



## PREDICTIVE VALUE OF MATERNAL C REACTIVE PROTEIN ESTIMATION FOR DETECTION OF CHORIOAMNIONITIS AND ITS HISTOLOGICAL CONFIRMATION IN WOMEN WITH PRETERM PREMATURE RUPTURE OF MEMBRANES

### Obstetrics & Gynaecology

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### ABSTRACT

The present study was conducted among 150 antenatal women before 37 weeks of gestational age presenting in obstetrics and gynaecology department of PMCH with preterm premature rupture of membranes, for a duration of 2 years.(dec 2015-dec 2017). CRP was found to be more sensitive (100%) but less specific (35.13%) than clinical signs of chorioamnionitis. So, we concluded that CRP may serve as a non-invasive screening test as it has high sensitivity to predict chorioamnionitis in cases of PPRM even in cases of subclinical chorioamnionitis and warn about timely delivery before there is severe fetal infection.

### KEYWORDS

CRP, Preterm Premature Rupture of Membranes

#### INTRODUCTION:

PPROM complicates approximately 2–4% of all pregnancies. Pregnancies with PPRM are often complicated by adverse intra-amniotic conditions such as microbial-invasion of the amniotic cavity and intra-amniotic inflammation in 30-40% of cases which is associated with significant maternal, perinatal, and long-term adverse outcomes.(Owen Stock et al 2015)[1]

Balancing the benefits of prolonging pregnancy to allow for maturation of the fetus against the risks of infection in cases of PPRM represents a major challenge for obstetricians. The key clinical findings associated with clinical chorioamnionitis include fever, uterine tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min) and purulent or foul smelling amniotic fluid. (Jeong Woo Park et al 2017)[2]. Tachycardia may be present in the absence of chorioamnionitis. Medications such as antihistamines, beta agonists and ephedrine may raise maternal or fetal heart rate. Fundal tenderness is difficult to interpret in the context of the pain of labor and may be masked by analgesics including epidural or confounded by the pain associated with placental abruption. Purulence or foul odor of amniotic fluid may or may not be appreciated by clinicians. (Michael P Sherman 2017)[3] Amniotic fluid interleukin-6 (IL-6) has been reported as a significant predictor but amniocentesis is an invasive procedure with accompanying risks, and a decreased amniotic fluid volume in cases of PPRM often makes it difficult or impossible to obtain it. Consequently, alternative approaches for non-invasive and rapid identification of chorioamnionitis are needed for women with PPRM.( Su Ah Kim et al 2016)[4] C-reactive protein is an acute phase protein secreted by the liver in response to inflammation. It is not specific for infection but is a marker used for the diagnosis of many inflammatory, infective and malignant conditions. (RD Trochez-M et al(2007)[5].

The aim of this study is to evaluate the diagnostic accuracy of CRP in the prediction of chorioamnionitis following PPRM. So that it can serve as biomarker that can detect chorioamnionitis early in its evolution, predict the development of intrauterine infection before it occurs and could substantially improve outcomes, both maternal and fetal.

#### MATERIAL & METHODS

This is a prospective observational study carried out in the department of obstetrics and gynaecology Patna Medical College and Hospital for duration of 2 years (Dec 2015-dec 2017) on a sample size of 150 patients.

All patients were at between 28 and 37 of weeks of gestation as best estimated by LMP, and confirmed by ultrasonography. A detailed history was taken at the time of admission and thorough examination was done. In all patients rupture of the membrane was diagnosed by sterile speculum examination using pooled fluid, fern test and Nitrazine paper test.

Pregnant mothers more than 37 weeks gestation ,with upper

respiratory tract infection, urinary tract infection, burn ,malignancy, heart disease, hepatitis, diabetes, rheumatic fever, rheumatic arthritis, SLE and pregnancy complications like twin pregnancy, malpresentation, preeclampsia, antepartum hemorrhage, polyhydramnios were excluded from the study.

Odour of the discharge whether foul smelling or not was also noted. Maternal serum samples were sent for C-reactive protein and total leucocyte estimation. Patients were managed with antibiotics and corticosteroid injection. After delivery placenta was sent to pathology department in 10% formalin for histopathological examination. Birth weight and APGAR score of newborns was noted. Fetal outcome was studied with respect to number of still born, neonatal deaths, perinatal deaths, NICU admission and infection.

Statistical analysis was done. Descriptive data were presented as mean± standard deviation and range values. Chi square test and student t- test were used for comparing the means of two groups. For all the tests, the probability value (p-value) of less than 0.05 was considered statistically significant.

#### OBSERVATION

Total 150 pregnant women were included, out of which 111(74%) were CRP positive and 39(26%) were CRP negative. CRP ≥6mg/l was taken as positive with range between (6.2mg/l- 23.4mg/l). CRP <6mg/l was negative with range between (0.8-5.8mg/l).

There was no statistically significant difference between two groups with respect to maternal age and parity. Mean gestational age of delivery in crp negative groups was significantly higher than those who were crp positive (p<0.01) Overall vaginal delivery was high (75.33%) but the difference was not statistically significant (p=0.12).

**Table 1: Comparison Of CRP With Mean Age**

CRP	MEAN age	SD	
CRP≥6mg/l	25.4234	4.9333	P>0.05
CRP<6mg/l	24.3590	4.4985	
Parity	Crp>6mg/l	Crp<6mg/l	
Primi	48(43.2%)	19(48.7)%	p-0.55
Multi	63(56.8%)	20(51.3)%	
Crp	Mean ga at delivery	sd	
CRP≥6mg/l	33.1315	2.0689	P<0.01
CRP<6mg/l	34.1821	2.0119	

39(26%) patients had increased CRP along with histological evidence of chorioamnionitis, 72(48%) had increased CRP without any histological evidence of chorioamnionitis, 39(26%) had normal CRP without histopathological evidence of chorioamnionitis.

**Table2: Comparison Of CRP With Clinical Signs Of Chorioamnionitis:**

	HPE-CHORIO		NO HPE-CHORIO		SEN %	SPE %	PPV %	NPV %
	NOR MAL	ABNO RMAL	NOR MAL	ABNO RMAL				
CRP≥6mg/l	0	39	39	72	100	35.13	35.13	100
TLC>15,000 /ul	21	18	25	86	46.15	22.52	17.31	54.34
FEVE R>100 .4 F	2	37	55	56	94.87	49.55	39.78	96.49
Ut. Tenderness	17	22	70	41	56.41	63.06	34.92	80.46
Foul vagina l disch	36	3	63	48	7.69	56.76	5.88	63.64
Materal hr>100/min	12	27	47	64	69.23	42.34	29.67	79.67
FHR>160/min	14	25	56	55	64.10	50.45	31.25	80

The table above shows that crp has better sensitivity but less specificity than other clinical signs of chorioamnionitis.

Neonates born to CRP positive mothers had poor neonatal outcome, which was measured in terms of APGAR score, birth weight, NICU admission, neonatal sepsis and perinatal mortality. In CRP positive patients 74.7% neonates had APGAR <7 whereas in CRP negative patients 41% had APGAR <7. Mean APGAR in CRP negative patients (7.4615 with SD 1.3050) which was significantly higher ( $p<0.01$ ) than mean APGAR in CRP positive patients (6.7838 with SD 1.4104). Mean birth weight of babies in CRP positive cases (2.1556 with SD 0.2602). Was significantly ( $p<0.001$ ) lower than mean birth weight of babies in CRP negative cases (2.3295 with SD 0.2264). Statistically significant ( $p<0.001$ ) difference was found in NICU admission of the babies born to CRP positive mothers (55.9%) and in CRP negative mothers (25.64%).

Neonatal sepsis and mortality was also higher in CRP positive patients. There was 9.9% of neonatal sepsis, 2.7% of IUD and 13.5% of neonatal death in CRP positive cases whereas in CRP negative cases there was 7.6% of neonatal sepsis, no IUD and 5.1% of neonatal deaths

#### DISCUSSION:

The present study tried to evaluate the relationship between maternal C- reactive protein value and chorioamnionitis so as to establish its usefulness in predicting and anticipating chorioamnionitis secondary to PPRM and whether increased CRP acts as a predictor of neonatal sepsis and poor neonatal outcome. Total 150 pregnant women were included, out of which 111 (74%) were CRP positive and 39 (26%) were CRP negative. CRP  $\geq 6$ mg/l was taken as positive. CRP <6mg/l was taken as negative.

Maximum patients were in the age group of 18-27 years.. The overall incidence of multigravida was high but the results were not significant ( $p=0.55$ ). According to the study conducted by **Viroj Wiwanitkit(2004)[6]** age , gestational age, parity and race doesn't affect CRP. Mean gestational age at delivery in CRP positive patients (33.1315 with SD 2.0689) was significantly lower ( $p<0.01$ ) than those of CRP negative patient (34.1821 with SD 2.0119). **Hsin Chu et al (2009)[7]** in his study concluded that histological chorioamnionitis was significantly correlated with lower gestational age at delivery (30.8 $\pm$ 4.1 weeks vs 33.0 $\pm$ 2.6 weeks  $p<0.05$ ) and higher CRP level in mother. **Xie AL et al (2012) [8]** also concluded that the gestational age of delivery was significantly lower than those of control group [(32.0 $\pm$ 1.5) weeks vs. (32.7 $\pm$ 1.5) weeks] in cases of increased CRP and histological chorioamnionitis. Overall vaginal delivery was high (75.33%) but the difference was not statistically significant ( $p=0.12$ ). In the study conducted by **Minakeshi Rana et al (2014) [9]** and **Ojaswini Patel et al (2017) [10]** also there were 67% vaginal deliveries.

In our study sensitivity and specificity of raised CRP was 100% and 35.13% respectively with positive predictive value and negative predictive value of 35.13% and 100% respectively. Sensitivity, specificity, positive predictive value and negative predictive value of leucocytosis was 46.15%,22.52%,17.31%,54.34% respectively. In a study conducted by **Dr. Sujata Deo et al (2016)[11]** sensitivity specificity, positive predictive value and negative predictive value of CRP was also 100%,50%, 29.27% and 100% respectively. Leucocytosis had a sensitivity, specificity, positive predictive value and negative predictive value of 66.7%, 94.4%, 57.14%, and 96.23% respectively which was higher than our study. But according to studies conducted by **Thomas Popowski et al (2011)[12]** & **Saini S et al (2003)[13]** sensitivity of CRP is >90% and is better marker than TLC for prediction of chorioamnionitis and early neonatal infection. According to **Chandra S et al (2012) [14]** and **Bauer ME et al (2017)[15]** also leucocytosis occurring during pregnancy is due to the physiologic stress induced by the pregnant state and also due to corticosteroid administration in women at risk for preterm delivery.

In the study CRP is more sensitive (100%) but less specific (35.13%) than maternal fever with specificity (49.55%), maternal tachycardia with specificity (42.34%), uterine tenderness with specificity (63.06%), foul smelling vaginal discharge specificity (56.76%) and fetal tachycardia with specificity (50.45%). The findings are consistent with the study conducted by **Sujata Deo et al(2016)[11]** who also concluded that CRP is more sensitive(100%) but less specific(36.89%) than maternal fever, maternal tachycardia and fetal tachycardia. In the studies conducted by **Lieberman et al (2000)[16]** and **Micheal A. Florich et al (2012)[17]** fever in pregnancy is confounded by factors such as epidural anesthesia, particularly among nulliparous women with prolong labour, also medications given during epidural anesthesia may induce maternal and fetal tachycardia. Studies conducted by **Smulian JC et al (1999)[18]**, **Apantaku O et al (2007)[19]** concluded that clinical chorioamnionitis were not supported by histological evidence for infection in 38.1% of cases suggesting other non-inflammatory causes of signs and symptoms. But according to **Danthanh Hoang et al(2012)[20]** there is a significant association between Histological chorioamnionitis and maternal fever.

In the study neonates born to CRP positive mothers had poor neonatal outcome. CRP positive patients had significantly lower APGAR (6.7838 $\pm$ 1.4104), mean birth weight of newborns(2.3295  $\pm$  0.2264) and higher NICU admission(55.9%).

Neonatal sepsis and mortality was also higher in CRP positive patients. There was 9.9% of neonatal sepsis, 2.7% of IUD and 13.5% of neonatal death in CRP positive cases whereas in CRP negative cases there was 7.6% of neonatal sepsis, no IUD and 5.1% of neonatal deaths. Studies conducted by **Kwak DW et al(2015)[21]**, **Lee SY et al(2012)[22]** also concluded that elevated maternal serum CRP in cases of PPRM was associated with low APGAR score, increased NICU admission and low birth weight. According to **Xie al et al (2012)[8]** Histological chorioamnionitis was significantly correlated with lower birth weight (1680  $\pm$  379) g and, higher serum CRP level in cases of PPRM.

**Thomas Popowaski, Francois Goffinet et al (2011) [12]** in their study found that CRP at admission in cases of PPRM can predict early neonatal infection with a sensitivity of >90% whereas studies conducted by **Canpolat FE et al (2011)[23]** & **Torbe A et al(2010)[24]** concluded that CRP had low sensitivity and specificity in predicting early neonatal infection.

#### CONCLUSION

CRP may serve as a non-invasive screening test as it has high sensitivity (>90%) to predict chorioamnionitis in cases of PPRM even in cases of subclinical chorioamnionitis. Timely detection by using this sensitive warning test would lead to optimum gestational age possible and timely delivery before there is severe fetal infection.

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