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Procalcitonin vs C-reactive protein in early detection of intrauterine infection in premature rupture of membranes and neonatal infections

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ABSTRACT

At any time during pregnancy intrauterine infection is an important risk factor for neonatal sepsis and is a frequent cause of mortality and morbidity in newborn infants. The aim of this study was to consider the patterns of procalcitonin (PCT) response in normal pregnancy and in pregnancies complicated with a premature rupture of the membranes, to compare the results of PCT with those of C-reactive protein (CRP) and to assess their diagnostic accuracy both to mothers and neonates. 120 mothers with singleton pregnancies were enrolled in this study. 60 pregnancies were complicated with a premature rupture of membranes, and 60 were control pregnancies. We analyzed PCT and CRP values, clinical chorioamnionitis, neonatal infection and other neonatal outcomes in both groups. We found significantly higher maternal serum concentrations of PCT and CRP in the Study group. Regarding our results, both markers are predictive for chorioamnionitis and neonatal infections, with almost similar significance.

Key words: clinical chorioamnionitis, neonatal infection, procalcitonin, C-reactive protein

Introduction

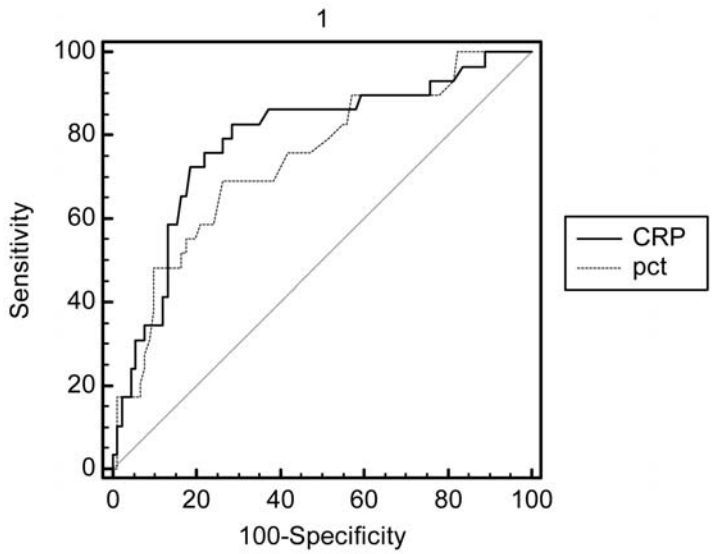
The diagnosis of early onset neonatal infection remains one of the greatest challenges in perinatal medicine. At birth the diagnosis must be based on the history of the pregnancy and take into account a number of risk factors, such as preterm premature rupture of membranes, along with (usually late to be recognised) subclinical intrauterine infection. Early onset neonatal infection is associated with an ascending infection from the cervix, and the intact membranes during pregnancy act as an effective barrier against infection of the amniotic fluid. (1) Intrauterine infection at any time during pregnancy is an important risk factor for neonatal sepsis and is a frequent cause of mortality and morbidity in newborn infants.

If promptly initiated, antibiotic therapy can reduce its sequelae and improve the prognosis. However, the number of tests that obstetrician can rely on for the early diagnosis of infection is quite limited. Culture tests are not immune from the risk of contamination and the measurement of interleukins in the amniotic fluid and maternal blood serum is not yet routine. The usefulness of procalcitonin (PCT) as a diagnostic tool of maternal-fetal infections is currently being evaluated, and the results of recent PCT studies regarding its usefulness for early diagnosis of neonatal sepsis have produced varying results. (2)

The aim of this study was to consider the patterns of PCT response in normal pregnancy and in pregnancies complicated with premature rupture of the membranes and to compare the results of PCT with those of C-reactive protein (CRP) and to assess their diagnostic accuracy both to mothers and neonates.

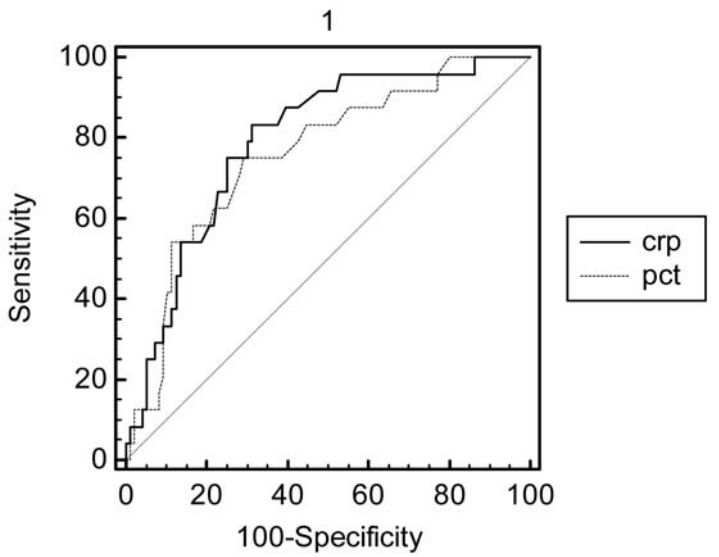
Materials and methods

A total of 120 mothers with singleton pregnancies were enrolled in this study. 60 pregnancies were complicated with the premature rupture of membranes, and 60 were control pregnancies. The study included pregnancies that ended as premature and term deliveries. Pregnancies with congenital fetal malformations were excluded from the study. Clinical chorioamnionitis was diagnosed when maternal temperature was



AUC CRP =0.789; the best cut-off > 7 mg/L; 82.8% sensitivity, 71.4%specificity
AUC PCT= 0.749; the best cut-off 0.053ng/L; 69% sensitivity, 73.6% specificity
AUC CRP/PCT, p= 0.3789
AUC, area under the curve
CRP, C reactive protein
PCT, procalcitonin

Figure 1. Receiver operating characteristics (ROC) curves for maternal CRP and PCT in prediction of chorioamnionitis;



AUC CRP =0.79; best cut-off: > 7 mg/l; 83.3%sensitivity, 68.7% specificity
AUC PCT =0.757; best cut-off 0.053ng/l; 69% sensitivity, 73.6% specificity
AUC CRP/PCT, p= 0.0345

AUC, area under the curve
CRP, C reactive protein
PCT, procalcitonin

Figure 2. Receiver operating characteristics (ROC) curves for maternal CRP and PCT in prediction of neonatal infections

≥38°C, leukocytosis >15.000x109/L, maternal (>100 beats/min) and fetal tachycardia (>160 beats/min). (3)

Early neonatal onset bacterial infection was recognized during the first 48 hours of life based on maternal findings and the presence of clinical signs in the neonate: respiratory (apnea, tachypnea >60/min, high ventilator settings or oxygen), cardiovascular (hypotension, poor peripheral perfusion, tachy/bradicardia), neurological (seizures, hypotonia), skin colour (pallor, cyanosis, jaundice) and positive blood culture. (3)

An immunoluminometric assay for the measurement of serum PCT concentration was performed with a Brahms KRYPTOR kit. The lowest detection limit of PCT using this method was 0.1 ng/ml.

All values are expressed as mean values. Statistical analyses were conducted using the non-parametric Mann Whitney test. Receiver operating characteristics (ROC) curves were used to determinate the diagnostic validity for predicting clinical chorioamnionitis and neonatal infections. Results were considered statistically significant at $p < 0.05$.

Results

We analysed 60 singleton pregnancies with premature rupture of membranes (PROM) as the Study group, and 60 singleton pregnancies without PROM as the Control group. We found a significantly lower gestational age (p=0.20), birth weight (p=0.27), and Apgar score in the first (p=0.48) and fifth minute (p=0.27) in the Study group. The incidence of clinical chorioamnionitis and neonatal infection was significantly higher in the Study group (p<0.001 and p=0.006). Neonates from the Study group had an almost four fold higher rate of NICU admission compared to neonates from the Control group (p=0.003). There was a significantly higher use of antibiotics during pregnancy in the Study group as well (p<0.001).

We found significantly higher maternal serum concentrations of PCT and CRP in the Study group.

The aim of this study was also to asses and to compare the diagnostic accuracy of PCT with those of CRP in the

prediction of chorioamnionitis (figure 1) and neonatal infection (figure 2).

Discussion

Sepsis is a condition that markedly influences mortality and morbidity in neonatal intensive care units. The main risk factors associated with neonatal sepsis are chorioamnionitis and preterm delivery. (4) One of the most important goals of recent research in the field of neonatology is to uncover a highly sensitive and specific method for early sepsis detection. Available laboratory tests lack the necessary sensitivity and specificity. This concentrates efforts on discovering new infection markers. (5)

The pathogenesis of premature rupture of membranes resulting in preterm birth remains unknown, but many hypotheses have been suggested. Intrauterine infection and subsequent inflammation may synergistically weaken the membranes because of the combined effects of microbia, host inflammatory cells and cytokine-regulated protease production. (6)

The frequency of perinatal infections and other pregnancy complications is adversely correlated to the gestational age at delivery, and sepsis is a condition that markedly influences mortality and morbidity in neonatal intensive care units. (7) In patients with preterm rupture of membranes, the incidence of a severe neonatal morbidity rate was reported as 55% in patients with chorioamnionitis and 18% in those without. (3) In our study group, 38% of patients had chorioamnionitis, out of which 30% had neonatal infection and 27% of those neonates were admitted to NICU. Clinical chorioamnionitis and antibiotics administration were significantly higher in the Study group ($p<0.001$) (table 1). The Study group had more preterm deliveries ($p=0.143$), and a lower Apgar score in first ($p=0.048$) and fifth ($p=0.027$) minute.

Although the usefulness of procalcitonin (PCT) in clinical practice is increasing, there is still not enough data available to establish the role of procalcitonin in the patophysiology of pregnancy.

In our study we found significantly higher PCT level in pregnancies complicated with preterm rupture of membranes (Study group) compared to the Control group ($p<0.001$) (table 2). The level of CRP in maternal serum in pregnancies complicated with preterm rupture of membranes was also elevated ($p=0.025$) (table 2). We therefore analysed the predictive value of CRP and PCT maternal levels for the diagnosis of chorioamnionitis (figure 1) and neonatal infection (figure 2). The AUC for both biomarkers showed relatively low, but still significant predictive values. We found AUC for CRP=0.78 and AUC for PCT=0.749 (figure1).

The predictive value of CRP in chorioamnionitis was no different when compared to the predictive value of PCT ($p= 0.3789$) (figure 1). Results from a study by Trochez-Martinez et al. found no positive correlation between CRP and chorioamnionitis, but results from Jarc et al. were almost similar to ours.

Table 1. Maternal and neonatal characteristics

	Study group (n=60)	Control group (n=60)	P-value
Age of mothers (years) (mean), min; max	28.5 (21-39)	27.5 (19-43)	.641
Preterm delivery	32 (53.3%)	24 (40%)	.143
Gestational age at delivery (weeks)(mean)	36.5 (24-41)	38 (24-42)	.020
Sectio cesarea	24 (40%)	19 (31.7%)	.341
Clinical chorioamnionitis	23 (38.3%)	6 (10%)	<0.001
Prenatal antibiotic administration	36 (60%)	14 (23.3%)	<0.001
Serclage	5 (8.3)%	11 (18.3%)	.107
Birth weight (g) (median)	3110 (290-3540)	3395 (480-4670)	.027
Apgar1 (points) (mean)	8.57 (0-10)	9.02 (0-10)	.048
Apgar2 (points) (mean)	9.12 (0-10)	9.42 (0-10)	.027
Neonatal infections	18 (30%)	6 (10%)	.006
NICU admissions	16 (26.7%)	4 (6.7%)	.003

NICU, neonatal intensive care unit

Table 2. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) concentrations

	Study group (n=60)	Control group (n=60)	p-value
PCT ng/L	0.074±0.008	0.041±0.0023	< .001
CRP mg/L	13.95±2.33	8.987±1.82	.025

(8,9) Analysing the detection of neonatal infection, we found a significantly higher predictive value of CRP compared to PCT ($p = 0.0345$) (figure 2).
A meta-analysis of six studies confirmed that CRP does not predict histological chorioamnionitis reliably. (8) Some authors reported 96% specificity and 88% sensitivity for CRP>13mg/L[10]. Some authors have not confirmed these findings with even higher concentrations of CRP. Fiski et al. reported 50% sensitivity and 80% specificity in their study. (11) Our results confirm this latter finding that neither CRP nor PCT in maternal blood after preterm rupture of membranes offer a precise diagnosis for subclinical chorioamnionitis. Predictive values of maternal PCT level for chorioamnionitis and neonatal infection, however, habe not been adequately studied yet. Popowski et al. found CRP to be a reliable predictive factor of early neonatal sepsis in PROM at 34-37 weeks of gestation. (12) The clinical significance of this study remains questionable, since pregnancy is usually terminated after preterm premature rupture of membranes at or after 34 weeks (through induction of labour or caesarean section).

Conclusion

Regarding our results, both markers are predictive for chorioamnionitis and neonatal infections, with almost similar significance. Future studies should focus on newer and potentially better diagnostic markers for the early diagnosis of chorioamnionitis and neonatal infection in pregnancies complicated with preterm rupture of membranes. Such markers would allow termination of pregnancy prior to a potentially adverse fetal outcome, but also assist in identifying cases in which prolonging pregnancy in beneficial.

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