Original Article

Study of Association of C-Reactive Protein with Maternal Chorioamnionitis and Early-Onset Neonatal Sepsis in Premature Rupture of Membranes Deliveries: A Diagnostic Dilemma

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Abstract

Introduction: Term prelabor rupture of membranes and preterm premature rupture of membranes (PROM), both pose significant risk to the mother and the fetus. Early identification of sepsis is essential as the mother has risk of chorioamnionitis and neonate is at the risk of early-onset sepsis. **Aim:** To evaluate the diagnostic value of positive maternal C-reactive protein (CRP) in association with maternal clinical chorioamnionitis and early-onset neonatal sepsis (EONS) in PROM deliveries after 28 weeks of gestation. **Methodology:** The study was conducted at People's College of Medical Science and Research Centre, Bhopal, from June 1, 2017, to May 31, 2018. Maternal serum CRP test was correlated to the signs of maternal chorioamnionitis and signs of EONS within 72 h of life. **Results:** The maternal CRP test was compared to clinical signs of chorioamnionitis. Sensitivity of CRP for diagnosing maternal chorioamnionitis was 48% (95% confidence interval [CI] −35.99–61.12), specificity was 81 (95% CI 71.55%–88.98%), and odds ratio of maternal chorioamnionitis was 4.1176 (95% CI 1.99–8.51) with $P < 0.0001$. Sensitivity of positive maternal CRP in diagnosing EONS was 56.67% (95% CI 43.24%–69.41%), specificity was 84.78% (95% CI 75.79%–91.42%), and odds ratio of neonatal sepsis in maternal CRP positive was 7.28 (95%CI 3.39–15.64) with $P < 0.0001$. **Conclusion:** Our study suggests that in PROM deliveries, if maternal CRP test is positive, then it indicates early delivery and neonate screening for EONS.

Keywords: *Early-onset neonatal sepsis, maternal chorioamnionitis, premature rupture of membranes*

Introduction

Spontaneous rupture of membranes at any time beyond 28 weeks of pregnancy but before the onset of labor is called premature rupture of membranes (PROM). Term prelabor rupture of membranes is the condition where the bag of membranes ruptures before the onset of labor. This poses significant risk to the mother and the fetus. Preterm PROM is one of the important causes of preterm birth where prematurity in addition to PROM can predispose to high perinatal morbidity and mortality along with maternal morbidity.[1] Early identification of sepsis is essential. The duration of leaking, 3 or more vaginal examinations after the rupture of membrane, is a significant risk factor for neonatal sepsis.[2-4]

The mother has the risk of chorioamnionitis and puerperal sepsis, and the neonate is at the risk of early-onset sepsis. The morbidity increases as there are more chances of operative delivery. Early diagnosis of chorioamnionitis and neonatal sepsis can reduce maternal and neonatal morbidity.[5]

C-reactive protein (CRP) is a serum protein which is synthesized in liver. Its rate of synthesis and secretion increases many times within few hours of injury or onset of inflammation and may reach up to 20 times. CRP is a blood test marker for inflammation in the body.[3,6] The present study was undertaken to evaluate the diagnostic value of positive maternal CRP in association with maternal clinical chorioamnionitis and early-onset neonatal sepsis (EONS) in PROM deliveries after 28 weeks of gestation.

Methodology

The study was conducted at the Department of Obstetrics and Gynecology, People's College of Medical Science and Research Centre, Bhopal, from June 1, 2017, to

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May 31, 2018. All pregnant women admitted to labor room with PROM having 28 weeks and above gestational age were included in the study. PROM was confirmed clinically by per speculum examination. Maternal serum CRP test was done in all the cases included in the study using RHELAX CRP reagent standardized to detect CRP concentration >0.6 mg/dl. This limit is traceable to the WHO International Reference Standard for Human CRP. Duration of leaking in hours was noted. If any signs of maternal chorioamnionitis such as fever (temperature >38°C), tachycardia (pulse >100/min), raised white blood cell (WBC) counts (>15,000/m^3), uterine tenderness, and foul smelling liquor if present were recorded, any two of these present were labeled as positive signs for maternal chorioamnionitis. Patients were followed till delivery. The neonates were observed for signs of EONS within the 72 h of life.[7-9]

The clinical signs of sepsis as per the International Pediatric Sepsis Consensus were considered as reference which included heart rate 100–180/min, respiratory rate >50 breaths/min, systolic blood pressure <65 mm of Hg. The tests done which suggested sepsis are raised WBC counts (>25 × 10^3), absolute neutrophil count positive, low platelet counts, CRP >1.2 mg/L, and positive blood culture positive. Cases having medical conditions such as chronic inflammatory disease, systemic lupus erythematosus, gastroenteric disease such as Crohn's disease, rheumatoid disease, and coronary artery disease where CRP can be positive and interfere with the diagnosis were excluded from the study.

Results

The total number of PROM deliveries during the study period was 152 out of total 747 (20.3%). Among them, 43.42% women developed maternal chorioamnionitis.

The maternal CRP test positive were compared to clinical signs of chorioamnionitis. True-positive cases were 32, true-negative cases were 70, false-negative cases were 34, false positive were 16 cases [Figure 1]. Sensitivity of CRP for diagnosing maternal chorioamnionitis was 48.48% (95% confidence interval [CI] −35.99–61.12), specificity 81.4% (95% CI 71.55–88.98); positive predictive value (PPV) 66.67% (95% CI 54.63%–76.86%); negative predictive value (NPV) 67.31% (95% CI 61.47%–72.65%); positive likelihood ratio 2.61 (95% CI 1.57–4.33); negative likelihood ratio 0.63 (95% CI 0.49–0.82); accuracy 67.11% (95% CI 59.03%–74.50%); and odds of having maternal chorioamnionitis in positive CRP group in comparison to CRP negative group was 4.1176 (95% CI 1.99–8.51) with *Z* statistics 3.817 significance level, $P < 0.0001$ [Table 1].

The prior probability (odds) was calculated as 43% (0.8) for maternal chorioamnionitis and 39% (0.7) for EONS [Figure 2].

Among all the 152 PROM mothers, 39.47% (60) of neonates developed early-onset sepsis. The maternal

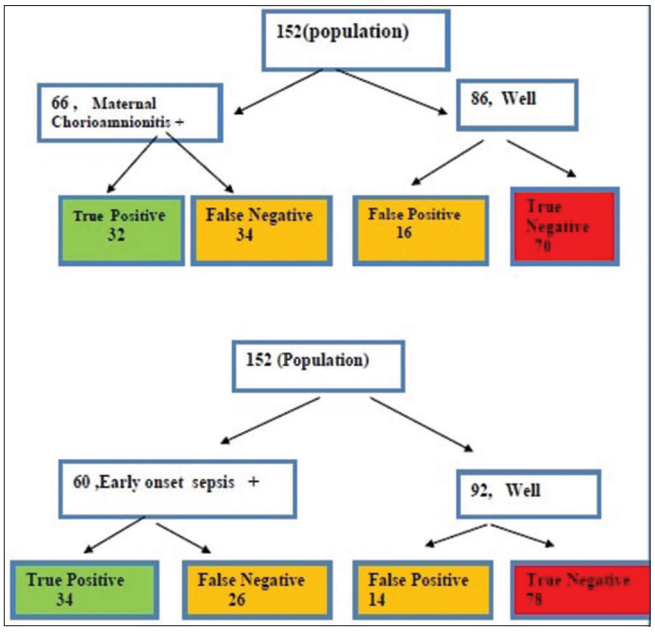

Figure 1: Population distribution of maternal C-reactive protein status, clinical chorioamnionitis, and early-onset neonatal sepsis

CRP positive test was compared to EONS. True-positive cases were 34, true-negative cases were 78, false negative 26, false-positive cases were 14 [Table 2]. Sensitivity of maternal CRP status in diagnosing EONS was 56.67% (95% CI 43.24%–69.41%), test specificity 84.78% (95% CI 75.79%–91.42%); PPV 70.83% (95% CI −58.82%–80.50%); NPV 75.00% (95% CI −68.92%–80.23%); positive likelihood ratio 3.72 (95% CI 2.19–6.33); and negative likelihood ratio 0.51 (95% CI 0.38–0.69). Test accuracy was calculated as 73.68% (95% CI −65.93%–80.49%. The odds ratio of neonatal sepsis in maternal CRP-positive group as compared to CRP-negative group was 7.28 (95% CI 3.39–15.64) with *Z* statistics 5.09 significance level ($P < 0.0001$). The prior probability (odds) was calculated as 39% (0.7) for EONS [Figure 3].

Maximum deliveries (63.16%) were by vaginal route whereas 36.84% delivered by cesarean section. Maximum cases of PROM delivered within 16 h of leaking 90.13%. Majority of cases were term (>37 weeks) and 13.81% cases were preterm.

Discussion

Jeon *et al*. have done a study in 2014 where they investigated the diagnostic importance of maternal CRP to diagnose EONS.[10]

They reported in their study that "Maternal CRP was quite high in neonatal sepsis group in comparison to control (3.55 ± 2.69 vs. 0.48 ± 0.31 mg/dL, $P = 0.0001$). The cutoff value for maternal CRP was >1.22 mg/dL. They reported a sensitivity of 71% and a specificity of 84% for predicting neonatal sepsis. Group having

Table 1: Maternal C-reactive protein test status and clinical chorioamnionitis

Test	Value	95% CI
Sensitivity	48.48%	35.99-61.12
Specificity	81.4%	71.55-88.98
Disease prevalence	43.42%	35.41-51.69
PPV	66.67%	54.63-76.86
NPV	67.31%	61.47-72.65
Positive likelihood ratio	2.61	1.57-4.33
Negative likelihood ratio	0.63	0.49-0.82
Posterior probability (odds): Positive test	67% (2.0)	55-77 (~1 in 1.5 with positive test are sick)
Posterior probability (odds): Negative test	33% (0.5)	27-39 (~1 in 1.5 with negative test are well)
Accuracy	67.11%	59.03-74.50

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

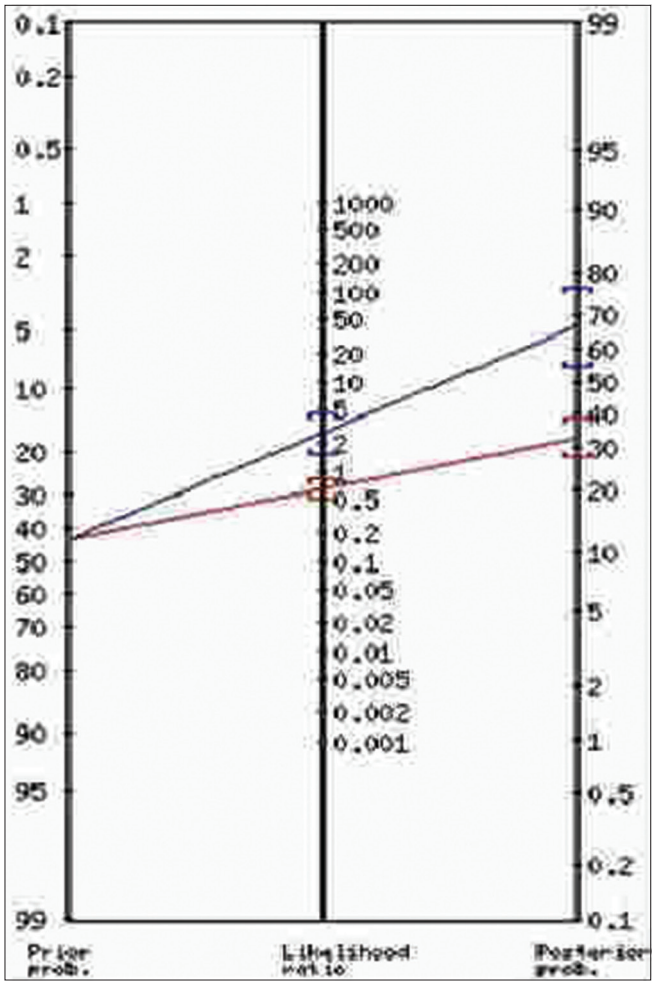

Figure 2: Prior probability (odds) 43% (0.8) maternal chorioamnionitis

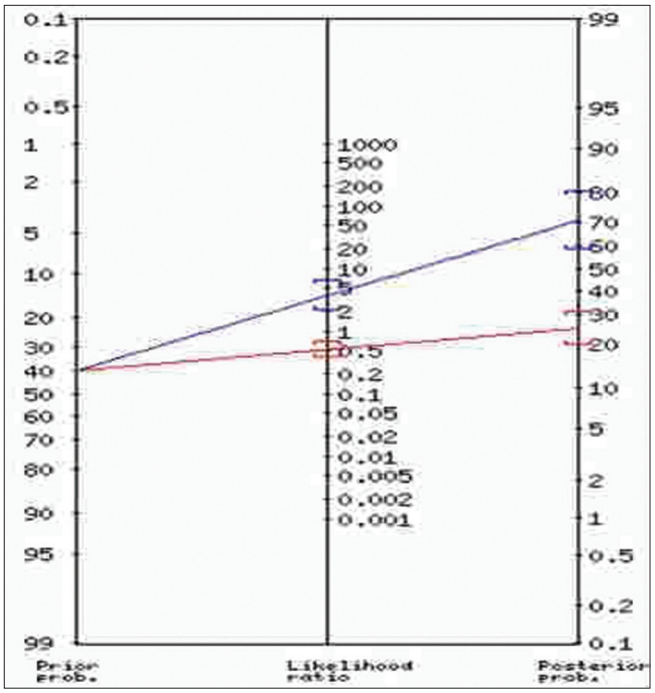

Figure 3: Prior probability (odds) 39% (0.7) in early-onset neonatal sepsis

maternal CRP positive had more neonatal sepsis than CRP-negative group (71% vs. 29%, $P < 0.001$). Odds ratio of neonatal sepsis in maternal CRP-positive group in comparison to CRP-negative group was 10.68 (95% CI: 4.313–26.428, $P < 0.001$).” They concluded that the risk of EONS significantly increased in the case of positive maternal CRP (≥1.22 mg/dL). In newborn of CRP-positive mother, a clinician may be alerted to earlier evaluation for possible neonatal infection before development of sepsis. In our study, the results were comparable to their results. Maternal CRP-positive accuracy was 73.68% for EONS. The odds ratio of neonatal sepsis in maternal CRP-positive group as compared CRP-negative group was 7.28 (95% CI 3.39–15.64, $P < 0.0001$).

Mehrotra reported a study in 2017 to determine the usefulness of CRP for evaluation of neonatal sepsis in tertiary care hospital.[11] He studied on 50 neonates and reported that 34 (68%) had positive CRP while 31 (62%) had positive blood culture. The sensitivity, specificity, PPV, and NPV of CRP were 90.32%, 42.10%, 71.79%, and 72.72%, respectively. He reported that qualitative method of estimating CRP which is cheap and rapid has moderate sensitivity. In our study, sensitivity (56.67%) was comparatively low and specificity was high (84.78%) while PPV (70.83%) and NPV (75%) were comparable to their results.

Table 2: Maternal C-reactive protein test status and early-onset neonatal sepsis

Test	Value	95% CI
Sensitivity	56.67%	43.24-69.41
Specificity	84.78%	75.79-91.42
Disease prevalence	39.47%	31.65-47.72
PPV	70.83%	58.82-80.50
NPV	75.00%	68.92-80.23
Positive likelihood ratio	3.72	2.19-6.33
Negative likelihood ratio	0.51	0.38-0.69
Posterior probability (odds): Positive test	71% (2.4)	59-81 (~1 in 1.4 with positive test are sick)
Posterior probability (odds): Negative test	25% (0.5)	20-31 (~1 in 1.3 with negative test are well)
Accuracy	73.68%	65.93-80.49

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

Lee *et al*. reported a study maternal serum CRP in predicting funisitis and EONS in women with preterm labor or preterm PROM.[12] They reported in their study that "sensitivity, specificity, PPV, and NPV of an elevated serum CRP level (≥8 mg/L) were 74.1%, 67.5%, 32.8%, and 92.4% for funisitis and 67.7%, 63.3%, 17.2%, and 94.6% for EONS, respectively. They concluded in their study that the maternal serum CRP level obtained up to 72 h before delivery is a good predictor of funisitis and EONS in women with preterm labor or preterm PROM. A low serum CRP level (<8 mg/L) has good NPV in excluding funisitis and EONS and may therefore be used as a noninvasive adjunct to clinical judgment to identify low-risk patients."

El-Mashad *et al*. reported in 2017 evaluated the value of CRP, interleukin (IL)-6, and IL-8 as early diagnostic biomarkers for ENOS.[5] Their results showed that "in the study group, 50% had positive cultures, while there were only 10% in the control group with $P = 0.001$. The sensitivity, specificity, PPV, and NPV for CRP were 88.6, 84.7, 86.9, and 90.4%; for IL-6 were 92.4, 97.6, 90.4, and 86.6%; and for IL-8 were 90.8, 88.9, 92.4, and 91.7%, respectively. The best sensitivity and NPV were for IL-6. They reported that IL-6 and IL-8 have great superiority than CRP when combined with other hematological markers. IL-6 was better diagnostic biomarker for ENOS than IL-8 and CRP." The IL-6 and IL-8 though improved the results were neither feasible nor cost effective at our setting.

Surayapalem *et al*. in 2017 reported 200 cases having spontaneous PROM of gestational age >37 weeks.[13] In their study, "PROM was common in age group of 20–24 years (35%) with mean age of 22.6 years and standard deviation of 2.8 years and was common in primigravida. In their study, majority of women were admitted within 6 h of PROM (41.5%) and mean duration of induction to delivery interval was 12.9 h. The mean duration between PROM to delivery in their study was 20.2 h which was statistically significant. Cesarean sections were more among primigravidas. Failure to progress was the common indication. Maternal morbidity was significant (17.5%). No maternal mortality was reported in their study. Perinatal mortality was 1.5%. Birth asphyxia was the most common cause. Perinatal morbidity was seen in 26%. *Escherichia coli* was the common organism found in cervical swab culture." In our study, 90.13% cases delivered in <16 h. Majority (63.16%) delivered by vaginal route and 36.84% required cesarean section. Our study also had no maternal and neonatal mortality.

Jaiswal *et al*. reported rate of maternal morbidity of 26%, with clinical chorioamnionitis in 11.9% followed by febrile illness in 10.5%.[14] In their study, perinatal morbidity reported was 30%. They diagnosed early-onset neonatal infection (EONI) clinically and reported that it was the most common cause for perinatal morbidity in their study which they noticed in 23.8% of cases (50 out of 210). They observed perinatal mortality in 1.43% (3 out of 210).

In our study, 43.42% (66) women developed maternal chorioamnionitis, 39.47% (60) neonates developed early-onset sepsis, and both maternal and neonatal sepsis were high in our study.

Khade and Bava[15] in their study reported maternal morbidity as 16% and perinatal morbidity as 33%. The most common causes were hyperbilirubinemia (23%) and respiratory distress syndrome (RDS) (21%). Perinatal mortality occurred in 15%. It was mainly due to RDS (53%). 25% neonates were delivered by cesarean. The most common indication for cesarean was malpresentation (36%) followed by fetal distress (24%).

Sharma and Dey reported in 2017 that the incidence of rupture of membrane in their study was 4.2%.[16] They reported that 92% of patients delivered within 24 h of rupture of membrane and 18% of them required cesarean section. Five neonates had RDS and one neonate had sepsis. They reported the induction of labor and delivery within 24 h of rupture of membranes associated with low incidence of maternal and neonatal adverse outcome.

Rewatkar *et al*. reported in their study that maternal serum CRP level and WBC count obtained at admission are predictors of chorioamnionitis and EONI although WBC

count alone is not a good indicator of them.[17] They reported that lowest best cutoff of serum CRP level >4.9 mg/l and lowest cutoff of WBC count 12,450/cumm have good predictive values for maternal chorioamnionitis and EONI. They proposed that maternal serum CRP level and WBC count should be used as screening test for EONI and chorioamnionitis rather than a diagnostic test.

Recommendations from the American College of Obstetrics and Gynecologists 2016 guidelines[4] suggests 7 days treatment of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin where expectant management is being done.

Conclusion

The odds ratio of maternal chorioamnionitis in positive CRP group is 4.1176 (95% CI 1.99–8.51) with $P < 0.0001$. The odds ratio of neonatal sepsis in maternal CRP positive group was 7.28 (95% CI 3.39–15.64) with Z statistics 5.09 significance level ($P < 0.0001$).

Both results suggest that in PROM deliveries, if maternal CRP test is done and if positive, it can indicate the need of early delivery and also neonate should be screened for EONS.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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