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High Sensitive C Reactive Protein to Diagnose Inflammatory Mediators in Preeclampsia

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Abstract

Preeclampsia is considered as a serious pregnancy complication. It's one of the most common causes of maternal morbidity and mortality. There is extensive evidence that activation of inflammation is considered as a major contributor in the preeclampsia pathogenesis. To assess serum highly sensitive C-reactive protein level in preeclampsia as an indicator of inflammation and to correlate Hs-CRP with blood pressure. The case-control study was carried out on 85 women attending the outpatient clinic of Al-Zahraa University hospital in the interval from March 2021 till November 2021 according to inclusive and exclusive criteria and tests were done at Allergy & Immunology Center Al-Azhar University. They were divided into two groups: a. Preeclamptic patient group (50 cases) b. Controls: involving 35 healthy normotensive gravid females. Two ml venous blood samples were collected from all females participating in the study for assessment of Hs-CRP level by ultra-sensitive immunoturbidometric technique (ELISA assay). In preeclampsia, serum Hs-CRP levels were significantly higher than normotensive pregnant females ($p<0.001$). Hs-CRP can assess low grade chronic inflammation. the degree of inflammation increase as Hs CRP rises. In preeclampsia, the systemic inflammatory response is overactive, resulting in production of reactive oxygen species and endothelial impairment. This is the main cause of the clinical symptoms of hypertension and proteinuria in preeclampsia. Early detection can minimize systemic inflammation and maternal death due to preeclampsia. Hence, Hs-CRP may be used as an important indicator of inflammation and severity of preeclampsia.

Keywords: High-sensitive C-reactive protein; Pre-eclampsia; pregnancy.

1. Introduction

Pre-eclampsia (PE) is a complex systemic condition. It is marked by gestation hyper-tension ≥140/90 associated with proteinuria or maternal organs damage or utero-placental dysfunction after 20th gestational week [1]. Pre-eclampsia is a frequent chief reason of motherly morbidities and mortalities. The exact pathogenesis of PE isn't yet identified. Proteinuria is considered by excretions of 300-mg a day, a urine protein/Cr ratio of 0.3, or a qualitative 1 dipstick reading [2]. A potential hypothesis for pathogenesis of pre-eclampsia is decreased placental perfusions as a consequence of shallow invasions of chorionic villi. This causes

elevated oxidative stress and stimulation of neutrophils and macrophages; this eventually indorses cytokine productions [3]. The productions of Hs-CRP are persuaded by pro-inflammatory cytokines, IL-1, -6, -17 and TNF-α in liver, while additional hepatic productions may contribute to systemic concentration [4]. The cytokines highlight biological influences on Hs-CRP by signaling via their receptors on liverwort cells. It stimulates dissimilar kinases and phosphatases resulting in the trans-location of several transcriptions on the Hs-CRP gene promoter and eventually causes Hs-CRP productions [4]. CRP of blood is considered as an acute-phase protein in which its levels rise throughout inflammations, tissue damages, infections and neoplasia. Elevated CRP levels were accompanying with severe PE [5].

2 .Patients and Methods

This was case-control research performed on 85 women attending out-patient clinic of at Al-Zahraa University hospital according to inclusive and exclusive criteria and tests were done at Allergy & Immunology Center Al-Zahraa university. They were allocated into 2 groups: preeclamptic patient group (50 cases) and Controls: including 35 healthy normotensive pregnant females. Inclusive criteria for the study group: Age group at least 18-yrs, gravidity ranging from PG to G5, gestational age ≥ 20week, patient not in labor having single viable pregnancy.

2.1. Inclusive criteria

Age group at least 18-yrs, gravidity ranging from PG to G5, gestational age ≥ 20week, patient not in labor having single viable pregnancy.

2.2. Exclusive criteria

Patients with a history of: Premature ruptures of membrane (PROM), renal conditions, DM, liver disease, systemic Lupus Erythematosus, systemic infections, cardio-vascular diseases and endocrine disorders.

2.3. All women were submitted for

Verbal and written Consent after they have been made aware of the purpose of the study. Detailed history: Personal history (name, age, occupation, residence), Obstetric history (gravidity, parity, pregnancy outcome), Contraceptive history and history: HTN or pre-eclampsia in preceding gestation, kidney disorder, DM, systemic lupus erythematosus, epilepsy, surgical and Family histories. Thorough examination that included: General examination: Weight, BMI, BP and pulse rate.

2.4. Abdominal and local clinical examination

- **Ultrasonography:** The 20^{th}-wk scans had both repetitive (reviewing of embryonic anatomy and bio-metric measures) and research (uterine and umbilical artery Doppler flowing velocimetry) element. Figure (1) [6].

- **Method:** All participants of the study were subjected to the following: Blood sampling: the 2mL of venous blood specimens were gathered under aseptic circumstances. The blood specimens were permitted to clot and centrifuge at 3k r/m for ten mins to get the clear serum, the serum specimens were utilized for the estimations of Hs-CRP by ultrasensitive immuno-turbidimetric technique (ELISA assay) via commercial kit (Roche, Germany).
- Hs CRP > 3 mg/L in preeclampsia.
- Hs CRP < 3 mg/L in normotensive pregnant women.

2.7. Statistical analysis

SPSS-23 (IBM, USA) and MedCalc-18.2.1 (Belgium) programs were utilized in statistical analysis of the data. Continuous numerical data has been introduced as mean and SD and among-group changes were matched via the un-paired t testing. Categorical variables have been introduced as numbers and percentages and changes were matched via Fisher's exact testing. Results considered significant at P <0.05.

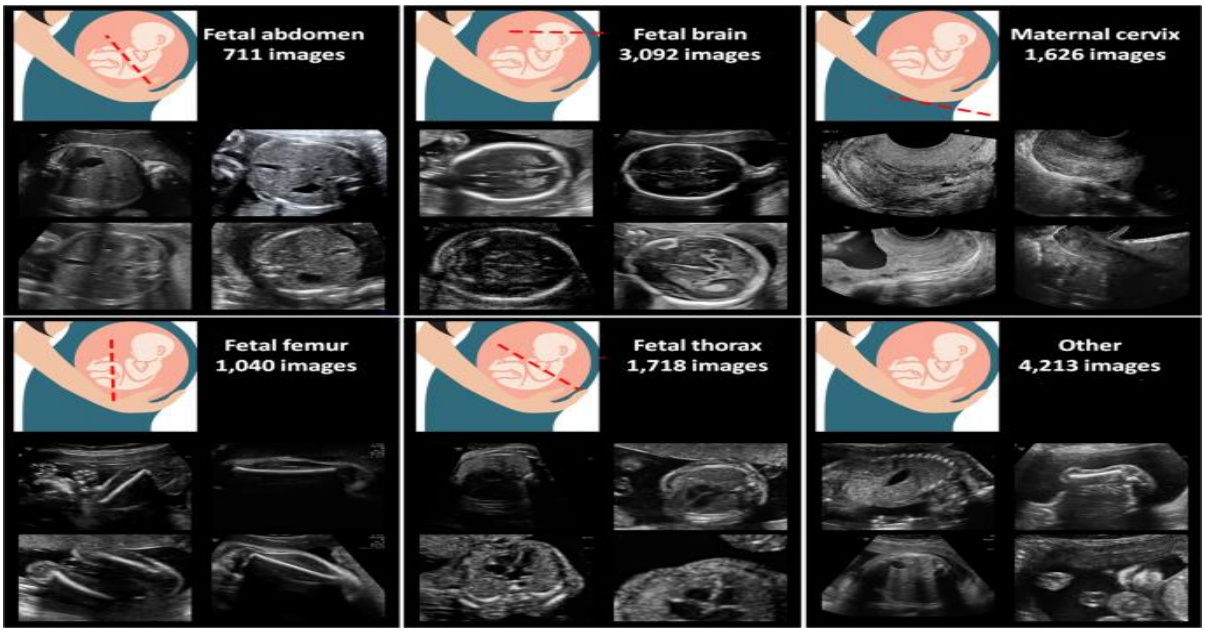

Figure (1): Ultrasound images display planes of volume acquisitions. [6].

3. Results

There was no statistical difference among the two groups in terms of demographics as shown in Table 1. Preeclampsia patients had considerably higher SBP and DBP than normal pregnant women. Both SBP and DBP were positively correlated with Hs CRP levels. (Figure2, Figure3). There was a significant difference in ALT and AST between the two groups. The levels of uric acid in the two groups were significantly different. ALT, AST and uric acid levels were all higher in preeclampsia group. There was no statistical difference between the two groups in terms of any test data. We revealed that Hs-CRP level was significantly high in PE group in comparison with normo-tensive group. Hs-CRP levels revealed to be significantly high in +3 proteinuria cases compared to +2 proteinuria patients compared to +1 proteinuria patients.

Table (1): The demographics have nonsignificant difference in both groups.

	Pre-eclampsia (n=50)	**Normo-tensive** (n=35)	**T**	**p**
Age (years) Mean ± SD	24.62 ± 5.09	25.15 ± 7.18	.401	.689
BMI (kg/m^2) Mean ± SD	27.12 ± 3.64	26.34 ± 2.39	1.11	.270
Gravidity Mean ± SD	2.38 ± 1.19	2.57 ± 1.36	**MU** 804	.511
Parity Mean ± SD	1.48 ± 0.839	1.54 ± 1.27	**MU** 831	.670

Table (2): SBP and DBP among the studied groups.

	Pre-eclampsia *(n=50)*	***Normo-tensive*** *(n=35)*	*t*	***p***
SBP *(mmHg)* *Mean ± SD*	164.8 ± 19.40	105.14 ± 9.19	**17**	**.000**
DBP *(mmHg)* *Mean ± SD*	104.6 ± 8.62	66.57 ± 7.25	**21**	**.000**

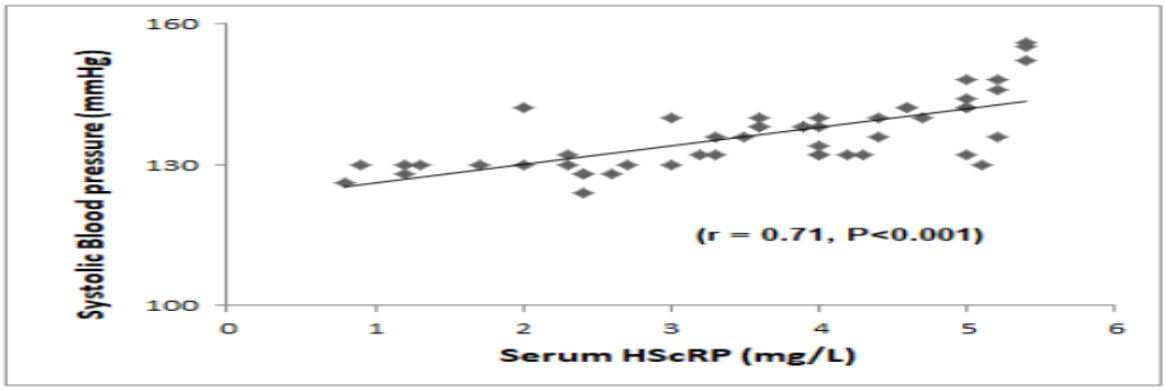

Figure (2): Correlation of Hs CRP with systolic blood pressure.

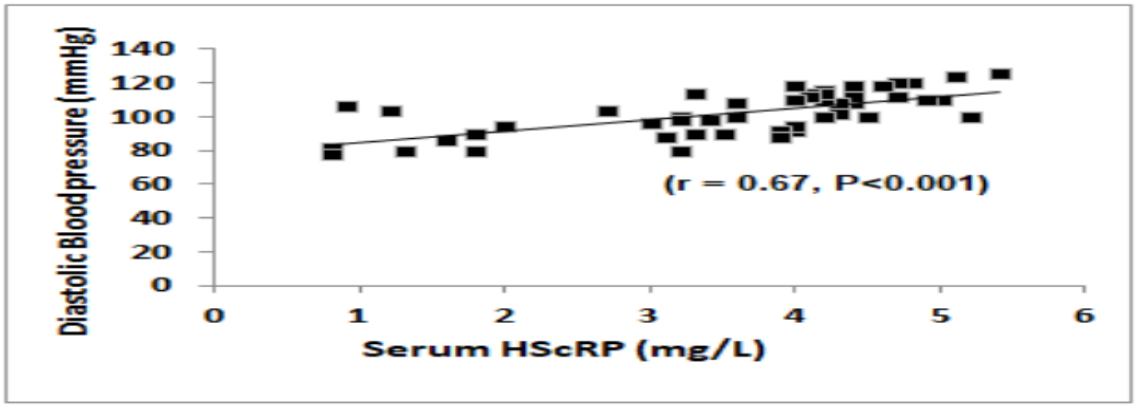

Figure (3): Correlation of Hs CRP with diastolic blood pressure.

Table (2): Laboratory results of the two groups.

	Pre-eclampsia *(n=50)*	***Normo-tensive*** *(n=35)*	***t***	***P***
Hb *(g/dL)* *Mean ± SD*	11.19 ± 1.21	11.68 ± 1.17	1.86	.066
TLC *(x 10^3/L)* *Mean± SD*	8.15 ± 2.32	8.41 ± 2.53	.489	.626
PLT *(x 10^3/L)* *Mean± SD*	287.54 ± 52.76	302.31 ± 45.14	1.35	.182
ALT *(U/L)* *Mean± SD*	42.11 ± 18.34	26.31 ± 7.76	**4.79**	**.000**
AST *(U/L)* *Mean± SD*	37.25 ± 15.63	23.47 ± 8.33	**4.76**	**.000**
RBS *(mg/dl)* *Mean ± SD*	137.75 ± 25.41	139.63 ± 26.88	.328	.744
Creatinine *(mg/dl)* *Median (Range)*	0.8 (0.7 - 1.2)	0.78 (0.6 - 1.2)	1.38	.171
Urea *(mg/dL)* *Mean ± SD*	13.25 ± 3.83	12.47 ± 3.6	.947	.346
Uric acid *(mg/dL)* *Mean ± SD*	4.37 ± 2.23	3.21 ± 1.16	**2.82**	**.006**

Table (4): Hs-CRP level in both groups.

	Pre-eclampsia *(n=50)*	***Normo-tensive*** *(n=35)*	***z***	***P***
hs-CRP *(mg/L)* *Mean ± SD.* *Range*	7.89 ± 3.4 3.2 - 20	1.37 ± 0.68 0.3 - 2.6	**7.82**	**<0.001**

Table (5): Hs-CRP in relation to proteinuria.

	+1 *(n=23)*	***+2*** *(n=24)*	***+3*** *(n=3)*	***kw***	***P***
hs-CRP *(mg/L)* *Mean ± SD.* *Range*	5.08 ± 1.28 3.2 - 6.9	9.58 ± 1.59 7.16 - 12.6	16.01 ± 3.53 13.3 - 20	**38.9**	**<0.001**

Table (6): Birth characteristics in both groups.

	Pre-eclampsia *(n=50)*	***Normo-tensive*** *(n=35)*	*t*	***p***
GA *(weeks)* *Mean ± SD*	30.43 ± 4.37	30.38 ± 2.88	**3.75**	**.000**
Birth weight *(kg)* *Mean ± SD*	2.84 ± 0.435	3.02 ± 0.314	**2.09**	**.039**
Apgar at 1 min *Mean ± SD*	6.73 ± 1.65	7.11 ± 0.964	1.22	.225
Apgar at 5 min *Mean ± SD*	9.71 ± 0.499	9.86 ± 1.21	.788	.433

A significant change was found among the study groups as regard GA and birth weight. There was a high significantly increase in GA and a significant decrease in birth weight in preeclampsia group**.**

4. Discussion

Plantar The demographics were non-significantly differed in the two groups. The present findings were in line with results of Sayyed & Pratinidhi, [7] as they revealed that the ages mean, and GA were not-significantly differed in both mild and severe pre-eclampsia in comparison controls. While, in the study of Kashanian et al., [8] the cases of study groups (both normo-tensive and pre-eclamptic) didn't show any significant change as regard gravidity; but maternal age (P-value<.05) and BMI (P-value<.05) were elevated in the PE group. GA was significantly lesser in the PE group. PE is one of the commonest encountered complications of gestation and this is a leading reason of motherly and newborn death worldwide. Pre-eclampsia is a disease of wide-spread vascular endothelial malfunctions and vasospasms that happens afterward the 20th gestational week and can be continued as late as 4 to 6-wks post-partum. It is clinically marked by HPT and proteinuria, with or with no pathologic edema [9]. The present work revealed that the commonest presentation was lower limb edema (82%) followed by epigastric pain (36%) and severe headache (32%). A significant change was found among the study groups as regard SBP and DBP. Our results were co-in siding with study of Jannesari & Kazemi, [10] as they reported that there was a significant variance among PE group in comparison with controls regarding SBP and DBP. Also, Udenze et al., [11] revealed that there was a significant variance among PE-group and controls regarding SBP and DBP. The current study showed that majority of the patients presented with +2proteinuria (48%) followed by +1 proteinuria (46%), while +3 proteinuria found in only 6% of the patients. A significant change was found among the

study groups as regard ALT, AST, and uric acid. Several concepts were proposed to clarify the reason of pre-eclampsia (3, 10) A potential suggestions for pathogenesis of pre-eclampsia is decreased placental perfusions as a consequence of shallow invasions. This result in elevated oxidative stress and activations of neutrophils and macro-phages; this eventually promote cytokine productions. The productions of Hs-CRP are persuaded by pro-inflammatory cytokines, IL-1, -6, - 17 and TNF-α in the liver, while additional hepatic productions may contribute to systemic concentration. The cytokines highlight biological influences on Hs-CRP by signaling via their receptors on hepatic cells. It triggers dissimilar kinases and phosphatases causing the trans-location of several transcription factors on the Hs-CRP gene promoter and eventually results in Hs-CRP productions. Placental dysfunctions or fats results in the expressions of the CRP in the liver or the placenta. Hs-CRP blinded to phosphocholines which are moved to neuro-kinin B, thus improving activations of the neuro-kinin 3 receptors. This cause organ damages and arterial HPT. These cytokines are accountable for inflammation response resulting in motherly endothelial dysfunctions and activations of homeostatic system in pre-eclampsia [12]. In the current work, Hs-CRP level was significantly high in pre-eclampsia in comparison with normo-tensive group. Levels of Hs-CRP revealed to be significantly increased in +3 proteinuria cases eclampsia in comparison with +2 proteinuria cases eclampsia in comparison with +1 proteinuria cases. The current findings were in harmony with results of Sayyed & Pratinidhi, [7] as they revealed that levels of Hs-CRP were significantly high in pre-eclampsia in comparison with controls. Furthermore, levels of Hs-CRP were significantly increased in severe pre-eclampsia in comparison with mild PE these results are in agreement with Bargale et al, [13] and Behboudi-Gandevani et al., [14]. Similarly, Kashanian et al., [8] revealed that sCRP of the 1st trimester was significantly elevated in the PE cases. sHs-CRPof >7 mg per L was detected in 26 (62 %) patients of PE vs. 22 (6 %) normo-tensive cases, which revealed a significant change (P-value= 0.001, RR = 12, 95% CI: 7–21). After adjusting for BMI, RR was valued to be 10.7 (95% CI: 7.9–14.2). sHs-CRPof >7 mg/L was detected in 17 (73.9 %) patients of severe PE vs. 22 (6.3%) in normo-tensive patients, which reveal a significant change (P value= 0.001, RR = 9.4, 95% CI: 4.5–19.5). Afterward adjusting for BMI, RR was valued to be 10.66 (95% CI: 7.3–15.2) resp. In the study done by Jannesari & Kazemi, [10] they matched the levels of Hs-CRP in cases with dissimilar severities of PE and those with controls. The findings revealed that the levels of the investigated markers were significantly elevated in PE cases. Despite elevated levels of Hs-CRP in PE cases than those with no PE, they have low sensitivity and specificity for predictions of PE. Also, Raio et al., [15] revealed that in control group, sHs-CRP exhibited a positive association with GA (r, 0.40; Pvalue < 0.001). In cases with PE, Hs-CRP levels were more than in GA-matching control group (18010±4763 vs. 3026±587 ng/ml; P value< 0.001). Mihu et al., [16] have matched the level of sCRP in cases with PE and control group. The study revealed that sCRP levels was significantly elevated in PE than controls and can be considered as a biomarker for PE severity. They suggested to usage CRP, a fast and comparatively cheap examination, in clinical practice mid pregnancies with PE. Hs-CRP is a biomarker of systemic low-grades inflammations, an acute phase reactant formed in the liver as a responding to stress, tissue injuries and is the most sensitive glycoprotein biomarker of inflammations in the human body [17]. In Iranian report by Farzadnia et al., [18] have revealed that Hs-CRP levels were elevated in sever than mild PE and controls and reported that it can be beneficial in expecting the PE severity. Furthermore,

Zaid et al., [19] stated that there was significant rise in mild-PE and severe-PE in comparison with controls and there was significant rise in severe PE in compared to mild PE and to controls. A significant rise was reported in mild and severe PE in comparison with controls and a significant rise was detected in severely PE compared to mild PE and to control group (P value< 0.05). In a report done by Adali et al., [20] on PE cases, regarding the correlation amid maternal sHs-CRP level and uterine artery Doppler veloci-metry was assessed. This report revealed that sHs-CRP levels are elevated in PE than normo-tensive cases. Hs-CRP as well has positive correlation with the MAP and its level was elevated in PE cases who had abnormal uterine artery Doppler velocimetry than PE cases with ordinary Doppler. They reported that the Hs-CRP level of motherly serum has an association with the severity of PE, which displays an endothelial dysfunction, and can be measured as a possible biomarker of pathologic utero-placental perfusions. Regarding neonatal outcome, a significant change was found among the groups as regard GA and birth weight. In accordance with our results, study of Arthur et al., [21] as they reported that a significant change was found among PE and control groups as regard GA. Similarly, Al-Tairi et al., [22] revealed that GA at birth was lower in the study PE case group in comparison with controls, which seems to have a significant correlation with PE (36.80 versus 38.10 wks. respectively, p value= 0.019). In the study of Mayrink et al., [23] PE cases having sustained elevated frequency of adverse outcome, counting CS (3.5-times), pre-term delivery less than 34 wks. of GA (3.9-times) and hospitalization >5-day (5.8-times) than control group. They as well had inferior perinatal outcome, counting lower birth weight (with mean 379 gm lower), small for GA babies (RR 2.4 [1.5–3.9]), 5-min Apgar scores <7 (RR 2.1 [1.0–4.3]), NICU admissions (RR 3.3 [1.6–6.9]) and Newborn Near Miss (3.6 [1.8–7.5]). Weakly weight gain, obesity and DBP ≥75 mmHg at 20 wks of GA were shown to be accompanying with PE. PE as well led to an elevated number of CS and extended hospitalization, as well as worse newborn outcome.

5. Conclusion

In preeclampsia, the systemic inflammatory response is overactive, resulting in production of reactive oxygen species and endothelial impairment. This is the main cause of the clinical symptoms of hypertension and proteinuria in preeclampsia. Early detection might minimize systemic inflammation and maternal death due to preeclampsia. Hence, Hs-CRP may be used as an important indicator of inflammation and severity severity of preeclampsia.

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