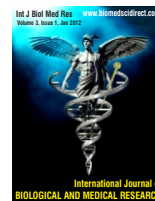


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Original Article

Pattern of C –reactive protein in pre eclampsia and normal pregnancy.

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ABSTRACT

Aim: To evaluate the pattern of C reactive protein in normal pregnancy and in preeclampsia. To know the positive correlation of CRP levels to the degree of blood pressure. Objective 1. To know the variation of C reactive protein in preeclampsia and normal pregnancy. 2. To know the positive correlation of C reactive protein levels to the degree of diastolic blood pressure. Study Design This study was conducted between July 2010 to June 2012 for the period of two years. Data for the study was collected from 100 patients attending the department of Obstetrics and Gynaecology in Sri Siddhartha Medical College Hospital and Research Centre. It included 50 pregnant women with preeclampsia as cases and 50 normotensive pregnant women as controls. Venous blood samples were collected at OPD or at the time of admission. Controls were included after meeting inclusion and exclusion criteria. Study was included after meeting inclusion and exclusion criteria. Venous blood was screened for plasmatic C reactive protein latex method. Results were interpreted in positive or negative. Then Immunoturbidometric method is done to measure C reactive protein in values. Results are analysed using Chi square test, Student t test, Fisher Exact test and Fisher exact test statistics. Results Blood parameters blood urea, serum uric acid, serum creatinine, SGOT, SGPT, ALP, RBS, platelet count were significantly higher in preeclampsia compared to control group values. In the preeclampsia group CRP levels are highly increased than control group. Correlation analysis showed a strong positive correlation between serum CRP levels and diastolic blood pressure and also with urine albumin. CRP by latex method is 84.3 times more likely positive in cases than controls ($p < 0.001$). CRP by turbidometric assay in controls Mean \pm SD 1.29 \pm 0.66 mg/dl. In preeclampsia mean \pm SD 4.85 \pm 1.45 mg/dl. Significantly higher values found in primigravida and with increase in duration of pregnancy. Conclusion Serum CRP levels increase in women with pre eclampsia. Elevated serum CRP levels in Preeclampsia were correlated with biochemical parameters of Preeclampsia. Determination of serum CRP levels may be used as a marker for the severity of Preeclampsia. Serum CRP levels are positively related to diastolic blood pressure and urinary protein excretion.

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1. Introduction

Preeclampsia is a common (7% of all pregnancies) disorder in which normal haemodynamic response is compromised. Preeclampsia is an important cause of maternal and fetal morbidity and mortality. [1]

In spite of its epidemiologic impact, the complete pathogenesis of this disease still remains unclear, underlining a multifactorial etiology. Endothelial cell dysfunction and inflammation are considered to have a crucial role in preeclampsia. A systemic inflammatory response involves both the immune system and clotting and fibrinolytic system.

Mediator of inflammatory response TNF- α , IL-1 is altered in women with preeclampsia including increased C- reactive protein. There may be a relationship between blood pressure and microalbuminuria and C- reactive protein modifies this association.

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An increased C- reactive protein can reflect the severity of preeclampsia especially by means of blood pressure and proteinuria.

C - reactive protein is a phylogenetically highly conserved plasma protein, with homologous in vertebrates and many invertebrates, that participates in the systemic response to inflammation. CRP is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or found on the surface of pathogens. CRP was discovered in Oswald Avery's laboratory during the course studies of patients with Streptococcus pneumonia infection. In humans, plasma levels of CRP may rise rapidly and markedly, as much as 1000-fold or more, after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes. CRP induction is part of a larger picture of reorchestration of liver gene expression during inflammatory states, the acute phase response. Induction of CRP in hepatocytes is principally regulated at the transcriptional level by the cytokine interleukin-6 (IL-6), an effect which can be enhanced by interleukin-1 β . Extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes. [2]

CRP has been associated with several diseases, involving endothelial dysfunction and systemic inflammation such as type II diabetes, metabolic syndrome and cardiovascular disease. Endothelial dysfunction and inflammation are involved in the pathogenesis of preeclampsia and other important complications of pregnancy, including gestational diabetes mellitus and fetal overgrowth. Hence its measurement has recently aroused considerable interest. [2]

2. Materials and Methods

Study was conducted for a period of two years from July 2010 to June 2012. Data for the study was collected from 100 patients attending the Department of Obstetrics and Gynaecology in Sri Siddhartha Medical College Hospital and Research centre. It included 50 pregnant women with preeclampsia as cases and 50 normotensive pregnant women as controls.

2.1 Inclusion Criteria

Control Group

1. Patients with singleton pregnancy of gestational age of first trimester to third trimester (gestational age based on LMP or first trimester ultrasound).
2. No chronic medical disorders like diabetes, renal disease, and hypertension.
3. Blood pressure less than 140/90 mm Hg.
4. Not in labour.
5. No vaginal or maternal infections.

PREECLAMPSIA GROUP

1. All singleton pregnant women from second trimester to third trimester irrespective of parity.
2. Not in labour and absence of premature rupture of membranes.
3. No evidence of chorioamnionitis.
4. BP > 140/90 mm Hg, proteinuria.

2.2 Exclusion Criteria

CONTROL GROUP

1. Diabetes.
2. Hypertension.
3. Other Cardiovascular illness.
4. Symptomatic diseases upper respiratory tract infections, vaginal infections, urinary tract infections.
5. Twins.

PREECLAMPSIA

1. Diabetes mellitus.
2. Renal disease.
3. Chronic Hypertension.
4. Symptomatic infectious diseases upper respiratory tract infections, vaginal infections, urinary tract infections.
5. Twins.

2.3 Study Protocol

In this study we estimated CRP in 100 pregnant women of which 50 were preeclampsia (study group) and 50 patients were normotensive pregnant women (control group). The correlation between CRP and severity of preeclampsia was estimated. CRP variation with other parameters and urine albumin was done.

Estimation of C reactive protein - Venous blood sample was collected during the regular antenatal check up at OPD or in the antenatal ward patients.

CRP TEST - Latex slide and tube test.

Principle: This test is based on the immunological reaction between CRP as an antigen and latex particle have been coated with antihuman CRP and sensitized to detect levels greater than 6 microgram per ml CRP. The latex slide test has the advantage of rapid performance in comparison to other tests for the detection of CRP. [3] Interpretation:

1. Qualitative Slide Test.

Observation	Conclusion
Coarse agglutination	Strongly positive
Finer agglutination	Weakly positive
Smooth suspension without any noticeable change	Negative

2. Semiquantitative Slide Test.

CRP level can be calculated in terms of micrograms per ml by multiplying the highest dilution giving clear cut agglutination with a factor of 6 (sensitivity of the antigen 6 microgram per ml).

Quantitative determination of CRP in human serum by turbidometric immunoassay.

Reference values:

0-1 mg/dl Measurement range 0-22 mg/dl.
 Detection limit 0.5 mg/dl Assigned values 0-13.46 mg/dl.

In this study CRP level are divided into: Normal range – 0-2mg/dl, Moderate increase – 2-3.5 mg/dl, Severe- >3.5 mg/dl.

3. Results

TABLE 1 shows that CRP is increased in all age groups. In 21-30 yrs in n=8 cases make 28.6%, in n=20 cases makes 71.4%, mean CRP is 4.96+/-1.43 mg/dl. In 31-40 yrs n=5 cases makes 41.7%, n=7 cases makes 58.3% mean CRP is 4.81+/-1.41 mg/dl. In 41-50 yrs n=2 cases showed elevated CRP. This shows as age advances CRP, 14 (28%) cases showed mild to moderate increase in CRP, mean CRP 4.84+/-1.46 mg/dl.

TABLE 1- Comparison of age in years with CRP-T in cases

Age in years	Number of patients	CRP-T (mg/dl)			Mean+/-SD
		Normal	Mild to Moderate increase	Maximal Increase	
18-20	8	1(12.5%)	1(12.5%)	6(75.0%)	4.41+/-1.82
21-30	28	-	8(28.6%)	20(71.4%)	4.96+/-1.43
31-40	12	-	5(41.7%)	7(58.3%)	4.81+/-1.41
41-50	2	-	0	2(100.0%)	5.25+/-0.81
Total	50	1(2.0%)	14(28.0%)	35(70.0%)	4.84+/-1.46

TABLE 2 shows in primigravida mean CRP level 4.98+/-1.52 mg/dl is more compared to 4.67+/- 1.38 mg/dl in multigravida. In primigravida 21 (75%) cases showed highly increased CRP and 6 (21.4%) cases mild to moderate increase in CRP, in one case it is normal. In multigravida n=14(63.6%) cases it is highly increased. In total 50 cases 35(70%) cases had highly elevated CRP and in 14(28%) cases mild to moderate increase in CRP, mean being 4.84+/-1.46 mg/dl.

TABLE 2- Comparison of obstetric index with CRP-T in cases.

Obstetric index	Number of patients	CRP-T (mg/dl)			Mean+/-SD
		Normal	Mild to Moderate increase	Maximal Increase	
Primi	28	1(3.6%)	6(21.4%)	21(75.0%)	4.98+/-1.52
Multi	22	-	8(36.4%)	14(63.6%)	4.67+/-1.38
Total	50	1(2.0%)	14(28.0%)	35(70.0%)	4.84+/-1.46

TABLE 3 in gestational age, less than 28 wks, out of 5 cases, 4(80%) showed maximal increase in CRP with mean 5.08+/-1.84 mg/dl. In 28-32 wks, out of 28 cases, 17 (60.7%), showed maximal increase and 10 (35.5%) mild to moderate increase in CRP with mean 4.14+/-1.41 mg/dl. In 32-37 wks, out of 14 cases 13 (92.9%) with maximal increase and 1(7.1%) case showed mild to moderate increase with increase with mean CRP 5.52+/-1.32 mg/dl. Out of 50 cases mean CRP was 4.84+/-1.46 mg/dl, 35(70%) showed higher and 14 (28%) mild to moderate levels.

TABLE 3- Comparison of gestation age with CRP-T in cases.

Gestational Age in wks	Number of patients	CRP-T (mg/dl)			Mean+/-SD
		Normal	Mild to Moderate increase	Maximal Increase	
<28	5	-	1(20.0%)	4(80.0%)	5.08+/-1.84
28-32	28	1(3.6%)	10(35.7%)	17(60.7%)	4.14+/-1.41
32-37	14	-	1(7.1%)	13(92.9%)	5.52+/-1.32
>37	3	-	2(66.7%)	1(33.3%)	4.17+/-1.25
Total	50	1(2.0%)	14(28.0%)	35(70.0%)	4.84+/-1.46

TABLE 4 shows maximal CRP was found with urine albumin 4+, 6(100%) cases showed 6.74+/-0.29 mg/dl. With 3+, 13(100%) cases show high CRP 5.91+/-0.81 mg/dl. With 2+, 13(92.9%) high and 1(7.1%) mild moderate increase in CRP 4.88+/-0.92 mg/dl. With 1+ albumin 2(15.4%) cases had high and 11(84.6%) cases had mild to moderate increase in CRP 3.5+/-0.70 mg/dl. In urine albumin NIL group mean CRP 2.58+/-0.62 mg/dl.

TABLE 4- Comparison of urine albumin with CRP-T in cases.

Urine albumin	Number of patients	CRP-T (mg/dl)			Mean+/-SD	
		Normal	Mild to Moderate increase	Maximal Increase		
Nil	4	1(25.0%)	2(50.0%)	1(25.0%)	2.58+/-0.62	2.58+/-0.62
1+	13	0	11(84.6%)	2(15.4%)	3.50+/-0.70	3.50+/-0.70
2+	14	0	1(7.1%)	13(92.9%)	4.88+/-0.92	4.88+/-0.92
3+	13	0	0	13(100.0%)	5.91+/-0.81	5.91+/-0.81
4+	6	0	0	6(100.0%)	6.74+/-0.29	6.74+/-0.29
Total	50	1(2.0%)	14(28.0%)	35(70.0%)	4.84+/-1.46	4.84+/-1.46

TABLE 5 shows mean CRP concentration is 4.85+/-1.45 mg/dl compared to 1.29+/-0.66 mg/dl in control group. CRP levels are significantly increased in cases. It is statistically significant.

TABLE 5-Comparison of levels of CRP-T (mg/dl) between two groups .

CRP-T (mg/dl)	Controls	Mild to Moderate increase
Min-Max	0.06-2.96	1.86-7.20
Mean+/-SD	1.29+/-0.66	4.85+/-1.45
95% CI	1.11-1.48	4.44-5.26

TABLE 6 shows as the blood pressure increases the CRP level also increased. There is positive correlation between diastolic blood pressure and CRP level.

TABLE 6- Comparison of BP with CRP-T (mg/dl) in cases.

BP	Number of patients	CRP-T (mg/dl)			Mean+/-SD
		Normal	Mild to Moderate increase	Maximal Increase	
Control	50	50	-	-	1.29+/-0.66
<140/90	0	-	-	-	4.11+/-1.29
140/90-160/110	29	1	13	15	5.86+/-0.97
>160/110	21	-	1	20	4.84+/-1.46
Total	50	1(2.0%)	14(28.0%)	35(70.0%)	

4. Discussion

Preeclampsia a disease of pregnancy is associated with endothelial cell damage or activation and hyper coagulation. There is increasing evidence that preeclampsia is a systemic inflammatory disease. CRP a sensitive marker of tissue damage and inflammation was proposed to play a role in eliciting the inflammatory response characteristic of preeclampsia. CRP acts as a scavenger and is responsible for the clearance of membranes and nuclear antigens. From early times many clinical trials have been done to differentiate different forms of preeclampsia and for early detection of its severe form and complications.

This study shows that as age advances CRP also increases. Out of 50 cases 35(70%) cases showed highly increased CRP, 14(28%) cases showed mild to moderate increase in CRP, mean CRP is 4.84+/-mg/dl. CRP levels are elevated in both primigravida and multigravida. In primigravida mean CRP level 4.98+/-1.52 mg/dl is more compared to 4.67+/-1.38 mg/dl in multigravida. This observation is comparable to various reports earlier by Wiliam et al.[4], Turnbull et al., Gabbe et al.[5], also state an increased incidence of PIH in primigravida.

CRP levels are higher around 28-37 wks in cases. As the duration of pregnancy increases the CRP levels also increase and are higher in range in preeclampsia than in controls. A positive relation has been observed between CRP levels and blood pressure (BP). Hence as CRP

increases SBP and DBP also increases. There is positive correlation between diastolic blood pressure and CRP level. The study conducted by E Teran, C Escudero et al [6, 7] also showed similar CRP was significantly higher in preeclamptic women. Selhattin et al [8] conducted a study to find the correlation of CRP with DBP, Urine albumin, other blood parameters of preeclampsia. Study showed a strong positive correlation between serum CRP levels and diastolic blood pressure, urine protein excretion. Yusuf ustan et al [9] study also showed significant correlation between MAP and CRP. This study is similar in comparison to results with other studies.

Urine albumin has shown strong positive relation with CRP levels. The present study results are comparable to study conducted by Selhattin kumru et al [8]. With comparison to CRP, as the blood parameters increased the levels of CRP also increased. As the elevated liver enzymes and renal functional tests indicate this severity of preeclampsia, so also the CRP increases. Study report by Selhattin et al is similar with the present study.

5. Conclusion

Serum CRP levels increase in women with pre eclampsia. Elevated serum CRP levels in Preeclampsia were correlated with biochemical parameters of Preeclampsia. Determination of serum CRP levels may be used as a marker for the severity of Preeclampsia. Serum CRP levels are positively related to diastolic blood pressure and urinary protein excretion.

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