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Significance of C-reactive protein in predicting fetal inflammatory response syndrome

Znaczenie białka C-reaktywnego w przewidywaniu zespołu płodowej reakcji zapalnej

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Abstract

Objectives: *The aim of the study was to identify and evaluate a possible correlation between C-reactive protein (CRP) concentration in maternal blood and the risk of developing fetal inflammatory syndrome (FIRS).*

Material and methods: *The study included 158 infants born at 22-34 weeks of gestation and their mothers. Umbilical cord blood cytokines were evaluated in immunoassay tests and maternal blood was tested for CRP concentration.*

Results: *The period of gestation was significantly shorter in the FIRS group as compared to the control group (29.5±3.1 vs. 32.2±2.4 weeks, p<0.001). Gestational age was ⩽30 weeks for 53.8% of the newborns in the FIRS group and 15.8% of the newborns in the control group (p<0.001). Maternal CRP before, during and after labor was significantly higher in the FIRS group as compared to the control group (p<0.001). Our study investigated the correlation between CRP in maternal blood and IL-6 concentration during the entire perinatal period (p<0.001).*

Conclusion: *CRP concentration in the FIRS group was significantly higher than in controls before, during, and after labor. Thus, it seems safe to conclude that changing concentration of inflammatory factors in maternal blood are closely related to FIRS. Elevated CRP in maternal blood might signify a progressing intrauterine infection and herald the development of FIRS.*

Key words: **intrauterine infection** / **CRP** / **preterm delivery** / **IL-6** /

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Streszczenie

Cel pracy: *Określenie zależności między stężeniem białka CRP w surowicy krwi matki i ryzykiem wystąpienia zespołu odpowiedzi zapalnej płodu (fetal inflammatory response syndrome – FIRS).*

Materiał i metodyka: *Badaniem objęto 158 noworodków urodzonych pomiędzy 22 a 34 tygodniem ciąży oraz ich matki. Oznaczano stężenie cytokinów w surowicy krwi pępowinowej za pomocą metody immunoenzymatycznej oraz stężenie CRP w surowicy krwi matki.*

Wyniki: *Ciąża trwała statystycznie krócej w grupie FIRS w porównaniu z grupą kontrolną (29,5±3,1 vs 32,2±2,4 tyg., p<0,001). Ciąża trwała ⩽30 tyg. w 53,8% przypadków w grupie FIRS oraz w 15,8% przypadków w grupie kontrolnej. Stężenie CRP w surowicy krwi matki przed, w czasie i po porodzie było statystycznie wyższe w grupie FIRS w porównaniu z grupą kontrolną (p<0,001). Badanie wykazało zależność między stężeniem CRP w surowicy krwi matki i stężeniem interleukiny – 6 podczas całego okresu perinatalnego (p<0,001).*

Wnioski: *Stężenie CRP w grupie FIRS było statystycznie wyższe w porównaniu z grupą kontrolną przed, w czasie i po porodzie. Można wyciągnąć wniosek, że zmiany stężenia czynników zapalnych w surowicy krwi matki są związane z FIRS. Wyższe stężenie CRP w surowicy krwi matki może wskazywać na progresujące zakażenie wewnątrzmaciczne i możliwy rozwój FIRS.*

Słowa kluczowe: **zakażenie wewnątrzmaciczne / CRP /poród przedwczesny / interleukina-6 /**

Introduction

Premature birth (PB) constitutes the main cause of prenatal mortality and morbidity in the developed countries, including Lithuania, where it affects 5-6% of all live births [1]. Prenatal mortality rate is significantly higher in premature infants as compared to full-term neonates. PB is responsible for 75-80% of deaths during the entire prenatal period and 40% of infant mortality cases [2].

The literature reports intrauterine infection (approx. 40 %), whose frequency is inversely proportional to the gestational age, to be the most frequent cause of prematurity in infants [3–5]. Intrauterine infection is typically chronic and asymptomatic, therefore it is difficult to predict premature birth. Intrauterine infection could evoke fetal infection and its inflammatory response, and initiate the fetal inflammatory response syndrome (FIRS). FIRS is the process of advanced fetal response to inflammation, which is defined by an increased IL-6 concentration ≥11 pg/ml in the umbilical cord blood plasma and inflammatory changes in the umbilical cord vessels - funisitis [6, 7]. The consequences of FIRS include severe fetal and neonatal disorders, as well as later remnant infant health problems such as cerebral palsy and chronic lung disease. Moreover, FIRS is related to increased risk of neonatal morbidity and mortality [6, 8–12].

In order to avoid life-threatening FIRS complications, researchers seek ways to identify high-risk pregnant women with the infection as soon as possible. Various studies attempted to identify the critical concentration values of inflammatory markers, which would allow to identify the intrauterine infection as the cause of premature birth. During our research, we focused our attention on the significance of C-reactive protein (CRP) quantity in maternal blood during the prenatal period, when predicting the development of FIRS.

Objectives

The aim of the study was to identify and evaluate a possible correlation between CRP concentration in maternal blood and the risk of developing FIRS in the neonate.

Material and methods

This case-control study was performed in Vilnius City Clinical Hospital between 2007-2009. Approximately 3.500 newborns (i.e. about 12% of all newborns in Lithuania) are born every year in this tertiary referral center. About 10-11% of all deliveries are premature.

Our study included 158 infants born at 22-34 weeks of gestation and their mothers. The eligibility criteria were as follows: 1) maternal age of >18 years; 2) gestational age of 22-34 weeks and 6 days; 3) properly attached placenta; 4) absence of diabetes, chronic cardiovascular and respiratory diseases, severe anemia (Hb<80.00 g/L), autoimmune or oncological diseases in the mother. The exclusion criterion were as follows: 1) stillbirth; 2) maternal alcoholism and/or drug addiction; 3) fetal malformations; 4) hemolytic disease of the newborn; 5) umbilical cord artery blood pH of <7.00; 6) birth trauma of the newborn; 7) maternal refusal to participate in the study.

All newborns and their mothers were investigated according to the same scheme: 1) umbilical cord blood cytokines IL-6 and tumor necrosis factor (TNF-α) were evaluated in each newborn; 2) depending on the concentration of the umbilical cord blood IL-6, the newborns were assigned to FIRS (IL-6 ≥11 pg/ml) or control (IL-6 <11 pg/ml) groups; 3) each mother was tested for CRP concentration in the blood before, during and after labor; 4) a correlation between CRP concentration in maternal blood and concentration of various cytokines in the umbilical cord blood was evaluated; 5) a correlation between CRP concentration in maternal blood before, during, and after labor and the development of FIRS was evaluated. In addition, the culture of cervical discharge, leukocytosis in maternal blood, histological placenta study, and bacteriologic newborn blood test were performed.

Immunological studies of cord blood cytokines were performed at the State Research Institute Center for Innovative Medicine. After birth, the umbilical blood cord vein was punctuated and 5 ml of blood were taken into a vacuum tube. Within 1h, the blood sample was centrifuged for 14 min. at 1.500 rpm/min and plasma was immediately frozen at -80˚C until assayed.

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IL-6 and TNF-α levels in the umbilical cord blood plasma were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits (Bender MedSystems, Austria) according to the manufacturer's protocols. The amount of cytokines for ELISA (Gen5 Microplate Data Collection & Analysis Software; BioTek Instruments, USA) was calculated.

Statistical analyses were performed using the SPSS statistics software version 15.0. Data are presented as mean±SD, median, minimum, and maximum. Quantitative variables of two independent groups were compared using the parametric Student *t*-test and non-parametric Mann-Whitney test. Spearman's test was used for assessing the correlation between the results. The p-value of <0.05 was considered as statistically significant. The specificity and sensitivity of testing were assessed by analyzing the receiver operator characteristic curves (ROC).

Local Bioethics Committee approved of the study (No. 14). Immunological studies of cord blood samples were funded by the Lithuanian State Science and Studies Foundation.

Results

The participants

Mean maternal age in the FIRS and the control groups was 27.3±6.5 and 28.3±5.2 years, respectively but the difference was not statistically significant (p>0.05). The number of leukocytes in maternal blood before and during labor was significantly higher in the FIRS group as compared to the control group (p=0.034 and 0.004, respectively). Our study detected a correlation between leukocyte count in maternal blood and IL-6 concentration during labor (p=0.05) and TNF-α concentration in the umbilical cord blood before and during labor (p=0.02 and 0.007, respectively) [2]. The culture of cervical discharge was done during the perinatal period in 42% of the mothers. The occurrence of a positive culture in the FIRS group was not significantly different from the control group (p>0.05). Histological study detected inflammatory changes in the placenta in 40.3% of the studied cases. The frequency of histological chorioamnionitis without funisitis and deciduitis did not differ between the two groups (p>0.05). Histological chorioamnionitis with funisitis was found in 51% of placentas in the FIRS group, while the control group demonstrated such changes in only 1% of the cases (p<0.001). No pathological changes were detected in 10% of placentas in the FIRS group.

The sex of the newborns was distributed almost equally, 49.4% - boys and 50.6% - girls (p=0.82). Mean gestational age (31.3±2.9 weeks) was statistically significantly (p<0.001) shorter in the FIRS group (29.5±3.1 weeks) than in the control group (32.2±2.4 weeks). The gestational age was ≤30 weeks in 53.8% of the newborns in the FIRS group and 15.8% of the controls (p < 0.001). Mean neonatal weight was 1.424.7±564.0 g and 2,006.35±554.1 g in the FIRS group and controls, respectively (p<0.001). Mean umbilical cord artery blood pH in the newborns was 7.3±0.1 and no differences between the groups were observed (p>0.05). Bacteriologic blood test was performed in 139 newborns. Positive blood cultures were found in 1 newborn from the FIRS group (*Listeria monocytogenes*) and 1 from the control group (*Klebsiella pneumonia*) (p=1.0).

Table I. Comparison of CRP concentration in maternal blood

CRP concentration	FIRS group n = 52	Control group n = 106	p value†
before labor (mg/l) mean±SD median [min – max]	**30.65±39.95** **16.52** [0.50-212.00]	10.91±33.77 3.38 [0.00-307.00]	**<0.001**
during labor (mg/l) mean±SD median [min – max]	**37.54±39.54** **29.53** [0.50–212.00]	7.83±11.05 3.38 [0.00–65.19]	**<0.001**
after labor (mg/l) mean±SD median [min – max]	**42.15±44.19** **29.53** [0.66–212.00]	12.86±18.22 4.14 [0.00-95.56]	**<0.001**

CRP: C-reactive protein; FIRS: fetal inflammatory response syndrome; †Mann–Whitney test; SD, standard deviation. Significant values are set in bold.

CRP concentration in maternal blood.

In our study, we compared CRP concentration in maternal blood before, during, and after labor (Table I).

While examining maternal blood samples during different periods, elevated levels of CRP before (30.65±39.95 mg/l), during (37.54±39.54 mg/l) and after (42.15±44.19 mg/l) labor were detected in the FIRS group (Table I). Total CRP concentration of these FIRS stages was significantly higher than in the control group (p<0.001). The critical values of CRP concentration in maternal blood for predicting the development of FIRS are presented in Table II and in Figures 1, 2 and 3.

The concentration of cytokines in the umbilical cord blood

Each newborn was tested for umbilical cord blood IL-6 and TNF-α cytokines. Our study detected a correlation between CRP concentration in maternal blood and IL-6 concentration in the umbilical cord before, during and after labor (p<0.001) (Table 3).

No significant difference was detected between CRP concentration in maternal blood and TNF-α concentration in the umbilical cord blood before, during and after labor (p=0.3, 0.1 and 0.1, respectively) (Table III).

Table II. Critical values of CRP in maternal blood for predicting the development of fetal inflammatory response syndrome

CRP concentration	Critical value	AUC	95% CI	Sensitivity %	Specificity %	NPV %	PPV %
before labor	6.37	0.7183	0.6171-0.8200	66.7	67.4	81.1	49.1
during labor	6.79	0.7678	0.6643-0.8673	71.4	70.8	84.0	53.6
after labor	10.18	0.7338	0.6340-0.8309	64.3	64.0	79.2	45.8

CI: confidence Interval; AUC: area under the ROC curve; PPV: positive predictive value; NPV: negative predictive value.

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Table III. Correlation between CRP concentration in maternal blood and cytokine concentration in the umbilical cord blood

CRP concentration	Spearman's correlation coefficient, r (p-value)	
	IL-6	TNF-α
before labor	**0.4 (<0.001)**	0.1 (0.3)
during labor	**0.4 (<0.001)**	0.2 (0.1)
after labor	**0.4 (<0.001)**	0.2 (0.1)

Significant values are set in bold

Discussion

Fetal inflammatory response syndrome is a fetal immune reactivation, or a systematic 'emission' of a number of cytokines which are known inflammatory markers. FIRS is often subclinical and associated with premature birth. Presumably, it causes a polyorganic fetal disorder [13]. FIRS is characterized by an increased amount of cytokines (especially IL-6) in the umbilical cord blood, also, by a histological expression of FIRS - funisitis (infiltration of inflammatory cells in umbilical cord vessels). FIRS is an outcome of an infection.

IL-6 is a cytokine of both, specific and non-specific immunities. When microbes and other cytokines (IL-1, TNF-α) act, it is synthesized by mononuclear phagocytes, endothelial cells, fibroblasts and activated T lymphocytes [14]. The IL-1, IL-6 and CRP secretion is stimulated due to the impact of substances produced by bacteria. Together with TNF-α, they stimulate prostaglandin E2 synthesis in an amniotic sac (or 'bag of waters'), in decidual plates and in the uterine muscle, and induce the production of metalloproteinases. Therefore, fetal membranes rupture prematurely and the cervix uteri is opening. Besides, IL-6 stimulates the production of acute phase reactants (CRP) in the liver. Thus, IL-1, IL-6 and CPR participate in the inflammatory response, and all together stimulate premature birth [15–18].

Contemporary medicine offers numerous methods of detecting intrauterine infection. Nevertheless, this process often lasts several days and is of low specificity and sensitivity [16]. Romero et al., detected elevated cytokine concentrations in the amniotic fluid of women who had been diagnosed with microbial invasion into the amniotic sac [19]. These authors tried to identify the marginal concentrations of IL-6, IL-1, interferons, TNF and IL-8 in women at risk of premature birth, together with developing amniotic infection or chorioamnionitis [20–22]. Also, concentrations of the inflammatory cytokines in maternal blood were assessed in cases of a premature rupture of the fetal membranes and premature uterine contractions and compared to cytokine concentrations of normal laboring women [23–27]. It was found that increased IL-6, IL-1 concentration in maternal blood correlated with the incidence of intrauterine infection and premature birth. Fetal disorder starts in the early pregnancy and there are no objective clinical signs. Therefore, prevention of intrauterine infection, based on maternal cytokine concentrations, must be started even during pregnancy [28].

CRP is synthesized in the liver. Blood serum of a healthy person contains very low levels of CRP, while in case of an acute inflammation it can increase 20-25 times. Hence, it belongs to the

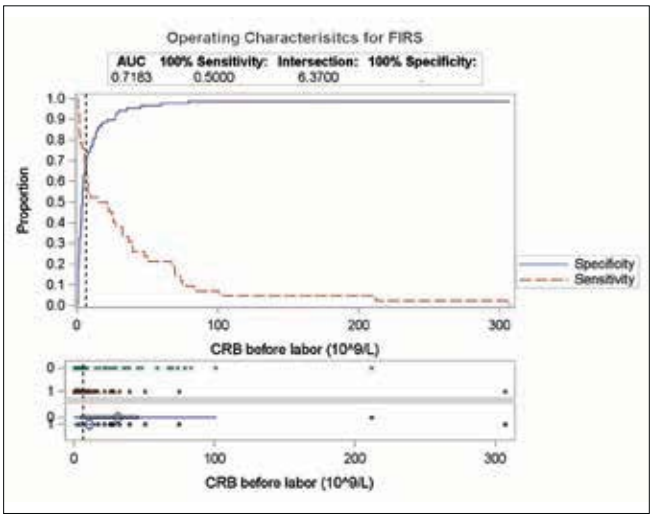

Figure 1. ROC curve analysis for determining the clinical values of CRP in maternal blood before labor.

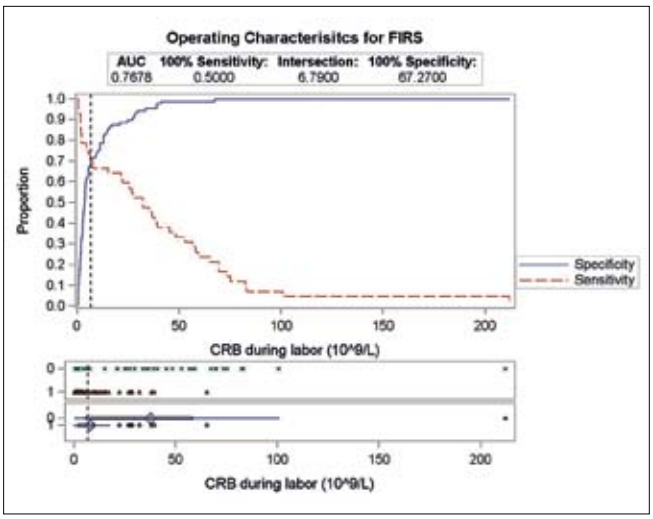

Figure 2. ROC curve analysis for determining the clinical values of CRP in maternal blood during labor.

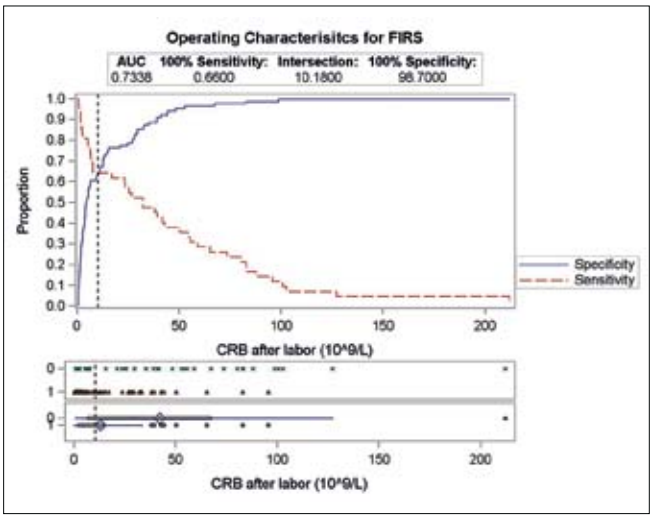

Figure 3. ROC curve analysis for determining the clinical values of CRP in maternal blood after labor.

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group of acute phase proteins (increase of its concentration in the blood is a response to the secretion of inflammatory cytokines, e.g. IL-6) [29].

Increased CRP activity may be observed not only in case of various inflammations. CRP activity has been found to rise even during pregnancy. Watts et al., established the average physiological concentration values of CRP during the entire gestation period based on their study of 81 pregnant women without any pregnancy complications. It turned out that mean CRP concentration in pregnant women is 1.5mg/dL higher than analogous indicators in non-pregnant women. Also, the length of pregnancy has no impact on these indicators. CRP concentration increases even more sharply during labor [29].

In our study, we focused on the correlation between FIRS and CRP levels in maternal blood during the prenatal period. We found the average CRP concentration in maternal blood to be above the normal range. In the FIRS group, CRP was significantly higher before, during and after labor as compared to the control group ($p<0.001$). Also, we identified a correlation ($p<0.001$) between CRP concentration in maternal blood and IL-6 concentration in the umbilical cord during the entire prenatal period.

Recently, a number of studies, substantiating a valuable association between CRP concentration in the maternal serum, FIRS and neonatal sepsis, have been carried out [28,30]. Sung Youn Lee et al., suggested measuring CRP concentration in maternal serum as a selection criterion when diagnosing early onset of neonatal sepsis or funisitis. A blood test could help to group women with premature birth and premature rupture of the fetal membranes into the low- and high-risk groups which would be further purposefully investigated (amniocentesis should be performed). According to these authors, CRP concentration in maternal serum of <8 mg/l has a good negative prognostic value in diagnosing neonatal sepsis or funisitis. It shows that a low CRP concentration could be a selection criterion to help protect mothers and newborns from unnecessary treatment (e.g., antibiotics, invasive treatment) [31]. The literature offers evidence indicating that elevated levels of CRP can be a marker for diagnosing proven sepsis in extremely preterm neonatal sepsis [32].

Conclusion

CRP concentration in the FIRS group was significantly higher than in the control group before, during, and after labor. Thus, one might speculate that changes in maternal blood inflammatory markers are closely related to FIRS, and elevated CRP concentration in maternal blood shows that the intrauterine infection is more progressed and, possibly, FIRS is developing.

Authors' contribution:

1. Daiva Bartkevičienė – concept, assumptions, study design, acquisition of data, article draft, revised article critically, corresponding author.
2. Ingrida Pilypienė – concept, assumptions, study design, acquisition of data, article draft, revised article critically.
3. Diana Ramašauskaitė – concept, assumptions, study design, acquisition of data, article draft, revised article critically.
4. Jolita Zakarevičienė – acquisition of data, article draft.
5. Dalia Laužikienė – concept, assumptions, study design, revised article critically.
6. Mindaugas Šilkūnas – concept, analysis and interpretation of data, article draft.
7. Rasa A. Vankevičiūtė – analysis and interpretation of data, article draft.
8. Brigita Vaigauskaitė – analysis and interpretation of data, article draft.
9. Gražina Drąsutienė – concept, assumptions, study design, revised article critically.
10. Irena Dumalakienė – study design, acquisition of data, analysis and interpretation of data, article draft, revised article critically.

Authors' statement

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- the manuscript has not been published in or submitted to any other journal.
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