ORIGINAL RESEARCH

Level of C-reactive protein as a predictor for preterm deliveries

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ABSTRACT

Background: CRP measurement is quick, non-invasive, and risk-free that can be a useful diagnostic test for evaluating and categorizing the risk levels and also anticipating the morbidity of both mother and fetus.

Aims: To identify the association between the level of C-Reactive protein (CRP) with preterm deliveries.

Materials and methods: It is Hospital based Prospective Observational study done for a period of 2 Years in 95 pregnant women with gestational age between 24 weeks to 36 weeks+6days, who present to emergency /labor room with regular uterine contractions, at least four in 20 minutes or eight in 60 minutes in presence or absence of cervical changes.Patients were then followed up till 7 days for preterm delivery. Further categorization of subjects was done into 2 groups:Group 1: Those who delivered preterm within 7 days of admission.Group 2: Those who did not deliver within 7 days of admission.

Results: 95 patients with premature uterine contractions were analysed for CRP levels and were followed up to find out if they underwent preterm delivery within 7 days of admission. The mean value of CRP was calculated in the 2 groups and was found to be higher in those who delivered within 7 days with a statistically significant p value 0.001. The curve generated cut off for CRP was ≥3.55 mg/l (AUC 0.809, SE 0.046, P <0.001), indicating a positive association for preterm delivery. With the derived cut off, the sensitivity, specificity, positive predictive value, negative predictive value of CRP for predicting preterm delivery was found to be 80.4 %, 75.5%, 80.7% and 75.2% respectively, with diagnostic accuracy of78.3%.

Conclusions: Prediction of preterm delivery by a simple biomarker like CRP could help in early intervention and subsequentprevention of preterm birth and its sequelae.

Keywords: Preterm labour, C-reactive protein, Premature uterine contractions

INTRODUCTION

Preterm labour (PTL) and delivery are among the most challenging obstetric complications encountered. PTL is the important single determinant of adverse infantoutcome in terms of both survival and quality of life. It complicates about 5- 10% of allpregnancies and about 30% it is due to deliberate medical intervention and in the remainder due to spontaneous PTL. PTL is associated with 75% of all perinatal deaths.[1]Around the world, preterm birth is an important perinatal health problem, and has high economic and social cost in terms of neonatal intensive care, for the families and health-care systems.Globally, prematurity is one of the leading causes of death inchildren under the age of 5 years and contributes to adverse perinatal outcomes. Also,after pneumonia, preterm birth is the second most common cause of

death in childrenless than 5 years.Almost 1 million children, i.e., 1 in 10 babies, die each year due tocomplications of preterm birth.[2]

Neonatal complications of preterm birth may include respiratory distress syndrome, hyaline membrane disease, broncho pulmonary dysplasia, pneumothorax, pneumonia/ sepsis, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, intraventricular haemorrhage, periventricular leukomalacia, unattended births, and perinatal death. Long term morbidities are also associated with preterm births which include learning disabilities due to mental development delay, visual andhearing disabilities and cerebral palsy. In India there are 3 519 100 preterm births every year which counts to 13.0 preterm births per 100 births.[2]This requires a simpleand cost-effective method enough to be introduced to predict preterm labour and preterm delivery so that early intervention can be taken and intensive ante-natal carecan be provided to reduce the perinatal morbidity and mortality.

In most cases, exact cause of PTL is not diagnosed and the aetiology is likely to be multifactorial. Antenatal identification of risk factors for preterm delivery, become important for primary prevention. High risk factors for preterm delivery in antenatal mothers can be predicted by clinical, biophysical and biochemical parameters. Clinicalpredictors are history of prior preterm birth, multiple pregnancy, presence of genital tract infection, symptoms of preterm labour which include pelvic pressure, backache, vaginal discharge or bleeding. Biophysical predictors are uterine contractions, Bishop's score of 4 or more, cervical length of 25 mm or less on transvaginal scan (TVS). Biochemical predictors are fetal fibronectin in cervicovaginal discharge, inflammatory markers in maternal serum like C-reactive protein (CRP), IL-6, IL-8, TNF- α. The association between CRP and pregnancy specific disorders like preeclampsia, preterm premature rupture of membranes (PPROM) has been observed in many studies but its correlation with the risk for preterm delivery is inconclusive.

CRP is one of the markers of inflammation and is an acute phase reactant. A prospective cohort study done by Moghaddam BL, et al. in 2012 concluded that CRP levels > 4 mg/L had statistically significant relationship with preterm premature rupture of membranes (PPROM) and preterm birth.Another study done by Spyros PB, et al.in 2012 concluded that measurement of maternal CRP at 11-13 weeks is unlikely to be useful in screening for spontaneous early preterm delivery.[3]

Very few studies have studied the relationship of CRP in cases of premature uterine contractions (PUCs) and its relation with preterm delivery. An observational study performed by Bayar M. et al, in January 2014 showed that 93 out of 100 women with premature uterine contractions had elevated level of CRP and 91% delivered prematurely while in the control group only 9 out of 100 women had elevated level of CRP and only 8% of them delivered preterm. Differences were statistically highly significant and they concluded that ―CRP can be used as a biomarker in prediction of premature delivery when it is associated with premature uterine contractions (PUCs).[4]

Therefore, in patients having PUCs, preterm labour should be arrested to prevent preterm delivery. Various methods advocated are bed rest, adequate hydration, antibiotic administration in case of evident infection, prophylactic cervical cerclage in women with short cervix and use of tocolytic agents to inhibit uterine contractions till coverage by antepartum corticosteroid therapy. The most extensively studied regimens of corticosteroid treatment for the prevention of RDS are two doses of betamethasone 12mg given in tramuscularly 24hours apart or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart Betamethasone treatment causes a larger reduction in RDS than dexamethasone.Commonly used tocolytic agents are Nifedipine-30 mg (10mg every 20 min for a total of three doses) followed by 10-20 mg every 6-8 hours , Magnesium sulphate-4 gm bolus followed by 2gm/hour. Another concern in present clinical practice is for unnecessary admissions and treatment for threatened preterm labour which contributes to exploding health

care costs.[5] By using CRP levels and thereby predicting preterm delivery, unnecessary hospital admissions can possibly be minimized. Studies to evaluate the role of CRP in predicting pre term delivery is relatively scarce in this part of the country. Hence the present study was undertaken to look for the level of maternal serum CRP levels for prediction of preterm delivery in those with premature uterine contractions.

MATERIALS AND METHODS

It is Hospital based Prospective Observational study done in CKMH,Warangalfor a period of 2 Years, November 2019 to October 2021 in 95 pregnant women with gestational age between 24 weeks to 36 weeks+6days, who present to emergency /labor room with regular uterine contractions, at least four in 20 minutes or eight in 60 minutes in presence or absence of cervical changes

SAMPLE SIZE ESTIMATION

Sample size was calculated using following formula: $Z\alpha^2 p (1-p)$

$n = e^2$ where $Z\alpha = 1.96$ at 95% Confidence interval

p = 0.56e is allowable error being 10% n = 95

INCLUSION CRITERIA

Pregnant women with singleton pregnancy with regular uterine contractions, at least four in 20 minutes or eight in 60 minutes with presence or absence of cervical changes, Gestational age between 24weeks to 36weeks+6days.

EXCLUSION CRITERIA

Pregnancy associated complications like gestational diabetes mellitus, pregnancy induced hypertension, placental abruption, Intra uterine growth retardation(IUGR) and Oligohydramnios, Systemic chronic illness (respiratory, renal and cardiovascular) 3) Known systemic infections.

This study was conducted on 95 pregnant women, who presented to emergency/ labour room with painful regular uterine contractions at least 4 in 20 minutes or 8 in 60 minutes with presence or absence of cervical changes. Contractions were confirmed clinically and by cardiotocography. Detailed clinical history was taken. General physical and obstetric examination including per speculum examination was done for all patients. The gestational age was calculated from the date of the LMP and confirmed by an ultrasound scan in early pregnancy. The subjects were selected considering inclusion and exclusion criteria. Informed written consent was taken from all patients. Routine antenatal investigations and specific investigations for evaluation of preterm labour like total leucocyte count, urine routine examination and culture- sensitivity, high vaginal swab (HVS) for evidence of vaginal infections, ultrasonography for measurement of AFI were done, as per hospital protocol. Additionally, maternal serum CRP test was performed for all the patients. The management of the preterm labour, including hospitalization and administration of tocolytics, was determined by the attending obstetrician according to the hospital protocol. Monitoring of cases were done and all patients tolerated nifedipine tocolysis. Blood sample for estimation of CRP was collected in a test tube without anticoagulant and allowed to be clotted. The serum was removed from the clot as soon as possible to avoid haemolysis and then the samples were kept frozen until tested by the lab. The level of CRP was measured through a quantitative highly sensitive immunoassay test(Latex Enhanced Immuno-Turbidimetric Assay).

Patients were then followed up till 7 days for preterm delivery. Further categorization of subjects was done into 2 groups:

Group 1: Those who delivered preterm within 7 days of admission.
Group 2: Those who did not deliver within 7 days of admission.

STATISTICAL ANALYSIS

Data obtained was entered in MS Excel initially. All the data analysis was performed using appropriate statistical software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft office was used to prepare the graphs. Chi Square test was used to compare the categorical data. P value of < 0.05 is considered as significant. Cut off value for predicting preterm delivery was assessed using receiver operating curve (ROC).

RESULTS

95 Pregnant women with singleton pregnancy with regular uterine contractions, at least four in 20 minutes or eight in 60 minutes with presence or absence of cervical changes and gestational age between 24weeks to 36weeks+6days were included in the present study
CRP levels were measured among these 95 females and they were followed up to find out if they progressed to delivery within 7 days. Of those, 48.4% (n=46) had a preterm delivery within 7 days while 51.6% (n= 49) did not deliver within 7 days. The baseline characteristics that were taken into account are as follows

Table 1: Distribution of patients according to patient details and time of delivery.

Age in years	**Delivery within 7 days**	**Delivery after 7 days**	**P value**
	N (%)	N (%)	
<20	3 (6.5)	4 (8.2)	0.493
21-25	20 (43.5)	26 (53.1)	
26-30	17 (37.0)	11 (22.4)	
>30	6 (13.0)	8 (16.3)	
Total	46 (100.0)	49 (100.0)	
Parity			
Primigravida	22 (47.8)	24 (49.0)	0.91
Multigravida	24 (52.2)	25 (51.0)	
Period of Gestation (in weeks)			
<28	1 (2.2)	2 (4.1)	0.1117
28-32	5 (10.9)	13 (26.5)	
32-36	40 (87.0)	34 (69.4)	

Majority of patients who delivered preterm were between 21-25 years (n= 20; 43.5%) and 26-30 years (n= 17; 37.0%) (Figure3; Table1). There was no significant statisticaldifference between different age groups; p value was 0.493.
The mean age of patients who delivered within 7 days was found to be 25.59 with a SD of 3.65 years, while that of patients who delivered after 7 days, mean age was 25.16 with a SD of 4.21 years.
The chance of delivering within 7 days, was comparable between primigravida and multigravida, with a non-significant p value of 0.91. 47.8% (n=22) of those who delivered within one week were primigravidae and 52.2% (n=24) were multigravidas (Figure 4; Table 2). Among patients who did not deliver within 1 week, 49.0% (n=24) were primigravidae, whereas 51% (n=25) were multigravida.

Among 46 patients who had preterm delivery within 7 days, majority of the patients, i.e., 87.0% (n=40) were in the late preterm group (Figure 5; Table 3). In the very preterm group, percentage of undelivered within 7 days (26.5%; n=13), is higher than the delivery group (10.9%; n=5). Statistically significant difference was not obtained in-between these 2 groups.

Table-2: Distribution of patients according to history of prior delivery and time of delivery

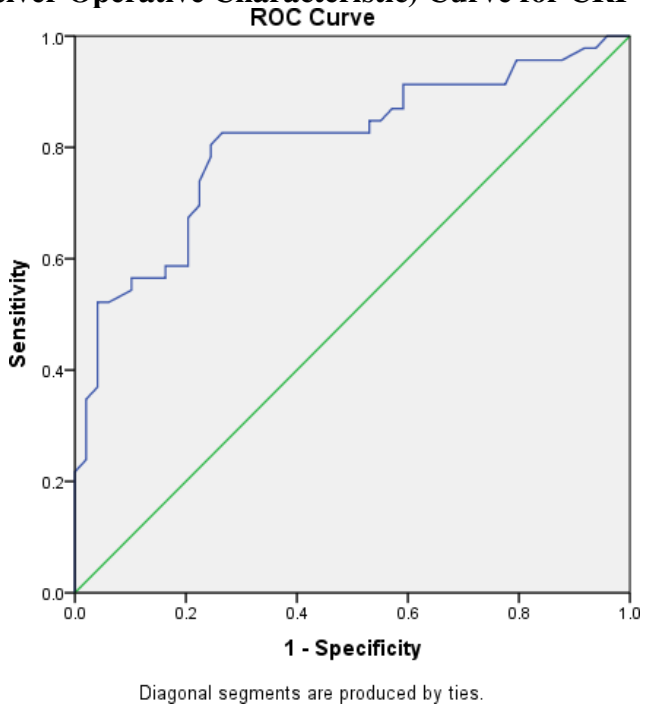
History of prior pre term delivery	Delivery within 7 days	Delivery after 7 days	P value
	N (%)	N (%)	
Yes	10 (21.7)	11 (22.4)	**0.**934
No	36 (78.3)	38 (77.6)	
Total	46 (100.0)	49 (100.0)	
History of tocolytic given	46 (48.4%)	49(51.6%)	0.66
Mean cervical dilatation of Os (in cm)	2.43 (1.28)	0.78 (0.73)	0.0001

Majority of the patients, i.e., 52.4% (n=11 out of 21) did not deliver within 7 days in spite of previous history of preterm delivery and the rest 47.6% (n=10) who had prior history of preterm delivery, delivered within 7 days (Figure 6; Table 4). p value is 0.93 which on evaluation with chi square test, indicates that there was no difference in the outcome between two groups. Tocolysis were given to all the patients among them 48.4%(n=46) were delivered and 51.6%(49) were not delivered. (Figure 7; Table5). Statistically significant difference was not obtained between these 2 groups. Mean cervical dilatation was compared between the two groups and was found to be higher in those who delivered within 7 days (mean 2.43cm) compared to those who did not deliver within 7 days (mean 0.78 cm). Difference was statistically significant with a p value of <0.001

Figure-1: Mean level of CRP in both groups

The mean value of CRP was calculated in the 2 groups and was found to be higher in those who delivered within 7 days, i.e., 7.13 mg/l compared to 2.73 mg/l in those who did not deliver within 7 days, with a statistically significant p value less than 0.001 (table 7).

Figure-2: ROC(Receiver Operative Characteristic) Curve for CRP values



On taking the derived cut-off of CRP as 3.55, the test group has a sensitivity of 80.4 % and specificity of 75.5% for predicting preterm delivery. CRP has a positive predictive value of 80.7% and negative predictive value of 75.2%, with a diagnostic accuracy of 78.3%. To determine the critical values that could predict preterm delivery, ROC curves were constructed for CRP. The curve generated cut-off for CRP was >3.55 (AUC 0.806, SE0.046, P <0.001), indicating an association for preterm delivery.

Table-3: Comparison between two groups with derived CRP cut-off

CRP (Cut off >3.55 mg/dl)	Delivery within 7 days	Delivery after 7 days	Total	P value
≤3.55	9 (19.6)	37 (75.5)	46 (48.4)	<0.001
>3.55	37 (80.4)	12 (24.5)	49 (51.6)	
Total	46 (100.0)	49 (100.0)	95 (100.0)	

On comparison of derived cut-off for CRP (3.55 Mg/l) between the two groups, the difference was statistically highly significant with p value of <0.001. Risk ratio was found to be 3.85 (2.10-7.08).

Table-4: Mean CRP levels at various gestational ages

Period of Gestation	Number of Patients	Mean CRP level (in mg/dl)
<28 weeks	3	2.00 (1.44)
28-32 weeks	18	3.93 (5.17)
32-36 weeks	74	5.21 (5.71)

Mean CRP values was found higher in patients with pre term labour belonging to the gestational age of more than 32 weeks, when compared with ones below 32 weeks.

Table-5: Relationship of tocolysis and mean CRP level in both the groups

Group	Number of Patients	Mean CRP level (in mg/dl)	Standard deviation	P Value
Delivered within 7 days	46	7.139565	7.0987705	<0.01
Delivered after 7 days	43	2.738776	1.8310762	

Significantly higher mean CRP values were observed in delivered group (7.139565 mg/l) than in those who did not deliver within 1 week (2.73 8776 mg/l), indicating marginal refractoriness for tocolysis in those with higher mean CRP levels.

DISCUSSION

There are few researches in the field of CRP to predict preterm delivery in those presenting with premature uterine contractions. Therefore, the results of this study may be of great value for the target population. Our results show that women with premature uterine contractions who had an abnormally high level of CRP were at high risk for preterm delivery within one week.

Among 95 pregnant women in this study who presented with premature uterine contractions, only 48.4% (n=46) of them delivered preterm within seven days and 51.6% (n=49) did not deliver within seven days. However, in a study done by Bayar M. et al. (2014), out of 100 women who presented with premature uterine contractions, 91% (n=91) underwent preterm delivery compared to 9% (n=9) who delivered at term.[4] Lesser number of patients in our study have delivered preterm as they are followed up only till 7 days. In study done by Kavita G. et al. (2016), out of 112 patients with symptoms of preterm labour, 55.3% (n=62) went in preterm labour and 44.64% (n=50)patients delivered at term.[6] Their result is at par with our study. Also, similar observation was done by Jamie B. et al. (2011), where 56.3% of the cohort (N=54 out of 96) delivered preterm.[7]

In the present study, we found out a significant difference in the mean CRP level between the two groups (as depicted in table 7), indicating a positive association between higher level of CRP and preterm delivery. Bayar M. et al. also found a positive correlation with higher mean CRP levels and preterm delivery.[4]Similarly, other studies by Pitiphat et al. (2005), Lohsoonthporn et al. (2007) and Torbe et al. (2004) found a statistically significant association between higher CRP concentrations and subsequent preterm delivery.[8,9]

In our study, the cut-off for CRP which was derived for the risk of preterm delivery in patients with premature uterine contractions is 3.55 mg/l (AUC 0.806). 51.6 % (n=49) patients had significantly elevated level of CRP > 3.55 mg/L. Of these, 80.4% (n=37out of 49) had a preterm delivery, whereas, only 19.6% (n=9 out of 46) delivered preterm even though CRP levels were less. The association thus derived was statistically highly significant with p value < 0.001.

Similarly, in study done by Kavita G. et al, there was a statistical significance between mean CRP value of patients delivered preterm and term (p=0.001) at cut off value 8 mg/L.[6] Bayar M.et al, also found that elevated level of CRP > 1mg/l in association with premature uterine contractions, was a risk factor for preterm delivery.[4]Also, Jamie B. et al. found that maternal serum CRP ≥ 4.34 mg/L was associated with an increased risk of preterm birth.[7] This cut-off is similar to our study. Another study by ZahraS et al. also showed that cut-off CRP level > 3.6 mg/l was a risk for preterm delivery in patients with symptoms of preterm labour.[10] Hvilsom et al. reported a significant association of elevated serum CRP levels >7.6 mg/l with a nearly twofold increased risk of delivery before 37 weeks gestation.[11]

At a cut-off CRP level (≥3.55 mg/l) derived in our study, the sensitivity is 80.4 % and specificity is 75.5%. CRP has positive predictive value of 80.7% and negative predictive value of 75.2% with diagnostic accuracy of 78.3%. In a study done by Bayar M.et al, with CRP level ≥ 1mg/l, sensitivity was 98.9%, specificity 66.7%, positive predictive value 96.8 % and negative predictive value 85.7%.8 Our results have lesser predictive value and diagnostic accuracy as compared to the study of Bayar M et al. where the used CRP cut off was 1mg/1. Similarly, Kavita G. et al found a cut off CRP of 8 mg/L for predicting preterm delivery showing sensitivity, specificity, positive and negative predictive value as 70.9%, 70%, 74.5% and 66% respectively.[6]These results are similar to our present study. Similarly, Zahra S et al. derived a near similar cut-off value of CRP >3.6. However, they had a still lower sensitivity of 41.3% and specificity of 89.3% to predict preterm labour.

We also observed that there is higher delivery rate in moderate to late preterm group (32 to 37 weeks) as compared to extremely and very preterm groups. However, no statistical

significance for preterm delivery was found among them (Table 1). This could be explained by the effect of tocolysis, which could be preferentially given to extremely preterm group.
Another observation was that tocolysis helped in preventing preterm delivery. Since this was a confounding factor, mean CRP levels were analyzed in those who receivedtocolysis. Significantly higher values were observed in delivery group (9.06 +/- 8.39 mg/l) than in those who did not deliver within 1 week (2.80+/- 1.85 mg/l), indicating marginal refractoriness for tocolysis in those with higher CRP levels. This is consistent with the study by Cammu et al. where elevated CRP levels were found to be higher in women who were refractory to tocolysis.[12] They inferred that underlyinginfectious morbidity could be a cause for refractoriness for tocolysis and resulting in preterm delivery.
Zahra S et al. (2014) also found higher CRP level in those who did not show response to the treatment and delivered prematurely.[13] It was also observed that higher cervical dilatation is associated with higher preterm delivery rate. CRP of lower range was found in moderate and late preterm group compared to extremely and very preterm group, with a higher chance of having a preterm delivery in moderate and late preterm group.[6]This is similar to the study of Kavita G et al. who found that with increasing gestational age, even with lower mean CRP value on admission, the chance of preterm delivery is high.

CONCLUSION

Findings of this study demonstrated that the maternal CRP level ≥3.55 mg/L in the absence of any medical/surgical or obstetric complication, can be used as suitable predictive marker for preterm birth with a reasonable diagnostic accuracy. All patients had received tocolysis to help in preventing preterm deliveries.Thisstudy showed that there is refractoriness to tocolysis in patients with higher mean CRP values, resulting in preterm delivery. This study showed that there was a positive association for preterm delivery with high levels of CRP. These observations may help us to avoid unnecessary interventions such as tocolysis, hospitalization, and activity restriction in patients presenting with symptoms of preterm labour. At the same time, prediction of preterm delivery by a simple biomarker like CRP could help in early intervention and subsequentprevention of preterm birth and its sequelae.

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