Correlation of Placental Growth Factor with Pre-Eclampsia during Mid Trimester of Pregnancy: A Case Control Study at Liaquat University of Medical and Health Sciences, Pakistan

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ABSTRACT

Introduction: Pre-Eclampsia (PE) is the common multisystem disorder which complicates the pregnancies 3-8% and a major cause of morbidity and mortality throughout the world.

Aim: To determine the correlation of placental growth factor with PE in mid trimester of pregnancy at Liaquat University of Medical and Health Sciences Jamshoro.

Materials and Methods: This Case-Control study was performed at Pathology Department with Department of Obstetrics and Gynaecology, Liaquat University of Medical and Health Sciences (LUMHS) Jamshoro/Hyderabad, during 12 months, from 6th February, 2017 to 5th February 2018. Pregnant women with mid trimester were enrolled in the study. Group A included females with PE, while Group B were normotensive females of same gestation. Their blood sample were collected and stored at -80°. Level of placental growth factor was measured on Elecsys system. Data was analysed via Statistical Package for the Social Sciences (SPSS) version 20.

Results: Total 384 PE females were selected and 50 females without hypertension were studied as control. Mean age of patients was 27.46±3.91 years. No significant variance was seen between mean of gestational age of patients and normal pregnant females; p-value 0.346. Mean of placental growth factor was insignificantly decreased 35.21±31.68 pg/mL among patients in contrast to normal women as 47.23±56.13 pg/mL, p=0.081. A negative correlation was found between blood pressure and placental growth factor, r-values -0.004 and -0.001, respectively.

Conclusion: It was concluded that serum placental growth factor was the poor marker for PE, as it showed weak negative correlation with PE.

INTRODUCTION

PE is the major cause of maternal morbidity and mortality [1]. It is characterised by hypertension, proteinuria and oedema. This further leads to seizures, stroke, intrauterine foetal growth restriction and even may leads to maternal and foetal death [2]. It is further divided as late and early onset PE on the basis of gestational age at presentation, before and after 34 weeks of gestation [3]. Extensive research was done for secondary prevention to control and treat the disease by conservative management that successfully reduced maternal morbidity and mortality on the cost of early delivery, hence increased neonatal prematurity and related perinatal morbidity and mortality [1,4,5]. Nevertheless, primary prevention to reduce its prevalence by understanding the pathology is unclear [6]. It has been asserted that during embryogenic period, dysfunction related to placental vascularisation and angiogenesis contribute significantly to the progression of this disease. Vascular Endothelial Growth Factor family (VEGF) that includes Placental Growth Factors (PGF) is key factor which was claimed to be involved in PE [7]. PGF, a glycoprotein part of VEGF family, is synthesised by placenta, which stimulates propagation, migration and triggering of endothelial cells. It has been postulated that impaired placentation in pregnancy leads to reduced maternal serum PGF. This reduction is evident from 11 weeks onwards [8]. It has been argued that these biochemical markers are released in response to placenta ischaemia [9]. sFlt-1, a tyrosine kinase protein and a variant of VEGF receptor 1 (R1), interferes with growth of blood vessel and it neutralises the action of PGF through interaction of pro-angiogenic factors that act as endothelial receptors and impedes endothelial function that propagates to PE [9-11]. Raised level of angiogenic

biochemical markers distinguish pre-eclamptics from normotensive pregnant patients [11,12]. In the course of recent years, PGF has been exhibited to be reduced among pregnant females with PE [13,14]. Reduced plasma concentrations of PGF are detectable at the time of PE [15]. Both factors have been seen to be correlated with raised risk of PE [16,17]. However, there is limited number of studies in this regard and no local study was found, despite of explicit search. Therefore, the purpose of present study was to assess the correlation of PGFs with PE in present setup, which not only prevents foeto-maternal mortality and morbidity, but also saves cost and resources spent for the admission and treatment of this catastrophic disease.

MATERIALS AND METHODS

This Case-Control study was carried out at Pathology Department with Department of Obstetrics and Gynaecology, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro/Hyderabad, during 12 months from 6th February, 2017 to 5th February, 2018. Ethical approval was taken (No. LUMHS/REC/272) before data collection. Sample size was calculated by taking the 30% prevalence of pre-ecmplsia [15], with 95% confidence interval. Thus, the sample size calculated was 384 pregnant women, out of them 50 normal women were selected as controls. All singleton pregnant women with mid trimester were enrolled in the study. The females with medical conditions like systemic lupus erythematosus, renal disease, diabetes mellitus, Antiphospholipid antibody syndrome, or any known autoimmune disease and users of chronic corticosteroid drug were excluded from this study. Pre-eclampsia was determined by systolic blood pressure (BP) ≥140 mmHg or a diastolic BP ≥90 mmHg

on two successive measurements. Maternal plasma specimens were isolated via 2,500 rpm centrifugation for 10 minutes. Aliquots of maternal plasma were stored at -80°. Levels for PGF were measured on fully automated Elecsys system. This assay is a sandwich immunoassays grounded on the electrochemiluminescence technology. The cut-off PGF values was set at 15.6-pg/mL as mentioned by manufacturer.

STATISTICAL ANALYSIS

All the information was recorded in self-made proforma. Analysis of data was done by a Statistical software Statistical Package for the Social Sciences (SPSS) version 20. Student t-test was applied and a p-value ≤0.05 was considered as significant.

RESULTS

In this study, 384 females with PE and 50 normotensive pregnant females as control were enrolled. Mean age of patients were 27.46±3.91 years and control's was 28.0±4.0 years, p-value 0.362. Mean gestational age of pre-eclamptic women was 25.08±2.34 weeks and controls were 25.42±2.61 weeks. Mean of the blood pressure was markedly higher as compared to normal women with p-value 0.0001 [Table/Fig-1].

Demographics	Pre-eclampsia n=384	Control n=50	p-value
Age	27.46±3.91 years	28.0±4.0 years	0.362
Gestational age	25.08±2.34 weeks	25.42±2.61 weeks	0.346
Systolic BP*	147.43±10.83 mmHg	111.90±6.91 mHg	0.001
Diastolic BP*	103.15±6.39 mmHg	72.10±7.36 mmHg	0.001

[Table/Fig-1]: Distribution of patients according to demographic characteristics n=434.
*BP: Blood pressure; p-value ≤0.05 was considered as significant.

Urinary proteins among pre-eclamptics and controls were statistically significant. Mean of PGF was found to be lower in patients with PE while higher in normotensives; however statistically nonsignificant, p-value 0.081 [Table/Fig-2].

Parameters		Blood pressure		p-value
		Pre-eclampsia n=384	Control n=50	
PGF	Mean	35.21±31.68 pg/mL	47.23±25.13 pg/mL	0.081
Urinary protein	Mean	1.54±0.72 mg/L	1.14±0.35 mg/L	0.001*

[Table/Fig-2]: Distribution according to mean of urinary protein and Placental Growth Factor (PGF) n=434.
*p-value ≤0.05 was considered as significant

There was a weak negative correlation between Systolic BP and placental growth hormone, r-value-0.004 [Table/Fig-3]. There was also a weak negative correlation amid diastolic BP and placental growth hormone, r-value-0.001 [Table/Fig-4].
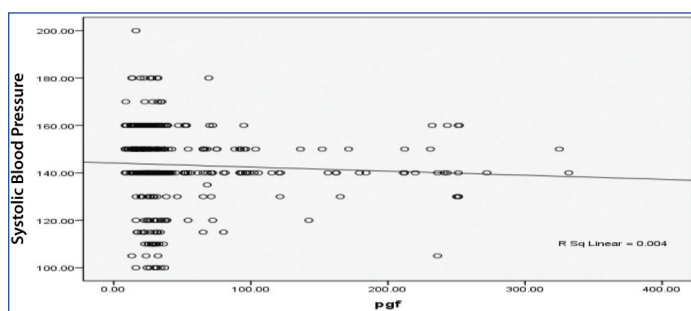
[Table/Fig-3]: Pearson correlation between Placental Growth Factor (PGF) and systolic blood pressure.

DISCUSSION

Placental Growth Factors is a predictive marker in development of PE, but limited data is available [18]. In this study, statistically no significant differences were found in basic characteristics among pregnant females who developed PE compared to normotensives.
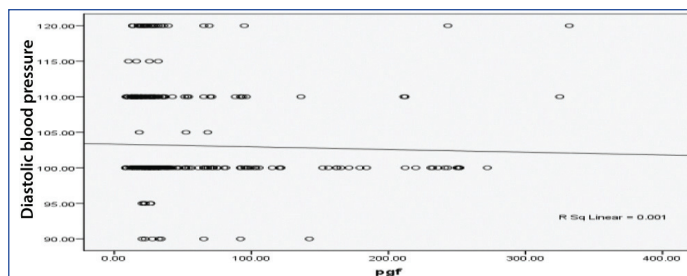
[Table/Fig-4]: Pearson correlation between PGF and diastolic blood pressure.

The mean age of patients was 27.46±3.91 years, which was almost similar to controls, p-value 0.362. A comparable study of Shibata E et al., reported that mean age of women with PE was 26.5±6.0 years and mean age of normal women was 26.2±7.1 years, which was statistically insignificant [19]. In this study, there was no significant variance between mean gestational age among both groups, p-value 0.346. Inconsistently, Hanita O et al., observed that in pre-eclamptics females, the gestational age at delivery was significantly lesser than those who didn't develop the condition (p<0.0005) [18]. This difference can possibly be because in present study, patients were with 2nd trimester, which is the lower gestational age as compared to Hanita O et al., [18].

In this study, mean placental growth factor was insignificantly decreased 35.21±31.68 pg/mL in patients, while in normotensives it was 47.23±25.13, p-value 0.081. Similar findings were found in a study of Gurnadi JI et al., [20]. This was further endorsed by Schmidt M et al., who reported that PGF levels from 15 to 18 weeks of gestational age were markedly lower than normal women [21]. Using a PGF level of 41.84 pg/mL as a cut-off, this test has a sensitivity of 0.87 and a specificity of 0.83 [21]. Sibiude J et al., reported that Mean PGF values (following log transformation) were significantly lower in cases those later developed PE than the subjects who didn't develop PE [22]. Lower values of PGF were as well significantly correlated with adverse outcome [22].

The present study exhibited PGF as a poor indicator of PE in mid trimester of pregnancy because there was weak negative correlation between systolic and diastolic BP and PGF (r-values-0.004 and -0.001, respectively) with 70% sensitivity and 60% specificity. Similarly, in the study of Elsheikh WA et al., ROC curve analysis for the probability of PGF to predict PE revealed that PGF can predict PE with sensitivity of 74%, specificity 50% [23]. Kleinrouweler CE et al., [24] conducted a systemic review and meta-analysis to examine the capacity of circulating PGF and other angiogenic factors to predict PE and reported that PGF exhibited modest however significantly different concentrations prior to 30 weeks of gestation among females who developed PE, nonetheless, the test accuracy (32% sensitivity) was worse for precise prediction of PE within clinical practice [24]. Conde-Agudelo ARR and Roberts JM, postulated that females have moderate to low risk to develop PE, the prognostic accuracy of angiogenic factors including PGF was high to moderate when measured in the course of the 2nd trimester (sensitivities ranging from 100% to 17%, specificities from 97% to 51%) [25]. On the other hand, many authors showed that low level of maternal PGF precede the clinical presentation of PE, provide a good indicator of SGA and severe PE and predict women who will develop early-onset PE [26,27]. However, McElrath TF et al., reported sensitivity 47% and specificity 62%, poor predictive value of PGF for prediction of PE [28]. In another study of Sung KU et al., observed that PGF is the useful marker during 1st trimester for hypertensive disorders in pregnancy [29]. However, PGF during 1st trimester may be more useful, though further large-scale studies of both, mid and first trimester are needed for further evaluation of the usefulness of this marker.

Limitation(s)

This study was single center study and only mid trimester women were included. Another limitation is lack of funding sources due to which control cases ratio could not maintained.

CONCLUSION(S)

It was concluded that serum plasma growth factor is non-significant for PE, as it showed weak negative correlation with pre-eclampsia. Large prospective multicenter studies are recommended to ascertain the association of these biochemical markers with pre-eclampsia before employment in clinical practice.

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