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Serum Placental Growth Factor and Uterine Artery pulsatility Index act complementary for Early Prediction and Stratification of Pre-eclampsia among Primigravidae

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Abstract

Objectives

To evaluate value of estimation of serum Placental Growth Factor (PLGF) and Uterine Artery Doppler (UAD) measurement of Pulsatility Index (PI) for prediction and categorization of Pre-Eclampsia (PE) among normotensive primigravidae.

Patients & Methods

396 normotensive primigravida gave blood sample at 12th Gestational Week (GW) for ELISA estimation of serum PLGF and undertook UAD-PI measurement at 20th GW and continued 4-wk follow-up till delivery for development of PE manifestations.

Results

Forty-seven women developed PE; 11 women developed early-onset PE and 8 women developed severe PE. Mean blood pressure measurements at time of PE development were significantly higher in PE women than controls, with early-onset PE compared to late-onset PE and in women had severe PE than those had mild PE. Estimated levels of PLGF were significantly lower and UAD-PI measurements were significantly higher in PE women than in controls and in women developed early-onset or severe PE than in those developed late-onset or mild PE, respectively. Statistical analyses showed that high UAD-PI measurements at 20th GW are specific and low serum PLGF estimated at 12th GW are sensitive early predictors for PE development especially early-onset PE. Low serum PLGF was significant sensitive, while UAD-PI was non-significant specific predictors for severe PE.

Conclusion

Estimation of serum PLGF at 12th GW is a non-invasive modality for screening primigravida for liability of developing PE. Low serum PLGF at 12th GW is a sensitive early predictor for PE especially severe PE. UAD-PI at 20th GW could assure the prediction of PE and

discriminate women at risk of early-onset PE. Thus, sequential use of both PLGF and UAD-PI could help to predict and stratify pregnant women at risk of PE.

Keywords: Early Prediction; Placental Growth Factor; Primigravida, Pre-Eclampsia, Uterine Artery Pulsatility Index

Introduction

Pregnancy complications such as fetal growth restriction and Pre-Eclampsia (PE) are diseases with limited biomarkers for prediction, and a complete lack of therapeutic options [1]. PE is one of the most frequent and difficult illnesses in pregnancy, which jeopardizes both mother and fetus [2]. Clinically, it is characterized by new onset maternal hypertension and proteinuria in a previously normotensive pregnant woman [3] and affects up to 1 out of 12 pregnancies [4]. In the new pyramid of pregnancy care, women were stratified into high-risk group that require close monitoring for high Blood Pressure (BP) and proteinuria at 24-31 weeks, intermediate-risk group that would have reassessment of risk for PE at 32 weeks to identify those who would require close monitoring and low-risk group [5].

Imbalance between angiogenic and antiangiogenic factors and disruption of endothelial function of spiral arteries may be implicated in pathogenesis of PE [6]. Placenta releases soluble angiogenic factors, which play an important role in modulation of placental endothelial function and its altered levels may be responsible for development of PE-related symptoms [7]. The most established potential diagnostics for PE are circulating placental proteins such as Placental Growth Factor (PLGF), pregnancy associated pregnancy protein-A and soluble FMS-like tyrosine kinase 1 (sFlt-1) [1]. PLGF and Vascular Endothelial Growth Factor A (VEGF-A) are the main angiogenic factors that play an important role in placental vascularization and maternal endothelial function [8], while sFlt-1, which is the soluble form of VEGF-receptor 1 is an anti-angiogenic factor that antagonizes and reduces the bioavailable concentration of VEGF and PLGF for normal placentation [9].

Uterine Artery (UAD) Doppler examination is used for determining the risk of hypertensive diseases of pregnancy [10], and in the 1st trimester UAD can be used to assess the risk of developing PE [11]. High UAD Pulsatility Index (PI) was associated with increased systemic arterial stiffness, whereas notching was related to increased stiffness in small arteries only; this indicates pathophysiological differences between the two Doppler parameters [12].

The current study tried to evaluate the value of estimation of serum PLGF at the 12th GW and determination of UAD-PI by color Doppler at the 20th GW for prediction and categorization of PE in normotensive primigravida women.

Materials and Methods

Design

Prospective case-controlled study.

Setting

Departments of Obstetrics & Gynecology, Clinical Pathology and Radiology, Faculty of Medicine, Menoufia University Hospital.

Patients & Methods

The study protocol was approved by the Local Ethical Committee. The study was started since

Jan 2015 till Dec 2018 to allow follow-up for the last enrolled case till delivery. The study plan was to include all primigravida attending antenatal care unit prior to the 12th Gestational Week (GW) for evaluation for eligibility and determination of baseline clinical data. Pregnant women at high risk for PE were excluded from the study, including those with past history of PE, type I or II diabetes mellitus, chronic hypertension, chronic renal disease, autoimmune disease as systemic lupus erythematosus or antiphospholipid syndrome, multiple pregnancy, and any other associated medical disorders as well as those at moderate risk for PE including those with Body Mass Index (BMI) >30, age ≥35 years and first degree family history of PE.

Only primigravida with singleton fetus and free of PE-risk factors who accepted to participate in the study, attend the clinic 4-weekly since 12th GW till delivery for follow-up and to donate blood sample on request to undergo the assigned investigations and to sign a fully informed written consent were enrolled in the study.

At each 4-week visit, enrolled women were followed-up for their Blood Pressure (BP) measurements, progress of pregnancy and fetal developmental progress. At the 20th GW, all women underwent TVU for assurance of normal placentation and its site and women with abnormal placental site were excluded from the study. Transvaginal Doppler was performed for determination of UAD-PI. Thereafter, women were asked to continue to attend the clinic 4-weekly till delivery for follow-up of BP and examination of mid-urine sample for protein content. Women who developed hypertensive manifestations throughout pregnancy course were categorized as PE group, while women who completed their pregnancy free of hypertensive manifestations were considered as controls and data of number of control women equal to those of PE group and within cross-matched age and body mass index were collected as control group.

Pre-ecalmpsia was diagnosed according to the American Society of Hypertension that PE is primarily characterized by hypertension and proteinuria, defined as a qualitative 1+ dipstick reading [13]. Severity of PE was stratified according to The American College of Obstetrics and Gynecology bulletins as mild or severe [14]. Severe PE was defined on the basis of BP level as ≥110 mmHg for Diastolic (DBP) and ≥160 mmHg for Systolic (SBP), proteinuria >5+ on a voided random urine and/or presence of systemic clinical manifestation including sudden oliguria, neurologic symptoms as headache, hyperreflexia, thrombocytopenia defined as platlet count <100,000/μL, hemolysis, or abnormal liver function. Regarding categorization of PE according time of onset, early PE onsets at <34 GW and late PE that onsets at >34 GW [15].

Transvaginal Ultrasound Technique

All the examinations were performed using GE Voluson S6 ultrasound machine (GE Medical Systems, Milwaukee, WI, USA). Transvaginal transducer (4.6–8 MHz) is placed in the anterior vaginal fornix and a sagittal section of cervix is obtained. Then, the vaginal probe is moved laterally till the para-cervical vascular plexus, uterine artery is identified using the color flow Doppler at the level of the cervicocorporeal junction and measurements are taken at this point before the uterine artery branches into the arcuate arteries.

Blood Sampling

At time of start of the 12th GW, all study participants gave 5 ml blood sample that was withdrawn under complete aseptic conditions, allowed to clot and then centrifuged at 3000 rpm for 10 minutes to separate serum that was collected in sterile Eppindorff tube and stored at -80^{o}C till be assayed.

Laboratory Investigations

Human Placental Growth Factor (PLGF) was measured with the Enzyme Linked Immunoassay (ELISA) kit (catalogue no. DPG00 SPG00 PDPG00, R&D systems Inc., Minneapolis, USA) by quantitative sandwich enzyme immunoassay technique [16] according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech MR 7000).

Statistical Analysis

Results were presented as mean±SD and analyzed using paired t-test, One-way ANOVA Test and Chi-square test (X^2 test). Test diagnostic value was calculated using the Receiver Operating Characteristic (ROC) curve analysis judged by the Area Under the Curve (AUC) that was compared versus null hypothesis that AUC=0.5. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Throughout the duration of the study (45 months), 497 primigravida were eligible for evaluation; 56 were excluded for not fulfilling inclusion criteria, 24 women declined to participate, and 21 women were lost during follow-up, and 396 women continued follow-up till delivery. Forty-seven women developed PE and the remaining women completed their pregnancy free of hypertensive manifestations (Figure 1: The flow diagram). Pregnant women in the control group (n=47) were chosen from the 349 PE-free participants being matched for age and BMI with those in the PE group.

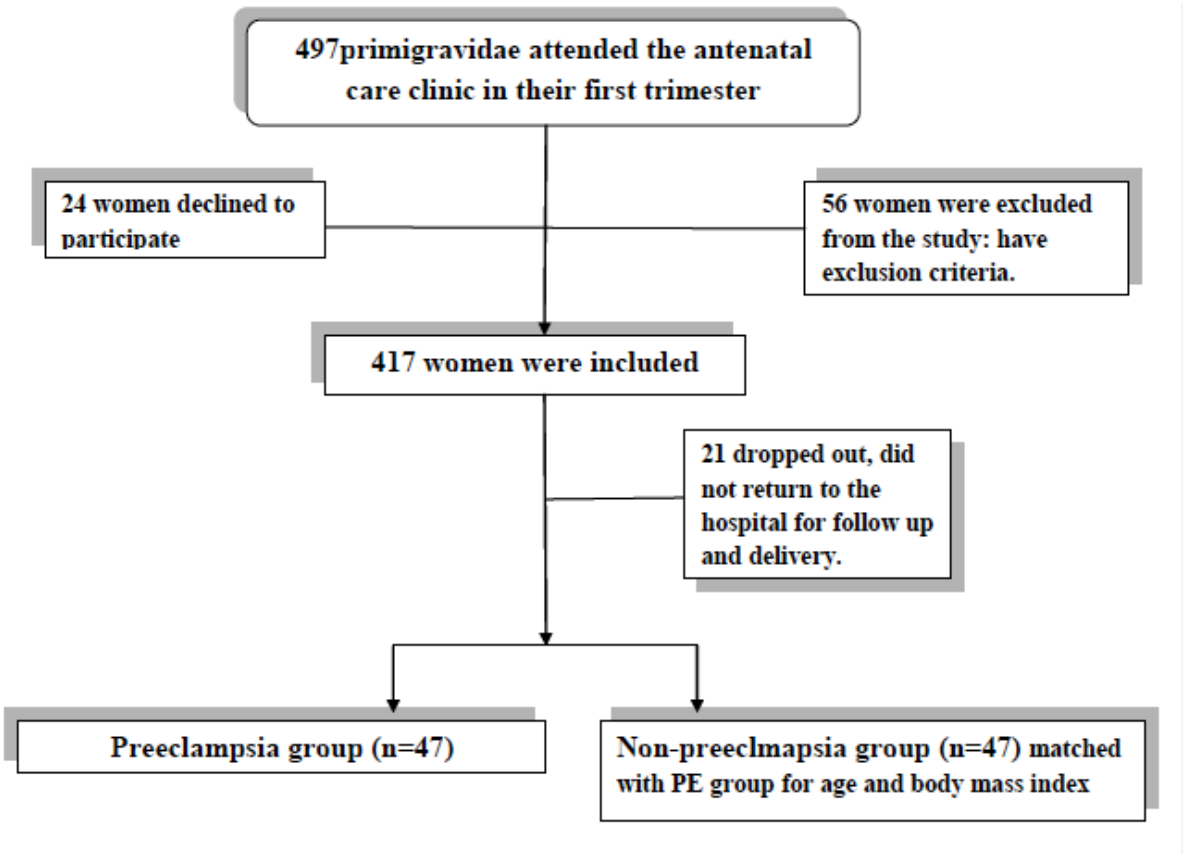

Figure 1: Flow diagram of recruitment and retention of women in the study.

Variables	Control group (n=47)	PE group (n=47)	P value
Age (years)	25.3±5	25.1±5.5	0.673
Weight (Kg)	73.7±6.3	76.2±9.1	0.342
Height (cm)	169.4±1.9	167±2.4	0.733
Body mass index (kg/m^2)	25.7±2.4	26.4±3.3	0.109
Systolic blood pressure (mmHg)	119.4±3.3	119.6±3.9	0.806
Diastolic blood pressure (mmHg	82.8±2.5	83.4±2.1	0.252
Protein in urine	0	0	0

Table 1: Enrolment data of women developed PE compared to control women.

Data are presented as mean±SD, P indicates significance of difference between both groups; P>0.05 indicates non-significant difference between both groups

Eleven women developed early PE; eight of them had mild and three had severe manifestations. Thirty-six women developed late PE; 31 women had mild and 5 had severe manifestations. Thus, 39 women developed mild and 8 women developed severe PE. Mean SBP and DBP measurements estimated at time of development of PE were significantly higher in women of PE group compared to control women and to their respective at enrolment measurements. Women had early PE developed high BP measurements than that of women developed late PE. Moreover, women had severe PE developed higher BP measurements that women developed mild PE (Table 2).

Parameter Group Time		SBP (mmHg)					DBP (mmHg)				
		Measurements	Significance of difference				Measurements	Significance of difference			
			P1	P2	P3	P4		P1	P2	P3	P4
Control	T1	119.6±3.4					82.7±2.4				
Total PE	T1	119.4±4.1					83.5±2.1				
	T2	152.9±7	<0.001				98±7.8	<0.001			
Early PE	T1	120.3±3					82.5±2.3				
	T2	156.6±8.9	<0.001				100±9.5	<0.001			
Late PE	T1	119.1±4.4					83.8±2				
	T2	151.8±6	<0.001	0.043			97.4±7.3	<0.001	0.35		
Mild PE	T1	119.3±4.1					83.3±2.2				
	T2	150.3±3.6	<0.001				94.5±1.1	<0.001			
Severe PE	T1	119.9±4.5					84.3±1.5				
	T2	166±3.7	<0.001				115.6±3.2	<0.001			

Table 2: Blood pressure measurements of women developed PE categorized according to severity and time of development compared to control women.

Data are presented as means (±SD); T1: At enrolment; T2: At time of development of PE; P1: significance versus control women; P2: significance versus at enrolment measurements; P3:

significance of difference between women had early and late PE; P4: significance of difference between women had mild and severe PE; P<0.05 indicates significant difference**;** P>0.05 indicates non-significant difference

Mean estimated levels of PLGF were significantly lower and mean UAD-PI measurements were significantly higher in PE women than in control women and in women developed early-onset or severe PE than in those developed late-onset or mild PE, respectively (Table 3).

Parameter		Control group	PE group				
			Total	Early	Late	Mild	Severe
PLGF (ng/ml)		334.1±41.9	263.5±61	219±19	277±63.1	275.5±58.7	205.1±32.8
	P1		<0.001	<0.001	<0.001	<0.001	<0.001
	P2				0.0045		0.0021
UAD-PI		0.71±0.058	0.768±0.076	0.942±0.2	1.175±0.2	0.87±0.145	0.914±0.186
	P1		<0.001	<0.001	<0.001	<0.001	<0.001
	P2				<0.001		0.0425

Table 3: Mean serum PLGF levels estimated at the 12th GW and UAD-PI determined at the 20th GW in control women and PE women categorized according to severity and time of development of PE.

Data are presented as means (±SD); PLGF: Placental growth factor; UAD-PI: Uterine artery pulsatality index; P1: significance versus control women; P2: significance of difference between women had early and late PE or mild and severe PE; P<0.05 indicates significant difference

Regression analysis defined low serum PLGF at the 12th GW as a predictor for later on development of PE (β=0.564, p<0.001) and severe PE (β=0.438, p=0.002), while defined high UAD-PI on Doppler examination at the 20th GW as predictor for development of early PE (β=0.633, p<0.001). Concerning sensitivity and specificity, ROC curve analysis defined high UAD-PI measurements at the 20th GW as specific (AUC=0.793, p<0.001) and low serum PLGF estimated at the 12th GW as sensitive (AUC=0.189, p=0.001) early predictors for development of PE (Fig. 2). Regarding timing for development of PE, high UAD-PI measurements at the 20th GW showed significantly high AUC (AUC= 0.913, p<0.001) for defining women liable for development of early-onset PE, while low serum PLGF as sensitive (AUC= 0.187, p=0.002) predictor for such event, (Fig. 3). On the other hand, serum PLGF was highly significant sensitive (AUC=0.091, p<0.001), while PI was found to be specific (AUC=0.662, p=0.153) despite being non-significant predictor for development of severe PE (Fig. 4).

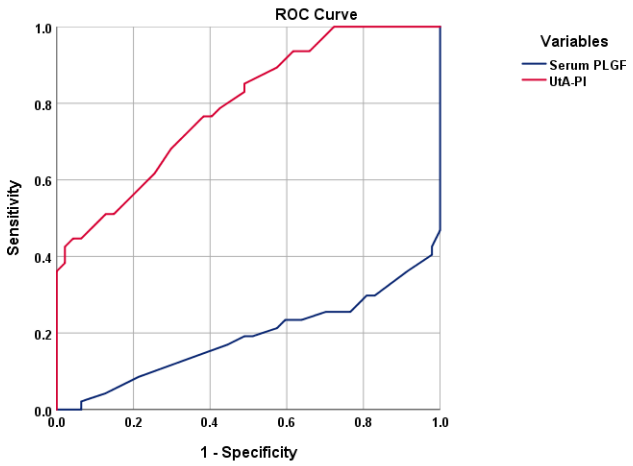

Figure 2: ROC curve for predictibility of estimated serum PLGF levels estimated at the 12th GW and UAD-PI measurements at the 20th GW for discrimination between women who will or not develop PE later during pregnancy course.

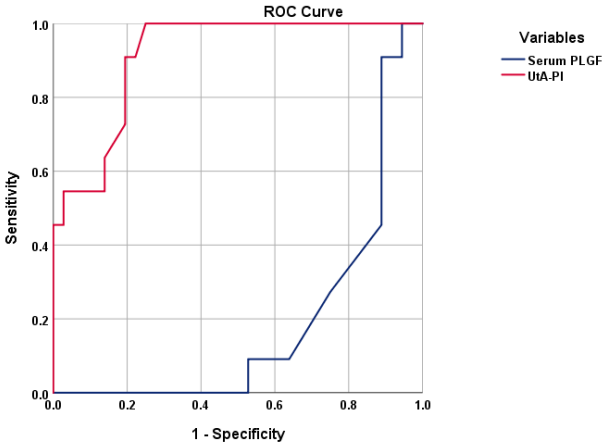

Figure 3: ROC curve for predictibility of estimated serum PLGF levels estimated at the 12th GW and UAD-PI measurements at the 20th GW for discrimination between women liable to develop ealy-onset PE later during pregnancy course.

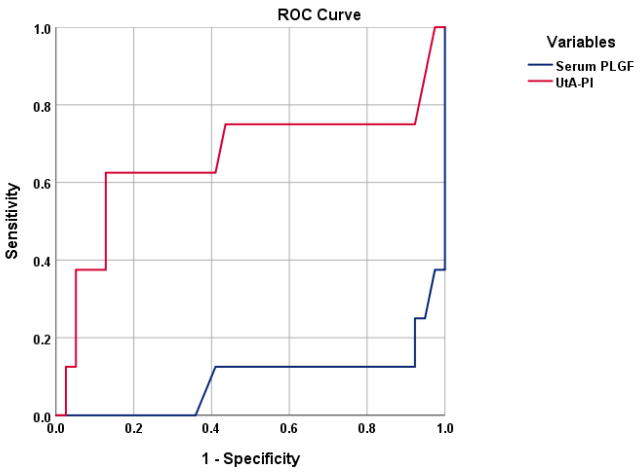

Figure 4: ROC curve for predictibility of estimated serum PLGF levels estimated at the 12th GW and UAD-PI measurements at the 20th GW for discrimination between women liable to develop severe PE later during pregnancy course.

Discussion

Estimated serum PLGF, at the 12th GW, in PE women, showed wide variance from levels of control women manifested as significantly lower PLGF especially in women developed early-onset PE than in controls and women who developed late-onset PE and in women who developed severe than in controls and in women who developed mild PE.

These results regarding predictability of low serum PLGF for oncoming PE go in hand with Chelli et al. [17] and Mayer et al. [18] who detected significantly lower PLGF levels in women who developed PE than in women who continued their pregnancy free of hypertensive manifestations. Also, Benovská et al. [19] reported decreased PLGF as early as 16 to 20 WG in serum of women who will develop PE than in women who had normal pregnancy. Also, the obtained results are in accordance with results of recent studies evaluated the placental angiogenic factors; PLGF and sFlt-1 where Caillon et al. [20] found low serum sFlt-1/PlGF ratio can rule out PE with high performance rate, while Yusuf et al. [21] found high ratio could predict early-onset and/or severe PE. Moreover, Herraiz et al. [22] reported that measuring the sFlt-1/PlGF ratio at 24-28 GW enables accurate prediction of PE and this performance is optimal to predict PE requiring delivery before 32 weeks.

As regards UAD-PI measured at the 20th GW, PE women showed significantly higher PI especially those who developed early-onset PE than in controls and women who developed late-onset PE and in women who developed severe than in controls and mild PE women. In a similar result, Khong et al. [23] found 1st trimester UAD Doppler performs better in the prediction of early-onset than late-onset PE.

The obtained results point to the possibility of prediction of oncoming PE as early as the 12th GW using estimation of serum PLGF and assuring the prediction at the 20th GW using Doppler determination of UAD-PI. In support of this assumption, statistical analyses defined low serum PLGF at the 12th GW as a significant sensitive predictor for later development of PE especially that associated with severe manifestations, while Doppler determined UAD-PI as a significant specific predictor for oncoming early-onset PE. The obtained results spotted light on the complementary diagnostic value of both parameters for early prediction of development of PE and determination of its severity and time of onset.

Similarly, Khong et al. [23] reported that UAD-PI as an isolated marker has sensitivity for prediction of early-onset PE in low risk pregnant women of 40-70%, but its sensitivity rises to 90% on combining 1st trimester UAD-PI with biochemical markers. Also, Puttapitakpong & Phupong [24] found combination of serum angiopoietin-2 levels and UAD may be a useful early 2nd trimester screening test for the prediction of early-onset PE. Moreover, Yu et al. [25] documented that the combination of biochemical markers and UAD improves the screening efficiency for PE prediction and 1st pregnancy-associated plasma protein-A and a disintegrin and metalloprotease-12 with 2nd trimester UAD-PI are associated with adverse pregnancy outcomes.

The results of the current study assured high sensitivity of low PLGF estimated at 12th GW for identification of primigravida susceptible to develop PE, so it can be used as an early non-invasive predictor that allows discrimination of women at risk for development of PE. In line with this assumption, Tarasevičienė et al. [26] found PLGF is superior to UAD pulsatality or resistance indexes for PE diagnosis. Also, Diguisto et al. [27] documented that PLGF in the 1st trimester is a useful marker for predicting PE, but neither sFlt-1 nor any UAD indices improved PE prediction.

As an indirect support of the obtained results, Spradley et al. [28], using animal model of PE, found administration of recombinant human PLGF abolished placental ischemia-induced hypertension, without major adverse consequences, so suggested that increased sFlt-1 and reduced PLGF resulting from placental ischemia contribute to maternal hypertension and recombinant human PLGF has a strong therapeutic potential in preeclampsia.

Conclusion

Estimation of serum PLGF at the 12th GW is a non-invasive modality for screening primigravida for liability of developing PE during course of pregnancy. Low serum PLGF at the 12th GW is a sensitive early predictor for PE especially that will present by severe manifestations. UAD at the 20th GW could assure the prediction of PE and discriminate women at risk of early-onset PE. Thus, sequential use of both PLGF and UAD-PI could help to predict and stratify pregnant women at risk of development of PE.

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