ORIGINAL RESEARCH

Factors That Influence The Status Of C-Reactive Protein Upon Neonatal Admission Subsequent To Delivery

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ABSTRACT

Objective: The aim of our study was to assess factors that influence the status of C - reactive protein upon neonatal admission subsequent to delivery.

Methods: The CRP of one hundred full-term infants was determined at 12, 24, and 48 hours of age. Perinatal variables such as mode of delivery, gestational age, maternal autoimmune diseases and others were documented. The electronic medical record system was utilized to gather data on the neonatal demographics and condition at the time of birth, in addition to the maternal medical history and medication usage during pregnancy. Utilizing statistical software, the potential correlation between perinatal factors and CRP at the time of postnatal admission was analyzed.

Results: The study examined a cohort of 100 neonates, of which 63 were male and 37 were female. The average gestational age (GA) of the infants was 35.74±3.30 weeks. In a multifactor logistic regression analysis, it was determined that maternal autoimmune diseases (P<0.002), premature rupture of membranes (PROM) within 18 hours (P=0.023), and larger GA (P<0.001) constituted independent risk factors for CRP≥8 mg/L. A cesarean section was an independent protective factor against CRP8 mg/L (P0.001).A total of 100 neonates were analyzed, including 63 males and 37 females with a mean gestational age (GA) of 35.74±3.30 weeks. Multifactor Logistic regression analysis: larger GA (P<0.001), premature rupture of membranes (PROM)≥18 h (P=0.023) and maternal autoimmune diseases (P<0.002) were independent risk factors for CRP≥8 mg/L. Cesarean delivery (P<0.001) was independent protective factor for CRP≥8 mg/L.

Conclusion: GA, PROM, maternal autoimmune diseases, cesarean delivery and maternal autoimmune diseases were all found to have an independent impact on neonatal CRP≥8 mg/L at admission. Additionally, GA and neonatal CRP≥8 mg/L on admission exhibited a nonlinear relationship.

INTRODUCTION

C reactive protein (CRP) is a liver-produced acute phase reactant protein that serves as an indicator of systemic inflammation. It has been established that C-reactive protein (CRP) plays a significant role in the inflammatory response, and its concentration is highly correlated with the overall health of the human body.[1] In critical situations such as bacterial infections, inflammation, tissue injury, and malignant tumors, it increases considerably.[2] The term "C-reactive protein" was initially defined in 1930 by Tillet and Francis. It was determined that the protein in question facilitates the binding of complement to foreign or damaged cells in response to inflammation, with concentrations reaching their maximum after fifty hours.[3]Elevated CRP levels have been identified as a risk factor for early-onset neonatal sepsis (EOS), a critical condition that can be fatal for infants. Neonatal sepsis ranks as the

third leading cause of mortality and morbidity among newborns during the initial month following delivery.[4] Approximately 1.5% of term neonates and 40% of very-low birth weight infants perish from EOS-associated mortality.[5,6] Although EOS has numerous etiological factors, group B Streptococcus (GBS), which is also referred to as Streptococcus agalactiae, plays a pivotal role.[7] Annual perinatal mortality in economically underdeveloped regions can be attributed to EOS, with an estimated 30 to 50% of cases following. Due to the high variability of the clinical spectrum and the subtle and non-specific signs and symptoms of neonatal sepsis that are clinically indistinguishable from those of non-infectious conditions, such as respiratory distress syndrome or difficult adaptation to extrauterine life, early recognition of EOS in newborns remains difficult.[8,9]Early diagnosis of neonatal sepsis (EOS) is challenging due to the lengthy testing period and atypical symptoms observed in early neonates, despite the fact that blood culture is the diagnostic gold standard.[10] There have been numerous proposals for biomarkers that can differentiate septic infants from healthy ones.[11] Hence, for the early detection of neonatal EOS, CRP, procalcitonin (PCT), and interleukin-6 (IL-6) are more informative biomarkers. An elevated CRP level signifies the presence of severe bacterial infections and is correlated with a heightened susceptibility to EOS.[12,13] The determination of CRP is the most utilized marker in neonatal intensive care units (NICUs) worldwide due to its critical function in the diagnosis of EOS and its extensive availability, simplicity, speed, and low cost.In actuality, CRP levels rise under all circumstances capable of instigating the inflammatory cascade and/or inducing tissue injury.Numerous prenatal, perinatal, and neonatal variables may impact CRP levels; therefore, an elevated CRP does not necessarily indicate septic status. Numerous past studies have documented that CRP levels are suggestive of EOS, resulting in the protracted administration of antibiotics in neonatal intensive care units (NICUs), which is typically the case when CRP levels are elevated. This inevitably results in the development and dissemination of antibiotic resistance as well as other adverse outcomes, including neonatal necrotizing enterocolitis (NEC) and late-onset sepsis (LOS), due to the excessive use of antibiotics. Furthermore, an overuse of antibiotics raises the potential for adverse bacterial colonization, the proliferation of resistant bacteria, and the development of hypersensitivity reactions.[14,15] In the differential diagnosis of EOS, the identification of independent variables that impact the interpretation of CRP could prove beneficial. CRP levels also increase physiologically during the initial days following birth in infants. When assessing a neonate in the initial hours of life, it is crucial to take into account both the typical kinetics of CRP and its response to potential confounding factors. This is necessary to prevent erroneous diagnoses and inappropriate treatment. The aim of our study is to assessfactors that influence the status of C - reactive proteinupon neonatal admission subsequent to delivery.

MATERIALS AND METHODS

At the hospital, a prospective investigation was conducted. One hundred healthy, term neonates who were born consecutively were enrolled. Upon admission, the CRP levels of each of the neonates mentioned above were assessed.The neonates were categorized into two groups based on whether or not they had a CRP value of ≥8 mg/L: the CRP≥8 mg/L group (50 cases, 32 males, 18 females, mean GA 37.71±3.51 weeks) and the CRP<8 mg/L group (50 cases, 31 males, 19 females, mean GA 35.66±3.11 weeks).Informed consent was obtained from the babies' s parents before the enrolment.The study involving human participants was reviewed and approved by the Ethical Committee.

Inclusion criteria

- Gestational age 34–42 weeks.
- At least one CRP determination in the first 48hoursof life.
- Sustained postnatal hospitalization devoid of complications, with healthy discharge from the facility at 48 hours (in the case of vaginal delivery) or 72 hours (in the case of caesarean section) after birth.
- Informed consent signed by a parent/legal guardian.

Exclusion criteria

- Babies with congenital heartmalformation, major congenital malformations and/or chromosomal anomalies; babies who received anti-hepatitis B vaccine.
- Babies whoneeded intensive assistance and were hospitalised in NICU.
- Acute intrapartum events such as cord prolapse, uterine rupture,sudden and sustained fetal bradycardia, shoulder dystocia and complicated breech extraction.
- Clinical signs of prenatal/perinatal asphyxia.

Determination of CRP

The CRP status was determined using the IMMAGE800 fully automated special protein analysis system and an immunoturbidimetric assay (CRP reagent, Beckman Coulter, USA). The cut-off values of CRP were 8 mg/L.[6,16]

Statistical analysis

Mean and standard deviation (SD) were utilized to represent a normally distributed continuous variable. The values of categorical variables were expressed as a percentage or a frequency. The differences between the CRP≥8 mg/L group and the CRP≥8 mg/L group were analyzed using χ 2 (categorical variables), Student's t-test (normal distribution), or Mann–Whitney U-test (skewed distribution). The potential correlation between gestational age, PROM, antenatal steroids, maternal autoimmune diseases, delivery mode, MAS, and the incidence of CRP≥8 mg/L was examined via univariate analysis and multiple logistic regression. Statistical significance was assigned to P-values<0.05.

RESULTS

The neonates were categorized into two groups based on whether or not they had a CRP value of ≥8 mg/L: the CRP≥8 mg/L group (50 cases, 32 males, 18 females, mean GA 34.15±2.56 weeks) and the CRP<8 mg/L group (50 cases, 31 males, 19 females, mean GA 37.34±3.77 weeks).

Table 1: Basic characteristics of the CRP≥8 mg/L group compared with the CRP<8 group.[Mean±SD, n (%)]

		CRP<8 mg/L(n=50)	CRP≥8 mg/L(n=50)	P-value
Gestational Age		34.15±2.56	37.34±3.77	0.002
Birth Weight		2325±655	2876±876	0.002
Maternal fever	no	48(96%)	46(92%)	0.342
	yes	2(4%)	4(8%)	
PROM	No	37(74%)	35(70%)	0.033
	Yes,<18 h	4(8%)	4(22%)	
	Yes,≥18 h	9(18%)	11(22%)	
Prenatal antibiotic use	no	43(86%)	44(88%)	0.245
	yes	7(14%)	6(12%)	
Prenatal dexamethasone use	no	39(78%)	43(86%)	0.002
	yes	11(22%)	7(14%)	
Placenta previa	no	44(88%)	48(96%)	0.003
	yes	6(12%)	2(4%)	
Maternal autoimmune diseases	no	47(94%)	45(90%)	0.001
	yes	3(6%)	5(10%)	
Gestational diabetes	no	45(90%)	44(88%)	0.654
	yes	5(10%)	6(12%)	
Pregnancy hypertension	no	46(92%)	46(92%)	0.876
	yes	4(8%)	4(8%)	
ICP	no	47(94%)	49(98%)	0.031
	yes	3(6%)	1(2%)	
Sex	Male	31(62%)	32(64%)	0.322
	female	19(38%)	18(36%)	
Delivery mode	Vaginal delivery	10(20%)	23(46%)	0.002
	Operative vaginal delivery	3(6%)	2(4%)	
	Cesarean delivery	37(74%)	25(50%)	
Apgar score	8-10	40(80%)	37(74%)	0.211
	4-7	7(14%)	9(18%)	
	0-3	3(6%)	4(8%)	
MAS	NO	48(96%)	46(92%)	0.003
	YEP	2(4%)	4(8%)	

Statistical distinctions were observed between the two groups with regard to the following indicators: gestational age (GA), birth weight (BW), premature rupture of membrane (PROM) (≥18 hours), antenatal steroids, placenta previa, maternal autoimmune diseases, intrahepatic cholestasis of pregnancy (ICP), cesarean delivery, meconium aspiration syndrome (MAS), and placenta previa. The GA and BW values were significantly greater in the CRP≥8 mg/L group compared to the CRP≤8 mg/L group. Neonatals exposed to PROM (≥18 hours), maternal autoimmune diseases, and MAS exhibited a significantly higher incidence rate of CRP≥8 mg/L. Conversely, exposure to antenatal steroids, placenta previa, ICP, and cesarean delivery resulted in a significantly reduced incidence rate of CRP≥8 mg/L.

Table 2: Univariate analysis for incidence of CRP≥8 mg/L [n=100, Mean±SD, n (%)]

		Statistics	OR (95%CI)	P-value
Maternal fever	no	98(98%)	1.1	
	yes	2(2%)	1.32	0.311
PROM	No	76(76%)	1.0	
	Yes,<18 h	10(10%)	1.13	0.875
	Yes,≥18 h	14(14%)	1.62	0.023
antenatal antibiotic use	no	88(88%)	1.0	
	yes	12(12%)	0.56	0.321
Prenatal dexamethasone use	no	79(79%)	0.1	
	yes	21(21%)	0.65	0.002
Placenta previa	no	92(92%)	0.1	
	yes	8(8%)	0.15	0.004
Maternal autoimmune diseases	no	97(97%)	0.1	
	yes	3(3%)	3.54	<0.002
Gestational diabetes	no	90(90%)	1.0	
	yes	10(10%)	1.22	0.644
Pregnancy hypertension	no	92(92%)	1.0	
	yes	8(8%)	1.22	0.866
ICP	no	96(96%)	1.1	
	yes	4(4%)	1.09	0.041
Sex	Male	63(63%)	1.0	
	female	37(37%)	1.01	0.362
Delivery mode	Vaginal delivery	26(26%)	1.0	
	Operative vaginal delivery	3(3%)	1.34	0.432
	Cesarean delivery	71(71%)	0.64	<0.001
Apgar score	8-10	79(79%)	1.0	
	4-7	17(17%)	1.21	0.234
	0-3	4(4%)	1.44	0.325
MAS	NO	98(98%)	1.0	
	YEs	2(2%)	4.32	0.004

By employing univariate logistic regression, we identified the following associations: GA and BW were positively correlated with CRP≥8 mg/L; for every one week increase in GA, the risk of CRP≥8 mg/L increased by 26% (P<0.001); antenatal steroids, placenta previa, and delivery mode (Cesarean delivery) were negatively correlated with CRP≥8 mg/L, reducing the risk by 53%, 82%, and 69% (All P<0.01, respectively); PROM (≥18 hours), maternal autoimmune diseases, and MAS were positively associated with CRP≥8 mg/L.

DISCUSSION

The status of CRP is highly correlated with the overall health of the human body. The status of this non-specific marker of inflammatory response fluctuates in the presence of malignancies, infections, autoimmune diseases, surgical procedures, cardiovascular disorders, and so forth. Variations in CRP levels in the blood are indicative of distinct pathological states. Proximity to diagnosis reduction, early disease progression prevention, and control are all critical factors that can be significantly aided by such modifications, which can improve physicians' disease judgment. We have conducted a comprehensive analysis of perinatal factors that may influence CRP status at birth, quantifying the amplitude of the impact of various factors on CRP status, and have discovered an unprecedented nonlinear relationship between gestational age and CRP status. These will aid medical professionals in the initial assessment of EOS.[1]Our research revealed that cesarean delivery was associated with a lower risk of CRP≥8 mg/L than vaginal delivery. Vogl SE et al.[17] discovered comparable findings in their investigation. This could be attributed to the fact that vaginal delivery induces an emergency state in neonates, which can trigger the body to generate an excessive quantity of hormones (e.g., glucocorticoids or catecholamine hormones), thereby interfering with neutrophil function and inflammatory factor production. Furthermore, forceps or vaginal delivery have the potential to induce specific tissue damage in neonates. The studies conducted by Perrone S et al.[5] and Bellieni CV et al.[18] documented a significant difference in the serum CRP levels between healthy neonates delivered vaginally and those delivered via cesarean section. The mode of administration is thus one of the most significant

determinants of serum CRP levels in neonates during the early postnatal period.The increase in serum C-reactive protein within 48 hours after birth was independently associated with maternal pregnancy and autoimmune disease, according to our research. The possible mechanism is that maternal autoantibodies enter the placenta and induce tissue damage in the neonates. Additionally, gestational age is a significant determinant of serum CRP levels during the initial postnatal phase. The studies conducted by Chiesa et al.[19] and Macallister et al.[20] documented that GA had a statistically significant positive impact on CRP. Furthermore, healthy preterm neonates exhibited a shorter and more minimal CRP response in comparison to healthy term newborns. Within 72 hours of birth, preterm neonates had lower CRP levels than full-term newborns, infected or uninfected, according to a study by Hofer et al[21]. Our research also revealed that as GA increased, so did the risk of CRP levels exceeding 8 mg/L.An investigation conducted by Hofer N et al[21] documented that in the early postnatal period, the serum CRP level of full term neonates diagnosed with MAS was notably elevated in comparison to the control group. Based on our univariate analysis, the incidence of CRP > 8 mg/L in MAS was 4.87 times higher than in the absence of MAS (P = 0.005). The incidence of CRP ≥ 8 mg/L in MAS was 2.89 times that of MAS without PROM, after adjusting for sex, GA, BW, maternal fever, placenta previa, antenatal antibiotic use, PROM, pregnancy hypertension, gestational diabetes, ICP, antenatal steroids, maternal autoimmune diseases, and delivery mode. This finding suggests that MAS had a positive correlation with CRP; however, the sample size may be a limitation of this study. Potentially independent risk factors for CRP > 8 mg/L were MAS. Two potential mechanisms exist. First, meconium contamination of amniotic fluid serves as an indicator of fetal maturity and is frequently observed in full-term infants; furthermore, the fact that a neonate is full-term is a significant contributor to the early-stage increase in serum CRP.[22]In conclusion, we believe that the interpretation of CRP status should be done in conjunction with the clinical condition of the neonate, rather than being relied upon exclusively to inform clinical antibiotic decision making.

CONCLUSION

CRP levels increase physiologically following birth. However, it is important to note that the interpretation of CRP values in healthy neonates can be influenced by various perinatal factors. Specifically, we discovered that CRP is significantly influenced by mode of delivery, gestational age, PROM, maternal autoimmune diseases, cesarean delivery, and maternal autoimmune diseases. Given the multitude of factors that contribute to the variation in CRP levels among healthy term infants, it is advisable to utilize reference CRP levels that are normal, accounting for gestational age, postnatal age, and method of delivery.

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