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First trimester prediction for preeclampsia using maternal characteristics, placental growth factor and estimated placental volume

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Abstract
Background: Preeclampsia is a frequent obstetric complication that results in mortality and morbidity in both the mother and the foetus. This study aims to evaluate the placental volume's sensitivity measured by 3D Ultrasonography, placental growth factor (PIGF) & maternal characteristics for predicting preeclampsia in the first trimester.
Methods: 85 pregnant women participated in this prospective research with clinical criteria of singleton pregnancy and the gestational age of 11-13 weeks at study enrolment. All patients were subjected to 3D placental ultrasound and specific investigation (PlGF). Human PLGF ELISA kits were used to determine the serum level in duplicate.
Results: Among our included females 27.1% were PG while 72.9% were multipara, 14.1% have past history of hypertension and 5.9% have past history of preeclampsia and 10.6% develop preeclampsia; 3 were early in pregnancy and 6 were late in pregnancy. Females with preeclampsia have statistically significant higher past history of hypertension and preeclampsia and have higher preterm labor than females without preeclampsia while them have lower PlGF and estimated placental volume than females without preeclampsia. At cut off level of < 108, estimated placental volume and PlGF have sensitivity of 96.1% and specificity of 88.9% for predicting preeclampsia.
Conclusion: Screening for pre-eclampsia at 11-13 weeks' gestation using placental volume and PIGF is associated with a high prediction rate with low false positive rate.

Keywords: First trimester prediction, preeclampsia, maternal, placental growth factor

Introduction

The probability of long-term cardiovascular and cerebrovascular disorders is elevated with preeclampsia. It is associated with a defect in the spiral arteries' trophoblastic invasion, which might be connected to a decline in placental perfusion and a rise in uterine artery vascular resistance [1].

Because the placenta is essential to fetal development and is responsible for supplying the fetus with nutrients and oxygen, a defective placentation throughout a pregnancy's first trimester may be a significant factor for estimating the probability of difficulties later in pregnancy. Pre-eclampsia develops because of poor placentation. Furthermore, there is a significant correlation between the birth weight and the placental size and form during delivery [2].

The development of a three-dimensional ultrasonography enhances precision and offers precise assessments of the placental volume throughout the first trimester of gestation. Like uterine perfusion, trophoblast invasion may be reflected in placental volume, but considerably earlier - during the first trimester. Particularly, it has been demonstrated that preeclampsia is substantially correlated with the assumption of a decreased early placental volume (PV) [3].

In order to predict pre-eclampsia, previous research has evaluated placental volume using 3D ultrasound during the first trimester. This may provide a more direct assessment of the abnormal placentation process hypothesized to signal the development of preeclampsia [4]. The sensitivity for detection of pre-eclampsia ranged from 38.5% to 63.4%. Maternal features and biomarkers were added to placental volume to screen for early and late pre-eclampsia in the first trimester [5].

Placental growth factor (PlGF), a polypeptide growth factor, belongs to the family of vascular endothelial growth factors that control the development of the placental villi in the early stages

of pregnancy. To guarantee a healthy pregnancy result, this regulatory function is crucial for developing placental blood circulation. Serum PlGF levels become functionally deficient when pregnant women with preeclampsia have high serum Fms in their circulation, such as tyrosine kinase (sFlt-1). Preeclampsia is characterized by a widespread endothelial damage brought on by a decreased serum PlGF level. When preeclampsia develops early in pregnancy, a low maternal serum PlGF level at 22-24 weeks of gestation is linked to an increased risk of postpartum hemorrhage [1].

A subset of women with an early and more significant manifestation of the condition are identified by the PlGF ratio, which is indicated by persistently decreased levels of PlGF during pregnancy and abnormal sFLT-1. To enable more focused study on pre-eclamptic subtypes of pre-eclampsia, angiogenic factors may be used to classify pre-eclamptic individuals [6].

Furthermore, PE predominantly impacts primigravidas, while some individuals may experience recurrence in later pregnancies. Pregestational diabetes, gestational diabetes, obesity, and other health issues are risk factors [5].

This study aims to evaluate the placental volume's sensitivity measured by 3D Ultrasonography, PIGF & maternal characteristics for predicting preeclampsia in the first trimester.

Patients and Methods

This prospective study was carried on 85 pregnant women, aged 18-34 years old, with clinical criteria of singleton pregnancy and the gestational age of 11-13 weeks at study enrolment.

The study was done from September 2021 to September 2022 after approval from the Ethical Committee Tanta University Hospital, Egypt. The patients gave their informed written consent. All maternal systemic disorders were considered exclusion criteria ex: chronic hypertension, diabetes mellitus, renal illness, collagen vascular disease, malignancies, fever, either recent or current infections, multiple pregnancies, auto immune diseases, women with uterine or foetal abnormalities (structural or chromosomal), and aspirin users.

All patients were subjected to complete history taking, complete physical examinations, laboratory investigations: (ABO grouping, RH typing, automated complete blood count, and urine analysis) and specific investigation (PlGF).

Placental growth factor (PlGF)

Venipuncture was used to take participants' blood samples, which was then collected via a serum-separator tube. Centrifugation was performed for 10 minutes at 10,000 RPM in order to extract the serum. Aliquoted serum samples were kept at -70 °C.

The serum concentrations were measured in duplicate using human PLGF ELISA kits. After the standards and samples were placed within wells, they were pre-coated for 2hours with a monoclonal antibody specific for PLGF, washed 4 times, and then incubated for another 2 hours with an enzyme-linked polyclonal antibody specific for PLGF. After a further washing step (4X), the addition of substrate solution (30 min in the dark) and stopping solution.

For every serum sample, the optical density at 450 nm and the optical correction at 540 nm were measured using a microplate reader. By comparing the results to measurements from standard curves, the concentrations of PLGF determined. Picograms per millilitre were used to describe PLGF concentrations.

3D placental ultrasound and detection of placental volume

Images were acquired during the first trimester visit and utilised to calculate the placental volume and vascularization indices. All of the photos were obtained using an ultrasound device that has a transducer operating at 4-8 MHz. In all cases, a similar prepared instrument power settings (actual power: 2 dB; filter: 2, actual power: cent, smooth: 4/5, FRQ: low, quality: 16, density: 6, enhance: 16, balance: GO150, and pulse repetition frequency: 0.9) were employed.

The 3D transabdominal placental volume was measured by setting the sweep angle at 85o perpendicular to the placental plate. The placenta was then divided into six parts, each acquired by rotating the preceding portion by 30 degrees. The uterine wall was not included while drawing the placenta's contour by manual tracing in each of the six planes. It was often thickened under the placenta at this stage of the pregnancy due to contraction or hypertrophy. An estimated 10 to 15 seconds were spent acquiring the images. A little lateral inclination of the transducer was employed to get posterior and laterally placed placental images. The regions marked in each of the six planes were being used by a software programme to calculate the volume. The 4D View computer software's VOCALTM programme was utilised.

Sample Size Calculation

This study based on study performed by Elkady *et al*., 2017 [7]. The following assumptions were taken into account while using Epi info STATCALC to calculate the sample size: - 95% two-sided confidence level, at an 80% power. & an error of 5% odds ratio calculated= 1.115. 89 was the final maximum sample size that could be obtained from the Epi-Info output. In order to account for any cases that may be dropped during follow-up, the sample size was raised to 100 cases.

Statistical analysis

Using SPSS v26, statistical analysis was performed. (IBM Inc., Chicago, IL, USA). The standard deviation (SD) and mean were used to represent quantitative variables, frequency and percentage (%) for qualitative variables.

Results

The age of the studied females ranged between 18-34 years with mean value of 26.882±4.057 years and their BMI ranged between 19-29 with mean value of 25.118±2.311. Among our included females 27.1% were PG while 72.9% were multipara, 14.1% have past history of hypertension and 5.9% have past history of preeclampsia and 10.6% develop preeclampsia; 3 were early in pregnancy and 6 were late in pregnancy. Table 1.

Table 1: The clinical characteristics and preeclampsia among the studied population

		N=85
Age (Y)		26.882±4.057
BMI		25.118±2.311
Gravidity		
Primigravida		23 (27.1%)
Multiparity		62 (72.9%)
Past history of hypertension		12 (14.1%)
Past history of preeclampsia		5 (5.9%)
Preeclampsia		9 (10.6%)
Time of Preeclampsia	Early	3/9 (33.3%)
	Late	6/9 (66.7%)

Data are presented by Mean ± SD or number (%). BMI: Body mass index

Females with preeclampsia have statistically significant higher past history of hypertension and preeclampsia and have higher preterm labor than females without preeclampsia while them have lower PlGF and estimated placental volume than females without preeclampsia. Table 2

Table 2: Comparison of obstetric data, placental growth factor and estimated placental volume of the studied population

		Preeclampsia	No Preeclampsia	
		N=9	N=76	P-value
Parity	PG	2 (22.2%)	21 (27.6%)	0.101
	1	0 (0%)	8 (10.5%)	
	2	0 (22.2%)	32 (42.1%)	
	3	5 (55.6%)	15 (19.7%)	
Past history of hypertension		5 (55.6%)	7 (9.2%)	<0.0001
Past history of preeclampsia		4 (44.4%)	1 (1.3%)	<0.0001
Type of labor	NVD	2 (22.2%)	43 (56.6%)	0.051
	CS	7 (77.8%)	33 (43.4%)	
GA at birth	Full-term	7 (77.8%)	75 (98.7%)	<0.0001
	Preterm	2 (22.2%)	1 (1.3%)	
PLGF		94.11±10.39	129.36±10.80	<0.0001
EPV		108.22±7.66	222.36±10.80	<0.0001

Data are presented by Mean ± SD or number (%). PG: Primigravida. NVD: normal vaginal delivery. CS: Cesarean Section. GA: Gestational Age. PLGF: placental growth factor. EPV: estimated placental volume

At cut off level of < 108, PlGF has sensitivity of 96.1% and specificity of 88.9% for predicting preeclampsia. Figure 1.

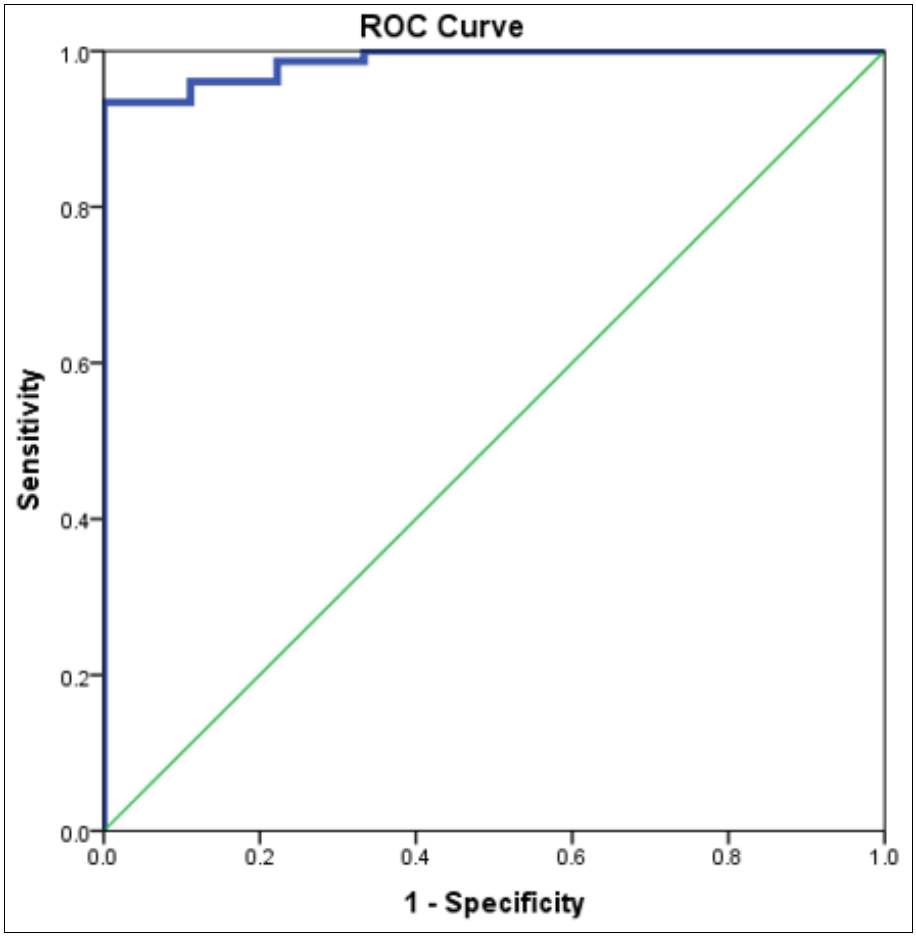

Fig 1: ROC curve for placental growth factor as a predictor for preeclampsia

At cut off level of < 108, estimated placental volume have sensitivity of 96.1% and specificity of 88.9% for predicting preeclampsia. Figure 2.

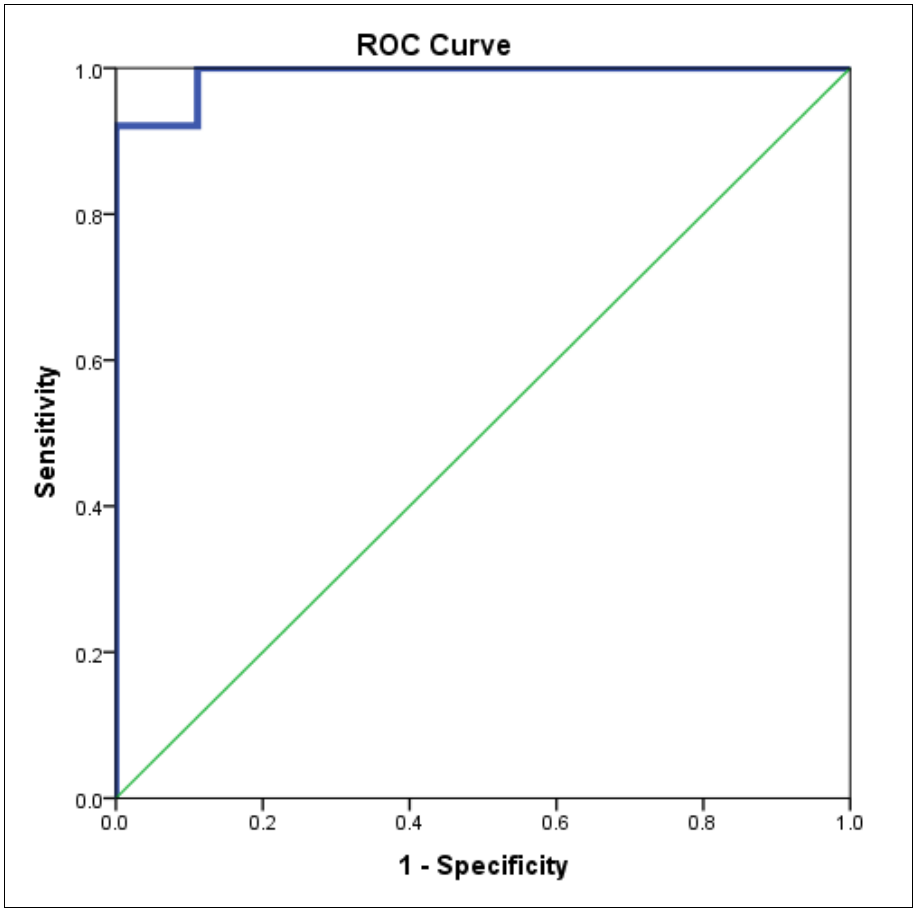

Fig 2: ROC curve for estimated placental volume as a predictor for preeclampsia

Discussion

Preeclampsia (PE) is a unique placenta-mediated illness that causes severe obstetrical systemic hypertension crisis during pregnancy and has an unclear aetiology. PE is still one of the primary causes of maternal and fetal mortality and morbidity worldwide. It affects 2-3% of pregnant women globally and up to 10% of pregnancies in developing countries. Over the past 10 years, a huge amount of research has been done on PE screening in those at greatest risk with the goal of lowering the disease's prevalence by pharmacologic intervention finding the ideal time and location for birth can also help minimise unfavourable perinatal outcomes for women who suffer from PE [8].

In this study, there was significant difference between females with preeclampsia and females without preeclampsia regarding GA at birth. This is in accordance with Kim *et al.* [9] who reported that there was a significant difference (p<.001) in the gestational age at birth between the PE and normal groups.

Regarding parity and the method of labour, there was no significant difference in this study between the preeclamptic and non-preeclamptic females. This agrees with Negm *et al.* [10] He said that there were no significant differences in mean number of deliveries or parity between the research's examined groups. This contradicts the results of Kashanian *et al.* [11] who examined the risk factors for preeclampsia and found that having more than one child is a significant protective factor against preeclampsia. This could be explained because during a first pregnancy, the mother's body is still adapting to the demands of pregnancy, including the development of the blood vessels supplying the placenta. In this study, females with preeclampsia have statistically significant lower PlGF than females without preeclampsia. This is in accordance with Negm *et al.* [10] who reported that, Patients with PE had reduced maternal PLGF levels than women in the control group when the study groups' levels were examined.

This is consistent with Mosimann *et al.* [12], who investigated the value of repeating first trimester PLGF in PE screening as well as the importance of timing it. Study by Akolekar *et al.* [13] has repeatedly demonstrated that, compared to women whose pregnancies are normal, those who get preterm PE have far lower PlGF levels in the first trimester. Moreover, a considerable correlation is observed between serum PlGF concentrations and the risk of PE, which is determined by the neonatal birthweight percentile and the gestation at the time of iatrogenic delivery.

In contrast, Sonek *et al.* [5] reported that, PlGF values did not reach statistical significance. On the other hand, the predicted median (MoM) level of 0.7 was in line with other research and implies that the limited sample size may have contributed to the lack of significance. This could be explained that the differences in findings between our study and them are due to differences in study design and sample size. Placental volume is diminished, and abnormal vascularity is seen in pregnancies that are determined to develop PE. At 11.0 to 13.6 weeks Collins *et al.* [14].

In this study, females with preeclampsia have significant lower estimated placental volume than females without preeclampsia. Our results are in agreement with Kim *et al.* [9] who reported that, Women who experienced PE tended to experience less EPV, and this difference became statistically significant.

This disagreed with Sonek *et al.* [5] who reported that, EPV seemed to be lower in individuals having preeclampsia, but this did not reach statistical significance. The difference between our study and them could be due to differences in the sample size or they may have different criteria for defining preeclampsia or

different ways of measuring placental volume, which could have influenced the results.

In this study, at cut off level of < 108 pg/mL, PlGF has sensitivity of 96.1% and specificity of 88.9% for predicting preeclampsia.

This agrees with Mazer Zumaeta *et al*. [15] who reported that, PlGF is the most accurate first-trimester indicator of PE, able to guess around 85% and 75% of births with PE < 34 and < 37 weeks' gestation, at a screen-positive rate of 10%.

Our results are supported by Agrawal *et al*. [16]. Who tried to see if PlGF could accurately predict PE in women without symptoms? The study found that when the test was conducted at or after 14 weeks of pregnancy as compared with early in the pregnancy, the predictive odds ratio (POR) increased dramatically. By increasing gestational age, its sensitivity grew significantly (51%-67%) without a notable loss in specificity (89%-83). The test's accuracy increased much more when it was performed at or after 19 weeks. This disagrees with Negm *et al*. [10] who reported that In terms of predicting early and late PE, PLGF's sensitivity was 43% and 37% and its specificity was 91% and 89%, respectively. Combined PLGF and Uterine Artery Doppler pulse index (UADPI) in their study proved to be 65.5% sensitivity, 98.8% specificity, 33.3% PPV and 93.5% NPV value. The differences in findings could be because to variations in the patient population, sample size, and study design.

This is also in contrary with Andrietti *et al*. [17] who found that screening in the early third trimester had a greater impact on PE prediction than evaluating PLGF in the first or second trimester. This may be since their screening at 30-34 weeks failed to increase the rate of identification of early PE when compared to biomarker readings acquired at 11-13 and/or 19-24 weeks. This is because they may be reporting on different aspects of the utility of PlGF as a biomarker for predicting pre-eclampsia.

At a fixed false-positive rate (FPR) of 10%, PlGF's detection rates (DR) for early- and late-onset PE are 55% and 33%, respectively [13].

In this study, at cut off level of < 108, estimated placental volume have sensitivity of 96.1% and specificity of 88.9% for predicting preeclampsia.

In contrary, Pregnancies shown to be at risk for PE have a decreased placental volume and abnormal vascularity at 11þ0 to 13þ6weeks, which could assist in determining the possibility of developing PE in the first trimester pregnancy Collins *et al*. [14].

Limitations: the number of women with PE was relatively small, with the inevitable wide CIs obtained for the performance of screening. The low incidence of PE is most likely the cause of this. The effectiveness and cost-benefit analysis of integrated intervention or prevention strategies based on positive early-risk prediction for PE should be conducted in future research, along with a large-scale evaluation of these predictive models.

Conclusion

Using placental volume and PIGF to screen for PE between weeks 11 and 13 of gestation has an elevated prediction rate and a decreased false positive rate.

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Conflict of Interest: Nil.

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