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A Study of Level of C-reactive Protein in Preterm Labor and Preterm Premature Rupture of Membranes

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Abstract

***Context*:** Preterm delivery is one of the most important causes of perinatal morbidity and mortality. Early detection of infection is most important during the conservative management of patients with preterm labor. CRP is one of the sensitive markers of systemic inflammation and hence, a suitable marker for predicting risk of preterm delivery. This study was thus planned with an aim to establish the association between maternal plasma CRP levels in pregnancy and risk of preterm delivery.

***Aims*:** To study the association between the level of CRP and preterm labor and PPROM.

Methods and Materials: The study included 150 women with singleton pregnancy with gestational age between 28-36+6 weeks who experienced PTL and PPROM. The study was conducted over a period of 24 months from November 2018 – October 2020. Venous blood samples were drawn from these patients and Serum CRP level was estimated.

***Results*:** 103 (68.7%) out of 150 patients enrolled in the study had elevated levels of Serum CRP >/=7 mg/L thus showing a significant statistical relation between S.CRP and PTL, PPROM. The mean S.CRP value being 12.0 ± 5.9 mg/L. The relation between S.CRP and its variation with gestational age was also found to be highly significant, showing the mean value of S.CRP to be highest among gestational age between 28-30 weeks and lowest among 35-36 weeks.

***Conclusions*:** CRP can thus be established as a biochemical marker for prediction of PTL and can be used as a non-invasive screening tool to detect cases that are at risk of PTL and PPROM.

Keywords: C-Reactive protein; Preterm labor; Preterm premature rupture of membranes.

Introduction

Preterm labor is defined by WHO as the onset of labor prior to the completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation.[1,2] The incidence of preterm labor varies from 10 to 15% of all pregnancies.[3]

Preterm Premature Rupture of Membranes (PPROM) is defined asthe spontaneous rupture of membranes before the onset of uterine contractions occuring after 28 weeks and before 37 weeks of gestation.[4]

Preterm labor remains a major management challenge particularly with regard to the respiratory and neurological outcome in infants.[5] Clinical and research experimental evidence indicate that preterm delivery results from amniochorionic-decidual or systemic inflammation.[6]

C-reactive protein (CRP) is one of the sensitive markers of systemic inflammation and is synthesized by liver in response to infection and tissue injury in body[7]. Higher concentrations of CRP have been associated with preterm delivery.[8,9,10] In the past decade elevated levels of CRP measured during gestation have been linked to adverse pregnancy outcomes such as preeclampsia and intrauterine growth restriction.[11] Systemic maternal infections can lead to cervical ripening and premature delivery through inflammatory cytokines and prostaglandin production.[12]

Although medical advances have improved the survival of preterm infants, little success has been attained in understanding and preventing preterm birth. This study was thus planned with an aim to establish prospectively the association between maternal plasma CRP levels in pregnancy and risk of subsequent preterm delivery.

Aim

To study the association between the level of serum C-reactive protein and preterm delivery and Preterm Premature Rupture of Membranes (PPROM).

Methods and Material

The proposed study was conductedover a period of 24 months from November 2018–October 2020 in Department of Obstetrics and Gynecology.

Study design: Descriptive study

***Study period*:** November 2018 – October 2020

Basis of Sample size

For qualitative variable

$$SS = \frac{Z\alpha^2 p(1-p)}{d^2}$$

$Z\alpha^2$ = Stdnormal variable

5% = 1.96

p = Prevalence

d = Absolute error

Eg: Prevalence of CRP >7 in preterm delivery = 70%

Sample size required (min)

$$\frac{3.8416 * 0.7 * 0.3}{0.01} = \frac{0.80674}{0.01} = 81$$

Inclusion criteria

- Women aged atleast 18 years and older with a singleton pregnancy.
- Gestational age between 28 to 37 weeks.
- Regular uterine contractions occurring at a frequency of at least 4 in 20 minutes or 8 in 60 minutes synchronizing with pain.
- Cervical dilatation greater than 1cm with effacement of cervix of more than or equal to 80%.
- Patients of preterm labor with intact or ruptured membranes.

Exclusion criteria

- Patients not willing to give consent for the study.
- Intra-uterine fetal death.
- Women with any medical complications such as hypertension, diabetes mellitus, pre eclampsia, eclampsia, thyroid disorders etc.
- Patients with pyrexia.
- Severe obstetric bleeding; either abruptio placenta or placenta previa.
- IUGR, signs of fetal hypoxia and structural malformations or chromosomal abnormalities of fetus.

Procedure of study

A detailed history was taken from all patients who met our inclusion criteria after informed and written consent. Patient characteristics including age, parity, educational status, social and environmental history, gestational age at admission, booked or unbooked, obstetric history, maternal medical conditions and any treatment taken was noted. General and complete systemic examination was carried out.

Venous blood samples were obtained from all patients to measure serum C-reactive protein concentrations . Samples were collected in a test tube without anticoagulant and allowed to clot. Serum was removed from the clot as soon as possible to avoid

hemolysis and kept frozen until tested by lab. The levels of C-Reactive protein was measured through a quantitative highly sensitive immunoassay test (ELISA). The reference value was 5mg/dl. Thus, high maternal serum c-reactive protein in pregnancies were defined as those in which maternal serum level was above >5 mg/dl.

Determinations

The sample for evaluating CRP was made to react with CRP latex reagent to form a precipitate which was measured turbidimetrically at 340nm.

Based on the data, level of CRP in preterm labour and PPROM was studied.

Statistical Analysis

Statistical analysis was performed by Using the IBM SPSS statistical package (version 22 for Windows) Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann–Whitney U-test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the Chi-square test or Fisher's exact test. For all statistical tests, a P< 0.05 was taken to indicate a significant difference. Microsoft word and excel was used to generate graphs and tables.

Table 1: Demographic Charateristics of Patients.

Variable	Value
Age (Mean age in years)	24.04
Gravidity	
Primi	68
Multi	82
Gestational age in weeks	
28-30	15
31-32	21
33-34	42
35-36	72

Demographic Characteristics of Patients (n=150)

Abbreviations: None

Table 2: Results of the Study.

Variable	Value
PTL	
With PPROM	76
With intact membranes	74
C- Reactive Protein	
≥7	103
<7	47
Mean CRP	
PTL with PPROM	13.0 mg/L
With intact membranes	10.8 mg/L

Abbreviations

- PTL – Preterm Labor
- PPROM – Preterm Premature Rupture Of Membranes
- CRP–C- Reactive Protein

Graph 1: Study Outcome - Serum C- Reactive Protein.

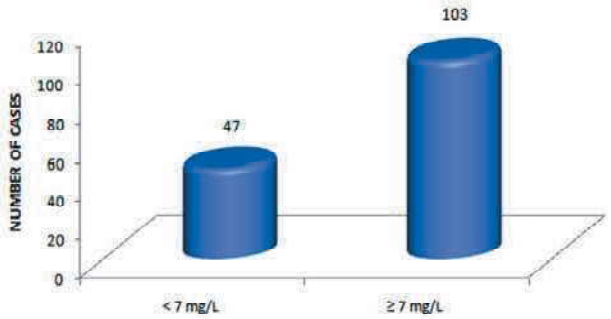
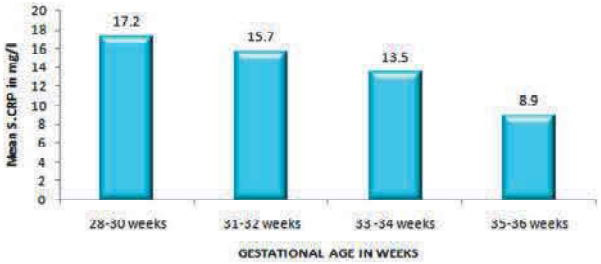
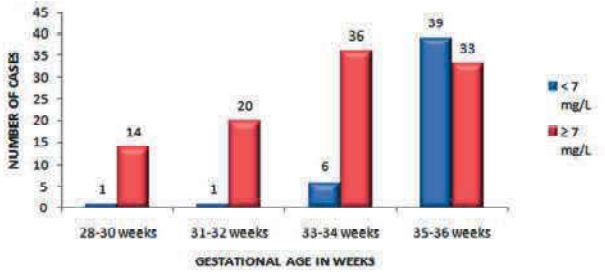


Fig. 2: Results of the Study.

(A) Graph 2A: Mean S.Crp (mg/L) in Different Gestational Age Groups.



(B) Graph 2B: Gestational Age with S.CRP.



Results

The present study was conducted over a period of 24 months from November 2018 to October 2020 on 150 cases who were admitted in the hospitals attached to JJM Medical College (Bapuji Hospital, Chigateri General Hospital, Women and Children Hospital) in Davangere.

These 150 patients fulfilled our study criteria as mentioned earlier. Venous blood samples were drawn from these patients and Serum CRP was estimated using a quantitative highly sensitive immunoassay test (ELISA).

In our study ,majority of women were from age group of 21 – 25 years, and 48% of them belonged to the gestational age of 35-36 weeks, 28% belonged to 33-34 weeks.

103 out of the 150 enrolled pregnant women had elevated levels of Serum C- Reactive Protein (≥ 7 mg/L) thus showing a significant statistical relation between preterm labor and S.CRP levels.

The mean S.CRP value being 12.0 ± 5.9 mg/L. The mean S.CRP value in patients with PPROM was 13.0± 5.8 mg/L and in those with preterm labor with intact membranes was 10.8 ± 5.7 mg/L.

Majority of cases with elevated S.CRP levels were seen among the gestational age group of 33-34 weeks.

The value of S.CRP was found to be highest among women with Gestational age between 28-30 weeks and lowest among gestational age between 35-36 weeks.

Thus in our study the statistical relation between the gestational age and serum levels of C- Reactive Protein was also found to be highly significant.

Thus Measurement of the level of C-reactive protein during pregnancy can be used as a biomarker for detection of subclinical infections that cause preterm uterine contractions.

Discussion

Preterm birth (PTB) is defined as childbirth occurring at less than 37 completed weeks (< 259 days) of gestation.[13] Preterm labor (PTL) is defined as occurrence of regular uterine contractions (4 or more in 20 minutes or 8 our study was intended to learn regarding the relationship or more in 60 minutes) and cervical effacement[14] >1cm in women with intact fetal membranes and gestational age < 37 weeks and after 28 weeks (20 weeks in developed countries).[15] In India, incidence of preterm labor is 23.3% and of preterm delivery varies between 10-69% in different settings. In one study, incidence of preterm labor was 22% and that of preterm deliveries 20.9%.[16]

C-Reactive protein is a sensitive marker of inflammation and tissue injury. In the present decade powered by increasing evidence from large multicenter trials, CRP has now emerged as one of the leading markers for inflammatory activity.

our study was intended to learn regarding the relationship between serum C-reactive protein (CRP) levels in maternal circulation and risk of preterm delivery. Maternal placenta concentrations of CRP aids in diagnosing subclinical infections in pregnant women who experience preterm labor and preterm premature rupture of membranes.

Majority (48%) of pregnant women in our study belonged to the gestational age of 35-36 weeks, 28% belonged to 33-34 weeks and only 10% of them belonged to 28-30 weeks. These findings are in accordance with the study conducted by Purvi K Patel, Dipa S Pitre and Suman P Bhooker.[17]

In the present study 103 out of 150 (68.7%) enrolled pregnant women had elevated levels of Serum C-Reactive Protein (>/7 mg/L) and only 47 (31.3%) of them had normal S.CRP levels. The mean S.CRP value being 12.0 ± 5.9 mg/L. Our study showed a significant statistical relation between preterm labor and S.CRP levels. The mean S.CRP value in patients with preterm labour with ruptured membranes was 13.0 ± 5.8 mg/L and in those with preterm labor with intact membranes was 10.8 ± 5.7 mg/L.

These results correlate with the study done by Tiwari D, Yadav S,[18] which concluded that CRP levels of >7mg/L to be significantly associated with preterm delivery independent of many other determinants of preterm delivery.

Likewise in our study the statistical relation between the gestational age and serum levels of C-Reactive Protein was also found to be highly significant. Majority of cases with elevated S.CRP levels were seen among the gestational age group of 33-34 weeks.

When association of S.CRP levels, and its variation with gestational age was evaluated in our study, the statistical relation was found to be highly significant. The mean value of S.CRP is found to be highest among women with Gestational age between 28-30weeks and lowest among gestational age between 35-36 weeks.

These findings are consistent with a study conducted by Pitiphat *et al*. (2005)[10] on plasma CRP in early pregnancy and preterm labor, in which they found a similar statistically significant association, with odd ratio of 2.55.

Similar results were also found in studies done by Lohsoonthporn *et al*. (2007)[19], Torbe A, Czajka et al. (2004)[20] and Dodds WG, Lams JD.[21]

Conclusion

In our study, a strong positive association between maternal Serum CRP "a sensitive biomarker" with preterm labor and PPROM was found.

To conclude we found that CRP levels of more than 7 mg/l was significantly associated with preterm

labor and PPROM independent of many other determinants of preterm delivery.

These results are consistent with the hypothesis that chronic low-grade inflammation may raise CRP levels and cause preterm delivery.

CRP can thus be established as a biochemical marker and a non-invasive screening tool associated with preterm labor and this valuable tool can guide in designing the most effective targeted intervention strategies aimed at women at risk for preterm birth.

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I, Dinesh Kumar Kashyap, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/-

(Dinesh Kumar Kashyap)