO hypertensive disorders cause significant maternal mortality, approximately for 16% in developed countries and 9% in Africa and Asia.[2]

It is associated with significant maternal and perinatal morbidity and mortality such as fetal growth restriction, preterm delivery, placental abruption, eclampsia, multi organ dysfunction and HELLP syndrome so there is a need to develop effective screening modalities in order to lessen the burden of this hypertensive disease of pregnancy.[3] The outcome of the preeclampsia depends to a large extent on risk factors, maternal vascular

responsiveness, screening performance and prevention effectiveness.[4-6] Screening constitutes a cumulative evaluation of history, demographics, blood pressure and uterine artery Doppler.[7] MUAPI of first trimester routine antenatal scan along with maternal factors combined screening is more than 70% sensitive in predicting preterm PE.[5]

At present, the FMF had developed an online calculator that predicts the risk for PE in pregnant woman in first trimester .FMF calculator uses an algorithm based on the Bayes theorem to assess the probability of developing PE using MUAPI and maternal factors.[8,9] Though it is a well-established tool, little information is available as to the effectiveness of the FMF calculator in the Indian subcontinent. This study addressed the same and thereby creating an effective tool for both clinicians and radiologists to implement early intervention for at risk patients of preterm PE.

Classification of PE

Preterm PE

It is defined based on the gestational age at the time of clinical diagnosis.

Term PE

It is defined as the presence of PE at or after 37 weeks of pregnancy.[10]

Early onset preeclampsia (EOPE)

It is defined as the PE with onset <34 weeks of gestation.[11,12]

Late onset preeclampsia (LOPE)

It is defined as the PE with onset greater or at 34 weeks of gestation.[12]

One of the most significant developments was the division of PE into EOPE and LOPE. Various cut-off values have been proposed, including 32 and 36 weeks of gestation, but the value of 34 weeks is the most generally used because neonatal morbidity reduces significantly after 34 weeks.[12]

EOPE associated with typical pathogenesis of preterm PE and associated with SGA births, abnormal Doppler indices, persistent hypertension and congenital abnormalities. The prevalence of placental under perfusion was higher in EOPE (58%) than in LOPE (33%).[13-15] The most common phenotype of PE is LOPE, which accounts for 90% of cases. LOPE seems to be the manifestation of a mismatch between the metabolic demands of the growing fetus close to term and maternal supply.[12,16]

First trimester prediction of PE

There are multiple maternal risk factors associated with the development of PE. Using this risk factors various approaches and studies have been conducted for early identification of women at risk of PE.

Screening based on National institute for health and clinical excellence (NICE) guidelines

The current method for screening PE is to use a checklist based on maternal demographic information and medical history as per NICE guidelines. Women at high risk of having PE are identified by the presence of any of the high-risk variables that is hypertension (Htn) in previous pregnancy, chronic Htn, chronic kidney disease, diabetes, autoimmune conditions or any two moderate-risk factors that is nulliparity, age ≥40 years, BMI ≥35 kg/m^2, family history of PE, interpregnancy interval >10 years, according to the NICE. High risk pregnant women was advised to take 75-150 mg of aspirin daily from 12 weeks until delivery, according to NICE guidelines.[17]

A checklist-based screening based on maternal history is no longer be considered sufficient for accurately predicting preterm PE. Pregnant women with or without risk factors according to NICE guidelines can develop PE.[8,17,18]

Alternative method of early risk prediction of preterm PE using maternal MUAPI, biochemical markers and medical history

The prediction of early or late PE was established using a competing risk model and Bayes algorithm incorporating maternal demographic factors, medical and obstetric history and biophysical and biochemical indicators at 11-13 weeks' gestation. The competing risks model is a new methodology for estimating patient-specific PE risks based on maternal factors and history. Bayes theorem is used to estimate priori risk for PE by combining maternal factors with potential biomarkers such as MAP, MUAPI, PAPP-A and PLGF.[19-22]

The detection rate of preterm PE using a combination of maternal variables, MAP, UTPI and PLGF was 82 percent, which was 41.6 percent higher than the NICE approach.[20] The algorithm was established based on a survey of 58,884 singleton pregnancies between 11 and 13 weeks of pregnancy, of which 1426 (2.4 percent) developed PE. At a fixed false-positive rate of 10%, the projected detection rates for preterm PE and all cases of PE were 77 percent and 54 percent, respectively.

In a prospective multicenter analysis of 8775 pregnancies, the algorithm's predictive ability was tested, including 239 (2.7%) cases developing PE. Preterm PE detection rate was 75% with a 10% false-positive rate. Based on three prospective nonintervention screening studies at 11-13 weeks of gestation in a total of 61,174

singleton pregnancies, including 1770 (2.9%) that developed PE, showed that screening using the algorithm in white women there is 10% screen-positive rate and 88% detection rate for EOPE and 69% for preterm.[20,23]

Secondary data analysis from the ASPRE trial of a total of more than 30,000 women with singleton pregnancies who underwent prospective screening for preterm PE found that screen positive women according to NICE guidelines who are screen negative by the Bayes based method, the risk of preterm PE is reduced to within or below background level.[24] Based on the above results risk-based screening using biomarkers is superior to a checklist-based method of screening.[18]

Maternal history and biomarkers for PE screening in the first trimester

Maternal history and demographics

Factors for assessment are maternal age, maternal weight, maternal height, maternal ethnicity (White, Afro-Caribbean, South Asian, East Asian), past obstetric history (nulliparous, parous without prior PE, parous with prior PE), interpregnancy interval in years between the birth of the last child. Gestational age at delivery (weeks) and birthweight of previous pregnancy beyond 24-week, family history of PE (mother), method of conception (spontaneous, ovulation induction, *in vitro* fertilization), smoking habit, history of CHTN, history of diabetes mellitus, SLE, APS.

Maternal biomarkers

Biochemical markers: PLGF and PAPPA-A

In early bio-chemical screening for PE, several biochemical markers have been proposed, of which PAPP-A, placental growth factor (PLGF) and placental protein-13 show promising results. These markers are thought to be involved in placentation or in the cascade of events leading from impaired placentation to development of clinical symptoms of PE.[25,26]

Several studies suggest that PLGF concentration in the first trimester is reduced in women who go on to develop PE. PAPP-A and PLGF levels are inversely correlated with the severity of the disease. Biochemical markers alone doesn't have good sensitivity.[19,26-28]

Mean arterial pressure (MAP)

MAP is a good predictor of PE with high specificity and negative predictive value but is only moderately effective due to low sensitivity and positive predictive value.[29,30] Performance of mean arterial blood pressure alone for the prediction of PE is low in a healthy nulliparous pregnant women group. A study of more than 5000 singleton pregnant women screened with a combination of MAP and maternal history, the detection rates for PE was 63% and 76% for EOPE.[31]

Multiple factors can affect the values of MAP in pregnant women. A COHORT study conducted on 70,000 pregnancies to evaluate the relationship between MAP and maternal characteristics, gestational age, maternal weight, height, Afro-Caribbean racial origin, cigarette smoking, family history of PE shows significant association.[18,31,32]

MUAPI

Pulsatility index (PI) is calculated by the following equation,

$$PI=\frac{peak\ systolic\ velocity-minimal\ diastolic\ velocity}{mean\ velocity}.$$

MUAPI is calculated by taking mean of bilateral uterine artery PI. MUAPI shows a significant and progressive decline throughout the gestation. The values show a decrease in the MUAPI between 11 weeks (mean PI 50th centile-1.79; 95th centile-2.70) and 34 weeks (mean PI 50th centile-0.70; 95th centile-0.99). Then it remains more stable until 41 weeks (mean PI 50th centile-0.65; 95th centile-0.89) The best predictor of PE is an increased MUAPI >95th centile.[33]

A large metanalysis of first trimester UTPI measurement for the prediction of PE included eight studies for the prediction of EOPE (n=41,692 women) and eleven studies for the prediction of PE of any gestation (n=39,179 women.[34] The first trimester abnormal UTPI is defined as greater than the 90th percentile, achieving detection rate of 48% at 8% false-positive rate, for the identification of EOPE.[34] Concluding that there are multiple studies demonstrating first-trimester uterine artery doppler is a useful tool for predicting preterm PE and EOPE as well as other adverse pregnancy outcomes.[34-36]

Combined risk assessment using FMF online calculator

Based on multiple combined risk assessment studies FMF developed an only free calculator for early prediction of preterm PE in first trimester (Figure 1). This application uses Bayes theorem to combine the prior risk from maternal factors and medical history with the results of various biophysical and biochemical measurements to estimate the risk for PE. We can obtain risks for PE based on maternal factors alone and in combination with any of the biomarkers. Based on existing evidence, the first-trimester combined test is most predictive of preterm PE and EOPE. Maternal factors, MAP, MUAPI and PlGF is compatible with reported several previous studies of screening for preterm PE by the Bayes' theorem-based method. The performance of screening for preterm PE of various combinations of the first trimester test, based on data from three previously reported prospective

nonintervention screening studies including a combined total of 61,174 singleton pregnancies, including 1770 (2.9%) that developed PE, the baseline screening test should be a combination of maternal risk factors with MAP and not maternal risk factors alone.[9,18]

Clinical application of FMF calculator

The clinical applications of FMF calculator are screening for PE at 11-14 weeks to identify group at high-risk for preterm-PE (<37 weeks); combined screening by maternal factors, uterine artery PI, mean arterial pressure and serum PLGF can predict 90% of early-PE and 75% of preterm-PE, at screen positive rate (SPR) of 10%; in a White population, for risk cut-off of 1 in 100 and 1 in 150 the respective SPR's are about 10% and 16%, the detection rate (DR) for early-PE is 88% and 94% and DR for preterm-PE are 69% and 81%; FMF online calculator is can be used as a routine screening tool for all pregnancies cost-effectively for predicting PE risk.

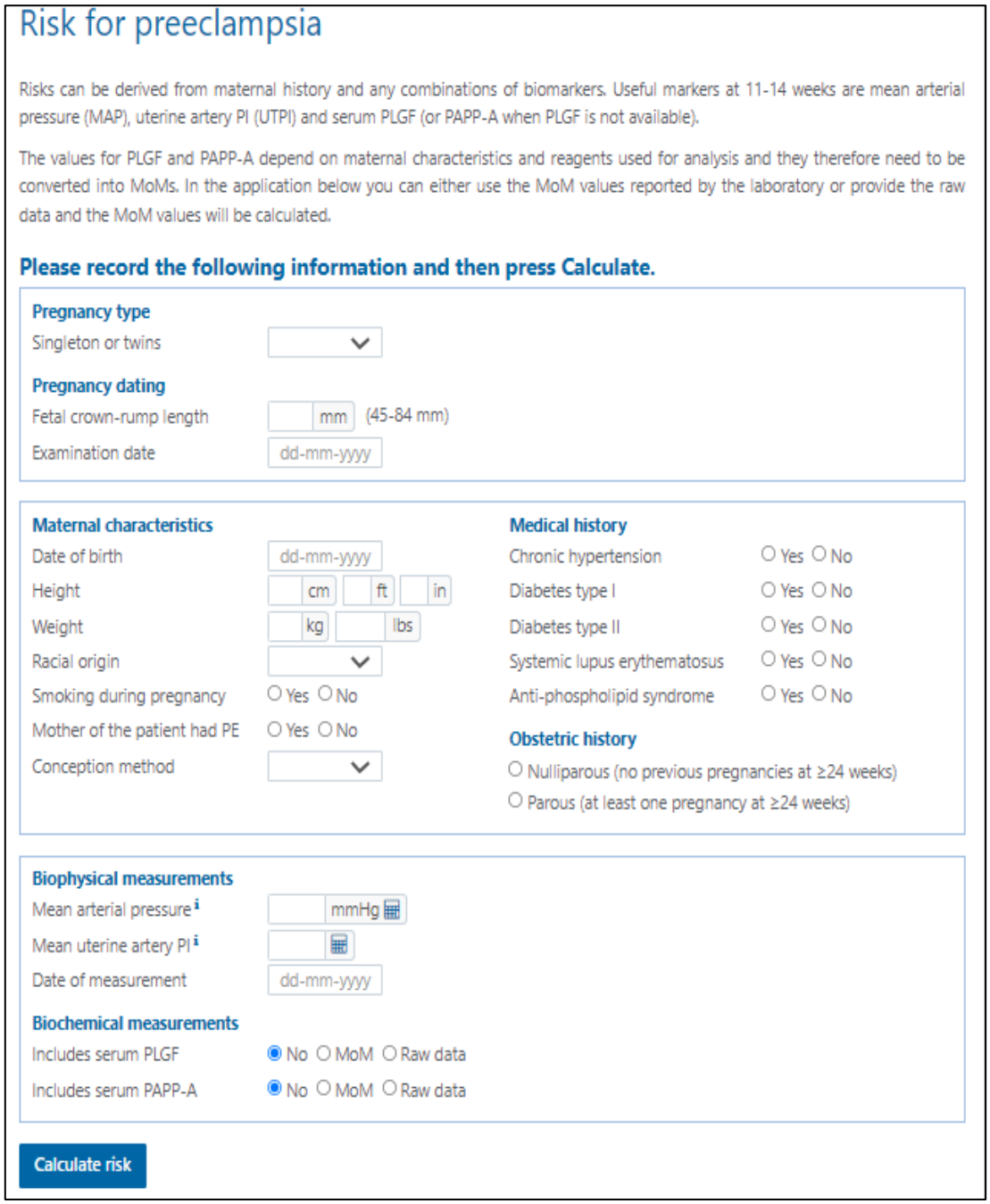

Figure 1: First trimester FMF calculator; (https://fetalmedicine.org/research /assess/ preeclampsia/first-trimester).

There was not much studies have been done of South Asian and Indian population. However, reasonable risk cut-off of less than 1 in 150 defined as the high-risk group.[9,18]

Aim

Aim of the study was to determine the effectiveness of first trimester FMF online calculator in predicting risk of PE in a tertiary care hospital in India so that it can be used as a screening tool as part of routine antenatal checkup.

METHODS

Diagnostic test evaluation of FMF calculator was performed with data collected from 316 pregnant women with singleton fetus of gestational age 11 week to 14+1 week fulfilling inclusion and exclusion criteria and who gave informed consent to participate in the study. The study was carried out at Amala institute of medical sciences, Thrissur, Kerala for a period of 18 months (December 2019 to May 2020).

Inclusion criteria

Pregnant women with singleton fetus of gestational age 11 week to 14+1 week confirmed by USG dating; patients with no congenital abnormalities diagnosed by USG; patients who provided informed written consent were included in the study.

Exclusion criteria

Patients with congenital anomaly in subsequent scans; patients lost to follow up were excluded.

Method of data collection (study procedure)

Collection of maternal obstetric history and maternal factors

Pregnant women who fulfilled the criteria for inclusion in the study were enrolled after obtaining informed consent. Patients were asked to complete a questionnaire on maternal age, racial origin, method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks) and previous pregnancy with PE (yes or no). The questionnaire was then reviewed by a doctor together with the subject and the maternal weight, height and BP were measured.

Procedure to measure MAP

Blood pressure measurement was done by standard mercury sphygmomanometer with patient in sitting position for at least 2-3 minutes with arm kept on table so that arm and heart were nearly at the same level. Either a normal or large adult cuff was used depending on the mid arm circumference. BP measurements are put into the risk calculator and the final MAP measurement will be automatically calculated.

Collection of data from routine first trimester ultrasound scan that included information on dating, number of fetuses, CRL and supplemented with an assessment of the mean uterine artery PI from radiology department.

Procedure to measure uterine artery PI

For the first-trimester transabdominal assessment of uterine artery resistance, a midsagittal section of the uterus and cervix was obtained initially. Using colour flow mapping, the transducer was gently tilted sideways, so that the uterine arteries were identified with high-velocity blood flow along the side of the cervix and uterus. The pulsed-wave Doppler sampling gate should be narrow (set at approximately 2 mm) and positioned on either the ascending or descending branch of the uterine artery at the point closest to the internal cervical os, with an insonation angle <30°. In order to verify that the uterine artery was being examined, the peak systolic velocity should be >60 cm/s. The PI was measured when at least three identical waveforms were obtained.

The information was then transcribed from the paper record form into the FMF online calculator and the risk for PE was estimated.

Risk estimator

The risk estimator was FMF online calculator for 1st trimester for PE.

Ethical approval

When a pregnant woman came for the routine antenatal checkup data was collected and risk according to FMF calculator was calculated. High risk cases were further evaluated by obstetrician with currently followed NICE guidelines and if the pregnant women fell into high-risk category according to NICE guidelines, they will be provided with options of preeclampsia prophylaxis and followed up.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records and by direct interview. The primary outcome measured was patient developed preeclampsia and gestational age at diagnosis. PE was

diagnosed according to International society for the study of hypertension in pregnancy (ISSHP) criteria.

Statistical analysis

The data of maternal factors and MUAPI and the risk predicted from FMF calculator was entered into excel work sheet and analysis performed using SPSS 23. Descriptive and inferential statistical analysis was carried out. Continuous variables are expressed as Mean±SD and categorical variables as frequency%. The diagnostic effectiveness of FMF calculator will be tested using sensitivity, specificity, positive and negative predictive values, likelihood ratios and diagnostic odds ratios.

RESULTS

In this diagnostic test evaluation study conducted with data collected from the 316 antenatal women till delivery. Most of the cases were between 20 to 43 years of age and 88.9% (281) of the subjects were primigravida and one patient (0.32%) was treated for infertility by ovulation induction. Out of 316 subjects 12 pregnant women were detected as high risk (1 in <150) group by FMF calculator and 304 cases were detected as low risk. 12 high risk subjects were further evaluated with currently followed NICE guidelines and was detected as low risk.

Assessment of FMF calculator

Diagnostic test evaluation was done using sensitivity specificity analysis. 316 cases were followed up till delivery. A total of 13 subjects developed preterm PE in the study population. The incidence of PE in the study subjects was 4.1% and preterm PE was 4.1% (95% CI: 2.42, 6.91). None of the patient developed term PE or EOPE in the study population. Out of the 12 high risk women detected by FMF calculator 9 subjects developed preterm PE and 3 women doesn't develop preterm PE on follow up. Out of 304 subjects in low-risk group 4 subjects developed preterm PE on follow-up. In the study population, sensitivity of FMF calculator was 69.2%, specificity was 99% with a positive predictive value (PPV) of 75 and negative predictive value (NPV) of 98.6. Diagnostic odds ratio of calculator was 225. Positive likelihood ratio of the calculator was 69.9 and negative likelihood ratio was 0.311. The area under receiver operating characteristic curve (AUROC) was 0.841 with 95% CI (0.711-0.972) (Table 1).

Table 1: Sensitivity, specificity table for first trimester FMF calculator in the study.

Preeclampsia high risk (<1 in 150)	Developed preterm preeclampsia		Total
	Yes	No	
Yes	9	3	12
No	4	300	304
Total	13	303	316

Sensitivity=69.2%, specificity=99%, PPV=75, NPV=98.6 positive likelihood ratio=69.9, negative likelihood ratio=0.311, diagnostic odds ratio=225, AUROC=0.841 with 95% CI (0.711-0.972).

DISCUSSION

The study was aimed to assessing the effectiveness of FMF calculator in predicting preeclampsia by using maternal history, MUAPI and MAP. Subjects in high-risk group were identified by risk cut of 1 in <150. All the subjects were followed up till delivery for development of PE and gestational age at diagnosis. The study spanned for a period of 18 months.

This study was done in 316 first trimester pregnant women meeting the inclusion and exclusion criteria. The mean age of the study population was 27. Among 316 subjects 281 subjects was primigravida.

In the study population none of patients had high-risk variables such as PE in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, autoimmune diseases or any two moderate-risk factors together as per NICE guidelines. 12 high risk subjects were further evaluated with currently following NICE guidelines and was detected as low risk.

FMF calculator predicted a high-risk population of 12 pregnant women (risk cut off 1 in 150) using its combined screening method algorithm. In the study population 13 pregnant women developed PE with an incidence of 4.1% and preterm PE was 4.1%. Mean gestational age at the time of diagnosis of preterm PE in the population was 35 weeks. None of the subject developed EOPE (<34 weeks) and term PE (>37 weeks). Among 12 subjects in high-risk population 9 subjects developed preterm preeclampsia and among the 304 subjects in low-risk group 4 subjects developed preterm PE. Three subjects in the high-risk population didn't develop PE. In this study sensitivity of FMF calculator was 69.2%, specificity was 99% with PPV of 75, NPV of 98.6, positive likelihood ratio of 69.9 and diagnostic odds ratio of 225. The AUROC was 0.841 with 95% CI (0.711-0.972) was high.

The sensitivity of FMF calculator for detection preterm PE using first trimester MAP, MUAPI and maternal factors was 69.2% which was comparable with the 68% detection rate as per FMF foundation by conducting multiple studies in White and Black populations.[9] Positive likelihood ratio of 69.9 indicated that the test can be used in clinical practice (a positive likelihood ratio of greater than 10 suggested excellent clinical application for the test). The odds ratio of 225 indicated that the odds for preterm PE in women identified as at high risk by the algorithm was 225 times more than the odds for development of preterm PE in women identified as low risk. The algorithm was highly specific so if a pregnant woman was identified as at high risk for the development of preterm PE, it was very likely that she will develop preterm PE. The AUROC was also high and indicated that the algorithm was able to differentiate between pregnant women at high or low risk for preterm PE.

Considering the multiple high-risk variables such as MAP, MUAPI, maternal factors separately, none of the variables was significantly associated with development of preterm preeclampsia in the study population.

In the study subjects MUAPI was within normal range (<95th percentile) with corresponding gestation age when compared with global population. Mean MUAPI of the study population was less than <95th percentile for the corresponding gestational age. 95th percentile of the study population was less than the 95th percentile of the global population in all corresponding weeks.

Limitations

Pregnancies with antenatal detection of congenital anomalies, syndromes and pregnant women with autoimmune diseases were a limitation for the study.

CONCLUSION

This study concludes that the algorithm used in FMF calculator using MAP, MUAPI and maternal factors in first trimester is highly specific and have high sensitivity for predicting preterm PE. The algorithm is effective in differentiating between pregnant women at high or low risk for preterm PE. This study also proves that considering each high-risk variable separately is not effective in predicting preeclampsia. The high positive likelihood ratio of the study suggest that this calculator can be used in routine clinical practice to identify women at high risk for developing preterm PE. Thus, FMF calculator is an effective of the tool for the first-trimester screening for predicting preterm PE in our population.

We recommend routine first trimester combined screening test for all pregnant women using MAP, MUAPI, maternal demographic factors and early identification of PE using free online FMF calculator thus help in reducing PE and associated complications cost effectively.

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