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MATERNAL CRP AS A PREDICTOR OF CHORIOAMNIONITIS IN WOMEN WITH PPROM

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Abstract

Introduction: Preterm prelabour rupture of the membranes (PPROM) refers to spontaneous rupture of membranes in the absence of labour pains, before 37 completed weeks of gestation. Chorioamnionitis (CAM) affects many pregnancies complicated by PPROM. Finding a serum factor that could accurately predict the presence of CAM could potentially lead to more efficient management of PPROM and improved neonatal outcomes. It has been claimed that estimation of C-reactive proteins (CRP) is helpful in the diagnosis of chorioamnionitis, and this study aims to appraise such claims

Objective: To determine the diagnostic accuracy of C-reactive protein in the detection of chorioamnionitis in women with PPROM and to test sensitivity/specificity/positive predictive valve/negative predictive value of CRP in diagnosing chorioamnionitis against histopathological examination of placenta.

Method: A study conducted on total 440 antenatal women, 220 cases of PROM and 220 cases with same gestation but without PPROM used as a control. A detailed obstetrical and menstrual history was taken and systemic and local examination was done. Subjects were managed expectantly with use of tocolytics, antibiotics and steroids. Frequent vital signs monitoring and hematological investigation were done. CRP levels were determined. After delivery placenta was sent for histopathological examination for the presence of chorioamnionitis.

Results: CRP 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 infection. On comparing C-reactive protein levels with other laboratory tests and indicators of infection (e.g. total leucocyte count, maternal fever, maternal tachycardia, fetal tachycardia) we found CRP level to be more sensitive (100%) but less specific (45.45%) in identifying chorioamnionitis. The positive predictive value was 31.4% and negative predictive value was 100%.

Conclusion: CRP is early and reliable indicator of histopathological and clinical chorioamnionitis in comparison of TLC and clinical parameter. Thus CRP can prove useful markers in identify early and subclinical infection which could lead to premature rupture of membrane.

Keywords: Preterm birth, C-reactive protein, PPROM, Chorioamnionitis.

Introduction

The management of patients with premature rupture of membrane poses one of the most serious dilemmas in obstetrics since they significantly increase the likelihood of prematurity and serious perinatal infection. Pathogens largely arise from the ascending route and the endogenous vaginal flora, and may cause chorioamnionitis[1].The incidence of PPROM is variable between 2-4.5% of all deliveries. It is responsible for 30% of preterm deliveries and contributes around 10% of perinatal mortality. Removal of barrier to ascending infection in PPROM dramatically increases the likelihood of the development of chorioamnionitis. Acute chorioamnionitis is a threat to both mother and fetus.[2]There are various serologic and amniotic fluid tests that may identify activation of the host immune and inflammatory responses as a consequence of the microbial invasion of the amniotic cavity, but these are not yet fully confirmed for clinical use.[3-5] Examples are C-reactive protein (CRP), leukocyte count, vaginal microbiological studies and histological study. These tests may identify the early stages of an infectious process, before the full clinical manifestations of chorioamnionitis.[6] CRP is annular pentameric protein in blood plasma. It is synthesized in the liver. Its main roles is to identify potentially toxic autogenous substances released from damaged tissues, to bound them, detoxify them and remove them from the blood.[7,8] The level of CRP in plasma greater than 1.5 mg/dl shows a highly significant correlation with levels of interleukin-6 (IL-6) in the amniotic fluid greater than 1500 Pg/ml. C-reactive protein can be used in prediction and as a screening test to detect the risk of premature delivery [9].

Material and Method

This present proposed study was conducted in Department of Obstetrics and Gynecology IGMC Shimla from august 2017 to July 2018. Study comprises of 440 patients, 220

cases with Singleton pregnancy with premature rupture of membrane>24 wks. Exclusion criteria included patient with any respiratory, urinary infection at the time of admission, any long standing diseases such as rheumatoid arthritis, twin gestation, patient with cardiac disease, diabetes or any complication and >37 weeks of gestation. 220 cases with same gestation but without PPROM were taken as control. In each patient routine investigation results were analysed. Along with clinical assessment of chorioamnionitis, CRP levels were studied. Sample for CRP levels was taken from antecubital vein at the time of admission and daily till the patient delivers. CRP determination 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.

After the delivery histopathological examination of placenta was done, Inflammation was considered mild when 15 / HPF number of polymorphs <15/HPF and moderate to severe when number of polymorphs>.

Result

Age-wise distribution of the patients was compared in both groups. The highest numbers of cases of PPROM were primigravida (48%) and mean gestational age was 34.02+2.43 weeks. Leucocytosis (>12000/m3) was present in 5.5% cases and vaginal swab culture was present in 7.4% cases of study group. CRP level was raised (>6 mg/dl) in 64% in study group and 40% in control group. Histopathological chorioamnionitis was present in 20% cases of study group and 5.23% cases in control group (Table 1).

Table 1: Characteristics of patients of study and control group

	Study (n=220)	Control (n=220)	p-value
Age(years)	24.33±2.06	25.45±2.31	>0.001(NS)
Parity(primipara)	48%	53%	>0.001(NS)
Leucocytosis	5.5%	0%	
Vaginal swab culture	7.4%	0%	
CRP level	64%	40%	<0.001 (S)
Histopathological change (chorioamniotis present)	20%	5.23%	

CRP ≥6mg/L

Table 2 showed mean CRP level in both group. In study group mean CRP level in CRP positive cases (64%) were 10.39+3.32 mg/dl while in CRP negative cases (36%) it was 2.68+1.86 mg/dl. In control group mean CRP level in CRP positive cases (40%) was 6.82+2.05 while in CRP negative cases(60%) it was 2.26+1.86 mg/dl. Although CRP was raised in both study and control group but mean CRP level was higher in study group (10.39+3.32 mg/dl) than control group (6.82+2.05 mg/dl) and this difference was statistically significant (p<0.001).

Table 2: Mean CRP in study and control group

Group	CRP level	Mean	p-value
Study group (n=220)	Positive(≥6mg/l)n=140(64%)	10.39±3.32	<0.001(S)
	Negative(<6mg/l)n=80(36%)	2.68±1.86	
Control group (n=220)	Positive(≥6mg/l)n=88(40%)	6.82±2.05	<0.001(S)
	Negative(<6mg/l)n=132(60%)	2.26±1.86	

Table 3 shows mean CRP levels in study group in relation to clinical chorioamnionitis. Among 220 patients of study group. 17% patients had features of clinical chorioamnionitis (i.e. maternal fever, tachycardia, leucocytosis and fetal tachycardia uterine tenderness and foul smelling discharge) with elevated C-reactive protein levels (>6 mg/L). They had mean CRP level of 12.16+2.96 mg/litre. 47% had no evidence of clinical chorioamnionitis but they had elevated CRP level with mean level of CRP level is 10.38+3.22. 36% had no evidence of clinical chorioamnionitis and their C-reactive protein levels were also in normal range.

Table 3: Mean CRP levels in study group in relation to clinical chorioamnionitis

Clinical chorioamnionitis and CRP Level	Patients in study group		Mean CRP level
	No.	Percentage	
Clinical chorioamnionitis with elevated CRP level	37	17	12.16±2.96
No Clinical chorioamnionitis with elevated CRP level	103	47	10.38±3.22
No Clinical chorioamnionitis with normal CRP level	80	36	2.58±2.55
Total	220	100	

Table 4 shows that 44 (20%) out of 220 patients with PPROM showed histopathological chorioamnionitis i.e. neutrophilic infiltration of chorioamnion on their placental examination. They also had elevated CRP value with mean of 12.32±2.55 mg/dl. 96 patients i.e. 44% had no evidence of histopathological chorioamnionitis with elevated CRP level. 80 patients i.e. 36% had no evidence of histopathological chorioamnionitis with normal CRP levels.

Table 4: Relationship of clinical symptoms in study and group with histopathological chorioamnionitis

Diagnostic group	Patients in study group (n=220)		Mean CRP level
	No.	Percentage	
Histopathological chorioamnionitis with elevated CRP	44	20	12.32±2.55
No Histopathological chorioamnionitis with elevated CRP	96	44	10.42±3.21
No Histopathological chorioamnionitis with normal CRP	80	36	2.56±1.56
Histopathological chorioamnionitis with normal CRP	-	-	-
Total	220	100	

Table 5 shows sensitivity and specificity of CRP level with different clinical features and laboratory test of chorioamnionitis in cases i.e. fever, maternal tachycardia, fetal tachycardia and total leucocyte counts. It showed that CRP level to be more sensitive (100%) but less specific (42.55%) in identifying clinical chorioamnionitis CRP also had the highest negative predictive value (100%) but least positive predictive value (22.85%) among all parameters.

Table 5: Sensitivity and Specificity of CRP with different clinical features in study group

Clinical feature	CRP level				Sensitivity	Specificity	Positive predictive value	Negative predictive value
	With clinical features		Without clinical features					
	Positive	Negative	Positive	Negative				
Fever(100.4°F)	32	0	108	80	100	42.55	22.85	100
Maternal tachycardia≥100	14	0	126	80	100	38.83	10	100
Featl tachycardia ≥160	26	0	114	80	100	41.23	18.57	100
TLC>12000	12	0	128	80	100	38.46	8.57	100

Table 6 shows the comparison of C-reactive protein determination and other tests in the identification of histopathologically diagnosed chorioamnionitis. It was found that histopathological chorioamnionitis was present in 44 patients in study group. CRP was raised in all patients who had positive histopathological chorioamnionitis. Maternal fever and fetal tachycardia significantly higher in patient who had positive histopathological chorioamnionitis whereas total leucocyte count (>12000/mm3) was raised only in 20 patients with positive histopathological chorioamnionitis. CRP level was highly sensitive i.e. (100%) and less specific (45.45%) in identification of histopathological chorioamnionitis.

Table 6: Comparison of CRP determination and other test in the identification of histopathological chorioamnionitis

Test	With histopathological chorioamnionitis		Without histopathological chorioamnionitis		Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Normal	Abnormal	Normal	Abnormal				
CRP (≥6mg/l)	0	44	80	96	100	45.45	31.4	100
Maternal fever	0	28	188	4	100	97.9	87.5	100
WBC>12000	50	20	116	24	25.64	83.09	45.45	67.04
FHR≥160	0	36	178	6	100	96.42	76.92	100

Discussion

Expectant management for preterm labour and preterm premature rupture of membranes is an accepted modality of treatment. 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 commonly used to predict infection are total leucocyte count, differential leucocyte count, urine culture and vaginal culture. These tests are by and large are unreliable. C-reactive protein appears to be the most sensitive acute phase protein; its rise 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 440 patients were studied. The control group consists of 220 antenatal patients of same gestation but without PPROM. Demographic, socioeconomic were comparable between control and study group.

In our study total leucocytes C count (>12000/mm3) was present in 20 patients of study group (10%) whereas CRP was raised (>6 mg/dl) in 140 patients (64%). Mean CRP level for CRP positive patients were 10.39±3.32. All patients who had TLC >12000/mm3, CRP was also raised in those patients. Thus all the patients with leucocytosis (>12000/mm3) had raised CRP level but not all patients with raised CRP level had leucocytosis. Hence that CRP is more reliable indicator in diagnosing chorioamnionitis, than TLC. It has been seen that very high levels of maternal plasma CRP level in early pregnancy was associated with preterm delivery.[10,11] A study found that pregnant women has higher level of CRP > 1 mg /and women were at high risk of preterm delivery is associated with premature uterine contractions.[9] It has also been studied that higher level of CRP in 1st trimester has been associated with preterm delivery.[12] Similar results found in a study that very high levels of maternal plasma CRP in early pregnancy was associated with increased risk of preterm delivery.[13]

On comparing C-reactive protein levels with other laboratory tests and indicators of infection it was found that CRP level are more sensitive identifying clinical chorioamnionitis. These results were in accordance with other studies. For diagnosing the chorioamnionitis gold standard test is histopathological examination of placenta. In this study CRP was raised in all patients with positive histopathological chorioamnionitis. Maternal fever and fetal tachycardia also present in all patients with positive histopathological chorioamnionnitis whereas TLC (>20200/mm3) was raised only in 20 patients. The sensitivity of CRP is 100%, specificity is 45.45%, positive predictive value of CRP 31.4% and negative predictive value of CRP is 100% in detection of histopathological

chorioamnionitis. Our study is also supported by other studies.[1]

Conclusion

It is concluded that CRP is the earliest and most reliable diagnostic marker of clinical as well as histological CAM in patients with PPROM. Pregnancy affects the WBC in a variable fashion. Only CRP determination accurately reflects chorioamnionitis with high sensitivity but it is less specific. If on admission CRP has increased then 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 till maximum possible fetal maturity with monitoring regarding for signs of infection.

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