Research article

Normal value and changes in CRP values on maternal and fetal umbilical cord blood with the labor and intrapartum interventions

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Abstract

Introduction: C-reactive protein (CRP) is widely used as an inflammatory marker. Since labour is an inflammatory process, CRP values vary during the intrapartum and postpartum period due to multiple factors.

Methods: A descriptive-analytical study was carried out at Castle Street Hospital for Women. Mothers who have term singleton pregnancies with uneventful antenatal periods and have undergone vaginal delivery were recruited for the study. Samples were obtained just after admission to the labour ward (S_1), 24 hours after the delivery (S_2), and the fetal umbilical cord blood (S_3). Reference ranges for S_2 and S_3 were determined using the interquartile range (IQR).

Results: Out of 300 mothers recruited for the study, the mean age was 26.73 years (95% Confidence interval 19.5-36.9). There were 266 samples of S_1,177 samples of S_2, and 173 samples of S_3 were collected. The reference range for S_2 is 12.70-150.83 mg/dl, and for S_3 is 0.1-8.1 mg/dL. The S_2 value is significantly associated with duration of labor (r=0.47, p=0.046), number of vaginal examinations (VEs) ($p < 0.001$), augmentation of labor (AOL) (p=0.001), method of cervical ripening (p=0.014) and intrapartum intervention ($p < 0.001$). The number of vaginal examinations (p=0.02) and augmentation of labor (p=0.025) are significantly associated with fetal umbilical cord blood (S_3).

Conclusion: Early postpartum CRP can be risen up to 151 mg/dL after 24 hours of vaginal delivery. It may be associated with prolonged labor, number of VEs performed, AOL, method of cervical ripening, and episiotomy. Fluctuation of normal CRP values during the periods of antenatal, intrapartum, and postpartum needs to be assessed in the Sri Lankan community.

Keywords: CRP, intrapartum, peripartum, cord blood CRP, maternal CRP, usefulness of CRP in obstetrics, CRP in pregnancy

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Introduction

C-reactive protein (CRP) is an acute-phase protein, of which the levels in the blood rise to 1000-fold in response to injuries, trauma, infection, inflammation, and neoplasia[1]. In addition, CRP levels are significantly elevated in certain physiological conditions such as normal pregnancy[2,3], delivery[1,4] and a decrease in the postpartum period[1,4], compared to non-pregnant females. Hence, patently, a higher variability and significant elevation of CRP levels are observed with pregnancy-related complications and interventions. Consequently, the interpretation of CRP levels during pregnancy is a dilemma, and it makes the test results highly non-specific[4,5]. Nonetheless, the CRP values are still used as a supportive tool for diagnosis and assessment of progression and therapeutic response of infectious or inflammatory conditions during pregnancy and postpartum[6-9].

Despite the fact that CRP values are used as supportive evidence for determining antenatal and postpartum complications, specified normal ranges of CRP levels during pregnancy and postpartum are yet unclear. Also, the evidence on the associations between postpartum maternal CRP levels with peripartum and perinatal outcomes is scarce hitherto.

Particularly the postpartum CRP values can be highly variable depending on a number of factors, including the spontaneous onset of labor, status of the fetal membranes at the onset of labor, induction of labor, intra-vaginal prostaglandin administration, augmentation of labor, type of anaesthesia, duration of the second stage of labor, number of vaginal examinations (VE) after the onset of labor, and blood loss at delivery. It is important to identify the exact associations between the maternal and umbilical cord CRP levels and the above factors. Such trends can be taken into consideration in interpreting CRP values for individual cases to differentiate ongoing infection from normal labor response in day-to-day clinical practice.

Hence, in this study, our primary objective was to determine the normal range of maternal CRP levels in the early normal puerperium. The secondary objectives were to compare the variation of maternal CRP levels and the cord blood CRP among the above variables.

Materials and methods

The study was conducted as a descriptive cross-sectional study with an analytical component at wards 1 and 2 of Castle Street Hospital for Women (CSHW). A total of 300 mothers were included in the study. The inclusion criteria were singleton pregnant mothers who were admitted for delivery at term (between 37 to 41 weeks of period of gestation) and underwent vaginal delivery. We excluded the mothers who were diagnosed or suspected of infection, mothers with ruptured membranes for more than 6 hours, mothers with autoimmune or connective tissue disorders, and mothers who develop intrapartum complications like postpartum haemorrhage, perineal tears and manual removal of placenta. Antenatal care data were collected to a structured data sheet from in-ward clinical records, antenatal care records, and investigation results. Maternal and umbilical cord blood samples were collected for CRP. Maternal blood was collected at the time of admission to the labor ward following spontaneous onset or induction of labor (S_1) and Following 24 hours of uncomplicated delivery (S_2). Cord blood was collected from the umbilical vein at the time of the delivery(S_3). CRP was measured in the Biochemistry Laboratory, CSHW, using rate nephelometry with a Beckman array system protein analyzer. Serum CRP concentrations were measured in all samples within 12 hours after blood collection. Participants were followed up with routine pertinent care in the unit, and related Intrapartum, postpartum, and neonatal clinical data were collected during the ward stay by the investigator.

The maternal mean CRP level during pre-labour and 24 hours postpartum were calculated, and the significant difference was by significant test (Wilcoxon sign test).

The association of S_2 with the following was analyzed.

1. Duration of labor (from time of onset of active labor to delivery of the baby)
2. Number of vaginal examinations (VEs)
3. Augmentation of labor
4. Method of cervical ripening (Foley catheter/ prostaglandin analogs)

In addition, the correlation between mean umbilical cord blood CRP level and maternal pre-labor and 24-hour postpartum CRP levels were analyzed. Also, the correlation between mean umbilical cord blood CRP and perinatal outcome measures was assessed.

The reference ranges were calculated after excluding the outliers. The values were converted to logarithm

values before the analysis as the data was skewed. Interquartile ranges were calculated, and antilogarithm values were calculated back.

Results

The mean age of the sample was 26.7±4.81 years. The population between 19-28 years was 64%. The mean period of amenorrhea was 38.9 ± 2.28 weeks, and the mean Body Mass Index (BMI) was 24.37±3.9 kg/m^2. The number of children is 0, 1,2 and 3 in 131 (43.7%), 118 (39.3%), 24 (8.0%) and 13 (4.3%) mothers respectively (Figure 1).

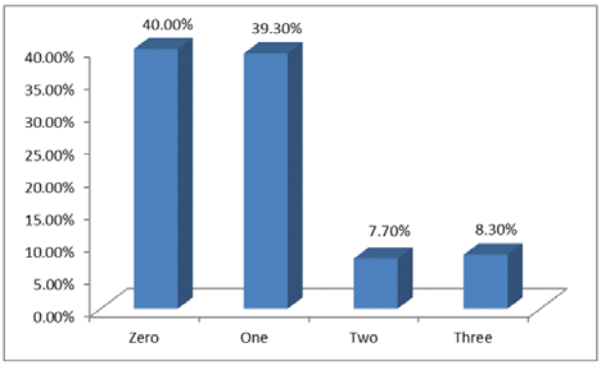

Figure 1. **Distribution of parity in the study sample.**

Out of 300 mothers recruited, 33 (11.0%) had hyperglycemia in pregnancy and 10 (3.3%) had hypertension in pregnancy.

There were 119 mothers (39.6%) who were admitted for the reason of abdominal pain, while another 20.3% were admitted for confinement. More than half (n=185, 61.6%) had spontaneous onset of labor, and 115 mothers (38.3%) were induced. Of them, 43 (14%) were induced with prostaglandin while 24.3% had Foley catheter induction.

The number of VE was considered only after being admitted to the labor ward. Out of which 124 mothers (41.3%) underwent two VEs following admission to the labor ward. Three VEs were done in 86 (28.7%), while 13 (4.3%) underwent four VEs. The mean labor duration was 281 ± 87.12 minutes.

The mean of the S_1 was 10.2 mg/dL (95% confidence interval (CI) 0.9-64.0) and the mean of the S_2 value was 71.28 mg/dL (95% CI 12.7-151.09), showing a significant difference between them (p<.001). The average CRP value of the cord blood was 2.2 mg/dL (95% CI 0.1-8.1).

The reference range for the postpartum CRP (S_2) was 12.70-150.83 mg/dL

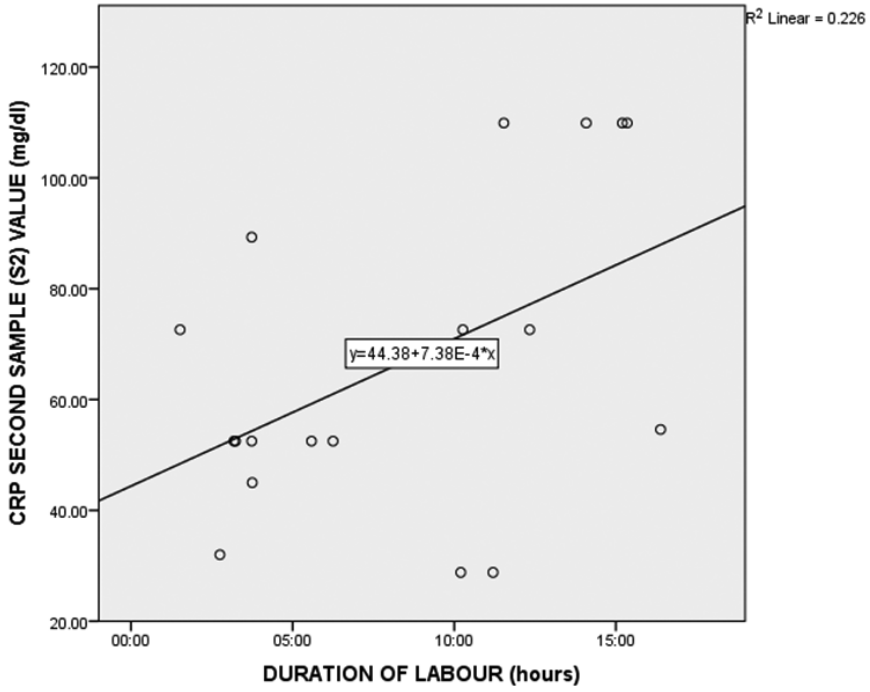

Figure 2. **Demonstrates the association between the duration of labor and the S_2 value. As it depicts there is a positive correlation between 2 variables (r=0.476, p=0.046).**

Table 1 depicts the association between different peripartum procedures and S_2 and S_3. The duration of labor and S_2 value showed a moderately positive significant correlation (r=0.47, p=0.046). Hence S_2 value rises as the duration of labor prolongs. The number of vaginal examinations is also associated with significant differences in S_2. However, the mean CRP value of those with 4 VEs is lower than in other patients. Vaginal examinations are performed during labor monitoring. When the augmentation is considered, a mean CRP of 64.77±35.88 mg/dL is noted in those who had IV oxytocin and there is a significant difference with those who hadn't (p=0.001). Foley catheter inserted mothers had mean S_2 of 59.87±33.78 mg/dL, whereas prostaglandin inserted patients had S_2 of 50.13±29.62 mg/dL (p=0.014).

Those who had undergone episiotomy and had minor perineal tears/lacerations during peripartum were considered as the group of mothers who had undergone intrapartum interventions. One hundred and four mothers (51.33%) underwent episiotomies out of the total sample of 300. Mann-Whitney U test showed a statistical significance of S_2 between those two groups (p<0.001).

The number of vaginal deliveries (p=0.02) and the method of labor augmentation (p=0.025) are significantly associated with fetal cord blood (S_3).

The mean birth weight was 3034.70±514.91g. According to Table 2, out of the 300 deliveries observed, 293 neonates (97.7%) had an APGAR score of 9 at the 1st minute after birth. Only 7 (2.3%) had an APGAR score of 8. However, 5 minutes after birth, all the neonates had 10 out of 10 APGAR scores. The 5-minute APGAR is 10 in all the babies. There were 22 babies admitted to PBU due to respiratory distress (n=8, 2.6%), meconium aspiration (n=10, 3.3%), and hypoglycemia (n=4, 1.3%). One child had to give inflation breaths, which she recovered within 1st minute.

Table 1. Association between different peripartum interventions and S_2 and S_3

Parameter	S_2 value (mg/dl) (n=177)		S_3 value (mg/dl) (n=173)	
	Mean ± SD	**Associations**	**Mean ± SD**	**Associations**
Number of vaginal examinations				
1 (n=124)	74.35±33.28	**p<0.001**	1.68±1.29	**p=0.020**
2 (n=86)	70.11±42.04		1.83±1.32	
3 (n=72)	81.63±20.90		3.46±3.332	
4 (n=13)	35.56±31.83		-	
Augmentation of labour				
Given (n=205)	64.77±35.88	**p=0.001**	2.35±2.20	**0.025**
Not given (n=95)	83.36±33.84		1.41±0.91	
Method of cervical ripening				
Foley catheter inser-tion(n=73)	59.87±33.78	**p=0.014**	2.70±3.30	**p<0.001**
Prostaglandin(n=42)	50.13±29.62		0.79±0.56	
Procedures				
Episiotomy (n=154)	77.71±34.43	**p<0.001**	2.30±2.08	**p<0.001**
No intervention (n=23)	28.23±2.88		2.18±2.05	

S_2: CRP second sample value (mg/dl) S_3: Cord blood sample value (mg/dl)

Neonatal outcomes

Table 2. Comparison between neonatal APGAR score and S_2, S_3 values

Parameters	S_2 value (Mean ± SD)	S_3 value (Mean ± SD)
APGAR score		
1 Minute		
8 (n=7)	61.21±31.13	2.12±1.04
9 (n=67)	57.17±35.49	2.27±1.53
10 (n=226)	70.74±35.25	2.02±0.96
5 Minutes		
10 (n=300)	71.28 ± 36.19	2.21 ± 2.00

The mean cord blood CRP value (S_3) was 2.21±2.00 mg/dL. The reference range for the cord blood CRP was 0.1-8.1 mg/dL.

Figure 3 shows the correlation between S_2 and S_3. Spearman correlation coefficient was 0.253 (p=0.03). Hence, a mild correlation between S_2 and S_3 can be concluded.

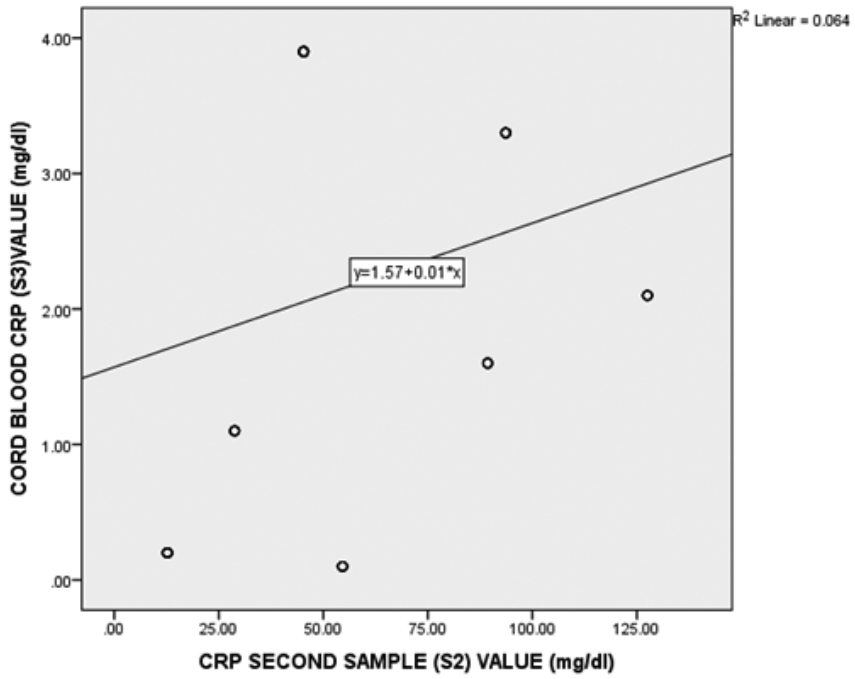

Figure 3. **Scatter plot demonstrating the correlation between S_2 and S_3.**

Discussion

CRP is an important serum inflammatory marker in day-to-day clinical practice. During the pregnancy, CRP value varies from its non-pregnant reference range. In this study, the mean of the S_1 was 10.2 mg/dL (95% Confidence Interval (CI) 0.9-64.0) and the mean of the S_2 value was 71.28 mg/dL (95% CI 12.7-151.09), showing a significant difference between them ($p<.001$). The average CRP value of the cord blood was 2.2 mg/dL (95% CI 0.1-8.1).

There is a positive correlation between the duration of labor and the S_2 value ($r=0.476$, $p=0.046$). The duration of labor and S_2 value showed a moderately positive significant correlation ($r=0.47$, $p=0.046$). Hence S_2 value rises as the duration of labor prolongs. The number of vaginal examinations is also associated with significant differences in S_2. However, the mean CRP value of those with 4 VEs is lower than in other patients. When the augmentation is considered, a mean CRP of 64.77±35.88 mg/dL is noted in those who had IV oxytocin and there is a significant difference with those who hadn't ($p=0.001$). Foley catheter-inserted mothers had mean S_2 of 59.87±33.78 mg/dL, whereas prostaglandin-inserted patients had S_2 of 50.13±29.62 mg/dL ($p=0.014$). Those who had undergone episiotomy and had minor perineal tears/lacerations during labor were considered as the group of mothers who had undergone intrapartum interventions. One hundred and four mothers (51.33%) underwent episiotomies out of the total sample of 300. Mann-Whitney U test showed a statistical significance of S_2 between those two groups ($p<0.001$). The number of vaginal examinations ($p=0.02$) and the method of labor augmentation ($p=0.025$) are significantly associated with fetal cord blood (S_3). There is a mild correlation between S_2 and S_3 ($r=0.253$, $p=0.030$).

The mean cord blood CRP value (S_3) was 2.21 ± 2.00 mg/dL. The reference range for the cord blood CRP was 0.1-8.1 mg/dL. The optimum reference range for CRP values during the immediate postpartum period was defined as between 12.70 - and 150.83 mg/dL.

Pregnancy imposes an inflammatory response in the mother[10]. A longitudinal study carried out including 47 participants claims CRP levels can be varied among different individuals. These fluctuations might be exhibited as a reduction, increment, or no change in the CRP value, for which the obvious cause could not be identified[10]. So, it is important to individualize the CRP trend. It is also worth noting, the other cytokines concentrations (IL-6, IL-12, IFN-γ, and GM-CSF) may be changed depending on the patient's BMI, and maternal age[11].

The elevated CRP values would compel the clinician to treat postpartum mothers with antibiotics. However, the "high CRP" levels are defined based on the cut-offs set for the normal adult population. Elevated CRP level may be a result of labor, multiple VEs, intrapartum interventions, etc. To avoid these problems, postpartum mothers need a separate reference range for CRP. Here within our study, we identified the CRP values between 12.70-150.83 mg/dL as the optimum reference range at immediate postpartum.

Earlier Watts et al. investigated the changes in CRP values during normal pregnancy. They had followed up on the healthy pregnant women from 22 weeks of POG to their term. Median CRP values for women not in labor were defined as 0.7-0.9 mg/dL. On the other hand, 95% of the values were ≤1.5mg/dL. The Median CRP value for women who are in labor at term was 1.3 mg/dL[10]. However, as per the current study, the mean of the 1st CRP value was 10.2 mg/dL (95% CI 0.9-64.0). The elevation of the mean CRP value in the study setup can be a normal variation of surveyed patients who were in labor. Contrarily, however, some literature suggests CRP value is significantly lower during the period of pregnancy with a further decrease at postpartum[12]. Nevertheless, elevated CRP levels were observed in obese maternal patients and CRP remains at higher levels even during their postpartum period[12].

Thus, whenever making a clinical judgment based on the CRP value, it is always better to compare the changes in CRP value rather than focusing on a single value.

The development of neonatal infection and its association with maternal CRP levels has been observed previously[11,13,14]. Research carried out at the University of Philadelphia on the variation of maternal serum and vaginal fluid CRP levels identified that both maternal serum and vaginal fluid CRP determinations after prelabor preterm rupture of the membrane are of poor predictive value in neonatal early-onset infection prediction[11]. However, a study conducted in 1990 suggests serum CRP is a useful and rapidly available adjunct to clinical assessment in the diagnosis and exclusion of bacterial infection in the early neonatal period. This has encouraged us to withhold or discontinue antibiotics and has a role in monitoring

response to treatment[13]. Another study carried out in India concludes that being a primi mother, prolonged labour, maternal fever, more than three VEs, rupture of the membrane more than 24 hours, foul smelling liquor, urinary tract infection, and cesarean sections significantly associated with elevated CRP levels after 24 hours of the postpartum period. The negative predictive value for elevated CRP levels at 24 hours was 97%[14]. In our research, the average maternal CRP value 24 hours after the delivery was 71.28mg/dL (SD=36.19). But surprisingly, only 7 neonates had an APGAR of 8. Those seven neonates also gained an APGAR of 10 after 5 minutes. In our study, we included only the singleton pregnant mothers who were admitted at term and undergone normal vaginal delivery, and we excluded most of the possible factors such as preterm labor, ruptured membrane more than 6 hours, antenatal infections, mothers who received antibiotics prior to labor, antenatal/intrapartum pyrexia, instrumental deliveries, and cesarean sections, which may be the cause of APGAR more than 8.

In our research, the cord blood CRP reference range was 0.1-8.1 mg/dL. This value is almost similar to the values available now. Therefore, a CRP value of 8.1 mg/dL can be used as a cut-off value to help the diagnosis of early neonatal infection and monitor the response to treatment in our setup. However, only 173 cord blood samples were collected in our study out of the total 300 study samples. The reference range for cord blood calculated in this study could be inaccurate due to this low number of cord blood samples, making it unreliable to apply during clinical practice.

Childbirth is an inflammatory process that results in elevated CRP levels during the immediate postpartum period. This makes it difficult to diagnose maternal and neonatal infections during this time period using the normal reference ranges of CRP. The goal of this study was to define the reference ranges of maternal and cord blood CRP levels. The optimum reference range for CRP values during the immediate postpartum period was defined as between 12.70 and 150.83 mg/dL. The cord blood CRP reference range was 0.1-8.1 mg/dL. These values make it feasible to interpret CRP values during the immediate postpartum period with fewer conflicts.

Limitations

In this study, the frequency of cord blood sampling was low. Hence, the reference range calculated for cord blood CRP is less reliable to be used in day-to-day practice. Furthermore, the sample collection time may have been altered due to practical reasons, even though it was primarily planned to withdraw blood after 24 hours of delivery. The study's results could have been affected by problems during sample handling, such as timing of sample collection and delayed sample transportation. Moreover, the result may have been affected by whether the collected blood was from the umbilical artery or the umbilical vein.

Conclusions and recommendations

The study identified the CRP values of 12.70-150.83 mg/dL and 0.1-8.1 mg/dL as the optimum reference range for maternal blood at immediate postpartum and cord blood, respectively. However, variations in CRP levels in normal pregnancies, complicated pregnancies, and patients with multiple co-morbidities should need to be studied thoroughly.

Furthermore, prolonged duration of labor, multiple vaginal examinations, augmentation of labor, method of cervical ripening, and episiotomy are associated with the rise of S_2. It is better to reduce the number of unnecessary VEs, carry out augmentation only in selected cases, and minimize intrapartum interventions during labor.

A cord blood CRP value of up to 8.1 mg/dL may be a normal response to the intrapartum interventions. Above that level might indicate early neonatal infection.

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