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Original Research Article

Evaluation of the role of CRP as an early predictor of chorioamnionitis in PPRM

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ABSTRACT

Background: Preterm birth is one of the most important cause of perinatal morbidity and mortality. PROM is defined as spontaneous rupture of membranes before the onset of uterine contraction. Objective of present study was to evaluate the role of CRP as an early predictor of Chorioamnionitis in PPRM.

Methods: A prospective study was done on 50 cases with PPRM and 50cases of control group without PPRM. All mothers and babies were observed from the time of admission to the time of discharge.

Results: C-reactive protein appears to be the most sensitive acute phase protein; rising of less than 24 hours makes it suitable to serve as a marker for diagnosing an infective process in early stage. On comparing C-reactive protein levels with other laboratory tests and indicators of infection (e.g. total leucocyte count DLC, maternal fever, maternal tachycardia, fetal tachycardia) we found CRP level to be more sensitive (100%) but less specific (69.56%) in identifying clinical Chorioamnionitis. The positive predictive value was 22.22% and negative predictive value was 100%.

Conclusions: In cases of PPRM, raised CRP is an early predictor of clinical Chorioamnionitis as well as histological Chorioamnionitis.

Keywords: CRP, Chorioamnionitis, PPRM

INTRODUCTION

Preterm birth is one of the most important cause of perinatal morbidity and mortality.¹ PROM is defined as spontaneous rupture of membranes before the onset of uterine contraction. If the rupture of the membranes occurs after 28 weeks but before 37 weeks of gestation it is termed as PPRM (Preterm Premature Rupture of Membrane). The incidence of PPRM is variable between 2-4.5% of all deliveries. It is responsible for 30% of preterm deliveries and contributes around 10% of perinatal mortality.² Removal of barrier to ascending infection in PPRM dramatically increases the likelihood of the development of chorioamnionitis.³ Acute CAM is a threat to both mother and fetus.⁴ Since expectant

management of PPRM less than 34 weeks of gestational age is broadly recommended, the placental results cannot be correlated with amniotic fluid results due to the long latency between sampling and delivery.⁵ Early infection is not reliably predicted by commonly used laboratory variables such as erythrocyte sedimentation rate, white blood cell count, neutrophil count or vaginal bacterial culture. Clinical signs such as fever and fetomaternal tachycardia usually appear late.⁶ One of the markers in maternal serum, which indicates an increased risk of preterm delivery, is the C-reactive protein CRP.⁷ CRP is an acute phase protein synthesized in the liver during infection. It is a sensitive marker of inflammation that remains stable in serum. Production of CRP is stimulated by release of pro inflammatory cytokines including

interleukin1, IL-6, INF-alpha. Although sometimes referred to as acute phase reactant, CRP accompanies both acute and chronic inflammatory disorder. Elevated concentration of CRP is seen both in the peripheral circulation and in the amniotic fluid in patients with intrauterine infection.⁸ CRP is being used in different parts of the world as early predictor of Chorioamnionitis. Perinatal mortality after PPRM is most commonly associated with infection and prematurity which leads to adverse neonatal outcomes as intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, bronchopulmonary dysplasia.⁹

Therefore, our main objective was to determine whether measuring individual or sequential CRP levels was useful for diagnosing CAM before onset of traditional clinical symptoms.

METHODS

This present proposed study was conducted in Department of Obstetrics and Gynecology, SGRDIMSR AMRITSAR on patients admitted in labor ward from June 2016 to June 2017. Written informed consent by each subject was sought before the study. The present study comprise of 100 patients, 50 cases with Singleton pregnancy with premature rupture of membrane >28 wks., excluding patient with any respiratory, urinary infection at the time of admission, any long standing diseases such as Rheumatoid Arthritis, Twin gestation, Patient with heart disease, diabetic mother or any complication and >34 weeks. of gestation. 50 cases with same gestation but without PPRM. In each patient, the first step was to study routine investigation results. Along with clinical assessment of Chorioamnionitis, next was to study CRP levels. Sample for study (Group A) and control mother (Group B) for CRP levels was taken from antecubital vein at the time of admission and daily till the patient delivers. CRP Determination This was done using latex agglutination method with the help of CRP reagent kit. For the purpose of analysis in the study, CRP values were considered abnormal when the values exceeded 6 mg/L. Patients were followed through labour and delivery.

Duration and type of labour, mode of delivery and indication of operative delivery was recorded. Finally, Histopathological examination of placenta was done, Inflammation was considered mild when number of polymorphs <15/HPF and moderate to severe when number of polymorphs >15/ HPF.

RESULTS

Above table shows age distribution in the study and control group. Maximum number of patients belongs to 20-24 yrs. in both study (64%) and control group (52%). Maximum number of patients was primigravida in both study group (40%) as well as control group (56%). In the study group 40 patients belongs to the gestational age 33-34 wks. I.e. maximum number, 9 (18%) patients belong to gestational age 29-32 wks., only 1 patient belong to less than 28 wks. gestational age group. In the present study mean gestational age of the study group was 33.4+2.109 wk. as compared to 33.36+1.208 wks. in the control group (Table 1).

Table 1: Demographic data of patients.

Demographic Data	Study Group A	Control Group B
Age (yrs.)	23.42±3.25	23±3.96
Gestational age (wks.)	33.4±2.109	33.36±1.208
Gravidity	2.04±1.2	1.68±0.36
Parity	1±1.13	0.56±0.75
Duration of PROM (hrs.)	60.16	

Table shows distribution of cases according to type of infectious morbidity. Out of 50, 18 patients (36%) showed inflammatory changes in placental histology and 4 among them (8%) presented with clinical CAM... in the study group out of 50 patients, 13 (24%) showed mild CAM on placental histopathology, 5 patients (10%) showed moderate to severe CAM. Rest 32 (64%) patients had no evidence of inflammation. In the control group 10 patients i.e. 20% had mild CAM; none of them showed moderate to severe CAM and all rest 80% patients had no evidence of inflammation (Table 2).

Table 2: Distribution of cases according to type of infectious morbidity (N = 50).

Type of Infectious Morbidity	%	No. of Patients	↑CRP	CRP value	Severity	
Clinical chorioamnionitis	8.00	4	8%	32ng	Severe	
Histological chorioamnionitis	28.00	14	(1)	2%	24ng	Severe-moderate
			(13)	26%	>12ng	Mild
Without infectious morbidity	64.00	32		<6ng		

Table shows CRP was elevated in all 4 cases of clinical CAM, thus the sensitivity of CRP is 100%. There were 14 false positive cases in which CRP was elevated but there no clinical CAM, thus specificity is 69.56% and

positive predictive value is 22.32% since there was no false negative because negative predictive value is 100%. In comparing the CRP levels with other parameters of infection clinically CRP has come out to be most

sensitive little less specific with high negative predictive value and little less positive predictive value. In sensitivity CRP ranges uppermost followed by maternal temperature, fetal tachycardia, TLC, lastly DLC. CRP becomes positive at least 48 hours before the other signs of infection. But Wiwanitkit V et al analysed different studies and found that CRP had sensitivity, specificity,

false positive and false negative of 72.8%, 76.4%, 23.6%, and 27.2% respectively in diagnosis of CAM.¹⁰ The overall prevalence of CAM was 41%, so this test has only fair role, but sensitivity and specificity shown by different authors are as: Sereepapong et al (56%,58%) Ibarra (94.1%, 100%) Teichmann et al (50%, 93.3%) (Table 3).¹¹⁻¹³

Table 3: Correlation of various parameters in predicting clinical CAM.

Parameters	Without clinical chorioamnionitis		With clinical chorioamnionitis		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Test normal	Test abnormal	Test normal	Test abnormal				
Fetal Tachycardia (>160/min.)	44	2	2	2	50.00	95.65	50.00	95.65
TLC (>11000/mm ³)	42	4	2	2	50.00	91.30	33.00	95.45
DLC (Polymerase >80%)	42	4	3	1	25.00	91.30	20.00	93.33
Maternal temperature (>38°C)	46	0	0	4	100.00	100.00	100.00	100.00
CRP (>6 mg/L)	32	14	0	4	100.00	69.56	22.22	100.00

Table 4: Accuracy of various parameters in predicting histopathological (mild-severe) chorioamnionitis.

Parameters	Without histopathological chorioamnionitis		With histopathological chorioamnionitis		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Test normal	Test abnormal	Test normal	Test abnormal				
Fetal Tachycardia (>160/min.)	30	2	16	2	11.11	93.75	50.00	65.21
TLC (>11000/mm ³)	30	2	14	4	22.22	93.75	66.66	68.18
DLC (Polymerase >80%)	29	3	16	2	11.11	90.62	40.00	64.44
Maternal temperature (>38°C)	32	0	14	4	22.22	100.00	100.00	69.56
CRP (>6mg/L)	32	0	4	14	77.77	100.00	100.00	88.88

Table shows correlation of various indicators of histological CAM and also compares the accuracy of various parameters in predicting histological CAM. There are 18 cases of histological CAM including mild to severe inflammation. CRP was elevated in 5 of these cases, thus sensitivity is 77.77%. There were 0 false positive hence specificity and positive predictive value is 100%. There was 4 false negative thus negative predictive value is 88.88%. In comparing the accuracy of various parameters in predicting histological CAM. CRP is the most specific in predicting histological CAM. Although the sensitivity is relatively less than specificity

but it is highest among all parameters. Positive predictive value and negative predictive value are also highest among all the parameters. As mild leucocyte infiltration may not be a true indicator of infection keeping this in view if only the cases showing moderate to severe inflammation are considered as true positive cases of pathological CAM. Then sensitivity of CRP in predicting it is 100%, specificity 100%, positive predictive value and negative predictive value is 100%.

Thus, elevated CRP level are found to be most sensitive parameter and correlate more accurately with histological

CAM keeping in view that mild inflammation is not a true indicator of infection (Table 4).

Table 5: Distribution of cases according to perinatal mortality.

Perinatal mortality	Study Group A		Control Group B	
	Number	Cause	Number	%
Live birth	45	-	50	100.00
Still birth	1 (CRP normal)	Prematurity	0	0.00
Neonatal deaths	4 (CRP high)	Sepsis and prematurity	0	00.00

Chi-square = 0.111 with 1 Degree of Freedom; P = 0.739

Table compares the perinatal mortality in the cases and control group. In the study group, out of total 50 patients 49 patients delivered live babies in which 4 died in the neonatal period (8%). There was 1 stillbirth due to extreme prematurity. In the control group there was no

mortality. Thus, the perinatal mortality has come out to be 10% in cases of spontaneous PPRM in the study group of patients. Prematurity increases the susceptibility of neonates to infection and thus multiple the risk of perinatal mortality in patients with PPRM as shown in present study also. Thus, prematurity directly and indirectly has maximum bearing of perinatal mortality as compared to sepsis.

So, the main cause of the conservative management in preterm cases of PPRM is to continue pregnancy till the fetus is mature and at the same time, monitor the pregnancy for the signs of the development of impending infection. There were in total 5 perinatal deaths in which CRP was increased in 4 (80%). 1 patient had CRP (<6 mg/dL). If we consider the perinatal mortality wholly or partly due to sepsis, CRP was increased in all 4 perinatal deaths. Thus, CRP has 100% sensitivity in predicting perinatal mortality due to sepsis (Table 5).

Table 6: Correlation of birth weight to perinatal mortality.

Birth weight (gms)	Study Group A			Control Group B		
	Number	PNM	%	Number	PNM	%
< 2000	12	4	33.33	2	0	0.00
2000 – 2500	28	1	3.57	18	0	0.00
> 2500	10	0	0.00	30	0	0.00

Table showed that 12 babies have less than < 2000 gm. at birth. Out of these there were 4 perinatal deaths i.e. 33.33%. Out of babies weighing between 2000-2500 gm. there was 1 mortality out of 28 (3.57%) and among babies weighing > 2500 gm. there was no perinatal mortality. 80% of the perinatal mortality seen in the babies weighing less than 2000 gm. whereas in control group there was no stillbirth (Table 6).

DISCUSSION

Expectant management for preterm labour and preterm premature rupture of membranes is now an accepted modality of treatment. Nevertheless, the main clinical concern is still the danger to the mother of acquiring Chorioamnionitis. Therefore, an approach to expectant management is based on monitoring for symptoms and signs of impending infection.

The laboratory indicators most often used to predict infection are total leucocyte count, differential leucocyte count, urine culture, vaginal culture, the tests are by and large, unreliable. C-reactive protein appears to be the most sensitive acute phase protein; rising in less than 24 hours makes it suitable to serve as a marker for diagnosing an infective process in early stage. In the present study, total 100 patients were studied. The control group consist of 50 antenatal patients (>28 completed

weeks) whereas study group consist of 50 antenatal patients with preterm premature rupture of membrane >28 weeks. Demographic, socioeconomic were comparable between control and study group. In our study maximum number of patients in study groups belong to 29-34 weeks of gestation. The results are in accordance with the previous studies.⁷ Latent period directly proportional to incidence of Chorioamnionitis with increase in latent period, there is increase in incidence of Chorioamnionitis and correlation is better with histological Chorioamnionitis then clinical CAM.

Then incidence of clinical CAM is 8% in which mean elevated CRP was 32 mg/L. Our results from this study is supported by relatively large cohort of women with PPRM that the presence of CAM is associated with higher maternal serum CRP concentrations.⁵

The control group shows CRP < 6 mg/L in all cases. On comparing C-reactive protein levels with other laboratory tests and indicators of infection (e.g. total leucocyte count DLC, maternal fever, maternal tachycardia, fetal tachycardia) we found CRP level to be more sensitive (100%) but less specific (69.56%) in identifying clinical Chorioamnionitis. The positive predictive value was 22.22% and negative predictive value was 100%. Present results were in accordance with other studies.^{14,15}

As we know that for diagnosing the Chorioamnionitis gold standard test is histopathological examination of placenta Histological CAM was found in 36% of patients with PROM. Mild inflammation was seen in 26% and moderate to severe in 10%. In control group mild inflammation was seen, none with moderate and severe CAM. There was no significant difference between number of cases showing mild inflammation between study and control group. Thus, mild inflammation is not a true indicator of CAM itself. Thus, if mild cases of inflammation are excluded regarding them insignificant CRP reaches the highest possible sensitivity and specificity, positive predictive value and negative predictive value.

The total perinatal mortality was 5 (10%) out of which 20% was attributed to sepsis and 20% to prematurity and 60% due to prematurity and sepsis. 80% of perinatal mortality was seen in the babies weighing <2000 gm. with weight <2kg Perinatal morbidity and mortality decreases as the birth weight increases. This is comparable to study by Cox and colleague 52% due to RDS.¹⁶ Thus prematurity has the maximum bearing of perinatal mortality directly as well as indirectly by increasing the susceptibility to infection. Maternal CRP levels were elevated in all 4 cases of perinatal mortality. Cord CRP was elevated in all cases of neonatal sepsis CRP detects neonatal sepsis with 100% sensitivity. Perinatal morbidity was found to be 10(20%) of which 8% was attributable to infection, 8% hyperbilirubinemia and 2% respiratory distress syndrome. CRP was elevated in all the cases that had sepsis. Thus, CRP predicts perinatal morbidity due to sepsis accurately. CRP was elevated in 70% cases of puerperal sepsis. The causes of fever in other cases were not sepsis as they responded to antimalarial.

CONCLUSION

It is concluded from the present study that CRP is the earliest and most reliable diagnostic marker of clinical as well as histological CAM so in patients with PPRM. If on admission has increase in CRP pregnancy should be terminated as soon as possible to salvage the baby as well as the mother. If the CRP is normal <6 mg/L at the time of admission the patient should be managed expectantly with a prospective follow up in order to allow the maximum possible fetal maturity and at the same time monitor the pregnancy regarding for signs of infection.

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