

MATERNAL C-REACTIVE PROTEIN IN PREGNANCY AND ITS RELATION WITH EARLY ONSET NEONATAL SEPSIS

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ABSTRACT

Objective: To determine association of early-onset neonatal sepsis in newborns of serum C-reactive protein positive mothers.

Study Design: Cross sectional analytical study.

Place and Duration of Study: Pediatrics department, Combined Military Hospital Quetta, from Sep 2016 to Mar 2018.

Methodology: A total of 105 neonates (both gender) of all mothers who were C-reactive protein positive were enrolled in this study using inclusion and exclusion criteria. Neonatal sepsis was diagnosed by clinical examination, which was carried out by senior pediatrician, blood complete picture and C-reactive protein. Neonates were treated as per departmental protocol.

Results: Out of total 105 patients, 46 (44%) were male and 59 (56%) were female neonates. Amongst the babies of 105 C-reactive protein positive mothers, 79 babies were having signs and symptoms of neonatal sepsis and 26 babies were having no signs and symptoms of neonatal sepsis with statistically significant relation between maternal C-reactive protein and neonatal sepsis of p -value <0.05 .

Conclusion: Increased maternal C-reactive protein level is associated with increased risk of neonatal sepsis. Maternal C-reactive protein may be used as a good screening tool for early detection of neonatal sepsis.

Keywords: C-reactive protein, Low birth weight, neonatal mortality, Neonatal sepsis, Pre term babies.

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INTRODUCTION

Neonatal sepsis is defined as systemic infection which occurs in newborn less or equal to four weeks of age. Based on age of onset early neonatal sepsis has been defined as bacterial meningitis or bacteremia in term infant <7 days or ≤ 3 days in newborn admitted in NICU. Early onset neonatal sepsis may also be caused by fungal or viral infection and need to be differentiated from bacterial infection¹. According to UNICEF report each year about 3 million neonates die globally with a world-wide neonatal mortality rate of about 4/1000 live births². About 1.4 million neonatal deaths are caused by neonatal sepsis. The burden of neonatal sepsis varies by geographical areas and neonatal and maternal risk factors. The use of intra partum antibiotics has reduced the incidence of neonatal sepsis^{3,4}. Fetal factors contributing to EONS include low birth weight, prematurity, instrument assisted delivery and congenital anomalies⁵. Maternal factors contributing to EONS include premature rupture of membranes, meconium stained amniotic fluids, multiple digital vaginal examinations and spontaneous onset of labour⁶.

Diagnosis of congenital infection is desirable for prompt treatment and to prevent long term disability of newborns with neonatal sepsis. Different modalities

have been introduced for congenital infection diagnosis but most of them are invasive including amniocentesis for amniotic fluids cytokines and white blood cell counts⁷. Maternal IL-6 has been shown to be good predictor of EONS. IL-6 is considered to be the primary trigger of C-reactive protein (CRP) so maternal CRP can also be predictive of congenital infections and EONS⁸.

CRP and ESR both are used for assessment of inflammation. ESR is a non-specific measure of inflammation. CRP measurement is a direct determination of an APP and its serum levels increases rapidly during inflammation and its variation is wider than that of ESR. Unlike ESR, anemia, polycythemia, spherocytosis, macrocytosis, or hypergammaglobulinemia has no effect on level of CRP. Serial monitoring is done to monitor the evolution of infectious, autoimmune, and other diseases⁹. The rationale of our study was to find relation of positive CRP in mothers with early neonatal sepsis within 7 days after birth. It would greatly help not only in early recognition of neonatal sepsis but also promote antibiotic stewardship, preventing injudicious use of antibiotics in this early age. Moreover it will be of great value in recognizing burden of sepsis among neonates for prompt initiation of treatment.

METHODOLOGY

This study was carried out at Neonatal intensive care unit of Combined Military Hospital Quetta, from

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September 2016 to March 2018. Study was reviewed and approved by ethics and research committee (CMH QTA-IRB/009 dated 22 Oct 2019). Sample size was calculated using World Health Organization (WHO) calculator (1.1) with confidence level=95%, anticipated population proportion=70%, absolute precision required=5% and sample size of 105. Non-probability consecutive sampling was used. It was an analytical study. All term and preterm infants, whose mothers were having positive CRP results, included in the study. Sampling technique used was non probability consecutive sampling. Inclusion criteria used was neonates of serum CRP positive mothers of either gender with neonatal age <72 hours. Twin babies, congenital anomalies, metabolic disorders and with maternal history of eclampsia, hepatitis, cardiovascular disease and rheumatoid disease were excluded from the study. The parents of the patients were explained accordingly and informed written consent was taken after assuring them, benefits and risks of the study and risks. Neonatal sepsis was diagnosed on the basis of history, clinical examination, which was carried out by senior pediatrician. All the lab investigations were reported by the concerned experienced pathologist having minimum of 5 years' experience. Patients were looked for symptoms and signs of neonatal sepsis like lethargy, refusal to feed, off color, vomiting, hypothermia and fits. Complete blood count and CRP were sent to laboratory. Necessary information including name, age and gender was recorded as per designed proforma. All the patients with neonatal sepsis were admitted and standard treatment as per departmental protocol was given. The patients were discharged once stable.

Data was entered and analyzed using SPSS-22. For qualitative variables, frequency and percentage were calculated. For quantitative variables, mean and standard deviation were calculated. Chi-square was applied and a p -value ≤ 0.05 was considered as significant.

Early-onset neonatal sepsis was defined as laboratory evidence of decreased platelet count ($<150,000/\mu\text{L}$) and positive CRP at ≤ 72 hr after birth with supporting clinical evidence of sepsis (lethargy, refusal to feed, off-color, febrile). CRP positive mothers were defined as mothers with serum CRP levels >6 mg/l.

RESULTS

Total number of patients in our study was 105. Out of 105 patients 46 (44%) neonates were boys and 59 (56%) neonates were girls. The relation of gestational age with early onset neonatal sepsis was shown in

table-I. Mean birth weight of babies included in the study was 2.51 ± 0.878 kg. Babies with birth weight <1.5 kg were 15, between 1.5 and 2.5kg were 33, between 2.5 and 3.5kg were 45 and >3.5 kg were 12. (table-II). The association of age in hours to early onset neonatal sepsis was shown in table 3. The correlation of quantitative maternal CRP with early onset neonatal sepsis was presented in table-IV.

Table-I: Gestational age (weeks) with respect to neonatal sepsis.

Gestational Age (weeks)	Neonatal Sepsis	
	Yes	No
<32	24 (22.8%)	2 (1.9%)
32-37	45 (42.8%)	3 (2.8%)
>37	10 (9.5%)	21 (20%)

Table-II: Birth weight (Kg) with respect to neonatal sepsis.

Birth Weight (Kg)	Neonatal Sepsis		p -value
	Yes	No	
<1.5	8 (7.6%)	7 (6.6%)	0.013
1.5-2.5	28 (26.6%)	5 (4.7%)	
2.5-3.5	37 (35.2%)	8 (7.6%)	
>3.5	6 (5.7%)	6 (5.7%)	

Table-III: Association of age of baby in hours with neonatal sepsis.

Age of Baby (Hours)	Neonatal Sepsis		p -value
	Yes	No	
<12	31 (29.5%)	12 (11.4%)	0.762
12-24	40 (38.1%)	11 (5.7%)	
>24	8 (7.6%)	3 (2.8%)	

Table-IV: Association maternal C-reactive protein and neonatal sepsis.

Maternal C-reactive protein	Neonatal Sepsis		p -value
	Yes	No	
>6-24	35 (33.3%)	17 (16.1%)	0.011
25-48	13 (12.3%)	7 (6.6%)	
>48	31 (29.5%)	2 (1.9%)	

Out of 105 mothers who were CRP positive, 79 had babies (35 males and 44 female neonates) who were having signs and symptoms/lab evidence of neonatal sepsis and babies of rest of the mother's i.e. 26 were having no signs and symptoms/lab evidence of neonatal sepsis with statistically significant relation between maternal CRP and neonatal sepsis p -value ≤ 0.05 .

DISCUSSION

Different number of inflammatory markers are used for early detection of infection in children including CRP, interleukins, procalcitonin and tumor necrosis factor etc. CRP is the most studied inflammatory marker and found to be the most valuable factor for detection of maternal infection during pregnancy.

CRP is a very sensitive marker of infection. It rises much earlier than the constitutional signs and symptoms of infection. It is a rapid, simple and a safe test of maternal infection detection. Raised CRP to a significant level during pregnancy indicates maternal infection¹⁰.

In this study, we also used CRP as an inflammatory marker for maternal infection as other inflammatory markers like interferons, interleukins were not available in our setup except procalcitonin which was not cost effective.

During pregnancy maternal infection is associated with increased morbidity and mortality. Moreover, intra uterine infection is a risk factor for preterm labor which not only further add to it but also affects good outcome badly. This is the reason that early detection and treatment of maternal infection during pregnancy is of great significance as this will help in decreasing neonatal mortality and morbidity¹¹.

The main feature of our study was the increased rate of neonatal sepsis with positive maternal CRP. It was further observed that with increasing maternal CRP (quantitative) more neonates developed neonatal sepsis. Statistically, significant relation was found between positive maternal CRP and early neonatal sepsis with p -value=0.011. Few studies have been done to show relation of maternal CRP with neonatal infection. Leena *et al*, showed that elevated maternal serum amyloid A, haptoglobin and CRP were related with positive amniotic fluid culture and neonatal sepsis¹².

Mithal *et al*, showed that positive maternal CRP is not only a good predictor of maternal infection but also of early neonatal sepsis¹³. The same findings were seen in our study as well. However, study done by Mehmet *et al*, showed no relation of positive maternal CRP with neonatal infection which was contrary to our results¹⁴.

Hao *et al*, studied comparing of role of maternal CRP and procalcitonin (PCT) as marker of intrauterine infection with that of neonatal sepsis. They concluded that maternal PCT had little value as a marker intrauterine infection but both cord blood and maternal blood CRP level could be used as a predictor of neonatal infection¹⁵.

Ivana *et al*, showed that positive maternal CRP was linked with microbial invasion of amniotic cavity (MIAC) and intra amniotic infection (IAI) and these patients were having the high quantitative values of CRP¹⁶. A recent study has shown that maternal CRP is of great value for EONS prediction and a maternal

CRP <8ng/l has a good negative predictive value for EONS and over treatment of these neonates (invasive intervention and antibiotics) may be avoided. In one study including 48 CRP positive mothers, 36 (70%) neonates had early onset neonatal sepsis¹⁷.

Another finding in our study was that the incidence of neonatal infection was significantly high in premature and low birth babies as compared to term and normal weight babies. Tshotetsi *et al*, also reported strong association between neonatal infection and preterm/low birth weight babies¹⁸.

To implement maternal CRP during pregnancy as a screening test for the detection of neonatal infection, it is necessary to carry out similar sort of studies in large and multiple centers. The shortcomings of our study are that it is a single centered study and the sample size was small and so the results drawn may not be implemented on general population.

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CONCLUSION

Maternal CRP was found to be an easily available, safe and noninvasive test. Increased maternal CRP level is associated with increased risk of neonatal sepsis. Maternal CRP may be used as a good screening tool for early detection of neonatal sepsis. Early detection and prompt treatment of neonatal sepsis may lead to improved neonatal outcome and may result in decreased neonatal mortality and morbidity.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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