C-reactive Protein as a Biochemical Marker of Idiopathic Preterm Delivery

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SUMMARY

Each birth which has happened before gestation period of 37 weeks of gestation and which is not related to a degree of birth difficulty is called premature birth. Different researches pointed out that C-reactive protein (CRP) can be used as a possible marker of idiopathic preterm delivery. Research goals were: To examine reliability of CRP in mothers serum as a marker of premature birth among pregnant women who had no of the known risks for premature birth. To determine critical value of CRP in pregnancies this ended up as a premature birth. To determine connection between value of CRP and low birth weight of the newborn. The research is done in a form of prospective study on 200 pregnant women. Research included pregnant women without known risks factors for premature birth with condition that those women had suitable antenatal protection. All pregnant women were divided in into two groups, experimental and control group. Experimental group is consisted of 150 pregnant women who were regularly controlled in ambulance. Control group consisted of 50 pregnant women who were hospitalized at the Department for Pathology of pregnancy due to threatening miscarriage symptoms of condition that tocolytic index were less than 4. The value of CRP in serum of all pregnant women was determined in period from 20 to 24th week of gestation. In further course of pregnancy we followed those pregnant women with more often premature birth and if premature birth occurred more often in pregnant women with increased value of CRP in relation to women who had normal values. As a critical value for CRP was taken >2 median value. Besides descriptive statistic methods in evaluating data processing were used test, student’s t-test, Fishers test and Mann-Whitney test. Results: Mean value of CRP in experimental group was 3.913 and in control group 14.92 (t=4.72, p<0.0001). Mean value of CRP was 18.17 in group of prematurely births and in women who gave birth on time 3.87 (t=5.72, p<0.0001). Value of CRP > 2 had 33 women who gave birth prematurely (16.5%). Conclusions: CRP can be used as a reliable marker of idiopathic premature birth. CRP value which is connected with development of premature birth is 4 mg/l. There is connection between the value of CRP >2 and low birth weight of the newborn.

Key words: preterm birth, C-reactive protein.

1. INTRODUCTION

Every birth that occurs before the age of 37th weeks of gestation, regardless of the delivery severity is called early (1). The frequency of preterm births in developed countries is 5-9%, with increasing level of underdevelopment and the growing number of premature deliveries, and up to 20% (2). Given the gestational age we differ:

- Extreme prematurity (to 28 weeks) with an incidence of 5%, severe prematurity (from 29th to 31st week) with an incidence of 15%, moderate prematurity (from 32nd to 33rd week) with an incidence of 20%, mild prematurity (from 34th to 36th week) with incidence of 60-70% (3).

Preterm birth makes 60-80% of perinatal mortality and morbidity, and is significantly influenced by gestation age. Two-thirds of the total mortality makes early deliveries up to 32 gestational weeks (4).

Methods for identifying high-risk pregnancies include clinical and biochemical markers of preterm delivery. Clinically relevant methods are: changes in the cervix, uterine contractions, vaginal bleeding and identification of epidemiological risk factors (5). One of the markers in maternal serum, which indicates an increased risk of preterm delivery is the C-reactive protein (CRP) (6).

CRP is in the serum of acutely ill, it have five identical polypeptide chains and is synthesized in the liver. Their main role is to identify potentially toxic autogenous substances released from damaged tissues, to bound them, and then detoxify them and remove from the blood. For its detection in the blood used are immunochromatic methods such as nephelometry or sensitive homogeneous enzyme immunoassays (7).

CRP is a hepatic globulin, and its increased levels in maternal serum are correlated with subclinical amnionitis and premature delivery (8). The level of CRP in plasma greater than 1.5 mg/d (15 mg/l) showed a highly significant correlation with levels of interleukin-6 (IL-6) in the amniotic fluid greater than 1500 pg/ml (9). Watts et al (1992) also showed that the value of CRP in the serum of a mother which is greater than 1.5 mg/dl (15 mg/l) showed a highly significant correlation with positive amniotic fluid culture (10).

2. GOALS

To examine the reliability of CRP in the serum of a mother as a marker of preterm delivery in pregnant women who do not have any of the known risks of preterm delivery. Determine the critical value of CRP in pregnancies which ended with early delivery. Determine whether there is a connection between CRP and low infant birth weight (<2500 grams).

3. MATERIAL AND METHODS

The study was conducted as a prospective study on a total of 200 pregnant women aged 18-35 years who have none of the known risk factors for preterm delivery. The study included only pregnant women regularly controlled.
The exact gestational age of pregnancy was determined by last menstrual period and ultrasound biometry in the first trimester, and confirmed with ultrasound in a period of 16 to 20 gestational weeks.

The pregnant women were divided into two groups: experimental and control groups. The experimental group included 150 women who had regular outpatient controls. The control group consisted of 50 pregnant women who were hospitalized at the Department of pregnancy pathologies (Clinic of Gynecology and Obstetrics, Tuzla) because of threatening abortion. The selection criteria for pregnant women are: tocolytic index less than 4, intact membranes and no contra indication for tocolytic therapy. Tocolytic index was determined by Kuvacic method (1994), and a score is obtained by scoring each of the symptoms of premature delivery, according to their severity (0-4 points) (11).

All subjects in the period from 20 to 24 gestational weeks from serum was determined the value of C-reactive protein. In the further course of pregnancy is followed by the occurrence of preterm delivery. Preterm birth was defined as the delivery of live infant before the age of 37th weeks of gestation (259 days of gestation), counting from the first day of the last menstrual period.

CRP was measured using nephelometry method at the Institute of Immunology, University Clinical Center in Tuzla. The manufacturer of the test is Dade Behring Limited, UK. Nephelometry is the measurement of light rays scattering. A mixture of antigen-antibody enters the beam of different wavelengths and the degree of scattering of light is measured by photoelectric cells as optical density. Theoretically nephelometry is a fast and simple method for the measurement of many antigens in biological fluids (12). As a critical value is taken value >2 (a value greater than two values of the median). The value is expressed in mg/l.

In processing the obtained values were used methods of descriptive statistics: mean, standard deviation and median. The results obtained in the experimental and the control groups are compared by the $\chi^2$ test, Student’s $t$-test, Fisher test and Mann-Whitney test.

## 4. RESULTS

The mean value in the control group was 14.92 mg/l with a standard deviation of 27.62 and median 3.39. In the experimental group, the mean value was 3.913 mg/l with standard deviation 4.67 and median 2.50. Mean values were tested by $t$-test. It is shown that there is a statistically significant difference between mean values of CRP in these two groups ($t=4.72, DF=1.99, p<0.0001$), and that the CRP values were significantly elevated in control group (Figure 1).

In the group of preterm deliveries mean value was 18.17 mg/l with a standard deviation of 28.624 and a median value of 7.2. In the group of deliveries on term mean value was 3.87 mg/l with a standard deviation of 6.89 and a median value of 2.0. Mean values were tested by $t$-test. It is shown that there is a statistically significant difference between mean values of CRP in these two groups ($t=5.72, DF=199, p<0.0001$). Applied Mann-Whitney test tested the statistical significance between the medians in the two groups. Median value of CRP between preterm and on term delivery was significantly different (Figure 2).

Following the work of Meyer et al (1995) we calculated the median concentrations of CRP and in preterm and on term deliveries. Calculated are the frequencies of occurrence of CRP concentration greater than two median values for on term delivery (value=2mg/l). Value greater than two median values in the case preterm deliveries had 33 pregnant women (16.5%) and in 37 pregnancies with on term delivery (18.5%). The value of less than two median values found among premature births in the 6 (3%) cases and in case of term delivery in 124 (62%) cases.

$\chi^2$ test proved that there is a correlation of preterm deliveries with a CRP concentration ($\chi^2=48.8, p<0.0001$). The same conclusions have been reached using Fisher exact test. Chance of occurrence of premature birth is 17.95 times higher if CRP is greater than two median values (95% CI: 6.65 to 55.45) (Figure 3).

Table 1 shows the value of CRP and low infant birth weight. In the experimental group, 48 (32%) women had a CRP >2 and low infant weight was present in 8 cases (5.34%). In the control group value of CRP >2 had 22 (44%)
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pregnant women, and 13 (26%) infants had weight <2499 grams.

$X^2$ test showed that there was a relationship between serum CRP concentration >2 and weight of infants in the control group ($\chi^2=11.12$, p=0.0009). Fisher’s exact test gives the same result (p=0.0005). Chance of infants of low birth weight was 12.04 times higher if the value of CRP is >2 (95% CI: 2.39 to 76.60).

$X^2$ test showed that there was a relationship between serum CRP concentration >2 and body weight of infants in the experimental group ($\chi^2=7.14$, p=0.0075). The same results were obtained using the Fisher exact test (p=0.005). Chance of infants with low birth weight is 6.6 times higher if the value of CRP is >2 (95% CI: 1.47 to 40.00).

Also calculated is the sensitivity and specificity of CRP as a diagnostic test. Test sensitivity was 84.6% and its specificity 76.5%. Logistic regression analysis led to the conclusion that the chances of premature birth increase 15.867 times if the value of CRP is >2 (95% CI: 5.82 to 43.24).

5. DISCUSSION

Some of the markers of infection can be detected in patients with pre-mature delivery; one of these markers is CRP. An increased level of CRP in the serum is a part of the acute phase of inflammatory reactions. Most women (86-88%) in case of threatening preterm delivery, accompanied by high levels of CRP level does not respond to tocolytic therapy, while pregnant women with normal levels of CRP have good response to tocolytic therapy in 77-94% of cases (13).

Research of Ghezzia et al (2002) showed that the value of CRP in amniotic fluid is higher in those women who had delivered prematurely (before 37 weeks gestation) compared to pregnant women who delivered at term. This study supports the theory that subclinical intrauterine or inflammatory processes in early gestation may be an important factor for preterm birth (14).

The mean value of CRP in a control group was 14.92 mg/L, while in the experimental group was 3.913 mg/L. There was a significant difference between these two groups. The mean value of CRP in case of birth completed prematurely was 18.17 mg/L, and in pregnant women who delivered on time 3.87 mg/L. It was also proved existence of statistically significant difference between these two groups. Value >2 (4 mg/L) was found in 33 pregnant women (16.5%) delivered prematurely.

The study included 35 pregnant women who delivered before term and 35 pregnant women who delivered at term, it is shown that CRP is significantly increased in pregnant women who delivered prematurely. Its value increased with the presence of perinatal infection (15).

Regarding whether there is a relationship between CRP value >2 and low infant birth weight (<2500 g). It is shown that the correlation exists in the control and experimental group. In the experimental group a chance for newborns with low birth weight is 6.6 times higher if the value of a CRP is >2, and in the control group a chance is 12.04 times higher.

6. CONCLUSIONS

- Based on the results the following conclusions were drawn.
- C-reactive protein (CRP) is a reliable marker of idiopathic preterm delivery in pregnant women who do not have any of the known risk for preterm delivery.
- Cut-off value of CRP, which was associated with the development of idiopathic preterm delivery was 4 mg/L.
- There is a correlation between CRP and low infant birth weight (<2500 g).

REFERENCES