Original Article

C- reactive protein levels in women with prelabour rupture of membrane and women with normal labour

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Abstract

Background: There is a very little information known about CRP in term pregnancies. It is a marker that is easily tested and is inexpensive. Although CRP has been used very effectively in diagnosing infection in the neonate, its clinical use and values have not been studied in term pregnancies. The level of CRP that is truly normal or clinically innocuous is not known. **Objectives:** This is a cross-sectional study to compare the CRP levels in antenatal women with PROM and women with normal labor and assess its utility to predict sepsis. **Methods:** This is a prospective study done over a period of one year and approved by the insititutional ethical committee (IRB. Min. No 11102[OBSERVE] dated 10.01.2018). Sample for CRP was collected from 112 antenatal women with prelabor rupture of membranes within 12 hours of admission (Group A) and from 112 antenatal women in spontaneous labor without rupture of membrane (Group B). CRP samples are processed by nephelometry method. **Results:** The median CRP value in Group A is 9.15 and Group B is 7.26, with no statistical difference. Chorioamnionitis, neonatal sepsis, and endometritis were similar in both the groups. **Conclusion:** CRP cannot be used as predictor for chorioamnionitis, endometritis, and neonatal sepsis. There was no significant difference in CRP levels between the two groups.

Keywords: CRP, infection, pregnancy, rupture of membranes

Introduction

C-reactive protein CRP is an acute phase reactant produced by hepatocytes in response to infection, trauma, chronic disorders, and malignancy[1]. The plasma half-life of CRP is 19 hours.[2] CRP levels are elevated even in the absence of clinical symptoms, and thus, it can be potentially used as a biochemical marker for subclinical infections.[3] Although CRP is a potential marker of infection in non-pregnant women, it is often found to be elevated in uncomplicated pregnancies,[4] i.e., even in the absence of infection.

The prelabor rupture of membrane (PROM) can lead to puerperal infection and neonatal and fetal infections.[3] PROM has multifactorial etiological causes of which infection with Group B streptococcus (GBS) is the most common. The incidence of women colonized by GBS is around 7.6% in South India.[5] GBS is also known to cause early-onset neonatal sepsis.[6] Another predisposing cause for PROM is chorioamnionitis which occurs due to the invasion of microorganisms through the genital tract. Intraamniotic infection risk is 15–35% following preterm PROM, and the risk of postpartum infection is about 15–25%.[7]

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Endometritis and postpartum wound infections are also common with PROM, and so it is reasonable to say that women with PROM are more likely to have a subclinical infection. Though very little information is known about CRP in term pregnancies, it can be a promising marker that could be useful in clinical practice as it is easy to measure the levels and is relatively inexpensive. Although CRP has been used very effectively in diagnosing infection in the neonate, its clinical use and levels have not been studied in term pregnancies and is not well established. The level of CRP that is truly normal or clinically innocuous is not known. Several practitioners currently make clinical decisions based on CRP levels. This practice is perhaps extrapolated from its use in diagnosis of sepsis in non-pregnant women. There is a need to know its reliability in diagnosing sepsis in pregnancy to avoid unnecessary intervention based on the CRP values. Infection is one of the important causes for prelabor rupture of membranes.

Therefore, we compared the levels of CRP in women with PROM with levels in women with normal spontaneous onset of labor. We also studied the correlation of CRP levels with chorioamnionitis, neonatal sepsis, and post-partum sepsis.

Methods

This observational cross-sectional study was conducted in the Department of Obstetrics & Gynecology, Christian Medical College and Hospital, Vellore. Tamil Nadu, Labor Ward, between February 2018 and January 2020, after Institutional Ethics Approval (IRB Min No -11102 [OBSERVE] dated 10.01.2018). We included two groups of women at term with a single live fetus in cephalic presentation with no significant risk factors. The first group had rupture of membrane within 12 hrs of admission (Group A), and the second had intact membranes with history of onset of spontaneous labor within 12 hours of admission (Group B). Women who had rupture of membrane or spontaneous labor before 12 hours at admission, preterm pregnancies (less than 37 weeks), multiple pregnancies, significant medical co-morbidities, significant bacterial or viral infection, previous LSCS or women who had induction of labor prior to labor were excluded.

The required sample size to compare CRP levels across the two groups was found to be 112 in each group, with 80% power and 5% level of significance when the anticipated effect size (difference in CRP) was 3 units. The variance in CRP levels was taken from pilot study done on 24 patients.

Thus, 112 women were assigned in each arm. Patient consent was taken, and CRP samples were obtained. Follow-up was done from labor records and progress records of mother. Baby details were extracted from the neonatal progress records and NICU records. CRP sample was processed immediately or stored overnight at 4 degrees centigrade pending testing. Sample was processed within 12 hours. CRP was performed by nephelometry (BN Prospec, Siemens, Marburg, Germany) using the hs-CRP kit (Cardiophase hsCRP, Siemens, Marburg, Germany) as per the protocol followed in the Department of Clinical Microbiology (an ISO15189: 2012 accredited laboratory), CMC, Vellore. The results of CRP levels were not available for clinical use.

Results

During the study period, 224 women were enrolled, with 112 women in each group. The women enrolled were within 37 – 40 + 6 weeks GA. High-risk pregnancies like multiple pregnancy, women with GDM, GHTN, preterm (<36 weeks GA), and other risk factors were excluded. The baseline characteristics of both the groups are depicted in Table 1. Table 2 shows overall intra- and postpartum characteristics in both groups.

Mean maternal age was 26 +/- 3.8 years. A large percentage of the women belonged to the middle class. Mean gestational age at the time of admission was 39.4 weeks. Seven women in Group A and four patients in Group B had intrapartum fever more than 100.4 degree (p-value 0.346). Maternal CRP level was similar among both the groups, median (IQR) of Group A was 9.15 (5.09,4.4), and Group B was 7.26 (3.54, 2.85). Endometritis, postnatal fever, UTI, wound infection, and neonatal complications were all similar in both the groups [Table 2].

The median (IQR) CRP levels of Groups A and B are 9.2 (5.1, 14.4) and 7.3 (3.5, 12.9), respectively. The difference of 1.3 (95% CI: -0.27, 2.95) among the two groups is statistically not significant (p-value = 0.200) though there was a slight elevation in Group A [Graph 1a (Box plot].

The receiver observer curve between the groups is depicted in Graph 1b.

The AUC is 0.562 (95% CI: 0.487, 0.638), and the CRP levels do not show a difference between Group A and Group B.

Only 19 women had clinical evidence of infection. They either had postnatal fever, evidence of endometriosis, or wound infection. The baseline description of women with or without infection is summarized in Table 3.

Table 1: Characteristics of Group A (PROM) and Group B (intact membranes)

	Mean (SD)			*P*
	Overall	Group A	Group B	
Age	26 (3.8)	25.9 (4.04)	26.09 (3.57)	0.713
Body mass index	24.7 (4.27)	24.34 (0.9)	25.05 (0.6)	0.212
Socioeconomic status				
Upper	10 (4.5)	2 (1.8)	8 (7.1)	0.152
Middle	210 (93.8)	108 (96.4)	102 (91.1)	
Lower	4 (1.8)	2 (1.8)	2 (1.8)	
GA at admission	39.04	38.98 (0.95)	39.11 (0.88)	0.270
Antenatal fever	11 (4.9)	6 (5.4)	5 (4.5)	0.746
Antibiotics used	7 (3.3)	4 (3.8)	3 (2.8)	0.701
Flu-like symptoms	5 (2.2)	2 (1.8)	3 (2.7)	0.651
Antibiotics used	1 (0.5)	1 (1)	0	

Table 2: Intra- and postpartum characteristics of both groups

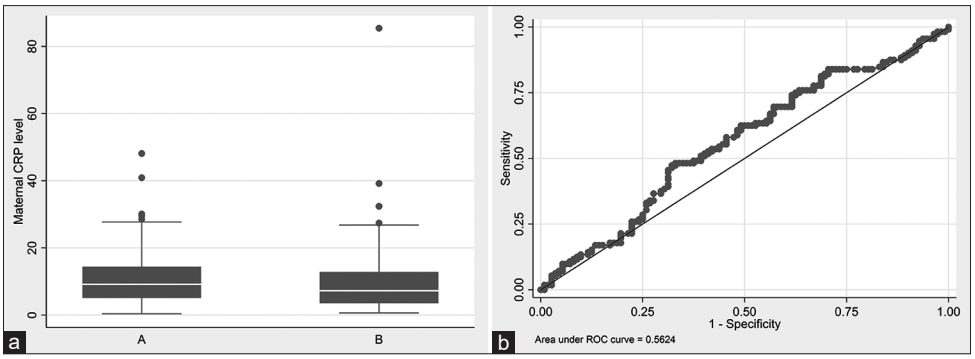
	Overall	Group A	Group B	*P*
Onset of labor				
Induced	60 (26.8)	52 (46.4)	8 (7.1)	<0.001
PGE 1	21 (11)	18 (16.4)	3 (3.7)	
Oxytocin	134 (70.2)	61 (55.5)	73 (90.1)	
Both	36 (18.8)	31 (28.2)	5 (6.2)	
Spontaneous	164 (73.2)	60 (53.6)	104 (92.9)	
Number of PV examinations				
Once	13 (5.9)	2 (1.8)	11 (9.8)	<0.001
Twice	52 (23.4)	17 (15.5)	35 (31.3)	
Thrice	120 (54.1)	63 (57.3)	57 (50.9)	
>thrice	37 (16.7)	28 (25.5)	9 (8)	
Fever >100.4 f	11 (4.9)	7 (6.3)	4 (3.6)	0.346
Intrapartum antibiotics	36 (16.5)	26 (24.1)	10 (9.1)	0.003
Change in the color of liquor during labor	7 (3.2)	6 (5.5)	1 (0.9)	0.055
Mode of delivery				
Normal	134 (59.8)	57 (50.9)	77 (68.8)	0.005
Instrumental	62 (27.7)	34 (30.4)	28 (25)	
LSCS	28 (12.5)	21 (18.8)	7 (6.3)	
Maternal CRP level Median (IQR)	7.79 (4.04, 13.55)	9.15 (5.09, 4.4)	7.26 (3.54, 2.85)	0.200
Postnatal fever	13 (5.8)	7 (6.3)	6 (5.4)	0.762
Endometritis	5 (26.3)	4 (44.4)	1 (10)	
UTI	2 (10.5)	1 (11.1)	1 (10)	
Wound infection	5 (26.3)	0 (0)	5 (50)	
Other	5 (26.3)	3 (33.3)	2 (20)	
Endometritis & UTI	1 (5.3)	0 (0)	1 (10)	
UTI & wound infection	1 (5.3)	1 (11.1)	0 (0)	
Postpartum antibiotics	14 (6.4)	8 (7.2)	6 (5.6)	0.617
Neonatal nursery admission	7 (3.2)	3 (2.7)	4 (3.6)	0.701
Neonatal antibiotic usage	25 (11.2)	19 (17)	6 (5.4)	<0.001

Table 3: Baseline characteristics of women with and without clinical infection

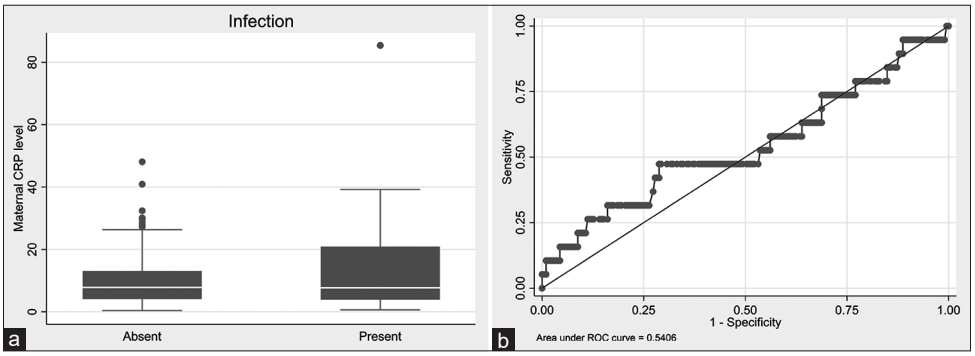
Variables	Overall *n*=224	Infection Absent *n*=205	Infection Present *n*=19	*P*
History				
Antenatal fever	11 (4.9)	11 (5.4)	0 (0.0)	0.299
Antibiotics used	7 (3.3)	6 (3.1)	1 (5.6)	0.576
Flu-like symptom	5 (2.2)	5 (2.4)	0 (0.0)	0.491
Fever >100f	11 (4.9)	9 (4.4)	2 (10.5)	0.239
Number of PV examination				
>3 times	37 (16.7)	33 (16.3)	4 (21.1)	0.843
Onset of labor				
Induced	60 (26.8)	57 (27.8)	3 (15.8)	0.258
PGE1	21 (11.0)	21 (12.1)	0 (0.0)	
Oxytocin use	134 (70.2)	120 (69.4)	14 (77.8)	
Intrapartum antibiotics	36 (16.5)	34 (17.0)	2 (11.1)	0.519
Mode of delivery				
Normal	134 (59.8)	129 (62.9)	5 (26.3)	0.001
Instrumental	62 (27.7)	55 (26.8)	7 (36.8)	
LSCS	28 (12.5)	21 (10.2)	7 (36.8)	
Postpartum				
Postpartum antibiotics	14 (6.4)	1 (0.5)	13 (76.5)	<0.001
Neonatal nursery admission	7 (3.2)	5 (2.5)	2 (10.5)	0.054
Neonatal antibiotic usage	25 (11.2)	22 (10.7)	3 (15.8)	0.503

The median (IQR) CRP levels of presence and absence of Infection are 7.7 (3.9, 20.9) and 7.8 (4.1, 13.1), respectively. The difference of -0.97 (95% CI: -5.76, 2.71) among the two groups is statistically not significant (p-value = 0.452) [Refer Graph 2a Box plot].

The receiver observer curve (Refer Graph 2b) for sensitivity and specificity for maternal CRP for predicting infection did not show any significance, in our study. The AUC is 0.5406 (95% CI: 0.384, 0.697), with the CRP levels not showing a difference with the presence or absence of infection.



Graph 1: (a) (Box plot): CRP among Groups A and B. (b) ROC of maternal CRP differentiating the study groups



Graph 2: (a) (Box plot): CRP levels for women with and without infection (b) ROC of maternal CRP differentiating the infected group

Discussion

CRP has been used as an acute-phase reactant in various diseases with good predictive value. It has also been used as a predictor for infection in preterm prelabor rupture of membranes.[8]

This study was done to assess the efficacy of CRP as a marker for infection in women with term prelabor rupture of membranes, and it was compared with women at term in spontaneous labor with intact membranes. The median value of CRP in the study population of 224 women was 7.79 (4.04, 13.55). There was no statistical difference in the levels of CRP between both the groups (p-value 0.20). In contrast, a study done in Poland showed significantly higher CRP levels in those who delivered vaginally in case of ruptured membranes than women with intact membranes.[9]

Women who had PROM had a higher incidence of cesarean section and endometritis with no difference in risk of neonatal sepsis or nursery admissions when compared to the group of women with intact membranes at the time of recruitment. However, these results did not show any statistical differences. Moreover, in women with clinical chorioamnionitis, CRP levels were found to be lesser than in those without chorioamnionitis.

Studies have compared CRP in women with elective caesearean sections and emergency caesearean sections. They found significantly higher levels of CRP among the women who underwent emergency LSCS.[10]

Furthermore, study done in pregnant women over 37 weeks with PROM or prolonged labor showed higher CRP levels in prolonged labor.[11]

A retrospective study conducted by Smith EJ *et al.*[12] in 2012 showed similar results, where CRP levels were not effective independent predictors of both clinical and histological chorioamnionitis, and neither was sequential testing statistically significant, to detect clinical or histological chorioamnionitis in women with preterm PROM.

A meta-analysis done by RD Trochez-Martinez showed that out of eight studies that were included, only three studies proved CRP as a good predictor for chorioamnionitis. In these three studies, serial monitoring of CRP was done.[13]

Serial monitoring of CRP may not be a feasible option in clinical practice as it would pose an unnecessary burden on the existing health system without much benefit to the patient who would often be managed by prophylactic antibiotics following 18 hours of rupture of membranes.

Conclusions

Women with PROM have slightly higher incidence of intrapartum infections and postpartum infections as compared to women with intact membranes in labor. Our study has shown that baseline CRP value in women with PROM is not significantly higher than in women with intact membranes. Although C-reactive protein is commonly used to identify infection in both adults and

children, its application in clinical practice during a pregnancy is questionable as it is known to be elevated in normal as well as abnormal pregnancies.

Limitations

The incidence of neonatal infections was not assessed. Relationship between CRP values and neonatal outcome is therefore unclear.

Author contributions

Dr. Susan Blossia, Dr. Richa Sasmita Tirkey, Dr. Beena Kingsbury, Dr. Hilda Yenuberi, Dr. John Jude, Dr. Santosh Benjamin, Dr. Jiji Elizabeth Mathews, and Dr. Swati Rathore were involved in the design, planning, conduct, and manuscript writing. Mrs. Gowri Mahasampath was involved in the data analysis and manuscript writing.

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Conflicts of interest

There are no conflicts of interest.

References

1. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
2. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. J Clin Invest 2003;111:1805-12.
3. Predictive value of procalcitonin or c-reactive protein for subclinical intrauterine infection in patients with premature rupture of membranes (PROM).-PubMed-NCBI. [Last accessed on 2019 Sep 10].
4. Szpakowski M, Nowak M, Oszukowski P, Wieczorek A, Skotnicka A. [C-reactive protein in normal pregnancy]. Ginekol Pol 1996;67:17-20.
5. Santhanam S, Jose R, Sahni RD, Thomas N, Beck MM. Prevalence of group B Streptococcal colonization among pregnant women and neonates in a tertiary hospital in India. J Turk Ger Gynecol Assoc 2017;18:181-4.
6. Heath PT, Jardine LA. Neonatal infections: Group B streptococcus. BMJ Clin Evid 2014;2014:0323.
7. Prelabor rupture of membranes: ACOG practice bulletin, Number 217. Obstet Gynecol 2020;135:e80-97.
8. Ronzoni S, Boucoiran I, Yudin MH, Coolen J, Pylypjuk C, Melamed N, *et al.* Guideline No. 430: Diagnosis and management of preterm prelabour rupture of membranes. J Obstet Gynaecol Can 2022;44:1193-208.e1
9. Joanna L, Aleksandra R, Dorota T, Andrzej T. Evaluation of C-reactive protein (CRP) plasma concentration among women during labour and in early puerperium. J Educ Health Sport 2018;8:569-79.
10. Marchocki Z, Vinturache A, Collins K, O' Reilly P, O'Donoghue K. Amniotic fluid C-reactive protein as a predictor of infection in caesarean section: A feasibility study. Sci Rep 2018;8:6372.
11. Fony NM, Nontji W. The difference between C-reactive protein (CRP) level in mother with preterm rupture membranes (PROM) and mothers with prolonged labor. Enfermería Clínica 2020;30(Suppl 2):10-3
12. Smith EJ, Muller CL, Sartorius JA, White DR, Maslow AS. C-reactive protein as a predictor of chorioamnionitis. J Am Osteopath Assoc 2012;112:660-4.
13. Trochez-Martinez RD, Smith P, Lamont RF. Use of C-reactive protein as a predictor of chorioamnionitis in preterm prelabour rupture of membranes: A systematic review. BJOG 2007;114:796-801.