Clinical significance of procalcitonin in cervico-vaginal secretions of women with preterm rupture of membranes

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Summary

Purpose: To compare vaginal fluid procalcitonin (PCT) concentrations in cases of preterm premature rupture of membranes (PPROM) and healthy pregnant women, and to determine whether the PCT concentrations are of value in the diagnosis of PPROM cases and clinical amnionitis. *Methods:* 50 cases with PPROM and 50 healthy pregnant women were enrolled in the study. In the PPROM group, analysis was conducted on PCT concentrations with reference to serum leucocytosis, serum C-reactive protein level and urine analysis, as well as to presence/absence of clinical amnionitis. Statistical analyses were carried out by using the statistical packages for SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). *Results:* Procalcitonin levels in the PPROM group were significantly higher than in cases of healthy pregnant women (1.17 vs 0.05 ng/ml; $p < 0.001$). In the PPROM group PCT concentrations between the patients with and without clinical amnionitis were comparable. Also, a significant correlation was observed between PCT and leucocytosis ($r = 0.64$; $p < 0.001$) and C-reactive protein ($r = 0.90$; $p < 0.001$). *Conclusion:* These findings suggest that the value of vaginal fluid PCT determinations can be useful for diagnostics of PPROM cases suspected of intrauterine infection.

Key words: Premature rupture of membranes; Procalcitonin; C-reactive protein.

Introduction

Preterm premature rupture of membranes (PPROM) is diagnosed when rupture of amniotic membranes occurs prior to the completion of the 36th week of gestation, and the incidence is reported to be between 6% and 10%, with almost 80% of these cases occurring at term [1, 2]. Preterm PROM is largely a clinical diagnosis. It is typically suggested by a history of watery vaginal discharge and confirmed on sterile speculum examination. The differential diagnosis includes leakage of urine (urinary incontinence); excessive vaginal discharge, such as physiologic discharge or bacterial vaginosis; and cervical mucus (show) as a sign of impending labor [3]. The perinatal complications of PPROM change with gestational age at rupture requiring a gestational age approach to treatment. There is little maternal benefit to conservative management, but there can be significant neonatal benefit, especially in the late second and early third trimester. The benefits of conservative management are mainly in prolonging pregnancy, which has the potential to decrease gestational age-related morbidity associated with preterm birth. This must be balanced with the risks of conservative management, which include cord prolapse, placental abruption, perinatal infection, emergent delivery for a non-reassuring fetal status and fetal death [4]. The number of clinical methods of detecting women suspected of subclinical intrauterine infection is modest and limited. Non-invasive methods of detecting intrauterine infection are desirable. Some mediators may be detected in vaginal or cervical secretions and it seems probable that the concentrations the vaginal compartment, especially after PROM, are representative of their intra-amniotic concentrations [5].

PCT is recognized as a specific marker of generalized bacterial infections [6, 7]. Although there is an increasing awareness of the usefulness of assessing PCT levels in clinical practice, there are only a few published data about PCT being evaluated during term and preterm parturition [8, 9].

The purpose of this study was to evaluate and compare concentrations of PCT in cervico-vaginal secretions in pregnancies complicated by PPROM and healthy pregnant women and to determine clinical significance PCT levels in clinical amnionitis cases.

Methods

This study was performed at Dicle University, School of Medicine, Department of Obstetrics and Gynecology, from September 2008 to September 2009 on 100 pregnant women. Written informed consent was obtained from all patients. The study consisted of 50 pregnant patients and a control group was created consisting of 50 normal pregnant women.

The study group consisted of patients admitted with a diagnosis of PPROM (24-36 weeks gestation). All patients in this group developed spontaneous rupture of membranes. PPROM was diagnosed by traditional methods such as vaginal fluid drainage, vaginal discharge and perineal wetness. Rupture of membranes was diagnosed by sterile speculum examination confirming fluid leakage from the cervical canal or pooling of fluid in the posterior vaginal fornix. All pregnant patients in this group were hospitalized at our clinic and followed-up until delivery. From admission to delivery patients received prophylactic antibiotics (sulbactam-ampiciline 1g 4x1 IV). Steroid therapy (betamethasone 12 mg 2x1 IM) was used in cases before 34 gestational weeks. Patients were restricted to bed rest,

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and fetal heart monitoring with uterine activity assessment was performed twice daily.

The control group consisted of pregnant women (20-37 weeks gestation), who were admitted to our clinic for routine control of pregnancy. This group was without complaints, vaginal discharge, or any infection and diagnosis of PPROM had been ruled out of by traditional methods.

In all patients of the study group, vaginal fluid was aspirated with a 5-ml plastic syringe from the cervical canal or the posterior vaginal fornix at the first examination. In the control group 5 ml sterile saline solution was administered to the posterior fornix and after 1 min aspirate was taken. The fluid specimens were collected in polypropylene tubes. For the measurement of PCT concentration, immunoluminometric assay was performed. Cervical dilatations (1 to 10 cm) and effacements (0 to 100%) were noted. In both groups blood samples for white blood cell count (WBC) and C-reactive protein (CRP) and urine analyses for leucocytes were taken. Also in both groups ultrasound examination was performed for detection of gestational week and amnionic fluid index (AFI).

The patient group was evaluated in terms of delivery type, maternal infection and fetal condition and they were also categorized according to clinical amnionitis situations. Fetal tachycardia (> 160/m), maternal fever (> 38°C), maternal tachycardia (> 100/m without any other explanation) or uterine sensitivity were evaluated as clinical amnionitis.

The mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogorov-Smirnov test. The chi-square test and Student's t-test evaluated associations between the categorical and continuous variables. Two-sided P values were considered statistically significant at $p < 0.05$. Statistical analyses were carried out by using the statistical packages for SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The demographic and clinical characteristics of groups are shown in Table 1. There were no significant differences in maternal and gestational age between groups. However cervical dilatation and effacements were significantly higher in the study group than the control group. Also AFI was significantly lower in the study group.

Serum WBC counts (10.97 vs 13.81k/ul; $p < 0.001$) and serum CRP level (6.22 vs 25.42 mg/l; $p = 0.005$) were found to be statistically different between the study and control group, and both of these values were higher in the study group.

Vaginal fluid concentrations of PCT in patients with PPROM were significantly higher than in the control group (1.17 vs 0.05 ng/ml; $p < 0.001$). Significant correlations were observed between PCT levels with CRP (r-0.90, $p < 0.001$) and WBC (r-0.64; $p < 0.001$).

Of the study group and control group cases leukocytes were detected in the urine analysis in 44% and 24%, respectively, and the difference was statistically significant ($p < 0.05$).

Study group cases were evaluated for clinical amnionitis within themselves and 24% of cases were detected. Detected and non detected clinical amnionitis cases were evaluated and vaginal fluid PCT concentrations (2.85 vs 0.22 ng/L $p < 0.001$), CRP (56.10 vs 8.16 mg/l $p < 0.001$) and WBC count (16.77 vs 12.15 k/l $p < 0.001$) were significantly higher in detected cases of clinical amnionitis. The 5 min Apgar score (6.43 vs 5.16 $p = 0.009$) was significantly higher in non detected clinical amnionitis cases versus detected cases.

Table 1. — *Demographic and clinical characteristics of the study and control groups*.

Characteristic	Study group (n = 50)	Control study (n = 50)	*p* value
Maternal age (years) (mean ± SD)	27.38 ± 6.02	27.72 ± 6.60	0.60
Parity (mean ± SD)	2.16 ± 2.24	3.36 ± 2.79	0.02
Gestational age (weeks) (mean ± SD)	30.40 ± 3.18	29.74 ± 4.04	0.36
Cervical dilatation (cm) (mean ± SD)	25.60 ± 17.39	8.40 ± 5.84	< 0.001
Cervical effacements (%) (mean ± SD)	1.61 ± 1.22	0.80 ± 0.53	< 0.001
AFI (cm) (mean ± SD)	4.86 ± 2.98	12.84 ± 1.73	< 0.001
WBC (g/l)	10.97	13.81	< 0.001
CRP (mg/l)	6.22	25.42	0.005
Procalcitonin (ng/l)	1.17	0.05	< 0.001

$p \leq 0.05$ is accepted to be statistically significant. CRP: C- reactive protein. AFI: Amiotic fluid index. WBC: White blood cells.

Twenty-eight (56.2%) patients of the study group were delivered by cesarean section and 21 (43.8%) patients were delivered vaginally. When delivery type was compared with clinical amnionitis, cesarean section rate was significantly higher in the clinical amnionitis group ($p = 0.035$).

Discussion

Rupture of the membranes is thought to result from the effects of physical forces in localized areas of membranes weakened by degradation of structural collagens [10]. The pathogenesis of PPROM resulting in preterm birth remains unknown, but many hypotheses have been suggested. These factors include maternal infection, genetic predisposition, mechanical damage, smoking, nutritional and vitamin deficiencies and plasminogen activation. Intrauterine infection and subsequent inflammation may synergistically weaken the membranes because of the combined effects of microbial, host inflammatory cells, and cytokine-regulated protease production [11]. The first goal of this study was to determine whether vaginal fluid PCT levels in PPROM cases and healthy pregnant women were different or comparable. It was observed that PCT levels in PPROM were significantly higher than in healthy pregnant women, thus adding additional evidence to confirm the hypothesis about the infectious etiology of PPROM.

The current management of patients with PPROM at a gestational age lower than 34 weeks consists of corticosteroid and antibiotic administration, and expectant management until fetal or maternal signs of infection become evident [12]. Optimal expectant management of PPROM requires early detection of chorioamnionitis. To date, no universally sensitive and specific marker for diagnosis of subclinical intrauterine infection has been identified.

Torbé *et al*. [13] found that increased vaginal fluid PCT level is associated with subclinical intraamnionitic infection in PPROM cases; likewise in our study high vaginal fluid PCT levels were detected in clinical amnionitis. Rizzo *et al*. [14] and Jun *et al*. [15] demonstrated that the measurement of interleukin-6 in cervical secretions of patients with PPROM is a noninvasive and sensitive method to identify the patient at risk for microbial invasion of the amniotic cavity, impending preterm delivery, or neonatal complications. Di Naro *et al*. [12] found that increased vaginal fluid C-reactive protein concentration is associated with intraamniotic infection and funisitis and that there is a significant correlation between amniotic fluid and vaginal fluid concentrations.

Conclusion

Procalcitonin is a new parameter used in the diagnosis of generalized or systemic infectious diseases. So far, not much is known about its use among pregnant women. In view of the probably infectious etiology of PPROM one of the purposes of this study was to determine whether vaginal fluid concentrations of PCT immediately after PPROM might have any value in the diagnosis of cases with suspected subclinical intrauterine infection.

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