Usefulness of Maternal Serum C-reactive Protein in Predicting Funisitis and Early-onset Neonatal Sepsis in Women with Preterm Prelabour Rupture of Membranes

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Objectives: To evaluate the usefulness of serum C-reactive protein (CRP) in women with preterm prelabour rupture of membranes (PPROM) in the prediction of funisitis and early-onset neonatal sepsis (EONS), to determine a CRP cutoff value for their prediction, and to identify other significant risk factors associated with funisitis and EONS.
Methods: This was a retrospective study conducted in a tertiary hospital in Hong Kong. Women with a singleton pregnancy at 24 to 34 weeks of gestation and had PPROM were recruited between January 2011 and December 2015. Maternal serum CRP level, histopathological diagnosis of the placenta, and incidence of EONS were evaluated.
Results: Among the 123 women recruited, funisitis was present in 21.1% of the women and EONS in 19.5% of the newborns. Maternal serum CRP level was associated with funisitis that was in turn associated with EONS. There was, however, no significant association between maternal serum CRP and EONS. Using a CRP cutoff value of 7.65 mg/l to predict funisitis, the sensitivity, specificity, positive predictive value, and negative predictive value were 65.4%, 78.4%, 44.7%, and 89.4%, respectively. The gestational age at delivery was the most significant risk factor for funisitis and EONS. Birth weight and Apgar score were significantly lower in women with funisitis and newborns with EONS than those without. Other risk factors for EONS included a positive high vaginal swab and placental swab cultures and the presence of group B *Streptococcus* in a high vaginal swab.
Conclusions: Maternal serum CRP may be helpful in the prediction of funisitis in women with PPROM. Nonetheless, the study did not show any association between maternal serum CRP and EONS. The CRP level should be interpreted with caution in a clinical setting. The gestational age at delivery was the most significant determining factor for funisitis and EONS.
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Keywords: Chorioamnionitis; C-reactive protein; Fetal membranes, premature rupture; Neonatal sepsis

Introduction

Preterm premature rupture of membranes (PPROM) occurs in 1% to 3% of all pregnancies and is responsible for approximately one-third of all preterm births[1]. Gestational age at membrane rupture and delivery has a significant impact on neonatal morbidity and mortality[2]. Balancing the benefits of prolonging pregnancy for fetal maturation with the risks of infection remains a challenge to obstetricians. On the other hand, prediction and early detection of intrauterine infection and in turn early-onset neonatal sepsis (EONS) would be helpful in such conditions.

Clinical signs such as fever and fetal heart rate abnormalities often present late. In fact, several studies have attempted to identify sensitive and specific diagnostic parameters for subclinical intrauterine infection and EONS[3-5]. Some involved analysis of amniotic fluid white cell count, cytokine level, or culture results[6-8] but all are invasive and involve a long turnaround time, thus they are not practical in day-to-day clinical practice.

C-reactive protein (CRP) is an acute phase protein secreted by the liver in response to inflammation. Although not specific to infection, maternal serum CRP is widely used in clinical practice in an attempt to detect occult infection. Numerous studies have investigated such a correlation but results have been controversial[9-12]. Furthermore, some studies focused on histological chorioamnionitis / funisitis rather than neonatal outcome[13]. To the best of our knowledge, no similar studies have been conducted in our local population on determining whether maternal serum

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CRP is of value in predicting funisitis and EONS in women with PPROM.

In this study, we aimed to evaluate the usefulness of maternal serum CRP in women with PPROM in the prediction of funisitis and in particular EONS, to determine a cutoff value for CRP in the prediction, and to identify other significant risk factors associated with funisitis and EONS.

Methods

This retrospective cohort study was conducted at Princess Margaret Hospital, a tertiary hospital in Hong Kong. The study was approved by the Hospital Authority Research Ethics Committee (Kowloon West Cluster), with patient consent waived.

Women admitted with a diagnosis of PPROM between January 2011 and December 2015 and delivered in the hospital were recruited. They were identified from the Obstetrics Clinical Information System, which is a well-established database containing maternal and neonatal information on all women who deliver in our hospital. The inclusion criteria of this study included: singleton pregnancy; gestational age at PPROM of >24 weeks and <34 weeks; no tocolytics, antibiotics, or steroids in the 7 days preceding admission; no clinical signs of chorioamnionitis; admission within 24 hours of PPROM; maternal serum CRP level available within 12 hours of admission and within 48 hours of delivery; and no major fetal congenital malformation. Non-Chinese women were excluded.

For each eligible woman, demographic data, pregnancy outcome, and neonatal outcome were retrieved from the medical records. Maternal data included maternal age; parity; gestational age at the time of PPROM and delivery; mode of delivery; maternal serum CRP levels; culture results; antenatal use of steroid, antibiotics, and tocolytics; and placental histology. Neonatal data included neonatal blood culture and surface swab results, birth weight, Apgar score at 1 and 5 minutes, and a diagnosis of EONS.

Rupture of membranes was diagnosed by sterile speculum examination that confirmed both pooling of amniotic fluid and a positive rapid dipstick test (Actim PROM; Medix Biochemica, Espoo, Finland). Antibiotics and steroids were administered in all women included in the study. Tocolytics were administered, if indicated, to delay delivery in order to complete the course of steroids. From admission until delivery, maternal serum CRP level was measured every 1 to 2 days depending on the clinical situation.

Concentration of CRP was measured by an immunoturbidimetric procedure using the Abbott Architect chemistry analyser (Abbott Laboratories, Abbott Park [IL], US). Clinical chorioamnionitis was defined as a body temperature of ≥37.8°C on two occasions at least 4 hours apart, and two or more of the following: uterine tenderness, foul-smelling vaginal discharge, maternal tachycardia (>100 beats/min), maternal leukoytosis (>15000/μl), or fetal tachycardia (>160 beats/min)[14].

In our unit, the standard practice is delivery at 34 weeks of gestation if there are no single features of clinical chorioamnionitis, and if the woman appears normal under close maternal and fetal surveillance. Delivery is strongly advised if there are frank signs of clinical chorioamnionitis. The option of delivery is discussed when the diagnostic criteria of clinical chorioamnionitis are partially fulfilled, or when there are early signs of maternal or fetal compromise.

The primary outcome was the incidence of funisitis and either confirmed or probable EONS. Definitions of various terms in this study are shown in Table 1[15,16].

Statistical Analysis

Statistical analysis was performed using PASW Statistics 18, Release version 18.0.0 (SPSS Inc., Chicago [IL], US). For categorical data, the Chi-square test and Fisher's exact test were used according to the data pattern. For continuous data with normal distribution, independent-samples *t* test was used. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

A receiver operating characteristic (ROC) curve using the points on the curve closest to the (0, 1) and Youden Index was used to establish a cutoff level of serum CRP in predicting funisitis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR–) for ability of serum CRP to identify funisitis were calculated.

Statistically significant variables were adopted as potential predictors and entered into a logistic regression analysis to look for significant factors of funisitis and suspected neonatal sepsis. The multiple logistic regression

Table 1. Definition used in this study[15,16]

Term	Definition in this study
Histological funisitis	Presence of neutrophils in the wall of the umbilical vessels
Confirmed systemic neonatal sepsis	Positive culture from blood or cerebrospinal fluid
Confirmed EONS	Sepsis manifested within 72 hours of birth
Probable EONS	Presence of one or more of the clinical signs of infection from (a) to (f), together with one or more of (g) to (j): (a) Respiratory distress (i.e. requiring ventilation, continuous positive airway pressure, or supplemental oxygen for >1 hour) (b) Apnoea (c) Lethargy (d) Abnormal level of consciousness (e) Circulatory compromise (i.e. hypotension, poor perfusion, need for inotropic support, or volume expansion) (f) Temperature instability (temperature <36°C or ≥38°C) for which the baby was treated with antibiotics for ≥5 days (g) Abnormal full blood count (i.e. white cell count <5 x 10^9 cells/l or > 30 x 10^9 cells/l, platelet count <100 000 cells/ml) (h) C-reactive protein >10 mg/l (i) Growth of a known virulent pathogen from a surface swab (j) Histological diagnosis of pneumonia in an early neonatal death

Abbreviation: EONS = early-onset neonatal sepsis

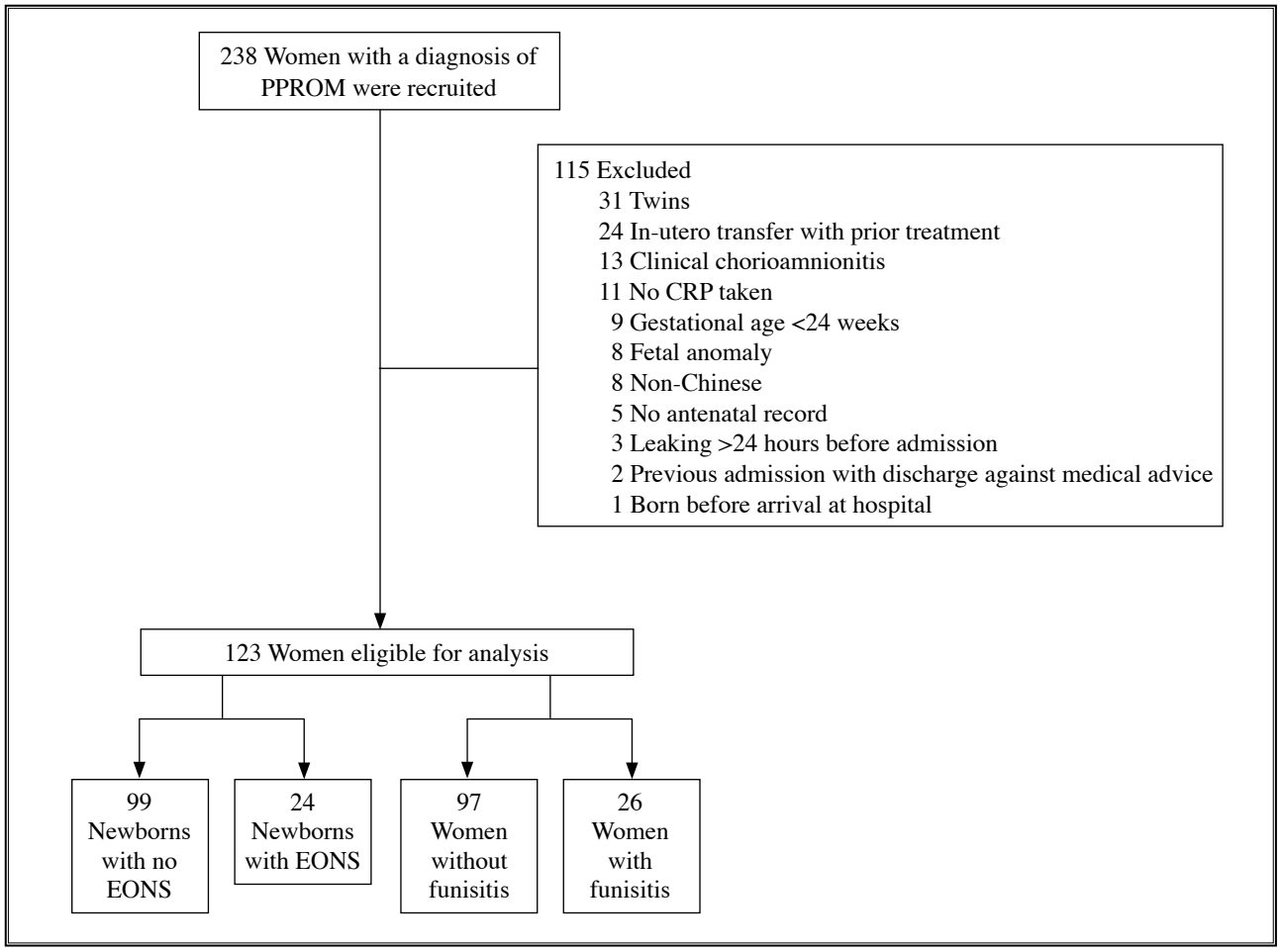

Figure 1. Flowchart showing the recruitment process and outcome (neonatal sepsis)

Abbreviations: CRP = C-reactive protein; EONS = early-onset neonatal sepsis; PPROM = preterm premature rupture of membranes

Table 2. Demographic and clinical characteristics of women and newborns with and without funisitis and early-onset neonatal sepsis*

Demographics / characteristics	Funisitis			Early-onset neonatal sepsis		
	Yes (n=26)	No (n=97)	p Value	Yes (n=24)	No (n=99)	p Value
Age (years)	31.27 ± 4.85	33.15 ± 4.60	0.069	33.00 ± 5.00	32.70 ± 4.64	0.778
Gravida	2 (1-3)	2 (1-4)	0.817	2 (1-3)	2 (1-3)	0.960
Parity	1 (0-1)	0 (0-1)	0.216	1 (0-1)	0 (0-1)	0.584
Maternal length of hospital stay (days)	6 (4-10)	5 (4-8)	0.654	7 (4-8)	5 (4-9)	0.916
Gestational age at PPROM (weeks)	28 (27-31)	32 (30-33)	<0.001	30 (26-32)	32 (30-33)	0.010
Gestational age at delivery (weeks)	30 (27-31)	32 (31-33)	<0.001	31 (27-32)	32 (31-33)	0.004
Days between PPROM and delivery	2 (1-5)	2 (0-5)	0.700	3 (1-5)	2 (1-5)	0.737
Temperature on admission (°C)	36.8 (36.6-37.2)	36.7 (36.5-37.0)	0.096	36.9 (36.6-37.1)	36.8 (36.6-37.1)	0.725
Mode of delivery			0.530			0.021
Normal vaginal delivery	17 (65.4%)	58 (59.8%)		20 (83.3%)	55 (55.6%)	
Instrumental delivery	0 (0%)	3 (3.1%)		0 (0%)	3 (3.0%)	
Lower-segment Caesarean section	8 (30.8%)	35 (36.1%)		3 (12.5%)	40 (40.4%)	
Classical Caesarean section	1 (3.8%)	1 (1.0%)		1 (4.2%)	1 (1.0%)	
Birth weight (g)	1145 (1034-1704)	1790 (1548-2030)	<0.001	1435 (1057-1773)	1790 (1490-2030)	0.002
Apgar score at 1 min	7 (7-8)	8 (7-9)	0.008	7 (6-9)	8 (7-9)	0.031
Apgar score at 5 mins	9 (9-10)	10 (9-10)	0.025	9 (9-10)	10 (9-10)	0.023
Pre-existing bacterial vaginosis	1 (3.8%)	2 (2.1%)	0.513	0 (0%)	3 (3.0%)	1.000
Use of tocolytics	14 (53.8%)	58 (59.8%)	0.585	12 (50.0%)	60 (60.6%)	0.344
Serum CRP level (mg/l)						
Day 1 (n=123)	9.85 (3.38-26.75)	4.90 (2.70-8.25)	0.029	6.90 (2.83-12.75)	4.90 (2.90-9.90)	0.459
Day 2 (n=61)	6.10 (4.25-25.50) [n=13]	3.55 (2.45-8.50) [n=48]	0.013	4.50 (2.75-12.50) [n=10]	4.40 (2.60-9.10) [n=51]	0.704
Day 3 (n=61)	6.45 (3.68-15.25) [n=16]	2.40 (1.06-6.35) [n=45]	0.002	3.60 (2.00-9.25) [n=13]	3.55 (2.00-7.70) [n=48]	0.853
Day 4 (n=43)	3.50 (2.00-10.95) [n=9]	2.30 (1.18-3.05) [n=34]	0.101	2.20 (1.10-4.80) [n=7]	2.30 (1.43-3.20) [n=36]	0.881
Day 5 (n=35)	2.3 (1.33-3.78) [n=10]	2.00 (1.00-3.25) [n=25]	0.373	2.00 (1.00-3.00) [n=9]	2.30 (1.00-3.33) [n=26]	0.659
Last serum CRP level before delivery (mg/l) [n=123]	11.00 (2.58-24.25)	4.20 (2.30-7.00)	0.002	4.10 (2.30-12.50)	4.60 (2.30-8.00)	0.883
% change in serum CRP level: (last–day 1)/day 1	0 (-27.3% to 68.8%)	0 (-32.4% to 0%)	0.090	0 (-11.9% to 9.1%)	0 (-32.4% to 0%)	0.960
High vaginal swab culture positive	8 (30.8%)	22 (22.7%)	0.394	10 (41.7%)	20 (20.2%)	0.028
Midstream urine culture positive	1 (12.5%) [n=8]	2 (6.1%) [n=33]	0.488	0 (0%)	3 (9.7%) [n=31]	0.564
Placental swab culture positive	9 (34.6%)	25 (25.8%)	0.371	13 (54.2%)	21 (21.2%)	0.001
Presence of group B *Streptococcus*	6 (23.1%)	10 (10.3%)	0.104	8 (33.3%)	8 (8.1%)	0.003
Perinatal death	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Histological funisitis	-	-	-	10 (41.7%)	16 (16.2%)	0.006

Abbreviations: CRP = C-reactive protein; PPROM = preterm premature rupture of membranes

* Data are shown as mean ± standard deviation, median (range), or No. (%) of subjects

analysis (backward / forward elimination procedure) was performed by including variables that were significant at the level of p<0.1 by univariate analysis and the importance of the demographic variable.

Results

Among the 238 deliveries with a diagnosis of PPROM, 123 met the inclusion criteria (Figure 1). Funisitis was present in 21.1% (26/123) of women and EONS in 19.5% (24/123) of newborns. None of the EONS had a positive blood or cerebrospinal fluid culture, and all were diagnosed on the basis of clinical and laboratory results using the definitions mentioned above.

Table 2 shows the demographic and clinical characteristics of patients with funisitis. Women with funisitis had a significantly lower median gestational age than those without funisitis at PPROM (28 vs. 32 weeks; p<0.001) and at delivery (30 vs. 32 weeks; p<0.001). Babies with funisitis had a lower median birth weight (1145 g vs. 1790 g; p<0.001) and Apgar score at 1 minute (7 vs. 8; p=0.008) and 5 minutes (9 vs. 10; p=0.025) after birth than those without funisitis. The median serum CRP level of women with funisitis was significantly higher on day 1, 2, and 3 of PPROM and before delivery than those without funisitis (p<0.05 for all). The first and last CRP levels did not show any significant percentage change in either group. The PPROM-to-delivery interval was comparable for the two groups.

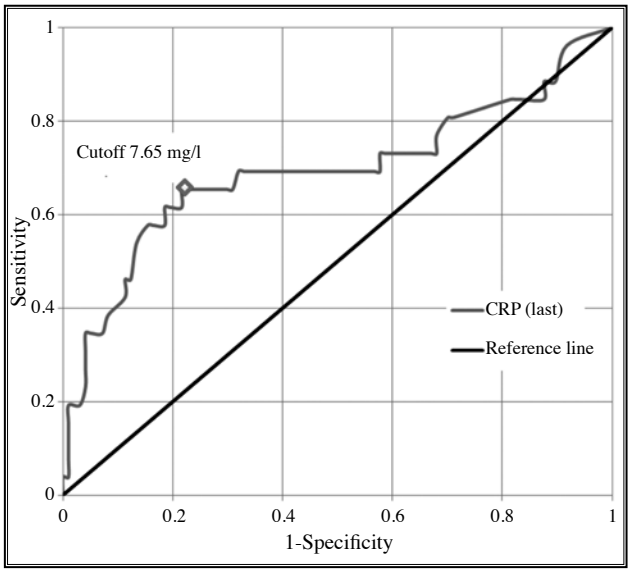

Figure 2. Receiver operating characteristic curve for the last maternal serum C-reactive protein (CRP) level for funisitis

Table 3. Logistic regression analysis of independent variables in predicting funisitis

Risk factor	OR (95% CI)	p Value
Maternal age	0.842 (0.745-0.952)	0.006
Gestational age at delivery	0.598 (0.467-0.765)	<0.001
Last serum CRP level	1.074 (1.029-1.122)	0.001

Abbreviations: CI = confidence interval; CRP = C-reactive protein; OR = odds ratio

Figure 2 shows the ROC curve of the last maternal serum CRP level before delivery in predicting funisitis. The curve is above the reference line indicating a significant relationship between CRP and funisitis (area under curve [AUC] = 0.693; 95% confidence interval [CI], 0.56-0.83; p<0.003). The best cutoff value for CRP to predict funisitis was 7.65 mg/l. Using this value, the sensitivity, specificity, PPV, and NPV were 65.4% (17/26), 78.4% (76/97), 44.7% (17/38), and 89.4% (76/85), respectively. The LR+ and LR– were 3.02 (95% CI, 1.89-4.84) and 0.44 (95% CI, 0.26-0.76), respectively. The ROC curves for CRP on day 1, 2, and 3 of PPROM were not plotted as the 95% CI of AUC crossed 0.5.

Table 3 shows the logistic regression analysis for funisitis. Maternal age, gestational age at delivery, and last maternal serum CRP level before delivery remained statistically significant after the analysis.

The demographic and clinical characteristics of patients with EONS are also shown in Table 2. Women who gave birth to babies with EONS had a significantly lower gestational age at PPROM (30 vs. 32 weeks; p=0.010) and delivery (31 vs. 32 weeks; p=0.004) than those without EONS. Babies with EONS had a lower birth weight (1435 g vs. 1790 g; p=0.002) and Apgar score at 1 minute (7 vs. 8; p=0.031) and 5 minutes (9 vs. 10; p=0.023) after birth than those without EONS. Of note, EONS was significantly associated with a positive high vaginal swab (p=0.028) and placental swab (p=0.001) cultures. The presence of group B *Streptococcus* in a high vaginal swab was significantly associated with EONS (p=0.003). The rates of histological chorioamnionitis and funisitis were higher in the EONS group than the non-EONS group. The PPROM-to-delivery interval was comparable for the two groups. Maternal serum CRP levels (including day 1-3 CRPs and last CRP before delivery) were, however, not associated with EONS.

Table 4 shows the logistic regression analysis for

Table 4. Logistic regression analysis of independent variables in predicting early-onset neonatal sepsis

Risk factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p Value
Gestational age at delivery	0.721 (0.585-0.889)	0.724 (0.587-0.892)	0.002
Placental swab organism: positive (reference group: negative)	4.405 (1.63-11.906)	4.485 (1.649-12.193)	0.003

Abbreviations: CI = confidence interval; OR = odds ratio

EONS. Gestational age at delivery and positive placental swab culture remained statistically significant after the analysis.

Discussion

Funisitis was present in 21.1% of women and EONS in 19.5% of newborns in this study. Maternal serum CRP was associated with funisitis that in turn was associated with EONS. There was, however, no significant association between maternal serum CRP and EONS. The gestational age at delivery was the most significant risk factor for both funisitis and EONS. The birth weight and Apgar scores were significantly lower in women with funisitis and newborns with EONS those those without.

Maternal serum CRP has been studied for years in the prediction of chorioamnionitis and / or neonatal sepsis in patients with PPROM. Funisitis is thought to be the counterpart of a fetal inflammatory response. Nonetheless, some studies have shown a positive correlation[5,17] while others have failed to do so[11,12].

In this study, the last maternal serum CRP before delivery was associated with funisitis. Of note, an odds ratio close to 1 and a relatively small AUC (95% CI, 0.56-0.83) made the prediction of funisitis imprecise. Using the ROC curve and a cutoff value of 7.65 mg/l for serum CRP, the sensitivity, specificity, and PPV were not high and again indicated the limited use of CRP. Despite this, a relatively high NPV (89.4%) made CRP a reasonable adjunct to allow expectant management in the presence of PPROM in predicting chorioamnionitis. This cutoff value also matched that in the study by Lee et al of 8 mg/l[18].

Although there is no clear evidence to support the use of CRP as an early diagnostic test of chorioamnionitis in PPROM, a literature review for serial CRP estimations showed that a CRP level of ≥20 mg/l may be predictive[19]. This correlation, however, was not observed in this study. The serial CRP values and percentage change between first and last CRP showed no significant difference between the groups with or without funisitis or EONS. A comparable PPROM-to-delivery interval might also suggest that infection was a cause rather than a consequence of PPROM.

In this study, a significant association between funisitis and EONS was found but not between CRP and EONS. There are three postulations regarding this seemingly conflicting finding. First, the diagnostic definition of EONS varies; the definition of EONS is challenging and despite numerous reviews, there is still no consensus among paediatricians. In fact, the definition used in this study was based on clinical, biochemical, and microbiological factors. Second, the lack of an association between CRP and EONS may be due to the early intervention (i.e. delivery) for other indications before infection occurred. Third, the sample size may not have been sufficient to show a positive correlation.

Despite the insignificant correlation between CRP and EONS, we identified several other risk factors for EONS. Gestational age at delivery remained the most significant risk factor after logistic regression, but a positive maternal culture (high vaginal swab and placental swab) and the presence of group B *Streptococcus* might also alert clinicians to the need for active management.

This study has several limitations. First, randomisation and data analysis were limited by the retrospective design. Second, there might have been an inconsistent time lag between CRP measurement and delivery leading to imprecise interpretation of data. Third, there were no data regarding the long-term baby outcome, which is an important factor when considering delivery, especially at an extremely premature gestation. Larger prospective randomised trials with long-term data are needed to provide stronger evidence. Until then, CRP should be interpreted with caution.

Conclusion

Maternal serum CRP is a non-invasive, inexpensive, and readily available test useful for many clinicians in the

clinical setting of PPROM. Based on this study, however, CRP may be linked to funisitis but not directly to EONS. Other risk factors should be taken into account when managing women with PPROM such as gestational age at delivery and positive maternal cultures, especially of group B *Streptococcus*.

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Declaration

The authors have disclosed no conflicts of interest.

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