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First trimester screening and prediction of preeclampsia by Application of Fetal Medicine Foundation Algorithm at Tanta University

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Abstract
Background: Preeclampsia (PE) is a complex illness linked to conception that affects a variety of bodily functions and is usually connected with perinatal morbidity and deaths. Early PE anticipation will reduce this linked morbidity and death by allowing for routine maternal and foetal monitoring and the use of preventative measures.
Aim of the work: the goal of this study is to investigate whether the measurement of maternal serum placental growth factor (PlGF) combined with uterine artery Doppler ultrasound, are useful in early predicting PE and to examine the diagnostic accuracy of the Fetal Medicine Foundation (FMF) Algorithm for the early screening and anticipation of the high- risk PE at 11-13 weeks conception in a group of pregnant women.
Patients and Methods: one hundred and twenty primigravida women with living, singleton fetus at 11-13 weeks conception without risk factors other than being primigravida attending antenatal care clinic at the Department of Obstetrics and Gynecology at Tanta University Hospitals. All cases were subjected to ; A signed informed written consent, proper history taking, full clinical examination, estimation of body mass index (BMI), blood pressures and determination of mean arterial blood pressure (MAP), ultrasound, Uterine artery doppler ultrasound examination with the determination of the mean Pulsatility index (PI) of the uterine arteries. Maternal serum levels of PlGF were also measured by specific immunoassay (ELISA). The measured values of MAP, mean uterine artery pulsatility index (PI) and PlGF were converted into multiples of the median (MoM). Then the FMF model was used for the determination of patient-specific risk of PE at 11-13 weeks conception in each case.
Results: The main results of the present study revealed that; Only 11 of 120 normal pregnant women were categorized as a high PE risk with a percentage of 9.2% and the rest 109 cases were low PE risk with a percentage of 90.8% by application of FMF algorithm**.** There was a significant difference between the high and low risks regarding the mean uterian UtA-Pi and PIGF levels at 11–13 weeks. Receiver operating characteristic curve (ROC) demonstrate to what extent it can be depended on PlGF, mean UtA-PI and MAP as a predictor for PE denoting the significant diagnostic performance for PIGF and mean uterine artery pulsatility index (PI). The optimal cutoff value of PlGF value using the ROC curve was ≤40 leading to a sensitivity of 90.91%, a specificity of 96.33%, a PPV of 71.4, a NPV of 99.1% and an accuracy of 95.83%. While the optimal cutoff measure of mean uterine artery PI value using the ROC curve was >1.91 leading to a sensitivity of 90.91%, a specificity of 96.33%, PPV of 71.4, NPV of 99.1% and an accuracy of 95.83%.
Conclusion: On the basis of these results, it could be concluded that the combined measurement of maternal serum PlGF concentrations and mean PI of the uterine arteries at 11–13 weeks of conception may help to predict the high-risk PE in primigravida when other parameters of PE anticipation are normal. And The FMF screening algorithm for the high-risk PE group performing satisfactorily. PE estimated by the competing risk model incorporated in the FMF algorithm may be applicable locally, and the earlier screening in conception would allow women at a higher risk to be monitored accordingly, participate in early intervention trials, and commence prophylactic therapy.

Keywords: Preeclampsia, placental growth factor, Pulsatility index, Fetal Medicine Foundation

Introduction
preeclampsia (PE) is one of the most dreaded conception problems. Several mechanisms have been linked to its development, which mostly affects women in their first trimester of conception and is caused by a combination of immunologic and hereditary factors, placental hypoperfusion,

oxidative stress, and other factors that result in vascular abnormalities, placental site trophoblast cell malfunction, shallow placenta insertion, and greater resistance to uterine artery blood circulation, even though the cause of PE is still under debate [1, 2].

Several epidemiologic and experimental researches have suggested that the abnormalities in circulating angiogenic factors released from the placenta are to blame for the maternal signs and symptoms of PE, despite the fact that the origin of the aberrant placentation is still being contested. Women with PE have significantly higher amounts of soluble fms-like tyrosine kinase 1, an antiangiogenic protein, in their blood than normal, but their levels of its ligand, placental growth factor (PlGF), are significantly lower. Preexisting PE symptoms are preceded by changes in these angiogenic factors, and the severity of the condition is correlated with these changes [3].

First-trimester screening may be significantly superior to a second-trimester approach. Predicting PE early will allow for frequent monitoring of the mother and foetus and the use of preventative measures, which will lower the associated morbidity and death [4].

PE has been largely prevented by preventative measures beginning in midconception. Before this could be examined, it is imperative to create a way of early and effective identification of the high-risk. It is unclear whether interventions beginning in the first trimester rather than the second would prove to be more beneficial in the prevention of PE [5].

A number of characteristics in the maternal history, such as nulliparity, a BMI, and a prior or familial history of PE, enhance the risk of developing PE [6]. Doppler studies of the uterine arteries and other biochemical blood indicators were used in several trials to predict PE. However, no approach that has a good predictive value has been developed to date [7].

Pregnant women can receive the majority of current screening techniques for early onset PE within the first trimester of their conception. Screening using a combination of biochemical markers, mean arterial pressure, uterine artery Doppler, and maternal risk factors [8].

The fetal medicine foundation (FMF) has created a different method of PE screening. According to studies using the most popular PE predictive algorithm, FMF, the mean arterial pressure (MAP) and mean uterine artery pulsatility index (UtA-PI) at eleven to thirteen weeks conception are higher in women who will later develop PE, and are especially increased in those who develop early-onset PE, compared with unaffected pregnancies, according to research using the most widely used predictive algorithm for PE is FMF [9].

Therefore, the detection rate (DR) increases with the addition of these markers to maternal variables, allowing for the diagnosis of more than 90% of preterm births that require delivery before 32 weeks and roughly 75% of all preterm births. From this standpoint, screening by maternal variables alone is inferior to the FMF algorithm [10].

Therefore, the purpose of the current study was to determine whether measuring maternal serum PlGF in conjunction with the mean PI of the uterine arteries can be used to predict PE in primigravida early on. Additionally, the FMF Algorithm's diagnostic accuracy for the early detection and anticipation of high-risk PE at 11–13 weeks of conception in a group of pregnant women was also examined.

Patients and Methods

This study included one hundred and twenty primigravida women with living, singleton fetus at 11-13 weeks conception without risk factors other than being primigravida attending antenatal care clinic at the Department of Obstetrics and Gynecology at Tanta University Hospitals and all procedures were assessed and approved ethically by Local Ethics Committee of Tanta University Hospitals. and they fulfilled the following.

Inclusion criteria

1. Age between 22-35 years.
2. Primigravida.
3. Connectional age between 11 and 13 weeks (assessed by the first day of the last menstrual period and confirmed by ultrasound).
4. Single viable intrauterine conception (confirmed by ultrasound).

Exclusion criteria were: Those women with; with a body mass index (BMI) ≥25 kg/m^2; pre-existing maternal diseases such as renal diseases and diabetes, autoimmune diseases, hypertension, intrauterine fetal death, fetal anomalies, and pelvic pathology. The duration of the study was from June 2021 till June 2022.

All cases were subjected to ; A signed informed written consent, full history taking then a general and abdominal examination to rule out any underlying medical conditions, estimation of BMI according to Battacharya *et al*., (2007) [11], blood pressures and determination of MAP according to standardized protocols [12], ultrasound to confirm the conceptional age, viability and any anomalies [13], evaluation of the uterine arteries using a doppler ultrasonography to calculate their mean pulsatility index (PI). At the initial antenatal care appointment, all patients had fundamental investigations to rule out any underlying medical conditions [14]. Specific immunoassays (ELISA) were used to measure the levels of PlGF in the maternal serum [15]. Multiples of the median (MoM) were created using the measured values of mean arterial pressure, UtA-Pi, and PlGF [16, 17]. The risk of PE specific to each patient was then determined at 11–13 weeks of conception using the Fetal Medicine Foundation (FMF) model [18]. Cases that didn't complete the study were replaced by new ones from the obstetric clinics. The newly discovered hypertension and proteinuria after 20 weeks of conception were used to diagnose PE. Hypertension is diagnosed when the systolic and/or diastolic blood pressures are checked twice, six hours apart. Using the dipstick approach, proteinuria was also identified when a 24-hour urine collection contained less than 300 mg of protein or when two readings were greater than one. Conceptional age was determined from the fetal crown-rump length (CRL).

Statistical analysis of the data

With the aid of the IBM SPSS software package version 20.0, data were fed into the computer and evaluated. (IBM Corp, Armonk, NY). The Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to confirm the normality of the distribution. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterise quantitative data (IQR). At the 5% level, significance of the results was determined. The receiver operating characteristic (ROC) curve was used to identify the ideal cutoff values for uterine artery PI, MAP and PIGF.

Results

One hundred twenty normal pregnant women were included, only 11 of them were categorized as a high PE risk with a percentage of 9.2% and the rest 109 cases were low PE risk with a percentage of 90.8% by application of FMF Agorithm (table 1).

Table 1: Distribution of the studied cases according to preeclampsia risk

Preeclampsia risk	No.	%
Low	109	90.8
High	11	9.2

Table 2 displays demographic information and clinical characteristics of expectant mothers. Insignificant variations in mother age, weight, height, BMI, or conceptional age between the low-risk and high-risks either by last menstrual period (LMP) or by ultrasound (US).

Table 2: Comparison between low and high preeclampsia risks according to the demographic data and the clinical features

	Total (n = 120)	Preeclampsia risk		t	p
		Low (n = 109)	High (n = 11)		
Age of pregnant women (years)					
Min. – Max.	22.0 – 35.0	22.0 – 35.0	22.0 – 28.0	0.956	0.341
Mean ± SD.	25.76 ± 2.43	25.83 ± 2.45	25.09 ± 2.21		
Median (IQR)	25.0 (24.0 – 27.0)	25.0(24.0 – 27.0)	25.0(23.50 – 27.0)		
Conceptional age (weeks)					
By LMP					
Min. – Max.	11.0 – 13.0	11.0 – 13.0	12.0 – 13.0	1.429	0.156
Mean ± SD.	12.13 ± 0.68	12.10 ± 0.70	12.41 ± 0.49		
Median (IQR)	12.0 (12.0 – 13.0)	12.0 (12.0 – 13.0)	12.0 (12.0 – 13.0)		
By US					
Min. – Max.	11.0 – 13.0	11.0 – 13.0	12.0 – 13.0	1.389	0.168
Mean ± SD.	12.08 ± 0.71	12.06 ± 0.72	12.36 ± 0.50		
Median (IQR)	12.0 (12.0 – 13.0)	12.0 (12.0 – 13.0)	12.0 (12.0 – 13.0)		
Height (cm)					
Min. – Max.	160.0 – 171.0	160.0 – 171.0	160.0 – 170.0	0.020	0.984
Mean ± SD.	166.5 ± 3.48	166.5 ± 3.40	166.5 ± 4.41		
Median (IQR)	168.0(165.0 – 170.0)	167.0(165.0 – 170.0)	168.0(162.5 – 170.0)		
Weight (kg)					
Min. – Max.	67.0 – 85.0	67.0 – 85.0	70.0 – 81.0	0.753	0.453
Mean ± SD.	73.97 ± 4.35	73.87 ± 4.40	74.91 ± 3.88		
Median (IQR)	73.50 (70.0 – 78.0)	73.0(70.0 – 78.0)	75.0(72.0 – 78.0)		
BMI (kg/m^2)					
Min. – Max.	24.20 – 29.70	24.20 – 29.70	24.90 – 29.30	0.898	0.371
Mean ± SD.	26.68 ± 1.44	26.65 ± 1.44	27.05 ± 1.43		
Median (IQR)	26.45(25.65 – 27.70)	26.40(25.60 – 27.70)	27.0 (25.85 – 28.10)		

Interquartile range (IQR) "SD" stands for "standard deviation." Value of the Student t-test to differentiate between those at low and high risk for preeclampsia

Table (3) shows the statistical comparison between the two studied groups according to the blood pressures. There were insignificant differences between two studied groups regarding systolic, diastolic blood pressure and mean arterial blood pressure.

Table 3: Comparison between low and high preeclampsia risks according to blood pressures

Blood pressure (mmHg)	Total (n = 120)	Preeclampsia risk		t	p
		Low (n = 109)	High (n = 11)		
Systolic					
Min. – Max.	100.0 – 125.0	100.0 – 125.0	120.0 – 125.0	1.765	0.080
Mean ± SD.	119.6 ± 4.46	119.4 ± 4.56	121.8 ± 2.52		
Median (IQR)	120.0(119.0 – 120.0)	120.0(119.0 – 120.0)	120.0(120.0 – 125.0)		
Diastolic					
Min. – Max.	60.0 – 85.0	60.0 – 85.0	75.0 – 85.0	1.085	0.280
Mean ± SD.	78.81 ± 5.87	78.62 ± 6.07	80.64 ± 2.84		
Median (IQR)	80.0 (76.50 – 81.50)	80.0(75.0 – 80.0)	80.0(80.0 – 81.50)		
Mean arterial blood pressure					
Min. – Max.	76.67 – 98.33	76.67 – 98.33	91.67 – 97.0	1.473	0.143
Mean ± SD.	92.39 ± 4.60	92.20 ± 4.76	94.33 ± 1.74		
Median (IQR)	93.33 (91.67 – 95.0)	93.33 (90.0 – 95.0)	95.0 (93.0 – 95.0)		

Interquartile range (IQR) "SD" stands for "standard deviation." Student's t-test p: p value for comparing between low and high preeclampsia risks

Also, there were insignificant differences between the two groups as regards the routine laboratory investigations including; Liver function tests, kidney functions, hemoglobin concentration, platelets count**,** thyroid profile, and Hb A_{IC}%. (Table 4).

Table 4: Comparison between low and high preeclampsia risks according to laboratory investigations

		Total (n = 120)	Preeclampsia risk		Test of Sig.	p
			Low (n = 109)	High (n = 11)		
Liver and kidney function tests	**ALT (IU/L)**					
	Min. – Max.	10.0 –34.0	10.0 –34.0	11.0 –29.0	t= 0.679	0.499
	Mean ± SD.	19.88 ±4.94	19.97 ±4.96	18.91 ±4.93		
	Median (IQR)	18.0(16.0 –22.50)	18.0 (16.0 –23.0)	17.0 (16.50 –20.5)		
	AST(IU/L)					
	Min. – Max.	11.0 –37.0	11.0 –37.0	13.0 –33.0	t= 0.068	0.946
	Mean ± SD.	20.48 ±6.14	20.50 ±6.18	20.36 ±5.99		
	Median (IQR)	18.0(16.0 –25.0)	18.0 (16.0 –25.0)	19.0 (16.0 –24.50)		
	Serum albumin(mg/dL)					
	Min. – Max.	3.50 –5.70	3.50 –5.70	3.80 –5.0	t= 0.230	0.818
	Mean ± SD.	4.41 ±0.50	4.41 ±0.51	4.45 ±0.42		
	Median (IQR)	4.50(3.90 –4.70)	4.50 (3.90 –4.70)	4.50 (4.20 –4.70)		
	Serum urea (mg/dL)					
	Min. –Max.	14.0 –39.0	14.0 –37.0	15.0 –39.0	t= 0.948	0.345
	Mean ± SD.	25.88 ±5.46	25.72 ±5.38	27.36 ±6.31		
	Median (IQR)	26.0(24.0 –28.50)	26.0(24.0 –28.0)	28.0(26.50 –29.0)		
	Serum creatinine(mg/dL)					
	Min. – Max.	0.50 –1.0	0.50 –0.90	0.50 –1.0	t= 1.493	0.138
	Mean ± SD.	0.72 ±0.11	0.72 ±0.11	0.77 ±0.16		
	Median (IQR)	0.70 (0.60 –0.80)	0.70 (0.60 –0.80)	0.80 (0.70 –0.90)		
CBC	**Hb g/dl**					
	Min. –Max.	10.43 –14.0	10.43 –14.0	11.0 –13.50	t= 1.348	0.180
	Mean ± SD.	12.44 ±0.76	12.47 ±0.76	12.15 ±0.73		
	Median (IQR)	12.43 (12.0 –13.0)	12.50 (12.0 –13.0)	12.0 (11.85 –12.50)		
	Platelets $10^3/cm^3$					
	Min. – Max.	160.0 –400.0	160.0 –400.0	180.0 –390.0	t= 0.064	0.949
	Mean ± SD.	284.4 ±59.32	284.3 ±59.78	285.5 ±57.18		
	Median (IQR)	279.0(260.0 –340.0)	280.0(260.0 –340.0)	270.0(260.0 –312.5)		
Thyroid profile	**TSH m U/L**					
	Min. – Max.	0.59 –4.0	0.59 –4.0	1.48 –3.32	t= 0.227	0.821
	Mean ± SD.	2.26 ±0.80	2.26 ±0.82	2.32 ±0.64		
	Median (IQR)	2.40 (1.67 –2.87)	2.36 (1.67 –2.87)	2.56 (1.78 –2.76)		
	Free T3 pg/ml					
	Min. – Max.	0.80 –4.30	0.80 –4.30	1.20 –3.80	t= 0.325	0.751
	Mean ± SD.	3.17 ±0.71	3.17 ±0.68	3.07 ±1.01		
	Median (IQR)	3.30 (2.75 –3.70)	3.30 (2.80 –3.60)	3.60 (2.50 –3.80)		
	Free T4 ng/dL					
	Min. – Max.	0.60 –1.90	0.60 –1.90	0.70 –1.80	U= 563.5	0.742
	Mean ± SD.	1.14 ±0.37	1.14 ±0.37	1.08 ±0.36		
	Median (IQR)	1.20 (0.80 –1.40)	1.20 (0.80 –1.40)	0.90 (0.85 –1.35)		
Hb AIC%						
Min. – Max.		4.20 –5.40	4.20 –5.40	4.50 –5.20	t= 0.226	0.821
Mean ± SD.		4.76 ±0.29	4.76 ±0.29	4.74 ±0.22		
Median (IQR)		4.80 (4.50 –5.0)	4.80 (4.50 –5.0)	4.70 (4.55 –4.85)		

IQR: Inter quartile range SD: Standard deviation t Student t-test U: Mann Whitney test p: p value for comparing between low and high preeclampsia risk*: Statistically significant at $p \leq 0.05$

Table (5) shows the statistical comparison between the two studied groups according to; Fetal crown -rump length which show insignificant difference between the two groups. Regarding right, left and mean uterine artery pulsatility index (UtA-PI), there were statistically significant increase of their values in high PE risk. Serum human PlGF level showed a statistically significant lower values in high PE risk when compared to the low PE risk one.

Table 5: Comparison between low and high preeclampsia risks according to different parameters

	Total (n = 120)	Preeclampsia risk		t	p
		Low (n = 109)	High (n = 11)		
Fetal crown -rump length mm					
Min. – Max.	41.0 – 74.0	41.0 – 74.0	54.0 – 74.0	1.559	0.122
Mean ± SD.	58.33 ± 11.71	57.81 ± 11.81	63.55 ± 9.61		
Median (IQR)	54.0 (54.0 – 74.0)	54.0 (54.0 – 74.0)	64.0 (54.0 – 74.0)		
Uterine artery(PI)					
Right					
Min. – Max.	0.80 – 2.0	0.80 – 1.99	1.92 – 2.0	24.218*	<0.001*
Mean ± SD.	1.38 ± 0.30	1.32 ± 0.26	1.95 ± 0.03		

Median (IQR)	1.40 (1.24 – 1.52)	1.38 (1.24 – 1.47)	1.95 (1.93 – 1.97)		
Left					
Min. – Max.	0.64 – 2.50	0.64 – 2.0	1.89 – 2.50	7.066*	<0.001*
Mean ± SD.	1.58 ± 0.34	1.53 ± 0.29	2.17 ± 0.23		
Median (IQR)	1.63 (1.53 – 1.75)	1.62 (1.52 – 1.65)	2.16 (2.0 – 2.39)		
Mean					
Min. – Max.	0.89 – 2.25	0.89 – 1.97	1.91 – 2.25	9.836*	<0.001*
Mean ± SD.	1.48 ± 0.28	1.42 ± 0.21	2.06 ± 0.12		
Median (IQR)	1.49 (1.34 – 1.57)	1.47(1.33 – 1.54)	2.06(1.96 – 2.16)		
Placental growth factor (ng/L)					
Min. – Max.	28.0 – 75.0	40.0 – 75.0	28.0 – 43.0	14.091*	<0.001*
Mean ± SD.	60.79 ± 11.23	63.61 ± 7.05	32.91 ± 4.70		
Median (IQR)	64.0 (59.0 – 68.0)	65.0 (60.0 – 68.0)	30.0 (29.50 – 35.0)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test p: p value for comparing between low and high preeclampsia risk
*: Statistically significant at $p \leq 0.05$

Table (6) shows the Multiple of Median (MoM) in the two studied groups regarding mean UtA-PI, mean arterial blood pressure and serum PlGF level in the present study. Regarding (MoM) of mean UtA-PI, there was statistically significant increase of their values in high PE risk. Concerning (MoM) of PlGF levels in the two studied groups, they show statistical significant decrease of their levels in high PE risk, while (MoM) of MAP showed insignificant difference between the two studied groups.

Table 6: Comparison between low and high preeclampsia risks according to Multiple of Median (MoM) of different parameters.

	Total (n = 120)	Preeclampsia risk		t	p
		Low (n = 109)	High (n = 11)		
MoM of mean uterine artery PI					
Min. – Max.	0.49 – 1.85	0.49 – 1.85	1.10 – 1.40	7.934*	<0.001*
Mean ± SD.	0.87 ± 0.19	0.84 ± 0.16	1.22 ± 0.09		
Median (IQR)	0.86 (0.76 – 0.94)	0.85 (0.76 – 0.92)	1.21 (1.14 – 1.27)		
MoM of mean arterial blood pressure					
Min. – Max.	0.84 – 1.13	0.84 – 1.13	0.92 – 1.11	1.931	0.080
Mean ± SD.	1.0 ± 0.06	1.0 ± 0.05	1.04 ± 0.08		
Median (IQR)	1.0 (0.96 – 1.03)	1.0 (0.96 – 1.03)	1.09 (1.0 – 1.09)		
MoM of placental growth factor					
Min. – Max.	0.45 – 1.18	0.61 – 1.18	0.45 – 0.86	11.445*	<0.001*
Mean ± SD.	0.96 ± 0.17	0.99 ± 0.11	0.58 ± 0.15		
Median (IQR)	1.0 (0.92 – 1.06)	1.02 (0.94 – 1.06)	0.55 (0.47 – 0.61)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test p: p value for comparing between low and high preeclampsia risk *: Statistically significant at $p \leq 0.05$

Table (7) and figure (1) illustrate the Receiver operating characteristic curve (ROC) to demonstrate to what extent it can be depended on PlGF, mean UtA-PI and MAP as a predictor for high-risk PE denoting the significant diagnostic performance for PIGF and mean UtA-PI. The optimal cut-off measure of PlGF value using the ROC curve was ≤ 40 leading to a sensitivity of 90.91%, a specificity of 96.33%, a PPV of 71.4, a NPV of 99.1% and an accuracy of 95.83%. While the optimal cut-off measure of UtA-PI using the ROC curve was >1.91 leading to a sensitivity of 90.91%, a specificity of 96.33%, a PPV of 71.4, a NPV of 99.1% and an accuracy of 95.83%.

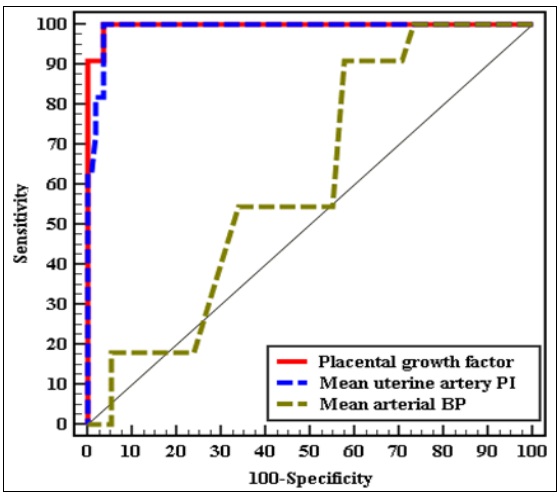

Fig 1: Prognostic performance for placental growth factor, mean uterine artery pulsatility index (PI) and mean arterial blood pressure to prognosis patients with high preeclampsia risk (n = 11) from low preeclampsia risk patients

Table 7: Validity (AUC, sensitivity, specificity) for placental growth factor, mean uterine artery pulsatility index (UtA-Pi) and mean arterial blood pressure to prognosis patients with high preeclampsia risk (n = 11) from low preeclampsia risk patients

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
Placental growth factor	0.997	<0.001*	0.989 – 1.004	≤40	90.91	96.33	71.4	99.1	95.83
Mean Uterine artery pulsatility index (UtA-Pi)	0.990	<0.001*	0.977 – 1.004	>1.91	90.91	96.33	71.4	99.1	95.83
Mean arterial blood pressure	0.614	0.213	0.472 – 0.757						

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals NPV: NPV PPV: PPV *: Statistically significant at $p \leq 0.05$

Discussion

Preeclampsia (PE) is one of the dangerous conception medical problems. PE-prone women are thought to have a defective placentation as early as the first trimester, according to current thinking. Predicting PE early will allow for frequent monitoring of the mother and foetus and the use of preventative measures, which will lower the associated morbidity and death [5].

The proliferation and migration of endothelial cells as well as vascular permeability are influenced by a number of angiogenic-related molecules, including PlGF, a proangiogenic member of the VEGF family. Placental dysfunction is more likely to emerge when pro- and antiangiogenic forces are out of balance [19]. Studies done during the second trimester show that blood pressure monitoring is a useful screening technique for the emergence of PE. Throughout conception, it is essential to maintain the mother's arterial blood pressure be kept under control [20].

In both the second and first trimesters of conception, researchers have previously looked into the measures of uterine artery Doppler studies in predicting PE. Vascular resistance in the placenta has been linked to the abnormal placental function that characterizes PE [21].

There have been numerous first trimester anticipation models created. Most of them have not undergone external validation or have failed it. However, it is important to point out that the FMF first trimester anticipation model has undertaken productive internal and external validation. This model combines maternal factors with measurements of mean arterial pressure, uterine artery pulsatility index, and serum PlGF [22].

The present study included 120 pregnant women at 11-13 weeks of conception and only 11 of them were categorized as a high PE risk with a percentage of 9.2% and the rest 109 cases were low PE risk with a percentage of 90.8% by application of FMF algorithm**.**

The results of the present study are in line with other previous studies that documented the importance of FMA in the early anticipation of high risk preeclamptic patients;

Lobo *et al*., (2019) [23] found that the FMF algorithm was demonstrated to be successful in predicting high risk PE in an early-onset variant of the illness in a Brazilian population.

Also in line with our observations, Stepan *et al*., (2020) [24] demonstrated that the FMF algorithm can be used to determine the risk for PE and may be improved upon. This algorithm combines information on risk factors of high risk preeclamptic women, such as placental perfusion (uterine artery pulsatility index [UtA-PI] plus mean arterial pressure), clinical characteristics (maternal factors/medical history), and biochemical markers of PIGF.

According to our results The FMF algorithm, while functioning satisfactorily, could still be improved, according to Prasad *et al*., (2021) [25] who also found that screening for preterm PE in India using the first trimester multi-marker screening approach would be an improvement over the current standard of screening by maternal characteristics alone. This is so that biophysical and biochemical markers are appropriately adjusted for native South Asian women.

Additionally, in line with the current study The FMF algorithm was found to be both practicable and successful in a public healthcare context for the anticipation of high-risk PE by screening at 11–13 weeks' conception, according to Cabunac *et al*., (2021) [26], Shen *et al*., (2021) [27] and Guy *et al*., (2021) [28].

The findings of Chaemsaithong *et al*., (2022) [29] are also consistent with our findings, which showed that the FMF's first trimester prediction model had successfully undergone internal and external validation. As a result, this screening performed better than the conventional method, which relied solely on maternal risk factors.

The current study found no statistically significant differences between the two analysed groups for routine laboratory tests, body mass index, or mean arterial blood pressure when comparing the high risk and low risk preeclamptic groups.

PE can be predicted with more accuracy in the second trimester of conception by the use of Uterine Artery Doppler study than in the first, according to research on the subject. It also played a significant part in foretelling severe or early-onset PE in low-risk populations [30].

Doppler studies of the uterine artery may be more predictive of PE if measured repeatedly in the first half of conception, according to research, which also found that using the first-trimester uterine artery Doppler in PE anticipation had an overall sensitivity of 26% and specificity of 91%. However, this will eliminate the possibility of beginning prophylaxis early [31, 32].

In the present study, there were statistically significant increases in the right, left, and mean UtA-PI values in the high PE risk compared to the low PE risk. The ROC curve's ideal cutoff PI value was >1.91, with accuracy of 95.83%, sensitivity of 90.91%, specificity of 96.33%, PPV of 71.4, and NPV of 99.1%.

Our findings are consistent with those of Salem and Ammer (2018) [5], who noted that the mean uterine artery (UtA-PI) at 11–13 weeks of conception in their study may help predict PE in primigravida when other PE anticipation parameters are normal and a lower cutoff value for uterine artery Doppler in their studies was (PI > 1.69), but they also came to the opposite conclusion. Additionally, they stated that in order to boost the uterine artery PI's predictive power, serum biochemical indicators should be added to it rather than using it alone as a regular diagnostic test.

Additionally, Oancea *et al*., results (2020) [32] concur with our findings, which established that uterine artery Doppler examination is a reliable non-invasive screening test for the emergence of PE in pregnancies at risk. This test is particularly appropriate in health systems with limited resources for assessing other biomarkers.

Also, Das *et al*., (2022) [33] discovered that uterine artery Doppler, performed in the first trimester at 11-13+6 weeks, is a reliable indicator of conception-related hypertension (including PE and conceptional hypertension).

In terms of serum levels of human PlGF in the two studied groups, the high PE risk had statistically lower levels than the low PE risk. The ROC curve's best PlGF cutoff value was 40, with accuracy of 95.78%, sensitivity of 90.91%, specificity of 96.33%, PPV of 71.4, and NPV of 99.1%.

Our findings are in-agreement with those of Myatt *et al*. (2012) [14] which showed a significant drop in serum PlGF levels in PE patients compared to controls, but not with our findings for the ROC curve, which had the highest area under the curve (0.61) with the highest sensitivity (32%), and specificity (80%).

Salem and Ammer's (2018) [5] findings are in accordance with our results, which showed that preeclamptic women had significantly lower serum PlGF concentrations than healthy women. This may be because PE is primarily caused by abnormal placentation, which reduces PIGF production. Pregnant women who will develop PE typically have lower first-trimester levels of serum PIGF. The best cutoff PlGF value using the ROC curve of their studies was 0.91 MoM, leading to a sensitivity of 90%, a specificity of 82.6%, a PPV of 36.5%, a NPV of 98.7%, and an accuracy of 83%. As for the ROC curve results of their study, they disagree with our results.

Saleh *et al*., (2016) [34] 's studies are also corroborated with our findings, which showed that pre-eclamptic patients and women with pre-existing conditions that predispose them to or mimic PE have significantly higher serum levels of the soluble fms-like tyrosine kinase-1 (sFlt-1), an inhibitor of PIGF, with subsequently lower (PlGF), compared to healthy pregnant women.

Agrawal *et al*. Findings (2019) [35] are consistent with our findings in that PlGF is frequently employed as a screening tool in the diagnosis of PE. which decreases in women who are going to get PE. This drop is known to occur before the onset of PE's actual symptoms, making it an effective screening tool for diagnosing the condition.

The findings of the present study are consistent with the results of Fillion *et al*., (2020) [36] and Fillion *et al*., (2021) [37] that documented decreased serum level of PIGF in preclampsia which may be due to the higher maternal blood levels of soluble fms-like tyrosine kinase-1 (sFlt-1), an inhibitor of PIGF, and subsequent lower levels of PlGF which appear before the clinical onset and is used for the anticipation of PE.

Additionally, our results with a significantly lower maternal blood PIGF level in high-risk PE, are consistent with the findings of Gbadegesin, *et al*., (2021) [38] Additionally, they showed that little is known about the mechanisms underlying the altered maternal plasma PIGF concentrations in women with PE. While inadequate remodeling of spiral arteries and neo-angiogenesis, which are crucial for health and growth in a typical conception, may arise from reduced oxygen tension in the placenta, in-vitro studies indicate that these factors' altered amounts may occur as a result.

Conclusion

The combined measurement of maternal serum PlGF concentrations and the mean PI of the uterine arteries at 11–13 weeks of conception may aid in the anticipation of high-risk PE in primigravida when other PE prediction criteria are normal, according to the present study.

The high-risk PE group's FMF screening methodology is operating satisfactorily. The competing risk model used by the FMF algorithm to predict PE may be applicable locally, and earlier prenatal screening would enable women with a higher risk to be monitored appropriately, take part in early intervention trials, and start preventative medication.

Recommendations

Our study's limited sample size was a major drawback. For this reason, we focused only on the foretelling of high-risk PE in general. Finding those at risk for getting PE early will enable for preventative therapy to be given. High-risk PE may be detected early with the use of a screening algorithm that incorporates the FMF, but further research with a large sample size is required to properly evaluate and strengthen its application.

Conflict of Interest

Not available

Financial Support

Not available

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