Original Article

The Relation between Deregulated Immune Milieu and Atherogenic Lipids Might Underlie the Development of Pregnancy-induced Hypertensive Disorders

Youssef Abdel Zaher, Ibrahiem M Rageh and Ali A. Morsy

Department of Obstetrics and Gynecology, Department of Clinical Pathology, Faculty of Medicine, Benha University, Egypt

ABSTRACT

Objectives: Evaluation of the relation between plasma lipoprotein(a) (LPA) and serum tumor necrosis factor-α (TNF-α) levels estimated in blood samples (S1 sample) obtained at the 6th gestational week (GW; T1 time) and the development of preeclampsia (PE) as judged by blood pressure measures at the time of diagnosis of PE (T2 time).

Patients and Methods: 140 newly pregnant women gave S1 sample at T1 time; during pregnancy 19 women developed early-onset PE (EOPE) and 51 women developed late-onset PE (LOPE); 16 women developed severe PE (SPE) and 54 women developed mild PE (MPE), while 70 women were normotensive (NT) till the end of pregnancy. At T2 time, all patients gave S2 sample for ELISA estimation of plasma LPA and serum TNF-α level in both samples.

Results: Serum TNF-α and plasma LPA levels were significantly higher in all S2 than S1 samples, in both samples of PE than NT women, and in both samples of women who developed EOPE and/or SPE than in samples of women who developed LOPE and/or MPE, respectively. Regression analysis of T1 data defined high body mass index; BMI (β=0.162, P=0.028), high S1 levels of TNF-α (β=0.424, P<0.001), and LPA (β=0.314, P<0.001) as predictors for development of PE as judged by SBP measures at T2 time. Correlation analysis showed a positive significant (P<0.001) correlation between at-T2-SBP measures with at-T1 BMI and S1 levels of TNF-α and LPA with a positive significant correlation between levels of both variables and with at-T1 BMI.

Conclusion: High serum levels of TNF-α and plasma LPA levels early in pregnancy could predict the development of PE and its severity.

Key Words: Early prediction, lipoprotein (a), preeclampsia, tumor Necrosis Factor-α.

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Corresponding Author: Youssef Abdel Zaher, Department of Obstetrics and Gynecology, Department of Clinical Pathology, Faculty of Medicine, Benha University, Egypt, **Tel.:** +20 10 9542 8295, **E-mail:** zahery065@gmail.com

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INTRODUCTION

Pregnancy-induced hypertension (PIH) is one of the leading causes of maternal and perinatal morbidity and mortality[1]. Preeclampsia (PE) is a serious complication of pregnancy that was characterized by new-onset hypertension around the 20th gestational week (GW) with or without proteinuria[2] and may complicate up to 5% of pregnancies worldwide[3]. The risk of maternal and perinatal complications is considerably higher in cases had early-onset PE (EOPE) and/or severe PE (SPE)[4].

Physiological adjustment of maternal lipid metabolism during pregnancy is essential and has a role in the progression of labor, and childbirth[5]. However, disturbed maternal lipid metabolism and altered lipid profile secondary to obesity is a risk factor for pregnancy-induced maternal diseases such as PIH and diabetes mellitus and is associated with various alterations in fetal metabolic status[6].

Lipoprotein(a), LPA is a particle with structural similarity to low-density lipoprotein (LDL) as regards the size, lipid composition, and the presence of apolipoprotein B100. LPA also contains apolipoprotein (a) that bounds to apolipoprotein B100 via non-covalent interactions and one single disulfide bridge and thus causes the difference between LDL and LPA in the density and electrophoretic mobility[7].

The LPA is atherogenic lipoprotein that was synthesized by the liver and has a strong genetic regulation by a single gene, so its plasma concentration is a hereditary character[8]. Plasma LPA was not affected by statins thus its turnover was not through LDL receptors[9], but was taken by macrophage (M) receptors to form foam cells responsible for the development and progression of atherosclerosis[10].

Pathogenesis of PE was found to be related activation of the inflammatory cascade in direction of inflammation[11] as evidenced by the increased placental number of resting

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natural killer (NK) and dendritic cells with a reduction in the proportion of activated NK cells[12]. Moreover, aberrant activation of the nuclear factor-Kappa B (NF-κB) pathway, which is a crucial mediator of inflammatory signaling, plays a crucial role in the pathogenesis of several disorders including PE[13].

OBJECTIVES

The relation between plasma LPA and serum tumor necrosis factor-α (TNF-α) was estimated early in pregnancy and the development and severity of PE as judged by blood pressure (BP) measures at the time of diagnosis of PE.

Design

Prospective comparative study

Setting

Obstetrics & Gynecology Department, and Department of Clinical Pathology, Faculty of Medicine, Benha University, Egypt

Ethical consideration

The approval of the study protocol was obtained from the Local Ethical Committee, Benha University at 10-2022 by number:RC:27-10-2022

Study participants

All newly pregnant women who attended the outpatient clinic for assurance of pregnancy were evaluated and those fulfilling the inclusion criteria were asked to attend the clinical pathology outpatient lab fasting for at least 12 hours to give blood samples for baseline investigations.

Exclusion criteria

The exclusion criteria included current essential hypertension, diabetes mellitus, renal impairment, or cardiovascular disorders, metabolic syndrome, body mass index (BMI)>35 kg/m^2, familial hypercholesterolemia, hereditary apolipoproteinemia, maintenance on immunosuppressive drugs, autoimmune disorders, attendance the clinic later than the time of pregnancy diagnosis, refusal to participate in the study, or being missed during follow-up.

Inclusion criteria

Newly pregnant women who attended the clinic at the time of pregnancy diagnosis; the 6th GW, free of exclusion criteria and had a single viable fetus during follow-up US examination and attended the follow-up visits were included in the study.

Diagnosis of PE

The diagnosis of PE depended on the development of hypertension during pregnancy in a previously normotensive (NT) woman and hypertension may be associated with proteinuria quantified as 1+ on a dipstick[14]. Regarding severity, PE was defined as mild (MPE) if systolic (SBP) and diastolic BP (DBP) were <160 and <110 mmHg, respectively with proteinuria of <2+ on a voided random urine sample and absence of systemic manifestations[15]. PE which was diagnosed before the 34th GW was considered EOPE[16].

Grouping

Women who developed PE at any time during follow-up visits were categorized as PE group. A similar number of women who continued their pregnancy with follow-up BP out-of-range diagnosis of PE and were cross-matched with PE women as regards age and BMI was categorized as the normotensive (NT) group.

Sampling and Investigations

Two blood samples were obtained at the time of enrolment and at the time of PE diagnosis (S1 and S2 samples). S2 samples were used for re-estimation of serum TNF-α and plasma LPA, while S1 samples were divided into three parts:

1. The 1st part was put in a fluoride-containing tube for estimation of fasting blood glucose[17].

2. The 2nd part was collected in heparin containing tube for estimation of plasma lipid profile and ELISA estimation of plasma LPA using an Abcam ELISA kit (Abcam Inc, Cambridge, USA; catalog no. ab212165)[18].

3. The 3rd part was allowed to clot and centrifuged at 2000rpm for separation of serum that was collected in a clean Eppendorf tube and stored at -20oC till being ELISA assayed for serum TNF-α[19] using Abcam ELISA kit (Abcam Inc, Cambridge, USA; catalog no. ab179886) according to the manufacturer instructions and results were read using a 96 well microplate ELISA reader (Dynatech, MR 7000).

Follow-up

Baseline BP measures and urine examination at the time of obtaining the S1 sample were recorded as T1 data and then all enrolled women were asked to attend the Obstetrics outpatient clinic for determination of BP and urine examination monthly till the development of PE or not and BP measures and urine examination data and S2 sample was obtained at that time and recorded as T2 data.

Study outcome

The relation between serum levels of TNF-α and plasma LPA in the S1 sample and development of PE, its type as regards timing and severity as judged by BP measures recorded as T2 data.

Statistical analysis

The obtained results were analyzed using One-way ANOVA and Chi-square (X2 test) tests. Regression analysis of T1 data was conducted to define the predictors for SBP at T2 time. Pearson's correlation analysis was used to evaluate the relation between the defined predictors using SPSS statistical analysis (IBM® SPSS® Statistics, Version 22, 2015; Armonk, USA) with *P value* at cutoff point of <0.05 was considered statistically significant.

RESULTS

The study included 70 PE and 70 NT women with comparable T1 data as shown in (Table 1).

Table 1: T1 data of patients of the studied groups

Data	NT group (n=70)	PE group (n=70)	*P value*
Age (years)	28.3±6	27.8±3.6	0.549
Body mass index (kg/m^2)	28.5±2.8	29.3±2.2	0.064
Primigravida	33 (47.1%)	40 (57.1%)	0.236
Fasting blood glucose (mg/dl)	91.9±10.2	94.7±9.3	0.093
Total cholesterol (mg/dl)	174.3±13	174.9±10	0.759
Triglycerides (mg/dl)	52.5±5.4	51±5.7	0.111
High-density lipoprotein (mg/dl)	44±4.3	42.7±4.5	0.082
Very low-density lipoprotein (mg/dl)	20±4.1	19±4.4	0.165
Low-density lipoprotein (mg/dl)	57.8±15.5	62.2±13.5	0.076

P>0.05 indicates the non-significant difference

Nineteen women developed EOPE and 16 women had SPE. Mean BP measures recorded in T2 data were significantly higher in PE women compared to their measures in T1 data and BP measures of NT women in T2 data. Also, the BP measures of women who developed EOPE and SPE were significantly higher than the BP measures of women who had LOPE and MPE, respectively. Interestingly, the BP measures of NT women in T2 data were significantly higher compared to their BP measures in T1 data, despite being lower than the levels diagnostic of PE (Table 2).

Table 2: T1 and T2 BP data of patients of the studied groups

Variable Group Sample	SBP (mmHg)			DBP (mmHg)		
	T1	T2	*P1-value*	T1	T2	*P1-value*
NT group (n=70)	118.8±4.8	120.6±5.2	0.036	77.7±3.9	79.9±4	0.001
PE group (n=70)	119.2±4.5	145.6±14.6	<0.001	78.2±5.3	101.5±8.2	<0.001
P2	0.589	<0.001		0.501	<0.001	
Early PE (n=19)	120.7±3.2	157.5±11.8	<0.001	79±6	105±7.6	<0.001
Late PE (n=51)	118.7±4.8	141.2±13.1	<0.001	78.2±5.1	100.3±7.9	<0.001
P	0.088	<0.001		0.569	0.03	
Mild PE (n=54)	119±4	139±8.8	<0.001	78±5.4	98±5.5	<0.001
Severe (n=16)	120±6.1	168±4.7	<0.001	79±4.8	113.5±1.7	<0.001
P	0.441	<0.001		0.510	<0.001	

P1 indicates the significance of the difference between T1 and T2 measures; P2 indicates the significance of the difference between each patient's categories; *P*<0.05 indicates a significant difference

Serum TNF-α levels increased significantly in S2 than S1 samples of all pregnant women, irrespective of the development of PE with significantly higher levels in PE than NT women in both samples. Also, serum levels of TNF-α were significantly higher in both samples of women who had EOPE than those who had LOPE with significantly higher levels estimated in S2 than in S1 of PE women, irrespective of the timing of development of PE. Similarly, serum levels of TNF-α in both samples were significantly higher in women who developed SPE than those who developed MPE with significantly higher levels in S2 than in S1 samples of all PE women. Plasma LPA levels were significantly higher in both S1 and S2 samples of PE than NT women with significantly higher in S2 of PE than their S1 samples, but the difference was non-significant between samples of NT women. Plasma LPA levels in women who developed EOPE or SPE were significantly higher in S2 than in their S1 samples and in S2 samples of women who developed LPE or MPE respectively. Plasma LPA levels in S2 samples of women who developed late PE were significantly higher than their S1 samples' levels, while the difference was non-significant between samples of women who developed MPE (Table 3).

Table 3: Serum TNF-α and plasma LPA levels estimated in S1 and S2 samples of studied patients

Variable Group Sample	Serum TNF-α (ng/ml)			Plasma Lp(a) (mg/dl)		
	S1 sample	S2 sample	*P1-value*	S1 sample	S2 sample	*P1-value*
NT group (n=70)	3.24±1.59	5.59±3	<0.001	12.87±3.6	13.4±4.7	0.495
PE group (n=70)	3.94±2.13	7.58±3.8	<0.001	14.3±4.4	23.1±16.4	<0.001
P2	0.030	0.0008		0.035	<0.001	
Early PE (n=19)	8.8±1.5	12.3±2	<0.001	17.8±4.7	33.8±20	0.0017
Late PE (n=51)	4.5±2.7	6±3	<0.001	11.7±3.5	19.1±13	0.0002
P2	<0.001	0.0078		<0.001	0.0006	
Mild PE (n=54)	5.11±3	7.22±2.5	0.012	12.9±4.3	14.9±5.7	0.144
Severe (n=16)	6.78±3.6	10.26±3.25	0.001	14.8±4.7	50.8±9.8	<0.001
P2	0.01	0.006		0.029	<0.001	

P1 indicates the significance of the difference between T1 and T2 measures; P2 indicates the significance of the difference between each patient's categories; *P*<0.05 indicates a significant difference

Regression analysis of T1 data defined high BMI (β=0.162, P=0.028), high serum levels of TNF-α (β=0.424, P<0.001), and plasma LPA (β=0.314, P<0.001) as predictors for development of PE as judged by SBP measures at T2 time. Pearson's correlation analysis showed a positive significant (*P*<0.001) correlation between SBP measures recorded in T2 data with at-enrolment BMI (Figure 1a), serum TNF-α (Figure 1b), and plasma LPA (Figure 1c). Further, serum levels of TNF-α and plasma LPA levels in S1 samples showed positive significant correlation with at enrolment BMI (Figures 2a,b) with a positive significant correlation between serum levels of TNF-α and plasma LPA levels in S1 samples (Table 4, Figure 3).

Table 4: Correlation analysis between SBP at T2 time and T1 data

	SBP at T2		BMI at T1		Plasma LPA in the S1 sample	
	"r"	*P*	"r"	*P*	"r"	*P*
BMI	0.375	<0.001	-	-	-	-
Serum levels of TNF-	0.514	<0.001	0.264	0.002	0.388	<0.001
Plasma LPA levels	0.468	<0.001	0.445	<0.001	-	-

"r": Pearson's correlation coefficient; *P*<0.05 indicates the significance of the value.

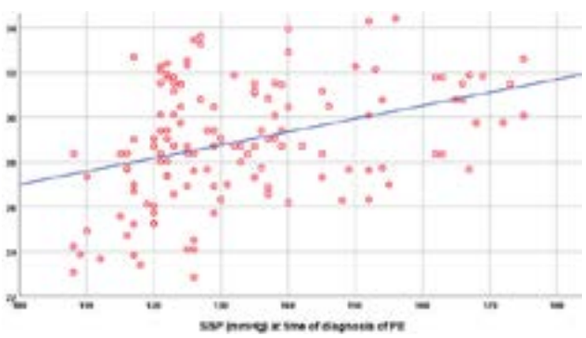

Fig. 1a: Pearson's correlation between at-enrolment BMI and SBP determined at T2 time

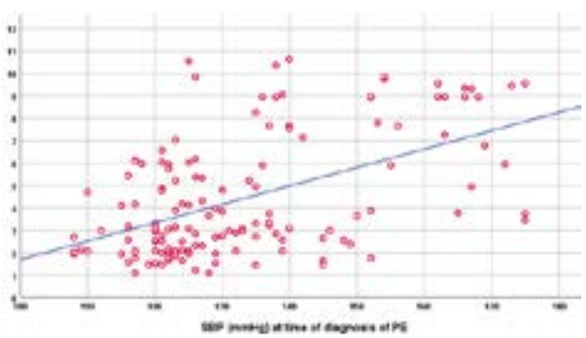

Fig. 1b: Pearson's correlation between serum levels of TNF-α estimated in the S1 sample and SBP determined at T2 time

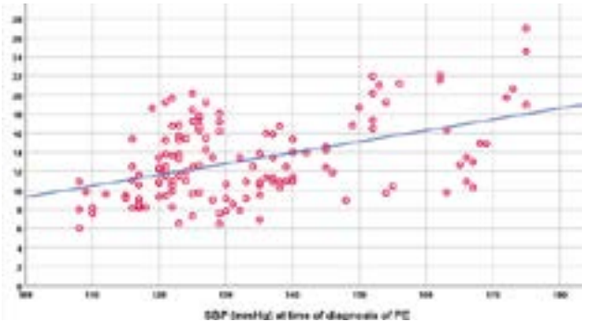

Fig. 1c: Pearson's correlation between plasma LPA levels estimated in S1 samples and SBP determined at T2 time

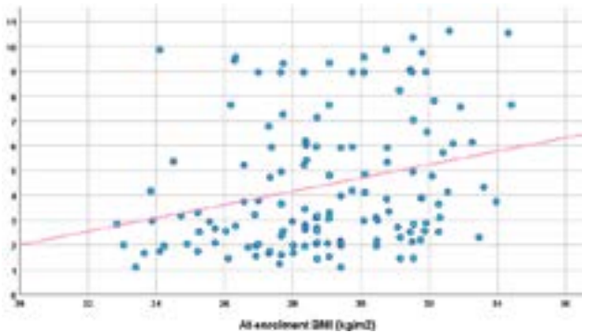

Fig. 2a: Correlation between at-enrolment BMI and serum TNF-α estimated in S1 samples

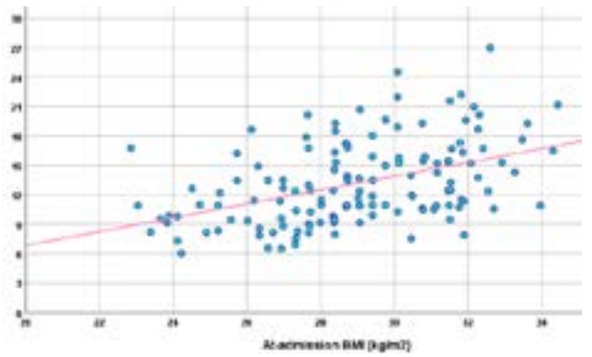

Fig. 2b: Correlation between at-enrolment BMI and plasma LPA estimated in S1 samples

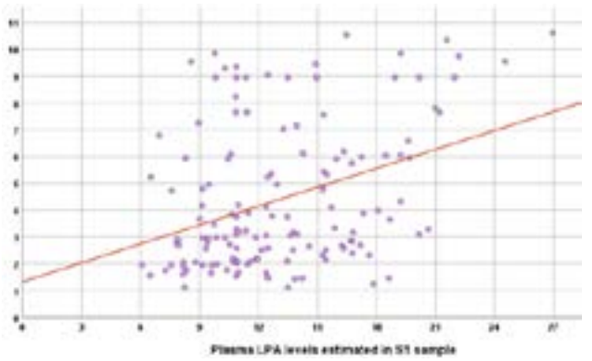

Fig. 3: Correlation between levels of serum TNF-α and plasma LPA estimated in S1 samples

DISCUSSION

The current study detected a significant elevation of blood pressure (BP) measures in all pregnant women, irrespective of reaching the diagnostic levels of pregnancy-induced hypertension (PIH). This finding indicating the hypertensive phenotype of pregnancy and multiple explanations were provided for the coincidence of hypertension and pregnancy, for example, micronutrient deficiencies with or without low levels of immunoglobulins were suggested to be risk factors for the development of high BP up to PE development[20], gut-placenta axis theory was supposed for the role of gut microbiota dysbiosis and altered levels of their active metabolites for the development of PE[21], placental malfunction secondary to activation of the RhoA/Rho-kinase pathway to induce overproduction of reactive oxygen species (ROS) by endothelial cells with down-regulation of the cellular HIF1α-UCA1 pathway that promote the trophoblastic adaptation to hypoxia may underlie the development of PIH[22], disturbed PLGF/sFlet ratio[23] and deregulated expression of vascular endothelial growth factor receptor 2[24] are also suggested as underlying mechanisms for PIH.

Serum levels of TNF-α were significantly higher in S2 than S1 samples of all patients, and in both samples of PE patients than in NT patients. This data spotlights a possible role of a disturbed immune milieu in direction of inflammation in the pathogenesis and/or aggravation of PIH. In support of this assumption Regression analysis defined high serum TNF-α early in pregnancy as a positive significant predictor for high blood pressure measures later in pregnancy.

In the evaluation of the role of the inflammatory process in PE development, trophoblast-derived extracellular vesicles from PE women were found to promote PE by inducing macrophage imbalance polarization from M2 to M1 phenotype with significant upregulation of M1 gene markers and downregulation of macrophage CD163 expression than in NT women, thus altering the classical inflammatory biological pathways in macrophages[25]. Another study found the placental tissue expression levels of the inflammatory proteins NLRP7 and PYCARD were higher in the placentas of PE versus NT samples and these proteins could be used as markers of prediction or progression of PE[26]. Another possible mechanism was the single nucleotide polymorphism (SNP) in TNF-α and interleukins-4, 6, 10, 17A, and 22 for the development of early-onset and severe PE[27].

The further study detected elevated plasma proinflammatory cytokines especially TNF-α and interleukin-17, which are potential mediators of autoregulatory loss with impaired pressure-induced vasoconstriction in PE and this myogenic vasoconstriction may affect small cerebral arteries and arterioles[28].

Plasma levels of LPA were found to be elevated in S2 than in S1 samples of PE women especially those who had severe PE with a significant difference between plasma LPA levels in samples of PE and NT women. Also, Regression analysis defined high LPA as a predictor for PE but was the predictor for severe PE. In line with these data, earlier studies detected high plasma LPA in samples of women who had PE than in women who did not develop PE[29,30] and a more recent study detected an increase level of LPA by 2-fold in women had PE and by 2.5-fold in women had stillbirth than in women who had normal pregnancy[31]. Also, a recent study found serum LPA levels showed a 2-fold increase in women who had PE than NT women, and LPA level > 40.5 mg/dL can predict severe PE in women who had mild PE, while at a cutoff level of > 52.5 mg/dL could be considered as a PE severity marker with high sensitivity and specificity[32].

In a trial to evaluate the pathogenic mechanism for the relation between altered levels of LPA and the development of PE, a study found LPA genetic variability with a high inflammatory response may indicate future cardiovascular events and rs9355296 and rs3798220 are independent risk factors for PE with a positive correlation between rs9355296 and the diagnostic criteria of PE[33].

The current study detected a positive significant correlation between plasma levels of LPA and serum TNF-α in S1 samples and both variables were positively correlated with at-enrolment BMI and SBP estimated at the time of obtaining S2 samples with a positive correlation between BMI SBP measures at the time of obtaining S2 sample. These findings illustrated a reciprocal relation between obesity, high serum TNF- and plasma LPA early in pregnancy, and the development of PIH later in pregnancy. These correlations coincided with previous studies that detected a correlation between serum LPA levels in PE women and tissue growth factor-β1 and PE severity[34], serum P-selectin, which mediates the interaction of monocytes, platelets, and endothelial cells, and the severity of PE[35], BMI in severely PE women[29], blood pressure and proteinuria[30], BMI and serum C-reactive protein levels and disease severity[36] and between LPA levels and PE disease severity[32].

A recent study suggested a mechanism for this relation depends on the generation of ROS causing oxidized phospholipids subspecies that were degraded enzymatically by activation of lipoprotein-associated phospholipase A2 forming lysophospholipids which in turn stimulate the production of the inflammatory cytokines; TNF-α and IL-6, promote the expression of adhesion molecules and attract macrophages to the arterial intima causing atherosclerotic changes[37].

CONCLUSION

Development of PE might be due to the interplay between maternal pre-conceptional obesity, deregulated immune milieu, and/or atherogenic lipid levels. High serum levels of TNF-α and plasma LPA levels early in pregnancy could predict the development of PE and its severity.

LIMITATION

Evaluation of oxidative milieu and anti-inflammatory milieu is the limitation of this study to assure the obtained conclusion and were to be evaluated in future studies.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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