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Research Article

THE CORRELATION BETWEEN A PREMATURE BIRTH AND THE LEVEL OF C-REACTIVE PROTEIN

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A B S T R A C T

Introduction: A premature birth, according to the records in the literature is accompanied with releasing of many biochemical mediators in the acute phase of inflammation (transfer, ceruloplasmin, protein C-reactive). Of particular interest is to discuss the correlation of between the said mediators and premature birth.

The Aim of the Study: The aim of the study was to analyze: Correlation between the pre-matured birth and CRP level. To discuss CRP level between the mother's blood and the fetus blood at normal and premature birth. To determine the report of CRP level in mother's blood and the fetus blood at premature birth comparing to normal birth.

Material and Methods: In the study are included 124 pregnant patients. In pregnancy and birth giving was of normal course (77) and in a group where the pregnancy is terminated as preterm birth (47). During the act of birth giving blood samples were taken from mother's cubic vein, from umbilical fetus vein.

The Results: Our results have shown that the level of CRP at premature birth in mother's blood is higher ($p<0.0002$) in comparison to CRP level at normal term birth. At premature birth the level of CRP in fetus blood is at higher level ($p<0.001$) comparing to CRP at normal term birth is explained with the fact that: due to presence of mother's infection, uterus-placental unit and fetus the biochemical mediators are released (interleukin, endotoxins, prostate glands, human necrosis factor, prosthesis and elastases), which by acting in the liver through a serial of numerous mediators raise the CRP synthesis on one side, whereas on the other side by acting in myometrium by intermediating and releasing of mediators initiate contracting of the uterus.

Conclusion: At premature birth the level of CRP in the mother's blood and fetal blood is at higher level compared to parameters of normal term birth. Therefore, we conclude that there is in close relation between the premature birth and CRP in mother's and fetal blood.

INTRODUCTION

With premature birth, we mean extraction of the fetus and other conception products after the week 22 of gestation and before the end of the week 37 of gestation. The birth rate of premature birth in the most developed industrialized countries is 6-8%. The factors that can cause premature birth can be of endogenous, exogenous nature, and socio-economic factors. Etiologic factors and other risk factors that can cause premature birth is divided into several groups: 1) maternal, 2) paternal, 3) fetal, 4) placenta, 5) horioamnional factors, 6) socio-economic factors, 7) traumas, 8) Genetic factors, 9) pituitary factors, 10) idiopathic factors, and 11) health education.

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Intra-amniotic infections are present in 25% at premature births in which there is no rupture of shadows sac.

From the etiopathophysiology point of view, we have identified a series of feto-maternal syndromes and some other disorders which on the side of a series of biochemical mechanisms initiate the appearance of contractions by the myometrium which then make the expulsion of fetus, placenta and the amnonial membranes. According to the data so far we can conclude that 1/3 of premature births occur due to feto-maternal disorders, 1/3 occurs due to the rupture of the amnonial membranes, whereas 1/3 is of unknown etiology. Infectiousness is an important factor for initiating premature birth. Chorioamnionitis and placenta inflammation are found in 25% of premature births. The premature premalignant can be initiated by the replication of bacteria in the amniotic fluid (3). In some studies, intra-amniotic infection was encountered even without the presence of sputum rupture as well as in 75% of cases the infection was subclinical.

Many bacteria produce phospholipase A_2 which acting on phospholipids in the amniotic and produce arachidonic acid from which prostaglandins are synthesized which then initiate contractions of uterus.

Many studies have shown the linkage in intra-amniotic and maternal infections and premature birth, even in cases with amniotic intakes (10, 7, 13). By examining of C-reactive protein at pregnancies at the end of the second trimester and at the beginning of the third trimester it has been verified that in one-third of pregnancies there is an increase in the concentration of this marker that occurs at the early stage of infections (2, 9). The C-reactive protein is the glycoprotein composed of 5 identical molecular monomers. The relative molecular weight is 107500D. The C-reactive protein is related to phosphoryl-holin and phosphoryl-ethanolamine as well as more polysaccharides of bacteria in degenerate tissues. Linkage of reactive (CRP) protein with microorganisms and phosphoryl-holin is also dependent on calcium ions. Linked C-reactive protein activates the classical compliment path that begins with C1q. The C-reactive protein also links even with receptors in the lymphocytes. In the blood of healthy persons, it is found in the concentration of (5-10mg / l). Concentrations of reactive (CRP) protein are increased at the inflammatory diseases by reaching concentrations up to 500mg/l. Increased concentrations can be found even in these diseases: colorectal cancer, breast cancer metastases, myocardial infarction, SNQ infections, postoperative complications and neonatal sepsis. Determination of C-reactive protein is a good test for differentiating bacterial infections from viral ones. At the acute inflammation, in high concentrations can also be found in these substances: transferrin, ceruloplasmin and α_1-antitrypsin. In the amniotic fluid some of these acute infectious phase reactants are also found (ceruloplasmin, transferrin and α_1-antitrypsin). In the amniotic fluid, the following substances have been found: Albumin, globulin, IgG, IgM, IgA, lecithin, lysolecithin, sphingomyelin, phosphatidyl-serine and bilirubin.

Some studies have shown that the inefficiency of the premature birth termination on the tokolitikside is much more expressed at pregnant women with higher concentrations of C-reactive protein compared to control group. The prophylactic treatment of antibiotics of pregnant women with more contractions tending to premature birth shows a good effect on termination of contractions, prolongation of gestate on and maternity outcomes without complications (5). The pre-mature birth with frequency 3 is present ed times higher at endometrial patients.

Minkoff et al with collaborators, 1984, found that Chlamydia trachomatis streptococcus ß-hemolytic, Neisseria gonorrhea, monocytegenes listeria, mycoplasma and trichomonas vaginitis are associated with a premature birth as well as the birth of the baby with a small weight. At pregnancies with amnionic membranes rupture the level of the immunoglobulin is increased. The increase of the level of these immunoglobulins (IgM, IgG, IgA) appears before the amniotic shrinkage and shows for the presumption of asymptomatic infection. From the clinical point of view is spotted that ß-hemolytic streptococcus is very virulent microorganism which appeared in the perinatal period. Streptococcus ß-hemolytic in the amniotic fluid penetrates through the ruptures of amniotic membranes and rarely through intact membranes (1).

In the recent studies, it has been proved that in the amniotic fluid there are a variety of antibacterial substances, such as lysozyme, transferrin, peroxidase, immunoglobulins, beta-lysine and zing-peptide complex. These antimicrobial factors represent the latest protective factor for the prevention of fetal sepsis.

The Aim of the Study

The aim of the paper was to determine the CRP level in maternal blood and the blood of the fetus at premature birth compared to birth on time.

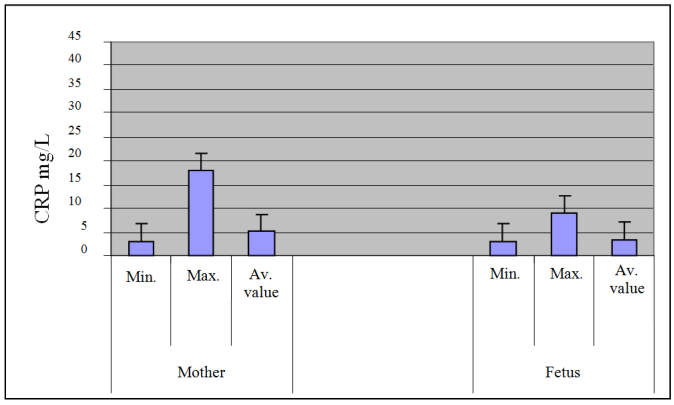
MATERIAL AND METHODS

The study included 124 pregnant women of them 77 pregnant women, pregnancies are normal, whereas, in 47 pregnancies, resulted with a pre term birth. A group of pregnant women with normal pregnancy (77) has been monitored throughout pregnancy by laboratory and ultrasonography aspects and we have found that pregnancy and birth are normal in normal form with the baby birth of normal weight which had responded to the age of gestation. A pregnancy group that ended with a pre term birth with the baby birth that had responded to the age of gestation, it was followed by ultrasonography and laboratory analysis and clinically. The gestational age was determined with the last menstruation period and was verified with the fetal biometry. The blood was taken at birth from the fetus from the umbilical vein as well as from the mother from the cubic vein. The laboratory analysis was performed at the Department of Microbiology and Biochemistry in the Faculty of Medicine in Pristina. Laboratory analyses were performed by using the immuno-turbidimetry method. Statistical analysis were performed with a variance analysis method (ANOVA) and t-test

RESULTS

Table 1 CRP values at term birth in mother's blood and fetal blood (No. 77)

Mother			Fetus		
Min.	Max.	Av. value	Min.	Max.	Av. value.
3.00	18.00	5.06	3.00	9.00	3.39



Graph 1 Graphic presentation of CRP concentration at term birth in mother's blood and fetal blood of (X ± SEM)

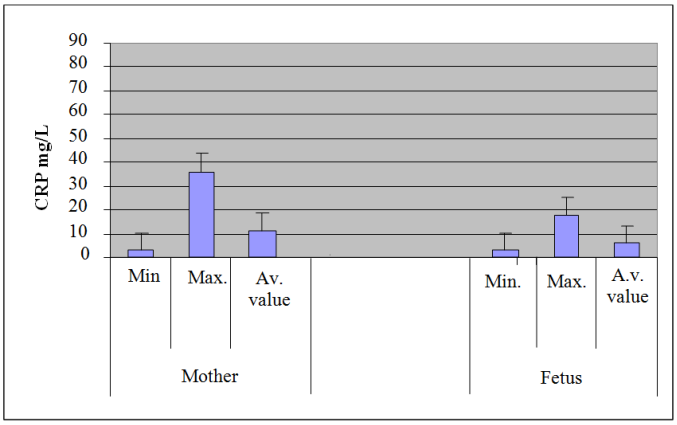
Mother vs. Fetus q (2.352) p> 0.05

One-way Analyze of Variance (ANOVA)
Tukey- Kramer Multiple Comparison Test

Programs: Instat 3 GrphPad

Table 2 CRP prematurely values at premature birth born in mother's blood and fetal blood (No. 47)

Mother			Fetus		
Min.	Max.	Av. value	Min.	Max.	Av. value
3.00	36.00	11.18	3.00	18.00	5.74



Graph 2 Graphic representation of CRP concentration prematurely in mother's blood and fetal blood (X ± SEM)

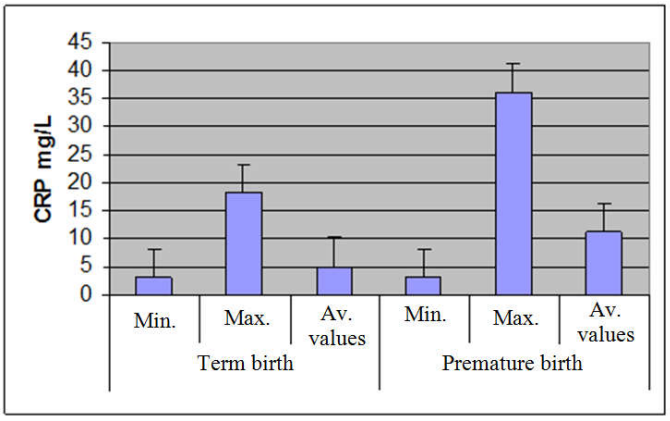
Mother vs Fetus q(3.671) p <0.05*

One-way Analyze of Variance (ANOVA)
Tukey- Kramer Multiple Comparison Test

Programs: Instat 3 GrphPad

Table 3 CRP values in mother's blood at birth on time and premature birth (No. 47)

CRP mg/L					
Term birth			Premature birth		
Min.	Max.	Av. values	Min.	Max.	Av values
3.00	18.00	4.98	3.00	36.00	11.17



Graph 3 Graphic presentation of CRP concentration in fetal blood at term birth and premature birth (X ± SEM)

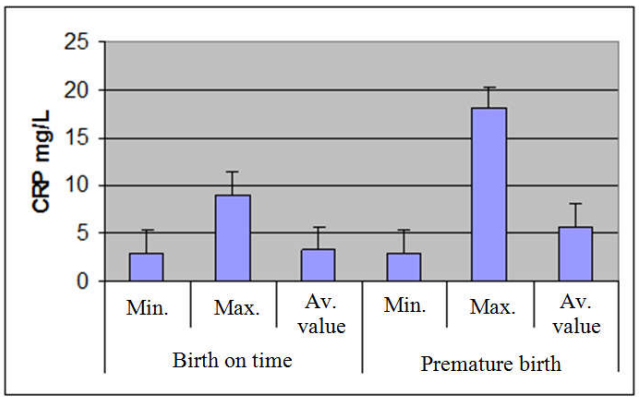
Unpaired t-test

P < 0.0002 ****
t = 3.842

Programs: Instant 3 GrphPad

Table 4 CRP values in fetus blood at birth on time and premature birth (No. 47)

CRP mg/L					
Birth on time			Premature birth		
Min.	Max.	Av. value	Min.	Max.	Av. value
3.00	9.00	3.26	3.00	18.00	5.74



Graph 4 Graphic presentation of CRP concentration in fetal blood at term birth and premature birth (X ± SEM)

Unpaired t test
P < 0.001 ***
t = 3.393

Programi:Instant 3 GrphPad

DISCUSSION

The constraints of the balance factors that initiate contractions as well as factors that inhibit the electrical activity of the myometrium can lead to premature birth. The factors that initiate the premature birth deaths can be derived from hypothalamus, pituitary, placenta, fetus, fluid amniotic, myometrium and cervix. Relaying on the nature of the action of the factors leading up to the birth of, for example, they may be of a mechanical, bioelectric, biochemical, ionic hormone and neural. The place of action of these agents is the myometrium in which the contractions are progressively increased which ultimately result with a premature birth.

In the appearance of premature birth, the following factors have an impact: distension of the uterine, the ratio between the volume uterine and progesterone levels, progesterone levels, estrogen ratio and progesterone, the effects of steroid suprarenal gland on the fetus (4), fetal oxytocin activity thymus origin, prostaglandins, the ratio between oxytocin and prostaglandins, placental inflammation, amniotic fluid infections, chorioamnionitis, deciduas infection, production of increase in endothelin due to amnion origin and prolactin level decrease in amnonial fluid.

CRP in mother's blood and fetal blood at premature birth is at higher level than at term birth ($p<0.05$). Such a phenomenon is explained by the fact that a premature birth of the CRP level in mother's blood is higher due to the infection. This phenomenon is explained by the fact that the mother of premature birth due to mother's infection and febrile conditions is released from some pyogenic substances (interleukins) which then with the help of some other mediators initiate uterine contraceptives in one side and on the other side with their action in the liver of the mother increase the synthesis of C-reactive protein as a parameter of the acute phase of infection. It is known that interleukins through prostaglandins cause the uterine contraction. Another theory that had to clarify CRP levels in the mother's blood and initiation of uterine contraction is the theory that is based on the fact that endotoxins of gram-negative bacteria in the liver blood acting on the liver make the growth of CRP level (acute infectious phase reactant) and on the other hand, these endotoxins acting on the fetoplacental unit (in amniotic shifts) make phospholipid release by releasing arachidonic acid and

finally synthesis of prostaglandins that initiate uterine contraction. Our findings correlate with the authors' data (2,9) who also met CRP growth in maternal blood of premature birth. Research shows that at 1/3 of premature births are causes of horio amniotic membrane infections and placental infections. These infections of the fetoplacental unit may be presented in the form of horizons without the rupture of the amniotic lesions (10,7,13) with the rupture of the horioamniotic membrane lesions and in 75% of the cases, these infections can also be presented in the subclinical form. High CRP values in early pregnancy are associated with premature birth (8). Walhace and Herrick 1988 have done amniocentesis in 25 pregnancies in the east with more amniointake and have found that in three cases they have found the presence of these microorganisms; Micrococcus, alpha-streptococcus, fusobacterium. The invasion of these microorganisms in the amniotic fluid as well as in mother's blood makes the release of endotoxin as well as interleukins acting in the liver of the mother by increasing the level of CRP and the action of these substances in the amniotic membranes which acting on phospholipids Of the cell membrane, through a series of mediators, release of the prostaglandins PgE_2 the $PgF_2\alpha$ which then initiate uterine contraction. The fact that the level of PgE_2 the $PgF_2\alpha$ is elevated is known. Another theory that had to clarify the tendency for premature birth and increase of CRP level is the theory of degeneration of amniocentral shingles on the side of bacterial products as well as inflammatory cell mediators who directly acting on the liver increase the level of CRP, but also with their action in amniotic supplements increases the level of prostaglandins. The microorganisms found in the cervical vaginal region produce a protease enzyme which inhibits ameliorate hydrolysis by causing its lesion and spreading infections in ascending pathways (5).

CRP values in premature fetal blood are at the highest level compared to CRP values at term birth ($p < 0.001$). This phenomenon is explained by the fact that early onset there is infection of the cytoplasmic unit as well as chorioamnionitis, due to bacterial invasion, release of endotoxin bacterial products as well as other cellular products interleukin I_1, interleukin I_6 and human necrosis factor which then reaches the blood the fetus and the action of these factors in the fetal liver stimulate the synthesis of C-reactive protein on one side, and on the other hand, these pharynx acting on horioamnical extensions make the release of prostaglandins which acting on myometrium initiate the uterine contraction. It has been shown that neutrophils peroxidase and elastase together with the synergistic effect of bacterial proteases cause degeneration of the amniotic shingles, and from which premature birth results. Protease and the elastase is released by neutrophils together with bacterial proteases can act on the fetal liver whenever the CRP level increases. The other theory that explains the increase in CRP levels in premature fetal blood is a theory based on the fact that gram-negative bacterial products, endotoxins, increase the synthesis of prostaglandins in the human amnion by acting on the macrophage. The level of prostaglandin is increased to pregnant women with a tendency to premature birth (11). The level of the phospholipase A_2 enzyme is increased to some types of bacteria found in the vagina. Interleukin I_1 (11), interleukin I_6 (12) and factor human necrosis synthesis activists are increased at the premature birth. These activators of prostaglandin synthesis through a trans-placental transfer reach the fetus, and by acting on the liver of the fetus stimulate the CRP synthesis in the liver.

CONCLUSION

At premature birth, the CRP level in mother's blood and in fetal blood is at higher level compared to these parameters at term birth. We may conclude that premature birth is in close correlation with CRP level in mother's blood and in fetal blood.

Litterature

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