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CLINICAL STUDY

Procalcitonin, neopterin and C-reactive protein in diagnostics of intrauterine infection and preterm delivery

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Abstract: *Objective:* The purpose of this study was to find out whether Procalcitoni,, Neopterin and C-reactive protein are sensitive and specific markers of intrauterine infection.
Methods: We evaluated 155 patients from 26. to 41. week of pregnancy at the time of delivery. We measured serum concentrations of procalcitonin (PCT), neopterin and C-reactive protein (CRP) from mother's blood sample at the beginning of delivery and from umbilical cord blood after delivery.
Results: In first group occurred in higher percentage (27.41 %) preterm delivery (26.–37. week of pregnancy), chorioamnionitis confirmed by histological examination (16.12 %) and preterm premature rupture of membranes (24.19 %). In this group occured perinatal infection of newborn in 61.29 %. In the second group preterm delivery (6.31 %)and perinatal infection of newborn (7.36 %) occured in lower percentage.
Conclusion: The results suggest that the simultaneous measurement of CRP, PCT and NPT in mother's blood sample before delivery and umbilical cord blood may provide an accurate early diagnosis of infection and then preterm delivery *(Tab. 1, Fig. 3, Ref. 18)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: procalcitonin, neopterin, C-reactive protein, preterm delivery, intrauterine infection.

Intrauterine infection is a major cause of premature labor. It is present in approximately 25 % of all preterm births. The differential diagnosis of intrauterine infection (chorioamnionitis) is very difficult because of absence of clinical signs of infection. Unfortunately, clinical signs of intrauterine infection do not appear until late in the course. The clinical syndrom of chorioamnionitis appears only in fraction of women with microbiologically proven intra-amniotic infection.

In the nineties new parameters – procalcitonin (PCT) and neopterin – were developed. Although their physiological role and regulation of their production is not sufficiently explained, procalcitonin and neopterin have been shown to be important, sensitive and specific markers of the severe inflammatory responses. These days procalcitonin is believed to be more specific marker of the severity of sepsis than cytokine interleukin 6 (IL-6) and C-reactive protein (CRP).

Procalcitonin is a 116-aminoacid peptide and precursor of calcitonine. High levels of PCT i serum have been reported in both adult and pediatric patients with severe bacterial infection (1, 2). Its production is induced by endotoxin and by pro-inflammatory cytokines – tumor necrosis factor-α (TNF-α), interleukin 1, interleukin 2 and interleukin 6. PCT is consistently released into the cicrulation 2–4 hours after injection of endotoxin and steadily increases up to 24 hours (4).

Neopterin is pteridine derivative synthesized from guanosine triphosphate in monocyte derived macrophages (8). The activity of this enzyme is greatly enhanced by interferon gamma (9). Serum concentrations of neopterin are increased in variety of infections (HIV, maesles, malaria, cytomegalovirus, Mycobacterium tuberculosis), chronic inflammatory states (Crohn's disease, ulcerative colitis, sarcoidosis), autoimune disorders, malignancies and also preterm delivery (10, 11).

Considering the infectious etiology of preterm labor, the purpose of this study was to evaluate plasma levels of PCT and neopterin in comparison with C-reactive protein in pregnancy complicated by intrauterine infection.

Methods

The prospective study included 155 patients who delivered at I. Department of Obstetrics and Gynaecology, Bratislava, Slovakia from december 2005 to March 2007.

We evaluated 155 patients from 26. to 41. week of pregnancy at the time of delivery. We measured serum concentractions of PCT, neopterin and CRP from mother's blood sample at the begining of delivery and from umbilical cord blood after delivery. The patients were divided into 2 groups: The first group

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Tab. 1. Characteristics of patients in details.

	Group I (PCT 0.05–3.5 ng/ml, average 0.437 ng/ml)	Group II (PCT 0.001–0.05 ng/ml, average 0.0103 ng/ml)
Amount of patienta (n=155)	60	95
Preterm labor	16 (27.41 %)	6 (6.31 %)
Preeclampsia	11 (18.33 %)	2 (2.1 %)
Chroioamnonitis	9 (16.12 %)	0 (0 %)
PPROM	14 (24.19 %)	7 (7.36 %)
GBS	6 (10 %)	21 (22.10 %)
Vaginal infections	21 (36.84 %)	22 (22.09 %)
TT>37.8 °C	10 (16.66 %)	5 (5.26 %)
Antibiotical treatment	27 (45.6 %)	25 (26.31 %)
Corticoid treatment	20 (33.33 %)	1 (1.05 %)
Perinatal infection of newborn	36 (61.29 %)	7 (7.36 %)

PPROM - Preterm Premature Rupture of Membranes, GBS - Group B streptococcus

consisted of patients where we measured concentractions of PCT in mother's blood sample higher than 0.05 ng/ml (0.05–2.690 ng/ml), in second group we measured physiological concentrations of PCT (0.001–0.05 ng/ml).

Serum concentrations of PCT was measured by immunolumimetric assay LUMItest PCT (BRAHMS diagnostica, Hennigsdorf/Berlin, Germany, normal values in adults: <0.05 ng/ml), serum neopterin concentrations was determined with ELISA (BRAHMS diagnostica, values in adults: <10 nmol/L were considered as elevated) and serum CRP concetrations were determined by NEPHELOMETRIC (DadeBehring, Bratislava, Slovak Republic, normal values: <5 mg/L).

Collected data included occurance of preterm labor, preterm premature rupture of membranes, histologically proven chorioamnionitis, vaginal infections, colonisation of vagina by Group B-streptococcus, tretment with antibiotics and corticoid therapy, and perinatal infection of newborn.

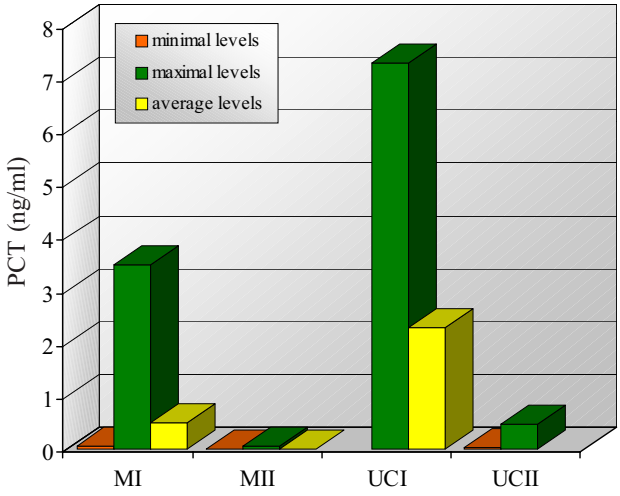

Fig. 1. Average values of procalcitonin in mother's blood sample and umbilical cord blood in the first and second groups. MI – mother's blood sample in the first group, MIL – mother's blood sample in the second group, UCI – umbilical cord blood sample in the first group, UCII – umbilical cord blood sample in the second group.

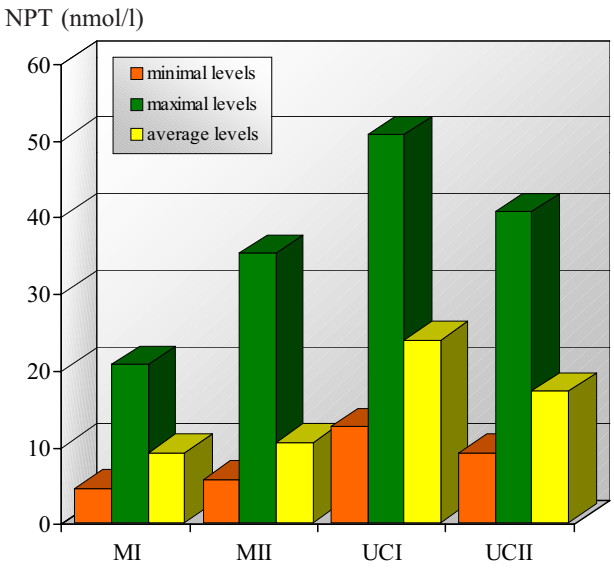

Fig. 2. Average values of neopterin in mother's blood sample and umbilical cord blood in the first and second groups. MI – mother's blood sample in the first group, MIL – mother's blood sample in the second group, UCI – umbilical cord blood sample in the first group, UCII – umbilical cord blood sample in the second group.

Results

In the first group occurred in higher percentage (27.41 %) preterm delivery (26th–37th week of pregnancy), chorioamnionitis confirmed by histological examination (16.12 %) and preterm premature rupture of membranes (24.19 %). In this group occured perinatal infection of newborn in 61.29 %. The most of the vaginal infections were caused by E. coli, Enterococcus faecalis (36.84 %), the prevalence of streptococcus B colonisation was only 10 %. We observed higher prevalence of preeclampsia (18.33 %) in this group. The comprehensive characteristics of patients is illustrated in table 1.

In the second group where we had measured physiological concentrations of procalcitonin preterm delivery occured in lower

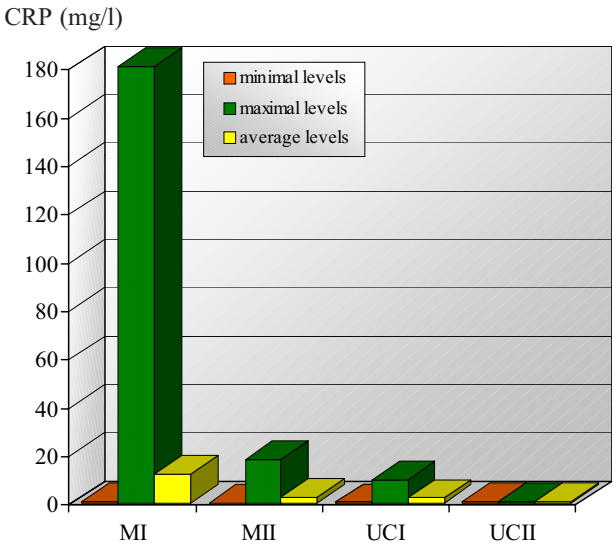

Fig. 3. Average values of C-reactive protein in mother's blood sample and umbilical cord blood in the first and second groups. MI – mother's blood sample in the first group, MIL – mother's blood sample in the second group, UCI – umbilical cord blood sample in the first group, UCII – umbilical cord blood sample in the second group.

percentage (6.31 %, $p<0.001$)) than in the first group. Histological confirmed chorioamnionitis did not occure in this group. Perinatal infection of newborn occured only in 7.36 %. Vaginal infection were caused mostly by Candida albicans , the prevalence of group B streptococcus was 22.10 %. PCT concentrations are illustrated in Figure 1.

Between the two groups we did not regard differences of neopterin in mother's blood sample (average concentraction of neopterin in the first group was 7.11 mmol/l and in the second group 8.63 nmol/L), but we regarded differences in umbilical cord blood samples of neopterin in first (average 23.78 nmol/l, $p<0.001$) and second group (average 17.6 nmol/L). Physiological levels of neopterin in adults are 5.3±.7 nmol/l, with upper limit 13.5 nmol/L and in umbilical cord blood physiological levels are 10.7–15.4 nmol/l with upper limit 24 nmol/L. Neopterin concentrations are illustrated in Figure 2.

We observed higher concentractions of C-reactive protein in mother's blood sample (average value 13.6 mg/L) where chorioamnionitis was confirmed by histological examination. We did not observe differences of concentration of C-reactive protein in umbilical cord blood in first (average value 1.9 mg/l) and second group (average value 0.20 mg/l). C-reactive protein concentrations are illustrated in Figure 3.

Discussion

The origin of PCT synthesis in the course of different diseases is not well understood. It is known that the parafollicular cells of thyroid gland are responsible for the production of PCT.

High levels of PCT in serum have been reported in both adult and pediatric patients with severe bacterial infection (1, 2). It is not known whether PCT is produced by placental tissues or wheter it can pass through placental barrier. Asssumna et al (14) hypothesised that the postnatal increase in procalcitonin indicates transplacental passage of maternal procalcitonin. However, procalcitonin concetrations in umbilical cord serum were found to be higher than in paired maternal samples at the birth in his and in our study, too. Therefore, the postnatal increase of procalcitonin cannot be explained by transplacental passage.

Neopterin is a pteridine derivate synthesized from guanosine triphosphate in monocyte-derived macrophages (8). High concentrations in serum and urine were found in patients who suffered from viral infections (10).

The aim of this study was to find out whether procalcitonin, neopterin and C-reactive protein are sensitive, specific and early markers of intrauterine infection. Because unfortunately, clinical signs of intrauterine infection do not appear until late in the course.

In the group where we measured higher levels of PCT occured in higher percentage preterm delivery (27.41 %), chorioamnionitis confirmed by histological examination (16.12 %) and preterm premature rupture of membranes (24.19 %). In this group occured perinatal infection of newborn in 61.29 %. We confirmed higher levels of PCT and nepterin in umbilical cord blood of newborns who later suffered with perinatal infection. We also confirmed that higher levels of PCT in mother's serum is related with intrauterine infection and preterm labor.

We did not regard differences of neopterin in mother's blood sample ($p=0.563$) and), but we regarded differences in umbilical cord blood samples of neopterin in first (23.78 nmol/l, $p\leq0.001$) and second group (17.6 nmol/l) what reflects immune activation of the fetal compartment. We cannot confirm neopterin as a marker of intrauterine infection in mother's blood sample. In general, neopterin concentrations increase with pregnancy up to third trimester and are higher than in nonpregnant women. Because neopterin production reflects cellular immune activation, it might be hypothesised that during pregnancy immunogenic stimuls are increasingly induced by placenta and fetus. Cord blood neopterin concentrations may reflect immune activation of the fetal compartment, which has previously been found to be isolated from the maternal compartment with the respect to neopterin metabolism (10). In this study we regarded differences in cord blood samples in first and second group ($p\leq0.001$). Earlier higher neopterin concentrations have been described in cord blood positive for infection of cytomegalovirus – CMV (17).

CRP is a circulating marker of inflammation,, trombosis, vascular injury, and it has been associated with underlying inflammatory processes (15). The role of measurment of CRP in clinical practise remains unclear for many diseases, although it has been proposed as helpful marker in diagnosis of chorioamnionitis (15). In the present study we observed higher concentractions of CRP in mother's blood sample (average value 13.6 mg/l) where chorioamnionitis was confirmed by histological examination. We did not observe differences of concentration of CRP in umbilical cord blood in the first (average value 1.9 mg/l) and the second group (average value 0.20 mg/l). The present study revealed

a high prevalence of chorioamnionitis among the study population, which underlines the need for efficient test for the condition. However, the sensitivity and specificity of C-reactive protein is only fair with high false positive and false negative rates. Hollý I (16) in his thesis investigated levels of CRP in 44 patients with false preterm labor. Positive levels occured only in 4 cases (9 %). He confirmed the assumption that levels of C-reactive protein rise with detection of clinical signs of infection.

Skrak et al (18) observed levels of procalcitonin, neopterin and C-reactive protein in use in potoperative setting after pediatric cardiac surgery. Their study showed that procalcitonin, neopterin nad C-reactive protein levels increase above normal in children after cardiac surgery. Due to rapid kinetics, procalcitonin and neopterin appear to be promising inflammatory markers in postoperative period.

Conclusion

A higher frequency of preterm delivery, chorioamnionitis confirmed by histological examination and preterm premature rupture of membranes occured in pregnant women with increased PCT serum concentrations and increased neopterin concentrations in umbilical cord blood. Also perinatal infection of the newborn was observed in 61.29 %. The results suggest that the maesurment of PCT in mother's blood sample and PCT and neopterin in umbilical cord blood sample may support earlier diagnosis of intaruterine infection.

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