

# Elevated maternal serum C-reactive protein levels and neonatal infection in term pregnancy

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## Abstract

**Background:** C-reactive protein (CRP) is an acute-phase reactant, and the CRP level has been reported to be slightly elevated in pregnant women. Although CRP has been extensively studied in early pregnancy, mid-pregnancy, and preterm premature rupture of the membranes (ROM), maternal CRP at term is insufficiently studied. This study aimed to analyze maternal CRP values and its relation to neonatal infection in term labor and delivery.

**Materials and methods:** Data of pregnant women who delivered their babies at our clinic were retrospectively collected. The enrollment criteria were;  $\geq 37$  weeks of gestation, and live singleton pregnancy. Maternal CRP level was measured at admission, and repeated daily until delivery. The women were classified into three groups: A, admission for induction/planned cesarean section; B, admission for labor onset with or without ROM; and C, admission for ROM without labor.

**Results:** A total of 4612 women (2133 nulliparas and 2479 multiparas) were enrolled. CRP levels at admission were higher in nulliparas than in multiparas (median [10th percentile, 90th percentile]: 0.2 [0.0, 1.3] vs. 0.1 [0.0, 0.8],  $p < 0.001$ ). In nulliparas, CRP at admission was higher in group B (0.2 [0.0, 1.5]) than in groups A (0.2 [0.0, 0.7]) and group C (0.1 [0.0, 0.8]) (both  $p < 0.001$ ). In multiparas, such difference was not observed. CRP levels were significantly higher on the delivery day than those at admission in both nulliparas and multiparas. A higher rate of neonatal care unit admission for infection and/or respiratory problems was observed in babies of women with elevated CRP ( $\geq 1.0$ mg/dl) than in babies of women without CRP elevation (30/804 vs. 37/3808,  $p < 0.001$ , odds ratio 3.95).

**Conclusion:** Maternal CRP levels may differ according to the indication for admission in nulliparous women. CRP levels increase during labor, and neonates of mothers with high CRP levels should be carefully observed for infection and respiratory problems.

## Introduction

Serum C-reactive protein (CRP) is an acute-phase protein that shows increased expression in the presence of infection, injury and inflammation [1]. The utility of CRP level measurement in obstetrics and gynecology has been extensively studied [2]. Previous studies reported that the CRP levels in women with normal pregnancy were similar to those in non-pregnant women [3-5], whereas later studies showed that the CRP levels were slightly higher in normal pregnancy than in a non-pregnant state [6-9]. CRP elevation is observed as early as at 4 weeks of gestation in normal pregnancy [10], and higher CRP levels in early pregnancy are associated with increased risks of preterm delivery [11-14], gestational diabetes [15], low birth weight [16-18] and preeclampsia [18]. Elevated CRP in mid-pregnancy is associated with preterm labor [19-21], gestational diabetes mellitus [22], preeclampsia [23], urgent cesarean delivery and low Apgar scores [21]. Maternal and umbilical cord CRP levels are higher in cases of idiopathic intrauterine growth restriction than in appropriate for gestational age cases [24]. Among women with preterm premature rupture of the membranes (ROM), or preterm labor, maternal CRP level is a predictor of intrauterine or neonatal infection [25-31]. Cord blood CRP level is associated with the duration of labor rather than the delivery mode [32], and measurement of cord blood CRP [33] and of neonatal CRP levels [34-37] can be performed to detect neonatal infection or sepsis.

However, maternal CRP at labor and delivery in term pregnancy has not been well studied thus far. In addition, the relevance of maternal CRP levels to neonatal infection in term pregnancy is less clear than in preterm ROM [38-40].

This study aimed to analyze maternal CRP value at admission for term delivery, and to examine the relationship between maternal CRP level and neonatal admission for infection and/or respiratory problems.

## Materials and methods

Data of pregnant women who delivered their babies at our obstetrics/gynecology clinic, located in Shizuoka City, central Japan, between January 2008 and December 2019 were retrospectively collected. The enrollment criteria were  $\geq 37$  weeks of gestation, and live singleton pregnancy. Cases with apparent non-obstetric infection, such as common cold, upper respiratory infection, urinary tract infection, periodontitis, and sinusitis, and cases with intrauterine fetal demise were excluded. Women admitted for birth were classified into three groups: group A, admitted for induction of labor and planned cesarean section (CS); group B, admitted for onset of labor with or without ROM; group C, admitted for prelabor ROM. CRP level was measured by using the latex agglutination immunoturbidimetric method (CRP-3100; Nihon Kohden, Tokyo, Japan) at admission, and repeated daily until delivery. Cases of neonatal admission for congenital anomalies

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and low birth weight were excluded. When maternal CRP levels were examined two or more times, the CRP level at admission and the final CRP level were compared.

Prophylactic antibiotics were intravenously administered to the women with ROM [41] and with elevated CRP level ( $\geq 1.0$ mg/dl). Induction of labor was performed with oxytocin infusion, and induction with a transcervical single-balloon catheter was considered for women with an unfavorable cervix. Amniotomy was performed when appropriate.

Data were analyzed with SPSS version 22.0 for Windows (IBM, Tokyo, Japan). A p-value of  $<0.05$  was considered statistically significant. This study was approved by the local ethics committee (no.20004).

**Results**

A total of 4612 women were enrolled, of whom 2133 were nulliparas, and 2479 were multiparas. Table 1 shows the demographic and clinical characteristics of the analyzed women. CRP levels at admission were higher among nulliparous women than among multiparous women (median [10th percentile, 90th percentile]: 0.2 [0.0, 1.3] vs. 0.1 [0.0, 0.8]) ( $p<0.001$ ) (Table 1).

In nulliparous women, CRP was significantly higher among those admitted for onset of labor (group B) (0.2 [0.0, 1.5]) than among those without labor (group A, 0.0 [0.0, 0.7],  $p<0.001$  and group C, 0.0 [0.0, 0.8],  $p<0.001$ ) (Table 2). Among multiparous women, CRP at admission

was similar among women irrespective of the presence or absence of labor and ROM ( $p=0.077$ ) (Table 2).

The CRP level significantly increased during the course of labor in both nulliparous and multiparous women (Table 3).

Neonates of the mothers with elevated CRP levels ( $\geq 1.0$ mg/dl) were more likely to be admitted to the neonatal care unit for suspicion of infection and/or respiratory problems than neonates of the mothers with low CRP levels ( $<1.0$ mg/dl) ( $p<0.001$ , odds ratio 3.95, 95% confidence interval 2.44-6.41) (Table 4). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 0.448, 0.830, 0.037, and 0.990, respectively (Table 4).

**Discussion**

Szpakowski *et al.* [7] reported that the median value of CRP level in term pregnant women was 0.2 mg/dl and that in women in term labor was significantly elevated to 0.8 mg/dl. In the study by Cicarelli LM *et al.* [42] the maternal CRP level was elevated at the moment of vaginal delivery ( $0.9 \pm 0.7$  mg/dl) compared with that at the admission for delivery ( $0.6 \pm 0.4$  mg/dl). Watts *et al.* [6] reported that the median CRP level for women not in labor ranged from 0.7 to 0.9 mg/dl, and that in women in labor was 1.3 mg/dl. These CRP values were higher than the CRP levels in our study (Tables 1 and 2).

Intraamniotic infection, or chorioamnionitis is a common condition in term and preterm parturients [43]. It is an infection of any

**Table 1.** Clinical characteristics of the analyzed pregnant women

	Nulliparas (n=2133)	Multiparas (n=2479)	p-Value
Age (years)	30.3 ± 4.4	32.6 ± 4.2	<0.001
Gestational age (days)	277.2 ± 7.0	274.8 ± 6.3	<0.001
Height (cm)	158.5 ± 5.3	158.3 ± 5.2	0.325
Prepregnancy weight (kg)	51.0 ± 6.8	51.6 ± 7.2	0.006
Body mass index (kg/m <sup>2</sup> )	20.3 ± 2.4	20.6 ± 2.8	<0.001
Epidural use, n (%)	109 (5.1)	76 (3.1)	<0.001 <sup>†</sup>
Cesarean section, n (%)	119 (5.6)	82 (3.3)	<0.001 <sup>†</sup>
Neonatal weight (g)	3003 ± 343	3087 ± 350	<0.001
CRP level at admission (mg/dl)	0.2 [0.0, 1.3]*	0.1 [0.0, 0.8]*	<0.001 <sup>‡</sup>

Data are presented as mean±standard deviation, or \*median [10th percentile, 90th percentile]  
 p-Value: unpaired t test, †Fisher's exact test, ‡Mann-Whitney U test  
 CRP: C-reactive protein

**Table 2.** CRP level at admission

	A: induction/planned CS		B: onset of labor		C: ROM		p-value for all	p-Value				
	n	CRP	n	CRP	n	CRP		A vs. B	A vs. C	B vs. C		
Total	537	0.0 [0.0, 0.7]	3226	0.2 [0.0, 1.1]	849	0.1 [0.0, 0.8]	<0.001	a	<0.001	0.540	<0.001	B
Nulliparas	247	0.0 [0.0, 0.7]	1353	0.2 [0.0, 1.5]	533	0.1 [0.0, 0.8]	<0.001	a	<0.001	>0.999	<0.001	B
Multiparas	290	0.1 [0.0, 0.8]	1873	0.1 [0.0, 0.8]	316	0.1 [0.0, 0.9]	0.077	a	0.070	0.476	>0.999	B
p-Value (nulliparas vs. multiparas)	0.462		<0.001		0.136			c				

CRP levels are presented as median [10th percentile, 90th percentile] (mg/dl)  
 p-Value □ a, Kruskal-Wallis test □ b, Mann-Whitney U test (Bonferroni correction); c, Mann-Whitney U test (without correction)  
 CS: Cesarean section, ROM: rupture of the membranes

**Table 3.** CRP level changes during the course of labor

	n	CRP at admission	final CRP	p-Value
Total	583	0.2 [0.0, 1.4]	1.7 [0.2, 7.7]	<0.001
Nulliparas	513	0.2 [0.0, 1.4]	1.9 [0.3, 8.0]	<0.001
Multiparas	70	0.2 [0.0, 1.0]	0.5 [0.0, 2.0]	<0.001

CRP level: median [10th percentile, 90th percentile] (mg/dl)  
 p-Value: Wilcoxon signed-rank test  
 CRP: C-reactive protein

**Table 4.** Maternal CRP level and neonatal admission

Neonatal admission	(+)	(-)
CRP $\geq$ 1.0 mg/dl	30	774
CRP<1.0 mg/dl	37	3771
p-Value (Fisher's exact test) <0.001, OR 3.95, 95% CI 2.44-6.41		
Sensitivity	0.448	95%CI 0.336-0.565
Specificity	0.830	95%CI 0.828-0.831
Positive predictive value	0.037	95%CI 0.028-0.047
Negative predictive value	0.990	95%CI 0.988-0.992

CRP: C-reactive protein, OR: odds ratio, CI: confidence interval

combination of the amniotic fluid, placenta, fetus, fetal membranes, or decidua [43]. Chorioamnionitis is associated with significant maternal, perinatal and long-term adverse outcomes [44], and is confirmed through microscopic examination of the delivered placenta and membranes. Therefore, chorioamnionitis cannot be diagnosed before the delivery of the placenta and membranes, posing clinical problems such as delays in antibiotic administration and maternal and neonatal infections. The clinical diagnosis of the chorioamnionitis is based on symptoms including maternal fever, uterine tenderness, purulent vaginal discharge, and maternal and fetal tachycardia [44]. However, uterine tenderness may be masked with epidural use, and fever may also be caused by epidural anesthesia [44]. Moreover, tachycardia may be present without chorioamnionitis [44]. As histological chorioamnionitis is associated with modest systemic inflammation in maternal blood [45], CRP has been studied as a marker for the detection of chorioamnionitis and for the prediction of neonatal infection. The risk factors for chorioamnionitis include nulliparity, longer duration of membrane rupture, and prolonged labor [44]. Intrapartum antibiotics are administered for the treatment of Intraamniotic infection [45]. Our results showed that CRP levels at admission were higher in nulliparous women than in multiparous women, and that CRP increased during the course of labor (Table 3). These findings were consistent with previous reports, although antibiotics were administered before the full manifestation of clinical chorioamnionitis in our cases.

Different cutoff levels of maternal CRP titers have been proposed for detecting chorioamnionitis and predicting neonatal infection. Park *et al.* [46] proposed that a maternal CRP cutoff level of chorioamnionitis was of 1.12 mg/dl. Jeon *et al.* [31] and Lee *et al.* [26] reported that maternal CRP cutoff level for neonatal infection was of 1.22 mg/dl, and 0.8 mg/dl, respectively. However, these cutoff levels were studied in the setting of preterm labor or preterm premature ROM. Popowski *et al.* [39] showed that the concentration of CRP level of  $\geq$ 0.5 mg/dl at admission for premature ROM, including 14.3% women before 37 weeks of gestation, was the most accurate infectious marker for the prediction of early-onset neonatal infection. In this study, CRP cutoff level was set at 1.0 mg/dl as de Meeus *et al.* [38] and Hirsh *et al.* [47] suggested. This cutoff showed a high specificity (0.83) and a very high NPV (0.99); however, the sensitivity (0.45) was not high, and the PPV (0.037) was very low (Table 4). This suggests that low maternal CRP level (<1.0 mg/dl) is rarely associated with neonatal infection or respiratory problems. The high NPV was consistent with other reports [26,39]. Lee *et al.* [26] set a maternal CRP cutoff level of 0.8mg/dl, and the NPV for early-onset neonatal sepsis was 94.6%. Popowski *et al.* [39] also reported a high NPV of 100% for early-onset neonatal infection.

Other inflammatory and infection markers, such as interleukin-6 [48,49], procalcitonin [29,45,50,51], white blood cell count [29,39,52] have also been used alone or in combination for detecting

chorioamnionitis and neonatal infection with widely ranging success rates. Among these markers, CRP is simple, non-invasive, and inexpensive to measure [46]. Asadi *et al.* [29] reported that among CRP, procalcitonin, and white blood cell count, maternal serum CRP level was found to be the most accurate predictor of chorioamnionitis in women with preterm premature ROM.

This study had some limitations. First, the delivered placenta and membranes were not microscopically examined. Therefore, we were unable to determine the precise rate of histological chorioamnionitis in women whose CRP levels were high or low. Second, antibiotics were administered before the full manifestation of the chorioamnionitis. If antibiotics were administered only after chorioamnionitis became clinically apparent, the number of neonates admitted to the intensive care unit might have increased and the results may have been different.

This study also had several strengths. The number of enrolled pregnant women in this study was >4000, which is higher than in other reports [25,26,28-32,38-40]. Moreover, only term pregnant women were enrolled. Maternal CRP level was separately analyzed according to parity and the indication for admission for labor.

In conclusion, maternal CRP levels increase during labor and delivery, and low CRP levels suggest a low likelihood of neonatal infection and respiratory problems.

## Conflict of interest

The author declares no conflicts of interest.

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