

Relationship between Maternal Serum C-Reactive Protein, Funisitis and Early-Onset Neonatal Sepsis

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Received: 16 July 2011
Accepted: 13 March 2012

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The aim of this study was to determine whether maternal serum C-reactive protein (CRP) is of value in predicting funisitis and early-onset neonatal sepsis (EONS) in women with preterm labor or preterm premature rupture of membranes (PROM). This retrospective cohort study included 306 consecutive women with preterm labor or preterm PROM who delivered preterm singleton neonates (23-35 weeks gestation) within 72 hr of CRP measurement. The CRP level was measured with a highly sensitive immunoassay. The sensitivity, specificity, positive predictive value, and negative predictive value 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. Logistic regression analysis demonstrated that elevated levels of serum CRP were significantly associated with funisitis and EONS, even after adjusting gestational age. The maternal serum CRP level obtained up to 72 hr before delivery is an independent predictor of funisitis and EONS in women with preterm labor or preterm PROM. A low serum CRP level (< 8 mg/L) has good negative predictive value in excluding funisitis and EONS, and may therefore be used as a non-invasive adjunct to clinical judgment to identify low-risk patients.

Key Words: C-Reactive Protein; Early-Onset Neonatal Sepsis; Funisitis; Preterm Labor; Preterm Premature Rupture of Membrane

INTRODUCTION

Microbial invasion of the amniotic cavity (MIAC) is considered to be the leading cause of preterm labor or preterm premature rupture of membranes (PROM), with an incidence of approximately 25% of all preterm births (1, 2). A subset of fetuses exposed to microorganisms in utero may elicit the fetal inflammatory response syndrome, including funisitis, which has been implicated as a cause of fetal or neonatal injury that leads to cerebral palsy and chronic lung disease (1, 3-6). Similarly, in the setting of MIAC a substantial number of preterm neonates are born with congenital sepsis, which has a high lethality rate (7) and survivors are at risk for other complications, such as severe retinopathy of prematurity or periventricular leukomalacia (8, 9). Therefore, the early identification of funisitis and congenital sepsis is a desirable clinical goal because a late diagnosis with delayed treatment of these early-onset diseases may increase the possibility of long-term sequelae and disability.

The early prenatal diagnosis of funisitis and/or congenital sepsis is difficult to achieve because the diagnosis of funisitis can only be made with certainty after delivery of the placenta and the diagnosis of congenital sepsis requires invasive procedures, such as cordocentesis. Therefore, several studies have attempted to develop sensitive and specific diagnostic parameters for

funisitis and congenital sepsis via analysis amniocentesis-obtained amniotic fluid (AF), such as the AF white blood cell count and cytokine levels, and such parameters have accordingly been reported as significant predictors (10-15); however, amniocentesis is also an invasive procedure with risks. A recent study has reported that the maternal serum interleukin-6 (IL-6) predicts individuals destined to develop funisitis up to 72 hr before delivery (16). Moreover, funisitis has been implicated as a valuable marker for early-onset neonatal sepsis (13, 17, 18). As IL-6 is thought to be the primary trigger of C-reactive protein (CRP) release (19), it follows that the maternal serum CRP can also be predictive of funisitis and early-onset neonatal sepsis. This information is clinically relevant because measurement of CRP is a non-invasive, rapid, inexpensive, and widely available test for detecting inflammation and tissue damage. The purpose of the current study, therefore, was to determine the diagnostic accuracy of the maternal serum CRP for the prediction of funisitis and early-onset neonatal sepsis in women with preterm labor or preterm premature rupture of membranes.

MATERIALS AND METHODS

Study design

This retrospective cohort study consisted of consecutive wom-

en who were admitted to the Seoul National University Bundang Hospital between January 2004 and December 2010 with the diagnosis of preterm labor and intact membranes or preterm PROM (gestational age < 36 weeks) who met the following criteria: 1) singleton gestation; 2) maternal blood drawn for determination of CRP levels on admission and weekly thereafter until delivery; 3) gestational age at birth > 23.0 weeks and < 36.0 weeks; 4) placental histopathologic examination after preterm delivery; 5) absence of a major congenital anomaly; 6) delivery within 72 hr of CRP measurement. This last criterion was used to preserve a meaningful temporal relationship between the CRP level, placental histology, and neonatal outcome. Throughout the study period, the maternal serum CRP level was routinely measured at the time of admission in women who were diagnosed with preterm labor or preterm PROM. It is the policy at our institution to send the placenta of all preterm babies for histopathologic examination.

Data storage and retrieval

A detailed database of all obstetric patients and neonates admitted to the neonatal intensive care unit at our institution has been maintained since 2004. Demographic, antenatal, delivery, and outcome information data for all preterm births are entered prospectively by research fellows and research assistants. The cohort data retrieved in the database includes maternal age, parity, gestational age at the time of admission and delivery, gender, mode of delivery, causes of preterm birth (preterm labor and preterm PROM), maternal serum CRP on admission, birth weight, Apgar scores at 1 and 5 min, clinical diagnosis of chorioamnionitis, placental pathologic diagnoses, antenatal use of medications (steroids and antibiotics), and the diagnosis of early-onset neonatal sepsis. The serum CRP levels, measured again at weekly intervals after admission, were abstracted from the electronic medical record in those patients who met entry criteria.

Definition of terminology

Preterm labor was defined as the presence of regular uterine contractions with a frequency of at least 2 every 10 min and cervical change that required hospitalization. Rupture of membranes was diagnosed by a sterile speculum examination confirming both pooling of amniotic fluid in the vagina and a positive nitrazine test. Corticosteroids and antibiotics were started if indicated. Clinical chorioamnionitis was defined as a body temperature $\geq 37.8^{\circ}\text{C}$ on 2 occasions at least 4 hr apart, and > 2 of the following criteria: uterine tenderness; malodorous vaginal discharge; maternal leukocytosis ($> 15,000/\mu\text{L}$); maternal tachycardia (> 100 beats/min); and fetal tachycardia (> 160 beats/min) (20). Histologic chorioamnionitis was diagnosed in the presence of acute inflammatory changes in any of the tissue samples (amnion, chorion-decidua, umbilical cord, and chorionic plate) using criteria published previously (11). Funisitis was

diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly. Early-onset neonatal sepsis was defined as the presence of confirmed or suspected sepsis at ≤ 72 hr after birth. Confirmed sepsis was diagnosed when either the blood culture and/or cerebrospinal fluid culture was positive. Suspected sepsis was diagnosed in the absence of a positive culture when two or more of the following previously validated hematologic criteria (21, 22) were observed: absolute neutrophil count $< 7,500/\mu\text{L}$ or $> 14,500/\mu\text{L}$; absolute band count $> 1,500/\mu\text{L}$; immature/total neutrophil ratio > 0.16 ; and platelet count $< 150,000/\mu\text{L}$.

C-reactive protein measurements

The CRP level was measured with a latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) using an automated analyzer (Toshiba 200FR; Toshiba, Tokyo, Japan). The detection limit of this assay is 0.1 mg/L. Both intra- and inter-assay coefficients of variation were $< 10\%$.

Statistical analysis

A Student's t-test or Mann-Whitney U-test was used for comparison of continuous variables. Comparisons of proportions were performed with a chi-squared-test or Fisher's exact test. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution of the data. A receiver operating characteristic (ROC) curve analysis was used to determine the relationship between the sensitivity (true-positive rate) and the false-positive rate, and to select the best cut-off value for the serum CRP in the prediction of funisitis and early-onset neonatal sepsis. Diagnostic indices were calculated (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPP], positive likelihood ratio [LR+], and negative likelihood ratio [LR-]) for the serum CRP to identify funisitis and early-onset neonatal sepsis. A logistic regression analysis was performed to determine the relationship between serum CRP levels and the occurrence of funisitis and early-onset neonatal sepsis after adjusting for baseline variables that have a significant correlation or a tendency with each of the outcome variables ($P < 0.15$), including gestational age, clinical chorioamnionitis, use of antenatal steroids and use of antenatal antibiotics (Table 1). In the logistic regression model, all factors were entered as dichotomous variables and the ROC curves were used to identify the best cut-off values for the dichotomization of variables. All reported P values were two-sided, and P values < 0.05 were considered statistically significant. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Ethics statement

The study protocol was reviewed and approved by the institutional review board of the Seoul National University Bundang Hospital (IRB No. B-1006/103-102). Informed consent was waived

by the board due to retrospective approach of this study.

RESULTS

Study population

During the study period, 514 women with a viable singleton preg-

Table 1. Demographic and clinical characteristics of women and their newborns according to the presence or absence of funisitis

Characteristics	Funisitis		P value
	Absent (n = 252)	Present (n = 54)	
Maternal characteristics at admission and hospital course			
Maternal age (yr)	31.0 ± 4.1	31.9 ± 3.5	0.177
Nulliparity	131 (52%)	27 (50%)	0.791
Gestational age at admission (weeks)	32.3 ± 3.0	29.7 ± 3.4	< 0.001
Cause of preterm delivery			0.243
Preterm labor	91 (36%)	15 (28%)	
Preterm PROM	161 (64%)	39 (72%)	
Antenatal antibiotics use	175 (69%)	47 (87%)	0.009
Antenatal corticosteroid use	122 (48%)	40 (74%)	0.001
Clinical chorioamnionitis	7 (3%)	14 (26%)	< 0.001
Serum CRP (mg/L)	10.9 ± 17.9	21.9 ± 17.3	< 0.001
Outcome characteristics			
Gestational age at delivery (weeks)	32.9 ± 2.6	30.5 ± 3.2	< 0.001
Cesarean delivery	89 (35%)	16 (30%)	0.424
Birth weight (g)	2,051 ± 564	1,629 ± 581	< 0.001
Male fetus	154 (61%)	31 (57%)	0.613
Apgar score < 7			
1 min	97 (39%)	29 (54%)	0.039
5 min	37 (15%)	14 (26%)	0.044
Histologic chorioamnionitis	89 (35%)	53 (98%)	< 0.001
Early-onset neonatal sepsis	20 (8%)	11 (20%)	0.006

Values are given as the mean ± standard deviation or No. (%). PROM, premature rupture of membranes; CRP, C-reactive protein.

nancy initially diagnosed with preterm labor or preterm PROM delivered between 23.1 and 35.6 weeks gestation. Of these 514 women, 3 (0.6%) were excluded due to neonatal deaths in the delivery room, 1 (0.2%) for major congenital malformations, and 117 (23%) for an incomplete data set (lack of placental pathology [n = 15] and lack of maternal serum CRP level on admission, or thereafter at weekly intervals until delivery [n = 102]). Eighty-seven additional women were excluded because of CRP measurement-to-delivery intervals > 72 hr. The remaining 306 women, who fit the study criteria, defined the study cohort: 106 women had preterm labor with intact membranes and 200 women had preterm PROM. No significant differences were noted between women with preterm PROM and intact membranes with respect to the mean CRP level and the rates of clinical chorioamnionitis and early-onset neonatal sepsis. However, women with preterm labor had a significantly lower gestational age at the time of admission and delivery and a higher rate of histologic chorioamnionitis than did women with preterm PROM (gestational age at delivery, 31.9 ± 2.9 vs 32.7 ± 2.8 weeks, *P* = 0.031; rate of histologic chorioamnionitis, 54.7% [58/106] vs 42% [84/200], *P* = 0.034). The reasons for not measuring CRP included immediate delivery following hospital admission and attending physician preference for the follow-up CRP measurements.

Funisitis was present in 17.6% of the cases (54/306) and early-onset neonatal sepsis was diagnosed in 10.4% of the cases (31/306). Of 31 neonates with early-onset neonatal sepsis, 6.5% (2/31) were diagnosed based on blood culture results and 93.5% (29/31) were clinically suspected to have sepsis. Microorganisms isolated from blood cultures included coagulase-negative

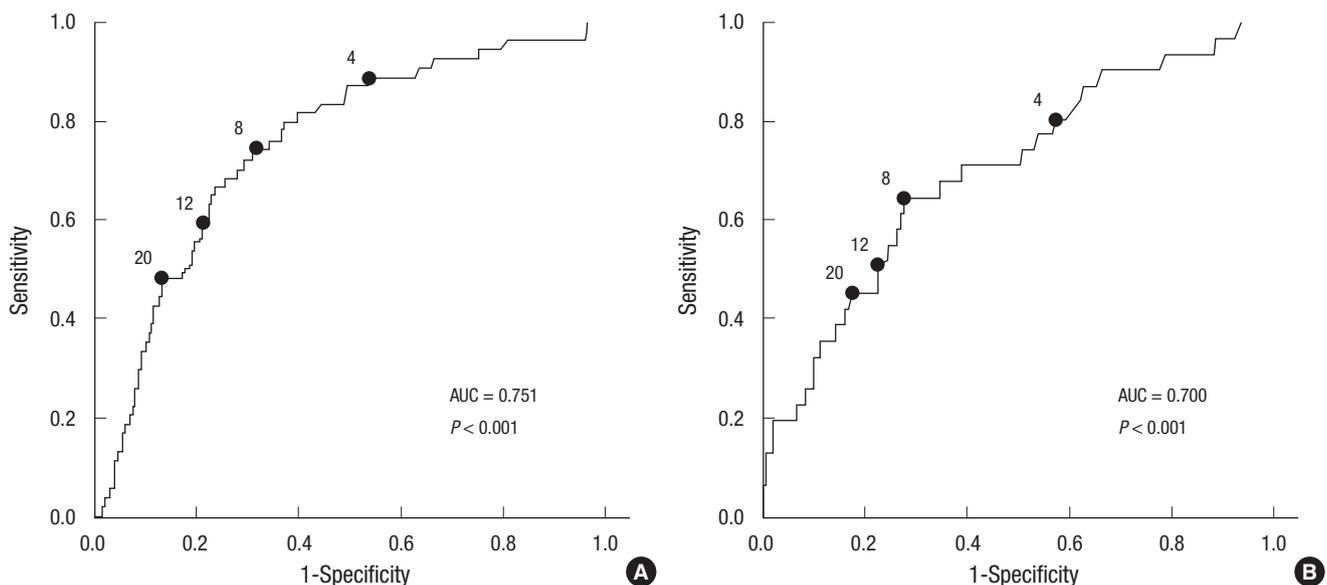


Fig. 1. Receiver operating characteristic (ROC) curves for maternal serum C-reactive protein (CRP). **(A)** For predicting funisitis. Numbers next to solid dots represent serum CRP levels (mg/L; area under the curve, 0.751; SE, 0.036; *P* < 0.001). **(B)** For predicting early-onset neonatal sepsis. Numbers next to solid dots represent serum CRP levels (mg/L; area under the curve, 0.700; SE, 0.051; *P* < 0.001).

Table 2. Diagnostic indices of different C-reactive protein levels in the prediction of funisitis and early-onset neonatal sepsis

	Sensitivity (% [n])	Specificity (% [n])	PPV (% [n])	NPV (% [n])	LR+ (95% CI)	LR- (95% CI)
CRP \geq 4 mg/L						
Funisitis	88.9 (48/54)	41.3 (104/252)	24.5 (48/196)	94.5 (104/110)	1.51 (1.32-1.74)	0.27 (0.13-0.58)
Early-onset neonatal sepsis	83.9 (26/31)	38.2 (105/275)	13.3 (26/196)	95.5 (105/110)	1.36 (1.13-1.63)	0.42 (0.19-0.96)
CRP \geq 8 mg/L						
Funisitis	74.1 (40/54)	67.5 (170/252)	32.8 (40/122)	92.4 (170/184)	2.28 (1.80-2.89)	0.38 (0.24-0.61)
Early-onset neonatal sepsis	67.7 (21/31)	63.3 (174/275)	17.2 (21/122)	94.6 (174/184)	1.84 (1.38-2.46)	0.51 (0.30-0.86)
CRP \geq 12 mg/L						
Funisitis	59.3 (32/54)	77.4 (195/252)	36.0 (32/89)	89.9 (195/217)	2.62 (1.91-3.60)	0.53 (0.38-0.73)
Early-onset neonatal sepsis	54.8 (17/31)	73.8 (203/275)	19.1 (17/89)	93.5 (203/217)	2.10 (1.44-3.05)	0.61 (0.41-0.91)
CRP \geq 20 mg/L						
Funisitis	48.1 (26/54)	86.9 (219/252)	44.1 (26/59)	88.7 (219/247)	3.68 (2.41-5.61)	0.60 (0.46-0.78)
Early-onset neonatal sepsis	41.9 (13/31)	83.3 (229/275)	22.0 (13/59)	92.7 (229/247)	2.51 (1.53-4.10)	0.70 (0.52-0.95)

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; CI, confidence interval; CRP, C-reactive protein.

Table 3. Logistic regression analyses of independent variables in predicting funisitis and early-onset neonatal sepsis

Variables	Odds ratio	95% CI	P value
Funisitis			
CRP \geq 8 mg/L	4.44	2.11-9.34	< 0.001
Gestational age at delivery \leq 32 weeks	2.74	1.25-6.03	0.012
Antenatal antibiotics	3.03	1.16-7.88	0.023
Antenatal corticosteroids	1.27	0.55-2.93	0.569
Clinical chorioamnionitis	6.97	2.41-20.2	< 0.001
Early-onset neonatal sepsis			
CRP \geq 8 mg/L	2.81	1.21-6.51	0.016
Gestational age at delivery \leq 32 weeks	1.55	0.68-3.57	0.298
Clinical chorioamnionitis	3.65	1.26-10.56	0.017

CI, confidence interval; CRP, C-reactive protein.

Staphylococcus (n = 1) and *Acinetobacter baumannii* (n = 1).

Relationship between serum CRP and funisitis

Table 1 shows the demographic and clinical characteristics of the women and their newborns according to the presence or absence of funisitis. Women with funisitis had a significantly lower mean gestational age at the time of admission and delivery, higher rates of clinical chorioamnionitis and histologic chorioamnionitis, were more likely to receive antenatal antibiotics and corticosteroids, and were more likely to deliver neonates with early-onset neonatal sepsis than women without funisitis. However, there were no significant differences in the mean maternal age and the distribution of women with preterm PROM and intact membranes between these two groups. The mean serum CRP levels were significantly higher in women with funisitis than in women without funisitis.

Fig. 1A is a ROC curve describing the values of the serum CRP levels in predicting funisitis. The curve constructed for the maternal serum CRP was above the 45° line, indicating a significant relationship with funisitis (area under the curve [AUC], 0.751; standard error [SE], 0.036; $P < 0.001$). The best cut-off value for CRP to predict funisitis was 8 mg/L. The sensitivity, specificity, PPV, NPV, LR+, and LR- of an elevated serum CRP level (\geq 8 mg/L) to predict funisitis are shown in Table 2.

Table 4. Demographic and clinical characteristics of women and their newborns according to the presence or absence of early-onset neonatal sepsis

Characteristics	Early-onset neonatal sepsis		P value
	Absent (n = 275)	Present (n = 31)	
Maternal characteristics at admission and hospital course			
Maternal age (yr)	31.2 \pm 4.1	31.2 \pm 2.7	0.921
Nulliparity	142 (52%)	16 (52%)	0.998
Gestational age at admission (weeks)	32.0 \pm 3.2	30.3 \pm 3.6	0.011
Cause of preterm delivery			0.769
Preterm labor	96 (35%)	10 (32%)	
Preterm PROM	179 (65%)	21 (68%)	
Antenatal antibiotics use	201 (73%)	21 (68%)	0.527
Antenatal corticosteroid use	145 (53%)	17 (55%)	0.823
Clinical chorioamnionitis	14 (5%)	7 (23%)	< 0.001
Serum CRP (mg/L)	11.0 \pm 13.9	28.7 \pm 36.8	< 0.001
Outcome characteristics			
Gestational age at delivery (weeks)	32.6 \pm 2.7	30.8 \pm 3.4	0.003
Cesarean delivery	90 (33%)	15 (48%)	0.082
Birth weight (g)	2,118 \pm 573	1,614 \pm 609	0.001
Male fetus	167 (61%)	18 (58%)	0.774
Apgar score < 7			
1 min	105 (38%)	21 (68%)	0.002
5 min	38 (14%)	13 (42%)	< 0.001
Histologic chorioamnionitis	123 (45%)	19 (61%)	0.08
Funisitis	43 (16%)	11 (36%)	0.006

Values are given as the mean \pm standard deviation or No. (%). PROM, premature rupture of membranes; CRP, C-reactive protein.

To control for the significant differences in gestational age at the time of delivery, clinical chorioamnionitis, use of antenatal steroids, and use of antenatal antibiotics, we performed logistic regression analysis. Using the cut-off values derived from the ROC curves, elevated levels (\geq 8 mg/L) of maternal serum CRP were significantly associated with funisitis, even after controlling for gestational age, chorioamnionitis, use of antenatal steroids, and use of antenatal antibiotics (odds ratio [OR], 4.44, 95% confidence interval [CI] 2.11-9.34; Table 3).

Relationship between serum CRP and early-onset neonatal sepsis

Table 4 describes the demographic and clinical characteristics

of the women and their newborns according to the presence or absence of early-onset neonatal sepsis. Women who delivered neonates with early-onset neonatal sepsis had a lower mean gestational age at the time of admission and significantly higher rates of clinical chorioamnionitis and funisitis when compared with women delivering neonates without early-onset neonatal sepsis. Neonates with early-onset neonatal sepsis were delivered earlier and had a lower mean birth weight and lower Apgar scores compared with those without early-onset neonatal sepsis. However, there were no significant differences in the mean maternal age, the prevalence of histologic chorioamnionitis, and the proportion of mothers receiving antenatal antibiotics or corticosteroids between mothers of neonates with early-onset neonatal sepsis compared with those who delivered without sepsis. The mean serum CRP levels were significantly higher in women delivering neonates with early-onset neonatal sepsis than women delivering neonates without early-onset neonatal sepsis.

A ROC curve was constructed and used to select cut-off values to dichotomize serum CRP levels as being increased or not increased (AUC, 0.700; SE, 0.051; $P < 0.001$; Fig. 1B). A cut-off value of 8 mg/L for serum C-reactive protein appeared to represent a reasonable compromise between the sensitivity and specificity, and was then used to calculate diagnostic indices for the prediction of early-onset neonatal sepsis. The sensitivity, specificity, PPV, NPV, LR+, and LR- to predict early-onset neonatal sepsis are shown in Table 2. To determine the significant independent predictive effect of CRP on early-onset neonatal sepsis, logistic regression analysis was performed. Based on this model, an elevated CRP level (≥ 8 mg/L) was significantly associated with early-onset neonatal sepsis after adjustment for gestational age at delivery and clinical chorioamnionitis (OR, 2.81; 95% CI, 1.21-6.51; Table 3).

DISCUSSION

A number of studies have assessed the relationship between early-onset neonatal sepsis and the maternal serum CRP level; some studies have demonstrated a significant association (12, 23, 24), while other studies have failed to do so (25, 26). This discrepancy among studies is probably attributable, in part, to a wide variety of time intervals between CRP measurement and delivery. Indeed, a recent study in which daily blood samples were collected from women with preterm PROM revealed that maternal serum IL-6 rises as much as 72 hr before the onset of labor or clinical infection (16). Therefore, the current study was restricted to the women who delivered within 72 hr of the CRP measurement, so that the CRP measurement, neonatal outcome, and histologic examination of the placenta could be compared in a temporally meaningful way, and showed that CRP measurement independently predicted early-onset neonatal sepsis. Nevertheless, in the current study the AUC for the maternal serum

CRP was relatively small (95% CI, 0.600-0.800) and the likelihood ratio was 1.84, which suggests that the usefulness of serum CRP alone as a predictor of early-onset neonatal sepsis is limited. These findings are in agreement with the recent study by van der Heyden et al. (24).

From a practical point of view, we propose that the maternal serum CRP level can be used as a screening test for early-onset neonatal sepsis and funisitis rather than a diagnostic test. Specifically, screening for early-onset neonatal sepsis and funisitis would begin with a maternal serum CRP measurement which can classify women with preterm labor or preterm PROM into high- and low-risk groups, and those at high-risk could then be targeted for appropriate risk-specific intervention (e.g., amniocentesis).

A maternal serum CRP < 8 mg/L has good negative predictive value for early-onset neonatal sepsis and funisitis, suggesting that a low CRP can identify women and their newborns who may safely avoid overtreatment (e.g., antibiotics and invasive intervention). These findings are consistent with the reports by Kurki et al. (26) and Ernest et al. (27) who demonstrated that negative CRP values before delivery strongly suggest the absence of chorioamnionitis and/or neonatal infection. The current study showed that approximately 60% of patients presenting with preterm labor or preterm PROM will be included into this category. This finding is supported in the literature, in which 67% of women presenting with preterm labor had a CRP < 8 mg/L (28). CRP has the potential to accurately identify a significant portion of women presenting with preterm labor or preterm PROM as low risk for early-onset neonatal sepsis and funisitis.

Several investigators have reported that the maternal serum CRP is valuable for the early diagnosis of histologic chorioamnionitis in the absence of clinical signs of infection (10-12, 23). However, to date there have been no reports on maternal serum CRP levels in relation to funisitis. Our finding that serum CRP levels are related to funisitis is novel, but not unexpected because a similar relationship has been demonstrated with IL-6, the primary cytokine responsible for the biosynthesis of CRP (16). Indeed, a significant relationship between maternal serum IL-6 and CRP level has been shown (29).

This is the first study to examine the independent predictive value of the maternal serum CRP level for funisitis. A fetal involvement assessment is an important step in the management of infection-associated preterm labor or preterm PROM. The difficulty with this assessment has led to development of a number of markers in umbilical cord plasma at birth and amniotic fluid. However, evaluating markers in these body fluids is rarely helpful in the early prediction of funisitis as access to these body fluids is limited in an ongoing pregnancy or may require the use of invasive techniques. In contrast, CRP test in maternal serum, as used in the current study, is non-invasive, inexpensive, and easily performed before delivery, thus allowing for serial test-

ing. Therefore, our finding that the serum CRP is independently predictive of funisitis can be beneficial to clinicians in counseling and clinical management of women with preterm labor or preterm PROM.

Our study had several limitations. First, the most important one is the retrospective design. However, most data (i.e., maternal, placental, and other perinatal parameters) were collected prior to inclusion in the study by means of an electronically-prepared Excel-based (Microsoft Corporation, Redmond, WA, USA) data collection tool. Thus, each data element was accurately documented and verified. Second, we included a heterogeneous group of women regarding the status of fetal membranes (e.g., intact or ruptured fetal membranes). However, we believe that our main results remain valid because elevated levels of serum CRP were significantly associated with both funisitis and early-onset neonatal sepsis after adjustment for the confounding variables (gestational age, clinical chorioamnionitis, and the state of fetal membranes).

In conclusion, a maternal serum CRP level obtained up to 72 hr before delivery is an independent predictor of funisitis and early-onset neonatal sepsis in women with preterm labor or preterm PROM but the usefulness is limited. A serum CRP level < 8 mg/L has a good negative predictive value in excluding funisitis and early-onset neonatal sepsis, and may therefore be a useful non-invasive adjunct to clinical judgment to identify low-risk patients. These findings need to be replicated prospectively in a second larger cohort because a recent study has found a significant influence of socio-demographic characteristics (e.g., race) on CRP values during normal pregnancy (30).

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