High Serum Levels of Cardiac Troponin I., Tumor Necrosis Factor-A and D-Dimer Could be Used as Early Predictors for Upcoming Preeclampsia and its Severity

Original Article

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ABSTRACT

Objectives: Evaluation of serum levels of high-sensitivity cardiac troponin I (cTnI), D-Dimer (D-Di) and Tumor necrosis factor-α (TNF-α) changes during pregnancy in women who developed preeclampsia (PE).

Patients and Methods: 70 PE women were diagnosed according to the American Society of Hypertension and were classified according to guidelines of American College of Obstetricians and Gynecologists. Also, 70 pregnant women free of hypertensive manifestations were enrolled as normotensive group (NT group). Two blood samples were obtained at the start of the 12th GW (S1 sample) and at time of diagnosis of PE (S2 sample) for ELISA estimation of cTnI, D-Di and TNF-α. Study outcomes included the relation between time and severity and change in serum levels of studied biomarkers and the ability of S1 sample levels as early predictors of development of PE and its severity

Results: PE women had significantly higher body mass index and fasting blood glucose levels than in NT women. Serum cTnI levels estimated in both samples of PE women were significantly higher than in NT women with increased levels in S2 than S1 by 1.46 folds and 2.44 folds than in S2 sample of NT women. Serum TNF-α and D-Di levels were significantly higher in both samples of all pregnant women in comparison to control levels and in PE than in NT women, and in S2 than S1 sample of PE women. Regression analysis defined high serum TNF-α and D-Di as significant positive early predictors for the possibility of development of PE especially early-onset, while high S1 sample serum D-Di and cTnI as the most significant early predictors for development of severe PE.

Conclusion: Estimation of serum TNF-α, D-Di and cTnI as an array early during pregnancy could identify women vulnerable to PE development and can be used as early predictors for early and/or severe PE.

Key Words: Cardiac troponin I, d-dimer, early prediction of PE, preeclampsia, tumor necrosis factor-α.

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INTRODUCTION

Hypertensive disorders in pregnancy (HDP) are a worldwide health problem that complicates up to 10% of pregnancies and is associated with increased maternal and neonatal morbidity and mortality[1]. HDP are associated with vascular dysfunction during pregnancy and an increased risk of long-term cardiovascular disease (CVD) in the mother[2]. Up to one third of women with HDP may develop hypertension (HTN) within a decade of an affected pregnancy[3]. Moreover, poorly-controlled HTN in the first trimester significantly increases maternal and fetal morbidity and mortality[4].

Preeclampsia (PE) is a systemic syndrome that continues to afflict 5% to 8% of all pregnancies throughout the world[5]. Pathogenesis of PE has not yet been fully elucidated, however, gestational kidney disease characterized by glomerular endothelial injury[6], imbalance in angiogenic factors[7], imbalanced cytokine network and altered levels of inflammatory and anti-inflammatory cytokines[8], disturbed levels of plasma decoy receptor 3 which is capable of inducing anti-apoptosis and anti-inflammation during pregnancy[9], dysregulation of long non-coding RNAs that could affect placentation, uteroplacental circulation, and endothelial cell function[10] are some of hypotheses that have been proposed to explain the development of PE.

During PE, the left ventricle undergoes concentric remodeling which often persists after delivery[11] and manifest as impaired myocardial contractility with increased peripheral resistance that depends on severity of hypertensive complications of pregnancy[12], so PE is strongly associated with heart failure later in life[11].

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Troponin (Tn) complex consisting of Tn I, T and C subunits, is a component of skeletal and cardiac muscle thin filaments and connects changes in intracellular Ca2+ concentration with generation of muscle contraction[13]. Increased serum Tn levels indicate higher risk for adverse outcome in patients with various cardiovascular diseases (CVD) beyond acute coronary syndrome[14]. High-sensitivity Tn assays shorten the time required to detect the first significant Tn elevation[15] and offer improvements for predicting major adverse cardiovascular events[16] or development of heart failure[17].

D-dimer (D-Di) is the smallest soluble fibrinolysis-specific degradation product found in the circulation[18] secondary to ordered breakdown of thrombi[19]. High serum D-Di is a manifestation of increased endogenous fibrinolytic activity and associated with the inflammation process[20].

Hypothesis

This study hypothesized a reciprocal relationship between development of HDP and pregnancy-induced inflammatory status on one-side and between HDP and activation of cardiac troponin complex that reflects the extent of insult on myocardial cells on the other side.

OBJECTIVES

Evaluation of serum levels of high-sensitivity cardiac troponin I (cTnI), D-Dimer (D-Di) and Tumor necrosis factor-α (TNF-α) changes during pregnancy in women who developed PE and the relation between these levels and PE severity as judged by blood pressure (BP) changes.

Design

Prospective comparative multicenter trial

Setting

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PATIENTS AND METHODS

According to the conditions cited in the approval of the study protocol by the Local Ethical Committee, all primigravida who attended the Antenatal Care Unit (ACU) of Menoufia University Hospital since Jan 2017, for assurance of being pregnant, were evaluated for eligibility for inclusion in the study. Exclusion criteria included presence of congenital heart diseases, valvular diseases, cardiomyopathy, myopathies, coagulopathy, infectious diseases, inflammatory states, manifest diabetes, endocrinopathy, essential HTN, renal, hepatic or cardiac diseases, family history of essential HTN, metabolic syndrome, or body mass index (BMI) >35 kg/m2. Also, women on regular exercise training, working require extensive muscular exercise, presenting after the 12thgestational week (GW) or refused to sign the written consent were excluded from the study. After assurance of pregnancy, gestational age was determined and women were clinically evaluated to determine baseline measurements of systolic and diastolic blood pressures (SBP, DBP), baseline BMI, and underwent routine investigations including complete blood count, kidney and liver function tests and urine analysis with special regard to presence of protein. All enrolled women were asked to sign written fully informed consent to attend the ACU 4-weekly till delivery for follow-up.

Diagnosis and categorization of pre-eclampsia (PE)

Preeclampsia (PE) was defined according to the American Society of Hypertension[21] as development of gestational HTN in a previously normotensive (NT) pregnant woman and is associated with proteinuria quantified as 1+ on dipstick. PE was categorized according to guidelines of American College of Obstetricians and Gynecologists as mild and severe according to BP measures obtained during follow-up visits, mild PE (MPE) was diagnosed if SBP and DBP were <160 and <110 mmHg, respectively with proteinuria of <2+ and absence of systemic manifestations. Severe PE (SPE) was diagnosed if elevated BP measures were associated with systemic manifestations or if SBP was ≥160 mmHg and DBP was ≥110 mmHg with proteinuria >2+ on a voided random urine[22]. Concerning timing of development of PE in relation to gestational age, PE was considered of early-onset (EPE) if diagnosed prior to 34 GW and late (LPE) if diagnosed after the 34th GW[23,24].

Groups

Enrolled women were categorized according to development of PE into two study groups:

1. PE group included pregnant women who developed PE during pregnancy.

2. NT group included number of pregnant women equal to that of PE women and were chosen from those who completed their pregnancy free of hypertensive manifestations and were age-matched to PE women.

For comparative purposes, ten non-pregnant women who were age-matched to women included in study groups and free of exclusion criteria were included as control group for laboratory data.

Laboratory investigations

Blood sampling

Two blood samples were obtained at the start of the 12th GW (S1 sample) and at time of diagnosis of PE (S2 sample) and only one sample was obtained from control women. Blood sample (5 ml) 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 -80oC till be assayed. Blood samples were collected and numbered by an assistant who was blinded about groups.

Investigations

Serum levels of high-sensitivity cardiac troponin I (cTnI), D-Dimer (D-Di) and tumor necrosis factor-α (TNF-α) were measured using enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000).

1. Human hsc-cTnI was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab223860, abcam, Cambridge, England) by quantitative sandwich enzyme immunoassay technique[25].

2. Human D-Di was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab260076, abcam, Cambridge, England) by quantitative sandwich enzyme immunoassay technique[26].

3. Human TNF-α was measured with the enzyme linked immunoassay (ELISA) kit (catalogue no. ab179886, abcam Inc., Cambridge, USA) by quantitative sandwich enzyme immunoassay technique[27].

Study outcomes

- Primary outcome is the relation between time of PE development and its severity and change in serum levels of studied biomarkers

- Secondary outcomes include

    1. The relation between the studied biomarkers
    2. The ability of S1 sample biomarkers' levels as early predictors of development of PE and its severity

Sample size calculation

Previously Joyal *et al*.[28] and Bozkurt *et al*.[29]compared serum Tn levels in normotensive (19 and 108, respectively) versus PE pregnant women (20 and 42, respectively) and detected higher serum cTn in PE women by 26.9% and 25% of levels estimated in NT women, respectively and documented that the difference was non-significant. The current study suggested a sample size of 61 women in each group to detect a 51% difference of serum cTnI levels between PE and NT women and to achieve study power of 85% and dropout of 5%. To guard against exclusion or missing of some cases during pregnancy course, the study was designed to include 70 patients per group.

Statistical Analysis

Obtained data were presented as mean±SD, median with interquartile range (IQR), numbers and percentages. Results were analyzed using paired t-test for intra-group comparisons, One-way ANOVA Test for intergroup comparisons, Mann-Whitney test and Chi-square test (X2 test) for non-parametric results. Possible relationships were investigated using Pearson linear regression analysis and Regression analysis (Stepwise method) was used for stratification of studied parameters as predictors for timing and severity of PE. For correlation and regression analyses, the studied parameters were evaluated versus the mean arterial pressure (MAP) calculated according to the equation: MAP = [(2 x diastolic) +systolic] / 3[30]. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. *P value* <0.05 was considered statistically significant.

RESULTS

During the study period, 70 PE women were enrolled in the study; 19 women (27.1%) had EPE and 51 women (72.9%) developed LPE. Sixteen women (22.9%) had severe and 54 women (77.1%) had mild manifestations (SPE & MPE, respectively). Seventy women of those had completed their pregnancy duration free of hypertensive manifestations and were age-matched to PE women were selected as NT group (Figure 1). Pre-eclamptic women had significantly higher body weight (BW) and BMI than NT women. Moreover, fasting blood glucose (FBG) levels in all women was in normal range but mean FBG was significantly higher in PE than in NT women (Table 1).

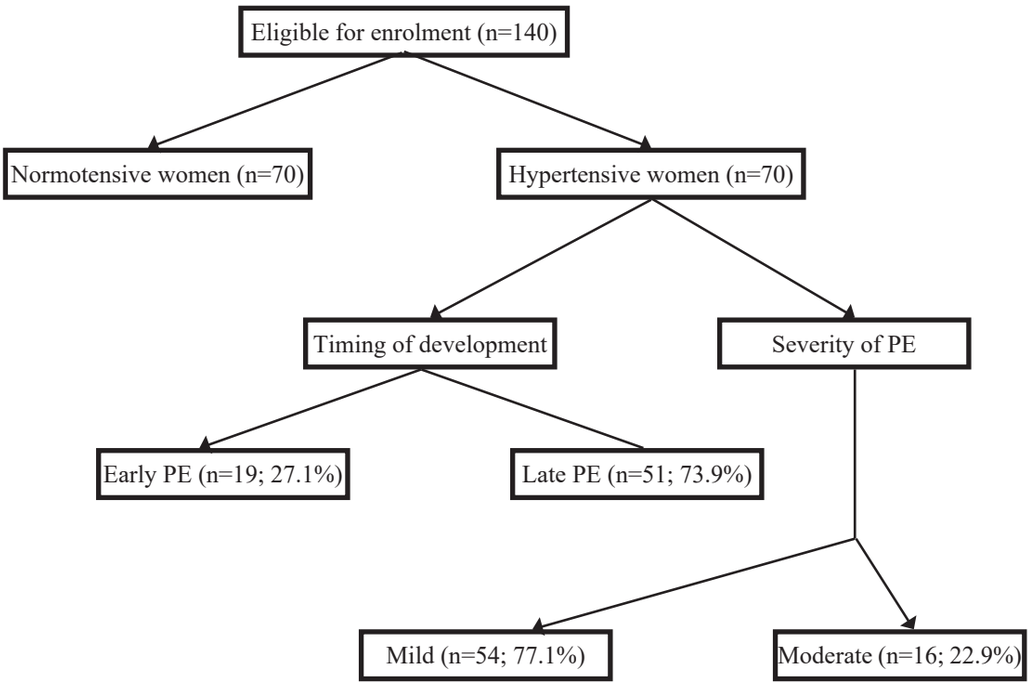

Fig. 1: Consort flow sheet

Table 1: Enrolment data of studied patients

Data		Group NT (n=70)	Group PE (n=70)	*P*
Age (years)		27.8±5.6	27.4±3.2	0.602
BMI data	Weight (kg)	79.2±6.4	84.8±6.6	0.019
	Height (cm)	170±2.4	169.8±1.9	0.561
	BMI (kg/m^2)	27.4±2.6	29.4±2.3	0.037
Fasting blood glucose (mg/dl)		90.8±9.2	94.6±9.3	0.015

Data are presented as mean, standard deviation; *P value* indicates significance of variance between groups; $p>0.05$ indicates non-significant difference; $p<0.05$ indicates significant difference

At time of enrolment, BP measures were non-significantly higher, while at time of PE diagnosis, BP measures were significantly higher in PE women in comparison to NT women. Furthermore, in comparison to BP measures estimated at time of enrolment, BP measures at time of PE diagnosis were non-significantly higher in NT women, but were significantly higher in PE women (Table 2).

Table 2: BP measures estimated at time of enrolment and diagnosis of PE in women of both groups

Time of estimation		Group NT (n=70)	Group PE (n=70)	*P*
At enrolment	SBP (mmHg)	116.9±4.2	117.9±3.9	0.149
	DBP (mmHg)	82.8±3.6	83±3.5	0.581
At diagnosis of PE	SBP (mmHg)	119.5±6	145.7±14.7	<0.0001
	P1=	0.062	<0.0001	
	DBP (mmHg)	84.7±3.6	101.5±8.2	<0.0001
	P1=	0.361	<0.0001	

Data are presented as mean, standard deviation; NT: Normotensive; PE: Pre-eclampsia; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *P value* indicates significance of variance of measures of the both groups; P1 indicates significance of difference in comparison to respective at enrolment measures; $p<0.05$ indicates significant difference; $p>0.05$ indicates non-significant difference.

Both SBP and DBP measures estimated at time of enrollment were non-significantly higher in women who developed severe or early PE in comparison to women who developed mild or late PE, respectively. At time of PE diagnosis, both SBP and DBP were significantly higher in women who developed SPE in comparison to those who developed MPE. However, women who developed EPE had significantly higher DBP, but non-significantly SBP in comparison to women who developed LPE (Table 3).

Table 3: BP measures of PE women categorized according to severity and timing of development of PE

Variables		Category	Severity		Timing	
			Mild PE	Severe PE	Early PE	Late PE
SBP (mmHg)	At enrolment	Measure	122±6.8	123±3.9	121.9±4.9	122.4±6.7
		P=	0.579		0.788	
	At diagnosis of PE	Measure	138.9±9.3	168±4.6	150.2±14.8	143.8±13.9
		P=	<0.001		0.112	
DBP (mmHg)	At enrolment	Measure	78±5.4	79±4.8	78.7±6.2	78.1±5
		P=	0.511		0.633	
	At diagnosis of PE	Measure	98±5.5	113.5±1.7	105.1±7.6	100.2±8.1
		P=	<0.001		0.0277	

Data are presented as mean, standard deviation; PE: Pre-eclampsia; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *P* indicates significance of difference; $P<0.05$ indicates significant difference, $P>0.05$ indicates non-significant difference

Serum cTnI levels estimated in S1 and S2 samples of PE women were significantly higher than cTnI levels estimated in corresponding samples of NT women. Mean serum level of cTnI in S2 sample of PE women was higher than that of S1 sample by 1.46 folds, and in comparison, to its level in S2 sample of NT women by 2.44 folds, while in S2 sample of NT women serum cTnI level was higher than its level in S1 sample by 1.36 folds. In S2 sample of SPE women, serum cTnI levels were significantly higher than in their S1 sample and in S2 sample of MPE by 1.9 folds and in S2 sample of EPE women than in their S1 sample by 1.68 folds and by 1.39 folds than levels estimated in S2 samples of LPE women, while serum cTnI levels in S2 sample of LPE women were higher than in their S1 sample by 1.36 folds

Serum TNF-α and D-Di levels estimated in all women were significantly higher in both S1 and S2 samples in comparison to control levels, while serum cTnI was undetected in controls. Serum TNF-α and D-Di levels estimated in both S1 and S2 samples were significantly higher in PE than in NT women. Moreover, serum levels of studied markers were significantly higher in S2 samples than in S1 sample of PE women, while in NT women, only serum TNF-α levels were significantly higher in S2 sample, but serum D-Di levels were insignificantly higher in S2 sample in comparison to levels estimated in S1 sample. Estimated serum D-Di levels were significantly higher in women developed severe and/or late PE in comparison to women who developed mild and/or early PE, respectively, in both S1 and S2 samples. On the other hand, serum TNF-α levels were significantly higher in S2 sample of EPE women in comparison to LPE, but were non-significantly higher in SPE women than in MPE women (Table 4).

Development of PE showed positive significant correlation of high BW, FBG and high serum levels of studied parameters, also PE severity showed positive significant correlation, while timing of PE development showed negative significant correlation with BW, BMI, FBG and levels of studied parameters estimated in S1 sample. Analysis of clinical and laboratory data determined at time of enrolment using Regression analysis defined high serum TNF-α and D-Di as significant positive early predictors for the possibility of development of PE especially EPE, while high S1 sample serum D-Di and cTnI as the most significant early predictors for development of severe PE (Table 5).

Table 4: Mean serum levels of TNF-α, cTnI and D-Di estimated in S1 and S2 samples of NT and PE women

Groups		Parameters	TNF-α (pg/ml)		cTnI (ng/ml)		D-Di (µg/ml)	
			S1 sample	S2 sample	S1 sample	S2 sample	S1 sample	S2 sample
Controls (n=10)*			0.252±0.13				0.175±0.03	
NT (n=70)		Level	1.83±0.78	4.76±2.14	0.143±0.123	0.195±0.184	0.419±0.07	0.432±0.09
		P1	<0.001	<0.001			<0.001	<0.001
		P2		<0.001		0.053		0.351
PE	Total	Level	8.599±3.9	15.6±6.94	0.251±0.168	0.517±0.269	0.682±0.21	1.343±0.39
		P1	<0.001	<0.001			<0.001	<0.001
		P2		<0.001		0.0002		<0.001
		P3	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	MPE	Level	8.39±3.98	14.9±7.15	0.306±0.151	0.393±0.215	0.6±0.16	1.149±0.09
		P2		<0.001		0.069		<0.001
	SPE	Level	9.31±3.66	17.9±5.8	0.394±0.209	0.75±0.27	0.957±0.088	2±0.25
		P2		<0.001		<0.001		<0.001
		P4	0.411	0.132	0.068	<0.001	<0.001	<0.001
	EPE	Level	10.5±3.29	18.4±5.1	0.355±0.14	0.598±0.19	0.647±0.22	1.28±0.34
		P2		<0.001		0.045		<0.001
	LPE	Level	7.89±3.9	14.56±7.29	0.316±0.177	0.429±0.285	0.775±0.17	1.518±0.46
		P2		<0.001		0.018		<0.001
		P5	0.012	0.039	0.483	0.647	0.022	0.019

Data are presented as mean, standard deviation; TNF-α: Tumor necrosis factor-α; cTnI: cardiac troponin I; D-Di: D-dimer; NT: Normotensive women; PE: Pre-eclamptic women; S1 Sample: sample obtained at time of enrolment in the study; S2 Sample: sample obtained at time of PE diagnosis; *: volunteer controls; MPE: Mild PE; SPE: Severe PE; EPE: Early PE; LPE: Late PE; P1 indicates significance of difference versus controls; P2 indicates significance of difference versus S1 levels; P3 indicates significance of difference versus NT group; P4 indicates significance of difference between MPE & SPE women; P5 indicates significance of difference between EPE & LPE women; $P<0.05$ indicates significant difference; $P>0.05$ indicates non-significant difference

Table 5: Statistical correlation and analysis for early predictors of PE development, severity and timing of development

		Development		Severity		Timing	
		Pearson's correlation					
		r	P	r	P	r	P
Body weight (kg)		0.178	0.036	0.312	0.009	-0.437	<0.001
BMI (kg/m^2)		0.160	0.059	0.315	0.008	-0.446	<0.001
FBG (mg/dl)		0.202	0.017	0.343	0.004	-0.486	<0.001
S1 level of	TNF-α (pg/ml)	0.825	<0.001	0.392	0.001	-0.721	<0.001
	cTnI (ng/ml)	0.562	<0.001	0.548	<0.001	-0.532	<0.001
	D-Di (µg/ml)	0.644	<0.001	0.760	<0.001	-0.492	<0.001
		Regression analysis					
		β	p	β	p	β	p
Body weight (kg)		0.059	0.487	0.177	0.145	-0.322	0.007
BMI (kg/m^2)		0.098	0.250	0.190	0.118	-0.299	0.012
FBG (mg/dl)		0.102	0.232	0.256	0.034	-0.286	0.017
S1 level of	TNF-α (pg/ml)	0.774	<0.001	0.304	0.011	-0.721	<0.001
	cTnI (ng/ml)	0.048	0.575	0.492	<0.001	-0.203	0.095
	D-Di (µg/ml)	0.328	0.001	0.760	<0.001	-0.451	<0.001

BMI: Body mass index; FBG: Fasting blood glucose; TNF-α: Tumor necrosis factor-α; cTnI: Cardiac troponin I; D-Di: D-dimer; S1 Sample: sample obtained at time of enrolment in the study; S2 Sample: sample obtained at time of PE diagnosis; r: Pearson correlation coefficient; β: Standardized coefficients; $P<0.05$ indicates significant difference; $P>0.05$ indicates non-significant difference

DISCUSSION

Serum cTnI levels estimated in S1 and S2 samples of PE women were significantly higher than that of NT women in both samples and in samples of SPE than MPE women. These findings suggest a possible relation between development and severity of PE and elevated serum cardiac marker; cTnI and spotlight on the risk imposed by PE on the heart, both functionally as manifested by elevated BP measures and structurally as reflected by high cTnI serum levels. In support of this suggestion, there was positive significant correlation between BP measures and cTnI levels of S1 sample and Regression analysis defined high cTnI level in S1 sample as an early predictor for development and severity of PE.

These results supported the earlier studies that reported elevated serum cTnI and cTnT in women with PDH and documented that these changes indicate some degrees of cardiac myofibrillar damage and cardiac dysfunction[31,32]. Also, the obtained results refuted the results obtained by other earlier studies[29,33] that detected no increase of serum cTnI in PE women.

In support of the obtained results, Alma *et al*.[34] detected 10 markers including C-reactive protein (CRP) and cTnI that could differentiate PE women from controls and found these markers to be elevated in women with heart failure with preserved ejection fraction (HFpEF), so suggested that both HFpEF and PE share a common pathogenic background and these markers may be used as prognostic tool.

Thereafter, Ekun *et al*.[35] reported that PE is associated with higher levels of cTnI and oxidative stress markers than NT healthy pregnant women, thus indicating the deleterious effects of PE on the cardiovascular system. Also, Morton & Morton[36] and Muijsers *et al*.,[37] detected elevated levels of cTnI in PE than NT women with a linear correlation between peak mean arterial pressure and log cTnI. Moreover, Ravichandran *et al*.[38] and Dockree *et al*.[39] found patients with HDP or PE had higher cardiac Tn concentrations, which was a strong independent predictor of HDP or PE.

In support of predictability of cTI estimation, hs-cTnI levels were statistically significantly higher in current hypertensive women with a history of preeclampsia compared with their normotensive counterparts. Therefore, hs-cTnI levels might improve risk prediction for women at the highest risk of cardiovascular disease. This suggestion goes in hand with the result of a narrative review documented that hs-cTnI in conjunction with disturbed inflammatory/anti-inflammatory ratio might be potentially eligible biomarkers for cardiovascular risk stratification of women with PE/HELLP syndrome and may contribute to the development of adequate preventive measures for PE or its adverse events[40].

Development of PE especially EPE was positively correlated with high serum TNF-α levels in S1 sample, while high serum D-Di was positively correlated with both severity and timing of PE development. Moreover, Regression analysis defined high S1 serum TNF-α levels as early predictor for development of PE especially EPE, while high serum D-Di levels as early predictor for development of early-onset severe PE. The reported relation between high serum TNF-α and D-Di and development of PE points to the role played by disturbed inflammatory milieu in pathogenesis of PE and the higher the extent of disturbance, the earlier the time of upcoming PE.

Similarly, Baboolall *et al*.[41] reported strong correlation between the period of gestation and plasma D-Di levels and using receiver operating characteristic curve assured a possible role of high plasma D-Di in predicting SPE. Lucena *et al*.[42] also found D-Di levels increased during pregnancy in NT and PE women but peaked earlier and was higher at 30-34 GW in PE than NT pregnant women. Recently, Liu *et al*.[43] detected high D-Di and activated partial thromboplastin time levels in PE and SPE than in normal pregnant women and Trisnawati *et al*.[44] reported that PE pregnant women have about five times higher levels of TNF-α than normal pregnant women

In trial to explore the pathogenesis of the reported relationships, In-*vitro* studies detected increased expression levels of NF-kB and TNF-α in the peripheral blood mononuclear cells of PE than in NT pregnant women and in EPE than in LPE with a strong correlation between NF-kB and TNF-α[45]. Also, in-*vitro* co-stimulation of placental cells by TNF-α and insulin-like growth factor-1 induced the genetic and epigenetic changes associated with preeclampsia[46]. Experimentally, using reduced uterine perfusion pressure (RUPP)-PE rat model, the detected high expression rates of cTnI, myoglobin, creatine kinase isoenzyme and brain natriuretic peptide indicated significant myocardial damage and IL-6 upregulation was found to deteriorate, while its down-regulation significantly relieved these abnormalities[47]. In *vivo* experiments demonstrated that MiR-133 plays a role in development and progression of PE through induction of higher levels of inflammatory cytokines especially TNF-α and affect placental tissue apoptosis through the Ras homolog gene family (Rho)/Rho-associated coiled-coil forming protein kinase signaling pathway[48].

At time of enrollment, PE women had significantly higher BMI and FBG levels and these high levels were significantly correlated with the development and severity of PE and can predict PE development. In line with these findings, Olson *et al*.[49] documented that pre-pregnancy obesity increased the chance of developing PE through an aggravated inflammatory response, angiogenic imbalance, and abnormal placentation because adipose tissue is a rich source of pro-inflammatory cytokines and complement proteins. Also, Alonso-Ventura *et al*.[50] reported that in

comparison to controls, PE women had significantly higher BMI, waist-to-hip ratio, blood glucose and total cholesterol, CRP with reduced HDL levels.

CONCLUSION

Activated pro-inflammatory cascade and fibrin degradation during pregnancy may predispose to development of PE that endangers cardiac function and structure. Estimation of serum TNF-α, D-Di and cTnI as an array early during pregnancy could identify women vulnerable to PE development and can be used as early predictors for early and/or severe PE. However, wider scale multicenter studies are mandatory to establish these results and to identify cutoff points for each marker for upcoming PE

CONFLICT OF INTERESTS

There are no conflicts of interest.

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