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C-Reactive protein as a predictive factor of preeclampsia

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ABSTRACT

Preeclampsia and eclampsia, the Hypertensive disorders of pregnancy, contribute significantly to still births, maternal and neonatal morbidity and mortality. C - reactive protein (CRP), a marker of tissue damage and inflammation, is elevated in serum in overt preeclampsia. There is still debate on its use as a predictive marker for preeclampsia during early pregnancy. The present study is an attempt to evaluate C - reactive protein (CRP) as a predictive factor of preeclampsia. Of the 70 cases studied, 30 were normal healthy pregnant women below 30 years of age and were in first trimester with no proteinuria. The remaining 40 pregnant women below 30 years of age with gestational age between 10-14 weeks and having BP of \geq 130/86mm of Hg and proteinuria \sim 200mg/l. In high risk preeclamptic women the level of plasma hsCRP was elevated significantly compared to values in normal pregnant controls. Plasma hsCRP assessment may serve as a predictive factor for preeclampsia.

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1.Introduction

Common disorders of pregnancy are Hypertensive Disorders, Gestational Diabetes, and premature birth. Maternal health is especially affected when preeclampsia or more severe complications such as eclampsia or HELLP syndrome develops. Worldwide, these syndromes contribute substantially to maternal morbidity and mortality as well as perinatal morbidity and mortality [1]. Preeclampsia is a common, yet incompletely understood, complication of pregnancy. Symptoms of preeclampsia include hypertension, proteinuria and associated general endothelial dysfunction [2]. The etiology of endothelial dysfunction in preeclampsia is not known, but it has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy [3]. Activated circulating leukocytes [4,5] increased production of reactive oxygen species [6] and increased release of inflammatory cytokines, such as Tumor necrosis factor α (TNF α) and Interleukin-6 (IL-6) [7,8] as well as abnormal activation of the clotting system [9] in women with preeclampsia compared with normotensive women, supports this hypothesis.

C - reactive protein (CRP) is an objective and sensitive index of overall inflammatory activity in the body [10]. The CRP

concentration in peripheral circulation is also known to be associated with Body Mass Index (BMI) and other marker of adiposity [11,12]. Plasma CRP levels rise in cases of acute infection, malignancy & inflammatory diseases. CRP can bind to chromatin (released from apoptotic or necrotic cells) and to small nuclear ribonucleoprotein particles. It has been proposed that CRP acts as a scavenger and is responsible for the clearance of membranes and nuclear antigens [13]. It has been suggested that CRP, in accordance with its proposed function, may play a role in eliciting the inflammatory response characteristics of preeclampsia [3]. Recently, it has been demonstrated that CRP enhanced opsonisation, and phagocytosis of apoptic cells is specific for and restricted to apoptic cells. Once the cells become necrotic, the effect of CRP is lacking [14]. CRP is elevated in women with overt preeclampsia [15]. but there is still debate about its potential use as an early marker of preeclampsia. Wolf et.al. has shown that CRP levels are elevated during first trimester in women who subsequently develop preeclampsia [16].

We propose to investigate whether CRP levels are elevated during the first trimester (10-14 Weeks) in women from low-risk population who subsequently develop preeclampsia.

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2. Materials and methods

The present study was conducted at Kempegowda Institute of Medical Sciences and Research Centre, VV Puram, Bangalore. The study was done on patients who attended the Out Patient Department of Obstetrics & Gynaecology. The ethical committee of Kempegowda Institute of Medical Sciences & Research Centre approved the study protocol. Informed consent was taken from individual subjects. The study comprised of 70 Primi pregnant women, aged below 30 years, who were of 10 to 14 weeks of gestation. 40 cases were taken in whom blood pressure was ≥ 130 Systolic pressure and ≥ 86 Diastolic pressure and Proteinuria ~ 200 mg/l. 30 Controls were normotensive pregnant women with no proteinuria. The diagnosis of preeclampsia was based on the working group members of National High Blood pressure education program (NHBPEP) [18] & defined as de novo appearance of Hypertension (Systolic blood pressure of ≥ 140 mm of Hg or Diastolic blood pressure of ≥ 90 mm of Hg) accompanied by new onset proteinuria, defined as ≥ 300 mg per 24 hrs ($\geq 1+$ reading on dipstick). Edema, being Non-specific & occurring in many normotensive pregnant women is no longer included in the diagnostic criteria for preeclampsia [17].

Pregnant women with family history of Hypertension, Diabetes mellitus, Ischaemic Heart Disease and any renal, cardiovascular, neurological complication were excluded from the study. A pre-structured and pre-tested Proforma was used to collect the data. 5 ml of 12 hour overnight fasting venous blood samples were collected from cases and controls. Estimation of serum total cholesterol, triglycerides, HDL cholesterol, blood urea, serum creatinine, total protein, Platelet count, Prothrombin time, and plasma high sensitive C-reactive protein were made with the samples collected. LDL cholesterol and VLDL cholesterol values were calculated from the values of total cholesterol, triglycerides and HDL cholesterol by applying Friedwal equation. Correspondingly urine sample was taken for urine sugar and urine protein.

Estimation of hsCRP is by Immunoturbidimetry. Turbidimetric Immunoassay is based on the principle of agglutination reaction for the ultrasensitive determination of C - reactive protein in human plasma. The test specimen is mixed with latex reagent and activation buffer and allowed to react. Presence of hsCRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured at wavelength between 505 - 578 nm. The increase in turbidity corresponds to the concentration of CRP in the test specimen.

Student t test and 2 was used to find the significance of difference between cases and controls for various parameters. Correlation co-efficient and regression analysis was done to find association between hsCRP and components of lipid profile.

3. Results

Mean Body Mass Index (BMI), Gestational Age and hsCRP levels among cases as compared to controls is presented in Table 1. The elevation in BMI and hsCRP is highly significant. Plasma hsCRP levels in controls and cases are also shown in Fig 1.

Predictive value of hs-CRP in high risk preeclampsia is projected in Table 2. Statistical analysis of hsCRP in cases and controls [large effect (1.35) with 95th percentile of control is 2.15 mg/L] suggest that women with high risk pregnancy are 43.5 times significantly more likely to have elevated hsCRP when compared to controls. This data is also projected in Fig 2.

The Lipid profile in controls and cases is tabulated in Table 3 and it is shown that only triglyceride and VLDL-Cholesterol are elevated significantly. Pearson Correlation of hs-CRP with BMI and Lipid parameters is presented in Table 4 and there is a positive correlation between plasma hs-CRP and the study parameters.

Blood urea, serum creatinine, serum protein, platelet count, prothrombin time were in normal limits in both the groups of study, Urinary Protein (albumin) was absent or present in traces in the cases and controls.

Table 1: BMI, Gestational age and hsCRP in Controls and Cases

Study Parameters (Mean SD)	Controls	Cases	P value
BMI (kg/m ²)	23.04 \pm 1.53	24.83 \pm 1.35	<0.001
Gestational Age (weeks)	12.13 \pm 1.46	12.47 \pm 1.26	0.29
hs-CRP (mg/L)	1.58 \pm 0.33	2.78 \pm 1.45	<0.001

Figure 1: hsCRP (mg/L) levels in controls and cases

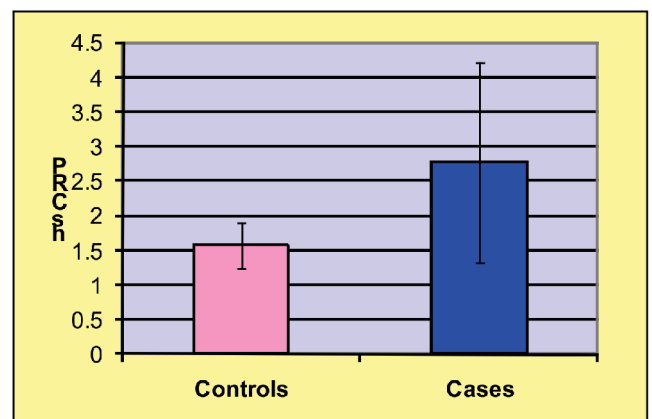


Table 2: Predictive value of hs-CRP (mg/L) in high risk preeclampsia

(95th percentile of controls is 2.15)

	Controls	Cases
hs-CRP(mg/L)	Controls (n-30)	Cases (n-40)
CRP <2.15	29 (96.7%)	16 (40.0%)
CRP >2.15	1 (3.3%)	24 (60.0%)
$\chi^2=23.776, P<0.001$		
Inference	Women with high risk pregnancies are 43.50 times significantly more likely to have elevated hs-CRP when compared to Controls	

Figure 2: Predictive value of hsCRP (mg/L) in controls and cases

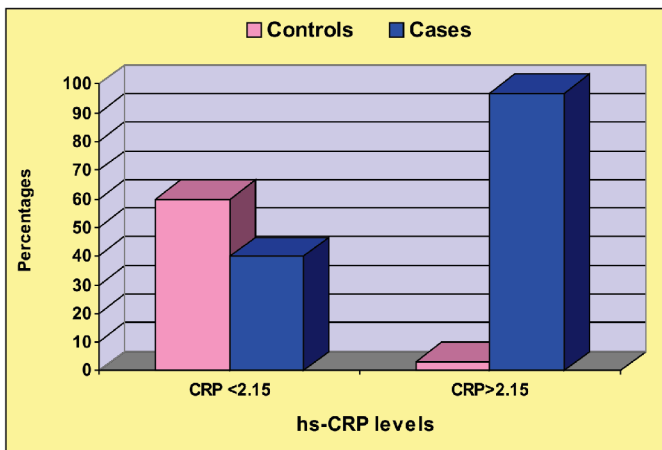


Table 3: Lipid profile in controls and cases

Lipid parameters	Controls	Cases	P value
Total Cholesterol mg/d	205.13±40.38	215.15±43.13	0.327
lHDL mg/d	42.77±8.30	45.18±7.69	0.215
lLDL mg/dl	118.53±31.27	129.98±38.51	0.188
TG mg/dl	184.23±42.36	210.98±45.47	0.015*
VLDL mg/dl	36.53±8.45	42.93±10.27	0.007**
Inference	TGL and VLDL are significantly increased in cases with P<0.05		

Table 4: Pearson correlation of hsCRP with study parameters

Study parameters	Pearson correlation co-efficient			
	Cases		Controls	
	R	P	R	P
BMI	-0.210	0.194	-0.016	0.935
Total cholesterol	-0.356	0.024	-0.220	0.242
HDL	-0.243	0.131	-0.027	0.887
LDL	-0.284	0.076	-0.096	0.615
TGL	0.070	0.667	-0.219	0.245
VLDL	-0.102	0.531	-0.221	0.240

4. Discussion

Preeclampsia is a multisystem disorder of human pregnancy. Clinically, preeclampsia is characterized by hypertension, proteinuria, edema and platelet aggregation. Pathophysiologically, the hallmark of preeclampsia include increased vasoconstriction resulting in maternal hypertension and reduced uteroplacental blood flow, disturbed vascular endothelial integrity with increased vascular permeability, and activation of the coagulation cascade [19]. C-reactive protein (CRP) is a marker of tissue damage and inflammation. Maternal levels of CRP are elevated in overt preeclampsia, but there is still a debate about its usefulness as a predictive marker for preeclampsia during the first and second trimester of pregnancy.

In the present study the mean age of the controls and the cases is 25.05± 3.29 and 23.10± 2.41 years respectively. The mean gestational age of cases is 12.47±1.26 weeks. The study done by M.L.Tjoa et al.[1]. in Netherland, involved 107 cases in the gestational age range of 10 to 14 weeks and a similarly Myles Wolf et al [16], in Boston have performed high resolution CRP assays in the first trimester (11 ± 2 weeks gestation) on 40 serum samples of cases who subsequently developed preeclampsia. Mean Body Mass index among cases is 24.83 ± 1.35 and we have recorded an elevation of plasma hs-CRP among cases. Similar findings have been made in a number of studies. Chung Fang Qiu et al [20], have reported that lean women BMI ≤ 25 kg / m² and elevated CRP were associated with a 2.5 fold increased risk of preeclampsia, but no similar association was observed in overweight women. Wolf M et al [16]. have reported that the first trimester CRP levels were significantly higher among women who developed preeclampsia. M L Tjoa, J M G Van Vugt et al [1] have observed significantly higher CRP levels in preeclamptic cases between 10 and 14 weeks of pregnancy. A cross sectional study done by Savvidou M D et al [21], in London presents a different picture in that the serum CRP

concentration in women who subsequently developed preeclampsia was not significantly different from that in women with uncomplicated pregnancies. As far as lipid parameters are concerned a significant increase in serum Triglycerides and VLDL cholesterol level is seen in cases and similar findings have also been reported by Hirschfield et al [22].

To conclude, our data suggest that CRP levels are already elevated in the first trimester of pregnant women who would subsequently develop preeclampsia.

5. Conclusion

There is a significant increase in Body Mass Index in cases as compared to the controls ($P < 0.001$).

Serum hsCRP levels were significantly elevated among cases as compared to controls ($P < 0.001$).

Both Triglycerides and VLDL Cholesterol levels were significantly higher in cases ($P < 0.05$) as compared to controls. HDL Cholesterol, LDL Cholesterol and Total Cholesterol levels were within normal limits in both cases and controls.

There is a significant positive correlation between hsCRP and BMI as well as Lipid Parameters.

In early pregnancy Blood Urea, Serum Creatinine, Total Protein, Platelet Count and Prothrombin Time were within normal limits in all the cases and controls indicating the absence of any pathology between 10-14 Weeks of gestation.

The present study suggests that hsCRP levels tend to be higher in women at the risk of developing preeclampsia than in healthy pregnant women.

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