ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 08 | August - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATION OF CRP AS A PRE-INDICATIVE MARKER IN WOMEN WITH PRETERM LABOUR AND PRETERM PRELABOUR RUPTURE OF MEMBRANE (PPROM)

Obstetrics & Gynaecology

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ABSTRACT

AIMS AND OBJECTIVES: To determine the diagnostic accuracy of C-reactive protein in the detection of chorioamnionitis in women with Preterm labour and PPROM and to test sensitivity/specificity/positive predictive value of CRP in diagnosing chorioamnionitis against gold standard of histopathological examination of placenta.

KEYWORDS

INTRODUCTION:

Preterm delivery is a worldwide public health problem, and it occurs in approximately 6-12% of all pregnancies. Preterm prelabour rupture of membranes (PPROM) is defined as amniotic fluid leakage before 37 weeks of gestation, and it represents approximately 20-40% of all preterm deliveries. Microbial invasion of amniotic cavity (MIAC) is identified in 30-40% of PPROM, particularly at early placental examination in up to 60% of all preterm deliveries.

The management of patients with preterm labour and 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. Potential pathogens largely arise from the ascending route and the endogenous vaginal flora, and may cause chorioamnionitis. Etiology of preterm birth is thought to be multifunctional. Cause factors linked to preterm birth include medical conditions of mother or fetus, genetic influences, environmental exposure, infertility treatments, behavioural and socioeconomic factors and iatrogenic prematurity.

By gestation age, 5% of preterm birth occurs at less than 28 weeks (extreme prematurity), 15% at 28-31 weeks (severe prematurity), 20% at 32-33 weeks (moderate prematurity), 60-70% at 34-36 weeks (late preterm). The incidence of preterm delivery was 5.4% when neither chorioamnionitis nor premature rupture of membranes (PROM) was present, 11.9% when chorioamnionitis was present without PROM, and 56.7% when both chorioamnionitis and PROM were present and suggest that occult antepartum infection of the genital tract is an important cause of preterm delivery.

Preterm labour can be prevented by early and prompt diagnosis of infection. Identification of high-risk pregnancies can be done by various methods including clinical and biochemical markers of preterm delivery, clinical methods are: change in the cervix, uterine contraction and vaginal bleeding and identification of various epidemiological risk factors. Measurement of inflammatory markers can be an alternative method to detect early infection of preterm labour. One of the markers in maternal serum, which indicates an increased risk of preterm delivery, is the C-reactive protein (CRP). CRP is annular (ring shaped) pentameric protein in blood plasma. It has five identical polypeptide chains and is synthesized in the liver. Their main roles are to identify potentially toxic autogenous substances released from damaged tissues, to bound them, and then detoxify them and remove from the blood. C-reactive protein can be used in prediction and as a screening test to detect the risk of premature delivery.

MATERIALS AND METHODS

A prospective study was carried out in Department of Obstetrics & Gynaecology, in collaboration with Department of Pathology and Microbiology, Nalanda Medical College and Hospital, Patna, India for one year from April 2019 March 2020. The study comprises of a total 120 antenatal women, who were admitted in the hospital. 60 cases were of the study group, and 60 of the control group. An informed consent was obtained from the patients.

Study group comprised of 60 pregnant women between >20 week of gestation with singleton pregnancy with preterm labour and or preterm premature rupture of membrane (PPROM) & control group comprised of 60 pregnant women at term >37 weeks to 40 weeks of gestation with singleton pregnancy without any other complication.

Exclusion criteria of study group were pregnancy complications (twin pregnancy, malpresentation, preeclampsia, antepartum, haemorrhage, polyhydramnios, uterine anomalies (cervical incompetence, malfunction of uterus), chronic diseases (hypertension, hepatitis, diabetes) and any medical condition such as rheumatic fever rheumatoid arthritis, LSE, history of recent bacterial or viral infection. A detailed obstetrical and menstrual history was recorded along with local and systemic examination. Obstetrical examination done and signs of chorioamnionitis were specially looked for, example maternal tachycardia, PR> 100 BPM, foetal tachycardia FHR > 160 BPM maternal fever >100. 4°F, uterine tenderness, foul smelling discharge per vaginum. Subjects were evaluated & managed with use of tocolytics, antibiotics and steroid as per hospital protocol.

C-reactive protein estimation was done in each patient of both groups. Blood sample was collected by venepuncture for routine haematological investigation like Hb%, TLC, DLC and C-reactive protein determination. Urine, vaginal swab culture and sensitivity test and routine antenatal investigation (if previously not done) were done. After delivery placenta in 10% formalin was sent to pathology department for histopathological examination with membrane. Chorioamnionitis was identified by the presence of Polymorphonuclear leucocyte infiltration of placental membrane and villi.

RESULTS

Age-wise distribution of patients was compared in the study group and control group. The highest number of cases of preterm labour and PPROM were primigravida (45.83%) and mean gestational age was 33.02 weeks. Leucocytosis (>12000/m_3) was present in 5% cases and vaginal swab culture was present in 5.83% cases of study group. CRP level was raised (>6 mg/dl) in 68.33% in study group and 47.5% in control group. Histopathological chorioamnionitis was present in 20% cases of study group and 5.83% cases in control group (Table 1).

Table I: Characteristics of patients of study group and control group

	Study (n=60)	Control (n=60)
Age (years)	25.33%+3.09%	24.95%+3.29%
Parity (primiparas)	45.83%	55.83%
Leucocytosis	5%	0
Vaginal swap culture	5.83%	0
CRP positive	68.33%	47.5%
Histopathological chorioamnionitis present	20%	5.83%

Table II showed mean CRP level in both groups. In study group mean

CRP level in CRP positive cases (68.33%) were 11.39 mg/dl while in CRP negative cases (31.67%) it was 3.68 mg/dl. In control group mean CRP level in CRP positive cases (47%) was 8.6 while in CRP negative cases it was 3.24mg/dl. Although CRP was raised in both study and control group (8.6 mg/dl) and this difference was statistically significant ($p<0.001$).

Table II: Mean CRP in study and control group

Group	CRP level	Range	Mean
Study Group (n=120)	Positive (>6 mg/dl) n=41 (68.33%)	6.2-18.4	11.39±3.33
	Negative (<6 mg/dl) n=19 (31.67%)	0.8-5.8	3.68±1.84
Control Group (n=120)	Positive (>6 mg/dl) n=28 (47%)	6.2-13	8.60±2.75
	Negative (<6mg/dl) n=32 (52.5%)	0.5-5.4	3.24±1.68

Table III shows mean CRP levels in study group in relation to clinical chorioamnionitis. Among 60 patients of study group. 14.17% patients had features of clinical chorioamnionitis (i.e., maternal fever, tachycardia, leucocytosis and foetal tachycardia uterine tenderness and foul-smelling discharge) with elevated C-reactive protein level (>6mg/L). They had mean CRP level of 14.16 mg/litre. 32 patients in study group i.e., 54.17% had no evidence of clinical chorioamnionitis but they had elevated CRP level with mean CRP level is 9.64mg/L. 19 patients i.e., 31.67% had no evidence of clinical chorioamnionitis and their C-reactive protein levels were also in normal range.

Table III: Mean CRP level in study group in relation to clinical chorioamnionitis

Clinical chorioamnionitis and CRP level	Patients in study group (n=60)			
	n	%	Range of CRP levels	Mean CRP levels
Clinical chorioamnionitis with elevated CRP level	9	14.17	7.4-16.2	14.16±2.96
No clinical chorioamnionitis with elevated CRP level	32	54.17	6.0-18.4	9.64±3.33
Non-clinical chorioamnionitis with normal CRP level	19	31.67	0.8-5.8	2.68±1.84
Total	60	100		

Table IV shows that 12 out of 60 patients with preterm delivery and PPROM showed histopathological chorioamnionitis i.e., neutrophilic infiltration of chorioamnion on their placental examination. They also had elevated CRP value with mean of 14.38 mg/dl. 29 patients i.e., 48.3% had no evidence of histopathological chorioamnionitis with elevated CRP level. 19 patients i.e., 31.67% had no evidence of histopathological chorioamnionitis with normal CRP levels.

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

Diagnostic Group	Patients in study group (n=60)		Range and Mean CRP level in study group (n=120)	
	No.	%	Range	Mean
Histopathological chorioamnionitis with elevated CRP levels	12	20	8.6-16.2	14.38±2.77
No histopathological chorioamnionitis with elevated CRP levels	29	48.3	6.0-18.4	10.39±3.33
No histopathological chorioamnionitis with normal CRP levels	19	31.67	0.8-5.8	2.68±1.84
Histopathological chorioamnionitis with normal CRP levels	--	--	--	--
Total	60	100		

Table V shows sensitivity and specificity of CRP level with different clinical features and laboratory test of chorioamnionitis in cases i.e., fever, maternal tachycardia, foetal tachycardia and total leucocyte counts. It showed that CRP level to be more sensitive (100%) but less specific (36.89%) in identifying clinical chorioamnionitis CRP also had the highest value (100%) but least positive predictive value 20.73% among all parameters.

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

Clinical features	CRP level				sensitivity	specificity	Positive predictive value	Negative predictive value
	With C/F		Without C/F					
	Positive	Negative	Positive	Negative				
Fever (100.4°F	9	0	32	19	100	36.89	20.73	100
Maternal tachycardia >100	5	0	36	19	100	34.23	10.98	100
Fetal tachycardia >160	7	0	35	19	100	35.51	15.85	100
TLC>12000	3	0	38	19	100	35.33	7.32	100

Table VI shows the comparison of C-reactive protein determination and other tests in the identification of histopathologically diagnosed chorioamnionitis. It was found that histopathological chorioamnionitis present in 12 patients in study group and 3 patients in control group. CRP was raised in all patients who had positive histopathological chorioamnionitis where as total leucocyte count (>12000/mm3) was raised only in 3 patients with positive histopathological chorioamnionitis. CRP level was highly sensitive i.e., (100%) and less specific (50%) in identification of histopathological chorioamnionitis.

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

Test	Histopathological CA		Without histopathology		Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Normal	Abnormal	Normal	Abnormal				
CRP	0	12	19	29	100	50	29.27	100
Maternal fever	0	6	51	3	100	95.37	7.59	100
WBC count	0	3	47	1	66.7	94.4	57.14	96.23
FHR	0	6	53	1	100	99.07	92.31	100

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 impeding 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 thousand folds in the initial stages of information. A short half-time of less than 24 hours makes it suitable to serve as marker for diagnosing an infective process in early stage.

In present study, total 120 patients were studied. The control group consists of 60 antenatal patients with full term pregnancy (>37 completed weeks) whereas study group consists of 60 antenatal patients with preterm labour and preterm premature rupture of membrane >20-37 weeks. Demographic, socioeconomic were comparable between control and study group.

In this study, maximum number of patients in study group belongs to 29-34 weeks of gestation.

In this study, CRP level was raised (>6mg/dl) in 41 patients (68.33%). All patients with leucocytosis >12000/mm_3, CRP was raised in those patients. Thus, all the patients with leucocytosis (>12000/mm_3) had raised CRP level but not all patients with raised CRP level had leucocytosis. So that CRP is more reliable indicator in diagnosing chorioamnionitis, than TLC and DLC. On comparing C-reactive protein levels with other laboratory tests and indicators of infection (e.g., total leucocyte count DLC, maternal fever, maternal tachycardia, foetal tachycardia) we found CRP level to be more sensitive (100%) but less specific (36.89%) in identifying clinical chorioamnionitis. The positive predictive value was 35.7% and negative predictive value was 100%. As we know that 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 foetal tachycardia also present in all patients with positive histopathological chorioamnionitis whereas TLC (>12000/mm_3) was raised only in 3 patients. The sensitivity of CRP is 100%, specificity is 50%, positive predictive value of CRP 29.27% and negative predictive value of CRP is 100% in detection of histopathological chorioamnionitis.

CONCLUSION

This study showed that many of the traditional laboratory test relied upon to predict the development of chorioamnionitis is unreliable. Pregnancy affects the WBC in a variable fashion. Physiological stress and beta-methasone administration significantly elevate WBC. Only CRP determination accurately reflected chorioamnionitis with high sensitivity but less specificity. However, elevated CRP levels correlated better with histopathological evidence of chorioamnionitis than with clinical features.

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