

## Pre-Eclampsia in Women with Raised C-Reactive Protein Levels Before 20<sup>th</sup> Week of Gestation; A Cohort Study

Komal Memon, Shazia Jabbar\*, Marvi Bozdar\*\*, Sumyya Ahmed\*\*\*, Shahzadi\*\*\*\*, Maryam Younus\*\*\*\*\*

Department of Obs & Gynae, RBUT Civil Hospital, Shikarpur Pakistan, \*Department of Obs & Gynae, Dow University of Health Sciences, Civil Hospital, Karachi Pakistan, \*\*Department of Obs & Gynae, Ghulam Muhammad Mahar Medical College, Civil hospital, Sukkur Pakistan, \*\*\*Department of Obs & Gynae, DHQ Sanghar Hospital, Pakistan, \*\*\*\*Department of Obs & Gynae, Rural Health Center, Hyderabad Tando Qaiser Pakistan, \*\*\*\*\*Department of Bio-Statistics, Institute of Business Management, Karachi Pakistan

### ABSTRACT

**Objective:** To assess the association of pre-eclampsia in women with raised CRP before 20 weeks of gestation.

**Study Design:** Prospective cohort study,

**Place and Duration of Study:** Department of Obstetrics and Gynaecology, Civil Hospital, Karachi Pakistan, from Jan to Aug 2019.

**Methodology:** One hundred and sixty-eight women were included. 84 of 168 women had raised CRP, called as Exposed-Group, and 84 had normal CRP, called as Unexposed-Group. Blood samples were sent to assay serum CRP. Patients were then followed up until the third trimester to observe whether women with elevated serum CRP >5 mg/l or women with normal levels of CRP developed pre-eclampsia.

**Results:** The average age of the women was 26.30±5.15 years. The pre-eclampsia was significantly high in the Exposed-Group as compared to the Unexposed-Group ( $p=0.019$ ). The pre-eclampsia was two times more likely in the Exposed-Group as compared to the Unexposed-Group (RR=1.73; 95% CI 1.07-2.79).

**Conclusion:** Pre-eclampsia is more likely to occur before 20 weeks of pregnancy in women having raised CRP. Therefore, effective monitoring of CRP could help in timely management and prevent severity.

**Keywords:** Body mass index, Pre-eclampsia, C-reactive protein, Pregnancy, Parity.

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### INTRODUCTION

Pre-eclampsia is defined as the onset of hypertension having  $\geq 90$ mm Hg of diastolic blood pressure along with  $\geq 300$ mg of proteinuria/day at  $\geq 20$  weeks of pregnancy. It affects around 10% of women during pregnancy, leading to significant perinatal and maternal morbidity and mortality.<sup>1</sup> The severe form of pre-eclampsia can result in low platelet count, abnormal coagulation in the body, stroke, cardiopulmonary complications and liver damage.<sup>2</sup> The statistics showed that every year, seventy thousand maternal deaths are reported worldwide.<sup>3</sup> The timely diagnosis of pre-eclampsia plays an important role in improving maternal outcomes.<sup>4</sup>

C-reactive protein (CRP) is a biomarker used to indicate inflammation in the body. The elevated levels of inflammation in the body suggest acute onset of inflammation.<sup>5</sup> The higher the CRP levels in the body, the more adverse the pathological response.<sup>6</sup> In obstetrics and gynaecology, CRP levels are used to

diagnose infections and predict complications related to preterm labour.<sup>6</sup> Previous research has shown a strong link between adverse maternal outcomes and elevated CRP levels. CRP promotes necrosis and apoptosis in the human body.<sup>7</sup> In pre-eclamptic women, there is higher oxidative stress and endothelial damage, which has been linked to higher CRP levels.<sup>8</sup> There is a strong correlation between elevated CRP and the severity of pre-eclampsia. CRP levels have also been used as prognostic markers in pre-eclampsia during third trimester. Literature has shown that the risk of having pre-eclampsia is 3.5 times higher in women with elevated CRP levels.<sup>9,10</sup>

Therefore, the present study aims to determine the association of pre-eclampsia in women with raised CRP before 20 weeks of gestation in tertiary care hospitals. The study will help us determine the therapeutic and diagnostic aspects of pre-eclampsia. Moreover, CRP levels can help in early screening and diagnosis, reducing severity and mortality in women with higher CRP. The close monitoring of CRP can effectively control the development of this disease and intervene promptly, which can effectively inhibit the progression of the disease.

**Correspondence:** Dr Maryam Younus, Department of Bio-Statistics, Institute of Business Management, Karachi Pakistan

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**METHODOLOG**

The prospective cohort study was conducted at the Department of Gynaecology & Obstetrics, Civil Hospital, Karachi Pakistan, from January to August 2019 after approval from the Institutional Review Board (Ref#35877) Sample size was computed using WHO sample size calculator taking statistics of Pre-eclampsia in women with raised CRP level as 22.2% and in women who had normal CRP level 7%.<sup>11</sup>

**Inclusion Criteria:** All pregnant women aged 18-45 with gestational ages less than 20 weeks (with raised and normal CRP) were included.

**Exclusion Criteria:** Patients with Maternal systemic disorders or drug use except for usual supplementation including folic acid, chronic hypertension, diabetes mellitus, collagen vascular diseases, renal disorders, any recent or present fever or infectious disease, malignancies or autoimmune diseases, multiple pregnancies, smoking and any vaginal bleeding (diagnoses confirmed on history or medical record) were excluded.

Informed consent from patients was taken before the start of the study. Study sample (n=168) comprised of 84 women with raised CRP (Exposed-Group) and 84 women with normal CRP (Unexposed-Group). The blood sample was sent to a well-equipped and skilled Laboratory for assaying serum CRP. The raised CRP cut-off value was more than 5mg/l patients were followed till third trimester to observe whether women with elevated serum CRP >5 mg/l or women with normal level of CRP were developed pre-eclampsia.

Pre-eclampsia was classified as positive gestational hypertension [systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg] after 20 weeks of gestation plus the presence of proteinuria. Using the urine dipstick method, women with a protein level of 1+ were classified as positive.<sup>11</sup>

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. Relative risk was also calculated, and a p-value of 0.05 was taken as significant.

**RESULTS**

There were 168 women were included as per inclusion criteria. Eighty-four had raised CRP, called the Exposed-Group, and 84 had normal CRP, called the Unexposed-Group. The mean BMI was 24.97±1.73 kg/m<sup>2</sup> and 24.76±1.47 kg/m<sup>2</sup> in Exposed and Unexposed-Groups, respectively. Most of the women underwent caesarean sections; in Exposed Group 51(60.71%) and in Unexposed Group 40(47.62%), women had Caesarean sections while the rest of them had a vaginal delivery. Pregnancy-induced hypertension was diagnosed in 5(5.95%) women among the exposed group and 9(10.71%) in the Unexposed Group. Both groups showed non-significant differences (p>0.05) (Table-I).

**Table-I: Descriptive Statistics of Study Subjects (n=168)**

Variables	Exposed-Group n=84	Unexposed-Group n=84	p-values
Age (Years)	27.02±5.39	25.57±4.81	0.067
BMI (Kg/m <sup>2</sup> )	24.97±1.73	24.76±1.47	0.397
<b>Parity</b>			
Primipera	21(25%)	22(26.19%)	0.963
2-5	53(63.1%)	53(63.1%)	
More than 5	10(11.9%)	9(10.7%)	
<b>Mode of Delivery</b>			
Cesarean Section	51(60.71%)	40(47.62%)	0.089
Spontaneous Vaginal Delivery	33(39.29%)	44(52.38%)	
<b>Pregnancy Induced Hypertension</b>			
Yes	5(5.95%)	9(10.71%)	0.264
No	79(94.05%)	75(89.29%)	

In the Exposed Group, 33(39.3%) women were pre-eclamptic, and in the Unexposed Group, 19(22.6%) women had pre-eclampsia, which indicated a significant association between elevated CRP and pre-eclampsia (RR: 1.73; CI 95%:1.07-2.79; p=0.019) (Table-II).

**Table-II: Association of Pre-Eclampsia in Women With and Without raised CRP before 20 weeks of Gestation (n=168)**

Pre-Eclampsia	Exposed-Group n=84	Unexposed-Group n=84	p-value	RR[95%CI]
Yes	33(39.3%)	19(22.6%)	0.019	1.73[1.07-2.79]
No	51(60.7%)	65(77.4%)		

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Associations regarding stratified groups also pregnant women the studies conducted by Sharmin et al. Ali *et al.* showed that CRP was higher in pre-

**Table-III: Association of Pre-Eclampsia with Raised CRP Before 20 Weeks of Gestation (n=168)**

Variables	Pre-Eclampsia	Exposed group	Unexposed group	p-value	RR[95%CI]
<b>Age Groups</b>					
≤25 years	Yes	11(28.9%)	8(15.4%)	0.119	1.88[0.84-4.22]
	No	27(71.1%)	44(84.6%)		
>25 years	Yes	22(47.8%)	11(34.4%)	0.237	1.39[0.79-2.45]
	No	24(52.2%)	21(65.6%)		
<b>Parity</b>					
Primipera	Yes	7(33.3%)	0(0%)	0.003	NA
	No	14(66.7%)	22(100%)		
2-5	Yes	18(34%)	15(28.3%)	0.529	1.30[0.57-2.97]
	No	35(66%)	38(71.7%)		
>5	Yes	8(80%)	4(44.4%)	0.109	5[0.65-38.15]
	No	2(20%)	5(55.6%)		
<b>Body Mass Index</b>					
18.5-24.9	Yes	7(25.9%)	6(19.4%)	0.549	1.34[1.07-3.50]
	No	20(74.1%)	25(80.6%)		
>24.9	Yes	26(45.6%)	13(24.5%)	0.021	1.86[1.07-3.23]
	No	31(54.4%)	40(75.5%)		
<b>Mode of Delivery</b>					
Caesarean Section	Yes	25(49%)	16(40%)	0.391	1.23[0.76-1.96]
	No	26(51%)	24(60%)		
Spontaneous Vaginal Delivery	Yes	8(24.2%)	3(6.8%)	0.031	3.55[1.02-12.38]
	No	25(75.8%)	41(93.2%)		

BMI>24.9 and normal delivery had significant effects ( $p$ -value<0.05) (Table-III).

### DISCUSSION

Pre-eclampsia is a threatening gestational disorder causing maternal and foetal complications, usually occurring after 20 weeks of gestation. Increased CRP causes severe inflammation, leading to multi-organ problems. Pregnancy, pre-eclampsia, and inflammation are interlinked.<sup>11</sup> Therefore, it is vital to determine the association between raised CRP and pre-eclampsia before 20 weeks of gestation to prevent morbid effects and aid in early diagnosis. The results showed that pregnant women having raised CRP levels were significantly 1.73 times at high risk of developing pre-eclampsia within 20 weeks of gestation.<sup>12</sup> Our results concur with another study that claimed that CRP levels are a good predictor of the severity of pre-eclampsia within the first trimester of pregnancy.<sup>13</sup> A cohort study claimed that CRP levels were elevated in the first trimester of pregnancy, followed by developing pre-eclampsia ( $p=0.001$ ).<sup>14</sup> Other studies also claimed raised CRP levels in pre-eclamptic.<sup>15-17</sup> In some studies, CRP levels were compared between pre- and non-pre-eclamptic

eclamptic pregnant patients, and further analysis revealed that CRP levels were highest in severe pre-eclamptic pregnant patients.<sup>18, 19</sup>

Our study results are in contradiction with a study conducted by Spracklen CN *et al.* that showed elevated CRP levels decreased the risk of developing preeclampsia.<sup>20</sup> This is because of different study designs and sample sizes. Another study found an increased risk of cardiovascular events in women having pre-eclampsia with raised CRP.<sup>21</sup> Pro-inflammatory cytokines are responsible for the production. Firm evidence has been established regarding the association among adverse pregnancy outcomes, raised CRP levels, and intrauterine growth inhibition.<sup>22</sup>

Moreover, the findings of a recent prospective cohort study showed that even after controlling for age, Gestational DM, and hypertension, a significant association between CRP levels and the development of maternal adverse outcomes like pre-eclampsia. Evidence also suggests an important relation between raised CRP levels and delivery before 37 weeks' of gestation.<sup>7</sup> We recommend conducting an in-depth risk factor analysis in women having pre-eclampsia with raised CRP.

### ssLIMITATION OF STUDY

This study has some limitations that must be acknowledged. To begin with, data on lifestyle factors, comorbidities, and risk factors associated with family history are not included in this analysis, and these factors may have influenced the outcomes. Further, the research is a single-centre study. More multicenter studies are needed to establish the results on a larger sample size to get generalizable results.

### CONCLUSION

In conclusion, the findings of this study established the association between elevated CRP and pre-eclampsia, as raised maternal serum CRP levels in mid-pregnancy might be associated with a greater risk of pre-eclampsia. Therefore, effective monitoring of CRP could help in timely management and prevent severity. CRP can be used as an important diagnostic tool in the identification of the severity of pre-eclampsia.

**Conflict of Interest:** None.

### Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KM & SJ: Conception, study design, drafting the manuscript, approval of the final version to be published.

MB & SM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

S & MY: Data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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