RESEARCH ARTICLE

Serum ferritin and C- reactive protein levels as indicators of severity of preeclampsia

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Abstract

Objective: To assess the role of inflammatory markers ferritin and C- reactive protein as indicators of preeclampsia severity.

Method: The case-control study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, from November 2021 to May 2022, and comprised pregnant women from the obstetrics ward and outpatient clinics aged 16-40 years having a viable singleton pregnancy and gestational age >32 weeks. They were divided into severe preeclampsia group A, non-severe preeclampsia group B and control group C. Serum ferritin and C-reactive protein levels were measured for all the subjects, and compared. Data was analysed using SPSS 26.

Results: Of the 87 pregnant women, 27(31%) were in group A with mean age 29.76±7.53 years and mean gestational age 35.63±1.92 weeks, 29(33.33%) were in group B with mean age 26.83±6.30 years and mean gestational age 36.24±1.72 weeks, and 31(35.63%) were in group C with mean age 26.00±5.73 years and mean gestational age 36.52±1.61 weeks. Ferritin levels in patient groups were significantly higher than in the control group ($p<0.05$), but it was not significantly different between the patient groups ($p>0.05$). C-reactive protein levels in the patient groups were significantly higher than in the control group ($p<0.05$), and they were also significantly higher in group A than in group B ($p<0.05$). At a cut-off value >101.8 ferritin had sensitivity 92.59% but specificity 20.69%, whereas C- reactive protein at a cut-off value >17.1 had sensitivity 66.67% but specificity 75.86%.

Conclusion: Serum C- reactive protein level was significantly associated with severity of preeclampsia with an acceptable grade of discriminative ability between severe preeclampsia and non-severe preeclampsia patients.

Key Words: Eclampsia, Protein, Gestational, Ambulatory, Ferritins

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Introduction

Preeclampsia (PE) is a common pregnancy-associated disorder characterised by new-onset hypertension (HTN) that occurs most often after 20 weeks of gestation and frequently near term[1]. The aetiology of PE remains unclear and multiple pathways have been postulated to be behind its pathogenesis[2].

The idea that PE is developing due to an exaggerated maternal systemic inflammatory response during pregnancy has attracted researchers to explore the possibility. Inflammatory marker C-reactive protein (CRP), has been investigated in PE particularly to evaluate its role as predictive or diagnostic tool,[3-5] but its clinical utility is still unestablished[6]. CRP is a protein and its level in the blood rises during inflammation, such as in infection or following a heart attack, surgery or trauma. It is the classical acute phase reactant that is synthesised by hepatocytes or placental cells following interleukin-6 (IL-6) secretion by macrophages and T cells[7].

Ferritin is used in human body to keep a balance between intra- and extra-cellular iron in an endeavour to protect from deleterious effect of excess iron uptake[8]. Ferritin thus serves as a safeguard to decrease generation of free radicals and to influence immunomodulation[9]. Iron, redox biology, and inflammation are inexorably linked[9,10]. Many studies have reported the presence of hyperferritinaemia in PE patients and its potential as a diagnostic tool[11,12].

Serum ferritin level was also reported to be not only higher in PE patients than in a control group, but to be associated with the severity of PE[13,14]. Similarly, many studies have reported such a role for CRP[15-18]. These latter reports have carried the potential of ability to stratify the risk in PE patients, to assess their prognosis and to influence the decision about their management.

The current study was planned to assess the role of inflammatory markers ferritin and CRP as indicators of preeclampsia severity. It was hypothesised that serum ferritin and CRP levels could discriminate between severe PE (SPE) and non-severe PE (NSPE) patients.

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Patients and Methods

The case-control study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, from November 2021 to May 2022. After approval form the ethics review committee of Mustansiriyah University, Baghdad, the sample size was calculated using the EpiInfo equation[19]. The sample was raised using consecutive sampling technique. Those included were pregnant women from the obstetrics ward and outpatient clinics aged 16-40 years having a viable singleton pregnancy and gestational age >32 weeks. Those excluded were women with gestational age <32 weeks, history of chronic conditions, like HTN, diabetes mellitus (DM), cardiac disease, neurological disorders, renal impairment, and premature rupture of membrane (PROM). Also excluded were smokers and those with multiple gestations, Rh isoimmunisation, foetal anomalies, maternal autoimmune disease, presence of chronic inflammatory disease and assisted conception.

Those enrolled were divided into SPE group A and NSPE group B as per the criteria of the American College of Obstetricians and Gynaecologists[1]. Those with normal pregnancy having no HTN or proteinuria and who remained normal for the rest of their pregnancy were included as control group C.

Data was collected after taking informed consent from the participants. A venous blood sample 10ml was drawn and divided into 2 tubes. The sample in the dipotassium ethylenediaminetetraacetic acid (EDTA-K2) tube was used for the measurement of haematological parameters, like Hb concentration, complete blood count (CBC), including the white blood cell (WBC) count and platelet (PLT) counts. The second plain tube without anticoagulant was centrifuged at 3000rpm and serum was divided into two portions; one for the basic biochemical laboratory tests, including urea, creatinine, uric acid, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), while the other was frozen at -20°C until analysed for ferritin and CRP concentrations.

The determination of proteinuria was done by dipsticks in a mid-urine stream. The dipstick was a first-line test and a positive result was confirmed by a turbidimetric sulfosalicylic acid (SSA) test, which was subjectively scored as, negative, trace, 1+, 2+, 3+, or 4+.

Concentration of serum ferritin was measured using sandwich-type enzyme-linked immunosorbent assay (ELISA) kits (DiaMetra Company, Germany).

CRP concentration was measured using an automated quantitative immunologically-enhanced turbidimetric assay using an analyser (Cobas C111, Roche Company, Germany).

Data was analysed using SPSS 26. Data was expressed as frequencies and percentages or as mean ± standard deviation, as appropriate. Analysis of variance (ANOVA) was used for 3-group comparisons, one-way ANOVA determined statistical significance, and Tukey's post-hoc analyses detected differences between the groups. Pearson correlation coefficient was used for testing the relationship between two parametric numerical variables. Receiver operator characteristics (ROC) curve analysis was used to assess the abilities of the study markers in discriminating between the two groups of PE patients, and measuring specificity and sensitivity of the studied markers. P<0.05 was considered statistically significant.

Results

Of the 87 pregnant women, 27(31%) were in group A with mean age 29.76±7.53 years and mean gestational age 35.63±1.92 weeks, 29(33.33%) were in group B with mean age 26.83±6.30 years and mean gestational age 36.24±1.72 weeks, and 31(35.63%) were in group C with mean age 26.00±5.73 years and mean gestational age 36.52±1.61 weeks. Ferritin levels in patient groups were significantly higher than in the control group (p<0.05), but it was not significantly different between the patient groups (p>0.05). CRP levels in the patient groups were significantly higher than in the control group (p<0.05), and they were also significantly higher in group A than in group B (p<0.05) (Table 1).

Table-1: Comparison of mean values among the study groups. Values carrying letters in common are not significantly different from each other while values with different letters are significantly different.

Variable (mean±SD)	SPE N=27	NSPE N=29	Controls N=31	*P*-value
Age /years	29.76±7.53 a	26.83±6.30 a	26.00±5.73a	0.08
GA in week	35.63±1.92 a	36.24±1.72 a	36.52±1.61a	0.15
Hb g/dl	12.45±2.15 a	12.56±2.69 a	11.79±0.72a	0.12
WBC 10^3/µL	12.46±4.63 a	10.95±3.55 ab	10.06±1.89 b	0.03
Platelets 10^3/µL	183.40±66.30 b	220.08±68.93 a	227.08±25.05a	0.01
Ferritin ng/ml	59.69±52.32 a	75.27± 75.54 a	12.06± 19.87b	< 0.0001
C-reactive protein mg/l	32.95± 29.55 a	13.07± 12.02 c	4.28± 4.52b	< 0.0001

Values carrying letters in common are not significantly different from each other, while values with different letters are significantly different.
GA: Gestational age, SPE: Severe preeclampsia, NSPE: Non-severe preeclampsia, Hb: Haemoglobin, WBC: White blood cells.

The correlation of ferritin with CRP levels showed no significance either in group A (r=- 0.29, o=0.14) or in group B (r=- 0.22, p=0.26).

Table-2: Cut-off values of ROC curve analysis for ferritin and CRP across the study groups.

Groups	Marker	Cut-off value	AUC	P-value	95% CI	SE	Sensitivity	Specificity
NSPE & Controls	Ferritin ng/ml	>7.765	0.910	<0.0001	0.807- 0.968	0.0391	96.55	77.42
	CRP mg/L	>10.31	0.823	<0.0001	0.711- 0.935	0.0571	41.38	93.55
SPE & Controls	Ferritin	>20.235	0.907	<0.0001	0.801- 0.967	0.0410	92.59	83.87
	CRP	>10	0.958	<0.0001	0.913- 1.000	0.023	74.07	93.55
SPE & NSPE	Ferritin	≤ 101.88	0.526	0.7461	0.388- 0.661	0.0789	92.59	20.69
	CRP mg/L	>17.1	0.755	0.0001	0.628- 0.883	0.0652	66.67	75.86

ROC: Receiver operating characteristic, SPE: Severe preeclampsia, NSPE: Non-severe preeclampsia, AUC: Area under the curve, CRP: C-reactive protein, CI: Confidence interval, SEL Standard error.

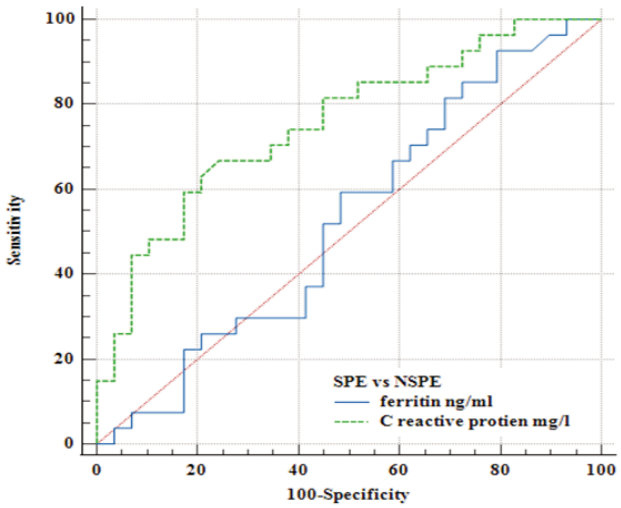

Figure: Receiver operating characteristic (ROC) curve analysis for ferritin values (area under the curve [AUC]=0.526, p<0.746), and CRP values (AUC=0.755, p<0.001) in the differentiation of severe preeclampsia (SPE) patients from non-severe preeclampsia (NSPE) patients.

At a cut-off value >101.8 ferritin had sensitivity 92.59% but specificity 20.69%, whereas C- reactive protein at a cut-off value >17.1 had sensitivity 66.67% but specificity 75.86% (Figure, Table 2).

Discussion

PE is a serious health problem around the world. It is recommended by some authorities that the combination of maternal high-risk factors with certain biomarkers could be useful in predicting the risk of PE, and to start an early clinical intervention in PE[20].

The current study found that ferritin levels were significantly higher in both SPE and NSPE groups than in controls. These results are in line with some previous studies which reported the presence of hyperserotonaemia in PE patients[11,12]. Although the current study found that the mean serum ferritin level was somewhat higher in SPE than in NSPE, the difference was not statistically significant, and this was confirmed by the results of ROC analysis. Such results are not consistent with many studies that reported a significant association of serum ferritin level with PE severity[13-18].

The proposed mechanism of the rise of serum ferritin level in PE may explain the current finding of no association of its serum level with PE severity as well as the further finding of no significant correlation between ferritin and CRP levels. Ferritin is often defined as an acute-phase protein that rises in inflammation irrespective of iron levels that makes identification of the cause of many iron disorders more difficult[21]. In such a process, it is unclear whether serum ferritin reflects or causes inflammation[10]. Ferritin was reported to induce the expression of pro- and anti-inflammatory cytokines, but cytokines themselves can induce ferritin expression as well[22,23]. Some studies have indicated that the dynamic regulation of ferritin differs in inflammatory status than in normal iron metabolism,[24] while others have indicated that the precise mechanism by which ferritin contributes to disease in immunological disorders remains elusive[10].

The current study found that mean serum CRP level was significantly higher in the NSPE group than in controls. This is in concordance with several studies[3-5] and favours the suggestion of using it as a potential diagnostic marker of PE[20]. The current study also found that mean serum CRP level was significantly higher in the SPE group than in NSPE group. Moreover, CRP levels showed an acceptable grade of discriminative ability between SPE and NSPE patients on ROC analysis. These findings are in line with many a number of studies[15-18].

Conclusion

Serum CRP level was significantly higher in SPE group than in the NSPE group, and had an acceptable discriminative ability between SPE and NSPE

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Conflict of Interest: None.

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