CEOG Clinical and Experimental Obstetrics & Gynecology

Predictive value of procalcitonin and IL-6 versus cervical length for the admission-to-delivery interval in preterm labour

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Summary

Objective: The authors aimed to determine whether concentrations of IL-6 and procalcitonin in maternal circulation can be used and compared with cervical length to predict the admission-to-delivery interval in preterm labour. *Materials and Methods:* Forty patients complicated with preterm labour between 24-34 weeks of gestation and having preterm birth were included in the study group. Forty-four healthy pregnant women at similar gestational ages and having term labour (≥ 37 weeks) were included in control group. Maternal concentrations of IL-6 was measured by an enzyme-linked immunosorbent assay (ELISA) and procalcitonin was measured by immunoturbidimetry with using human procalcitonin reagent kit. Transvaginal ultrasound to assess cervical length was performed. *Results:* Receiver operator characteristic (ROC) analysis results of IL-6 and procalcitonin for prediction of preterm delivery (PTD) < 48 hours, < seven days, < 32 weeks, < 34 weeks, and < 37 weeks were not statistically significant ($p > 0.05$).). It was shown through ROC analysis, that only cervical length had area under curve (AUC) 0.692 (0.511–0.873, $p = 0.044$) at cut off value ≤ 3.64 cm, AUC 0.758 (0.574–0.943, $p = 0.015$) at cut off value ≤ 3.50 cm, AUC 0.716 (0.553–0.879, $p = 0.032$) at cut off value < 3.80 cm, in predicting PTD within seven days, <32 weeks and < 37 week, respectively. *Conclusion:* This study suggests that in preterm labour, although IL-6 and procalcitonin have unsatisfactory predictive value for the admission-to-delivery interval, cervical length has better predictive values for the admission-to-delivery interval.

Key words: Procalcitonin; IL-6; Cervical length; Preterm labour; Preterm delivery.

Introduction

Preterm delivery (PTD) is a major community health problem throughout the world. It is defined as birth before 37 weeks gestation and occurs in 12.0% to 13.0% of pregnancies in the United States [1]. Estimated PTD rates in most countries of Europe vary from 5% to 8% [2]. In the last decade, the incidence of spontaneous PTD has increased by more than 50% [3]. Although there have been dramatic advances in neonatal care, PTD is still a significant cause (about 60–80%) [4] of neonatal morbidity and mortality [5].

The causes of spontaneous PTD (in 70% of cases) are mostly unknown [6]. It is a multifactorial disease caused by several etiologic factors which has overlapping pathophysiologic pathways [7]. Four major pathogenic pathways for PTD, have been suggested: inflammation, pathological uterine distension, activation of the hypothalamic-pituitary-adrenal axis, and decidual hemorrhage. All these pathways result in a biochemical reaction causing activation of uterotonins, like prostaglandins and induce labour [7]. Among the pathways, infection and the host inflammatory response to infection (e.g. cytokine activation) are among the most commonly [8] found pathogenic pathways blamed for PTD [9].

One of most important mediators associated with infection that it may affect the risk of PTD is interleukin 6 (IL-6). It has a role in inflammation and in the maturation of B cells. It is generally produced at sites of acute and chronic inflammation, then secreted into the serum and induces inflammatory response by IL-6 receptor alpha. It causes production of prostaglandins and leads to cervical ripening and uterine contractions [10]. Therefore an increase in concentration of IL-6 in cervical and amniotic fluid has been associated with microbial invasion of the amniotic cavity in patients threatened with PTD [11].

Recently procalcitonin, a prohormone consisting of 116 amino acids, has been determined as a specific marker of generalized bacterial infections [12]. In healthy individuals, it should be less than 0.5 ng/ml, but in conditions causing systemic inflammatory response syndrome or sepsis, it rapidly increases to high levels [13]. Although, in modern clinical practice, importance of procalcitonin have been increasing continuously, but there are only a few published data on procalcitonin in pregnancy [14].

It is known that 80% of PTD occur after 34 weeks of gestation and prognosis for these preterm babies is mostly very good. However, risk of complications related to prematurity significantly increase in deliveries between 24 and 32 weeks. Therefore, methods and biological markers

Revised manuscript accepted for publication June 23, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIV, n. 1, 2017
doi: 10.12891/ceog3180.2017

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are needed in order to predict accurately the admission-to-delivery interval in those women at high risk of PTD. By this way, unnecessary hospital admissions, hospital transfers, treatments including steroids and tocolytic treatments might be inhibited, and the management of PTD might be improved [15]. In present study, the authors aimed to determine whether concentrations of IL-6 and procalcitonin in maternal circulation can be used and compared with cervical length to predict the admission-to-delivery interval in preterm labour.

Materials and Methods

This prospective cohort study was conducted at Adnan Menderes University Hospital from January 2013 to April 2014. The institutional review board approved the study and informed consent was obtained from all of the patients.

A total of 40 patients with singleton pregnancies complicated with preterm labour admitted to the present hospital between 24 and 34 weeks of pregnancy and having preterm birth were included in the study group. In control group, 44 healthy pregnant women at similar gestational ages with study group and having term labour (≥ 37 weeks) were included. Maternal characteristics (age, obstetric history, and history of preterm labour in previous deliveries) were obtained by interview at the time of hospital applications. Exclusion criteria were: (1) patients having vaginal bleeding, cervical dilatation greater than five cm, and effacement 80%, (2) pregnancies lasting with PTD due to medical causes such as abruption of placentae, fetal distress, cord prolapse, (3) multiple pregnancy, (4) fetal anomalies, (5) preterm premature membrane rupture, and (6) smokers.

Study group included women who fulfilled the following admission criteria: pregnant with a single fetus of 24–34 weeks' gestation, had two or more painful and persistent uterine contractions in ten minutes, established by tococardiography. In all cases fetal heart rates were recorded by ultrasonography or tococardiography. Tocolysis was started when regular uterine contractions were associated with cervical change. As tocolytic treatment, ten mg nidilat (nifedipine) was applied to patients in two dosage periods; loading and maintenance dosages. It consisted of an initial oral dose of ten mg nifedipine, three doses repeated at 20-minute intervals for one hour, and the maintenance regimen consisted of ten mg taken orally every six hours for a further 24 hours, with a total maximum dose of 60 mg. Nifedipine treatment was terminated after 48 hours in patients whose uterine contractions had stopped. Maternal corticosteroids were applied to facilitate fetal pulmonary maturation. Corticosteroid regimen included 12 mg betamethasone or betamethasone disodiumphospate applied intramuscularly, repeated at 24-hour intervals.

Blood sample handling and peptide assay

Venous blood samples were collected from all cases within two hours before administration of any drugs in the study in order to determine levels of white blood cell (WBC), C-reactive protein (CRP), IL-6, and procalcitonin. All complete blood count (CBC) analyses were performed in the hematology laboratory of the present hospital. CBC analysis was performed by using a Mindray BC 6800 analyzer. The CRP levels were measured by immunoturbidimetry using CRP reagent kit in the COBAS E411 instrument. Procalcitonin was measured by immunoturbidimetry by using human procalcitonin reagent kit in COBAS E411 instrument. This assay measures concentrations between 0.02 and 5,000 ng/ml.

The blood samples (five ml) were collected in separate tubes and were immediately centrifuged for 15 minutes at 1000 ×g at 4°C within 30 minutes of collection. Plasma was separated into vials and stored at −80 °C until measurement. IL-6 levels were measured by human IL-6 platinium ELISA kit.

Cervical length was measured by using a 6.5-MHz transvaginal ultrasound probe according to the Fetal Medicine Foundation criteria. The mean of three measurements was taken and presence of funneling was recorded.

As the outcome variables of the study, preterm deliveries within 48 hours, first seven days, deliveries < 32 weeks, < 34 weeks, < 37 weeks, and mode of delivery were recorded. Apgar scores at one and five minutes and birth weights were obtained. Spearman correlations were also computed to quantify associations between procalcitonin, IL-6, WBC, CRP, and obstetric measures. Receiver

Table 1. — *Demographic characteristics, obstetric, and biochemical variables of study and control groups. (mean ± SD, %)*

	Study group (n=40)	Control group (n=44)	*p*
Maternal age (years)	26.2±5.2 (18-38)	26.84±5.32	0.58
Gravidity(n)			
1	18 (45%)	15 (34.1%)	
2	13 (32.5%)	17 (38.6%)	0.57
≥ 3	9 (22.5%)	12 (17.3%)	
Parity(n)			
0	19 (47.5%)	18 (40.9%)	
1	14 (35%)	16 (36.4%)	0.61
≥ 2	7 (17.5%)	10 (22.7%)	
Obstetric history (n,%)			
VB[1]	13 (32.5%)	14 (31.8%)	
CS[2]	8 (20%)	13 (29.5%)	0.3
None	19 (47.5%)	17 (38.6%)	
Maternal DM[3] (n,%)	1 (2.5%)	7 (15.9%)	0.03
Maternal HT[4] (n, %)	3 (7.5%)	5(11.4%)	0.55
Gestational age at presentation (weeks)	29.85±3.35 (24-34)	29.09±2.9	0.27
Previous preterm delivery (n, %)	2 (5%)	2(4.5%)	0.92
Cervical dilatation (cm)	1.61±1.38	1.54±1.17	0.81
Cervical effacement (%)	28.50±22.48	27.27±1.94	0.79
Cervical length (cm)	3.53±1.03	4.04±0.99	0.025
Gestational age at delivery (weeks)	32.82±3.82 (24-39)	37.86±1.47	<0.01
Interval admission-delivery (hours)	532.80±608.62	1458.54±546.81	<0.01
Mode of delivery (%)			
CS[2]	24 (60%)	31(70.5%)	0.320
VB[1]	16 (40%)	13(29.5%)	
Birth weight (grams)	2109.25±779.19	2977.61±547.84	<0.01
1-minute Apgar score	7.3±2.17	8.59±0.59	0.002
5-minute Apgar score	8.62±1.77	9.50±0.62	0.003
WBC[5] ($\times 10^9$/L)	12.01±3.46	11.42±4.08	0.47
CRP[6](mg/L)	18.61±17.74	10.52±15.23	0.29
Procalcitonin (ng/ml)	0.98±0.35	0.84±0.8	<0.01
IL-6[7] (pg/ml)	0.43±0.48	0.21±0.52	0.04

VB[1]: vaginal birth, CS[2]: cesarean section, DM[3]: diabetes mellitus, HT[4]: hypertension, WBC[5]: white blood cell, CRP[6]: C-reactive protein, IL-6[7]: interleukin-6.

Table 2. — *Area under the curve (AUC), 95% CI, and cut-off point of cervical length, IL6 (pg/ml), procalcitonin, CRP, and WBC for delivery at < 48 hours, < seven days, < 32 weeks, < 34 weeks, and < 37 weeks.*

		48 hours	7 days	32 weeks	34 weeks	37 weeks
WBC[1](×10[9]/L)	AUC[4] 7(95% Cl)	0.492 (0.278-0.706)	0.448 (0.263-0.633)	0.620 (0.415-0.825)	0.545 (0.364-0.726)	0.525 (0.320-0.731)
	Cut-off point	> 11.65	> 11.65	> 11.74	> 11.65	> 11.65
	p	0.940	0.586	0.261	0.626	0.802
CRP[2]	AUC[4]7 (95% Cl)	0.506 (0.301-0.712)	0.599 (0.412-0.785)	0.608 (0.423-0.794)	0.500 (0.318-0.682)	0.436 (0.250-0.622)
	Cut-off point	> 13.86	> 13.86	> 14.79	> 13.5	> 13.5
	p	0.952	0.301	0.310	1.0	0.526
IL-6[3] (pg/ml)	AUC[4] 7 (95% Cl)	0.481 (0.258-0.704)	0.571 (0.381-0.760)	0.603 (0.414-0.793)	0.481 (0.297-0.665)	0.490 (0.287-0.692)
	Cut-off point	> 0.34	> 0.38	≥ 0.36	> 0.36	≥ 0.36
	p	0.856	0.459	0.333	0.839	0.918
Procalcitonin	AUC[4] (95% Cl)	0.508 (0.256-0.960)	0.592 (0.382-0.802)	0.575 (0.344-0.806)	0.556(0.370-0.743)	0.504 (0.329-0.680)
(ng/ml)	Cut-off point	> 1.05	> 1.05	> 1.05	> 1.05	> 1.05
	p	0.940	0.335	0.482	0.542	0.965)
Cervical length	AUC[4] (95% Cl)	0.639 (0.414-0.865)	0.692 (0.511-0.873)	0.758 (0.574-0.943)	0.607 (0.430-0.783)	0.716 (0.553-0.879)
	Cut-off point	< 3.74	≤ 3.64	≤ 3.50	< 3.74	< 3.80
	p	0.178	0.044	0.015	0.250	0.032

WBC[1]: white blood cell, CRP[2]: C-reaktive protein, IL-6 [3]: interleukin 6; AUC[4]: area under the curve.

Table 3. — *Cox regression analysis of Cx length for interval admission-delivery.*

	Interval examination-delivery	B	SE	Wald	df	Sig	Exp (B)	95,0% CI for Exp (B)	
								Lower	Upper
Cx[1] length	7 days	- 0.794	0.235	11.387	1	0.001	0.452	0.285	0.717
	< 32 weeks	- 0.531	0.208	6.490	1	0.011	0.588	0.391	0.885
	< 37 weeks	- 0.626	0.190	10.815	1	0.001	0.535	0.368	0.777

Cx[1]: cervix, statistical significance $p < 0.05$.

operator characteristic curve (ROC) analysis was used to establish the cutoff value of WBC, CRP, IL-6, procalcitonin, and cervical length that optimized the prediction of admission-to-delivery interval. Cox regression analysis was used to establish the value of WBC, CRP, IL-6, procalcitonin, and cervical length in prediction of admission-to-delivery interval. Statistical analysis was performed using the SPSS statistical software (version 18.0). $P < 0.05$ was regarded as statistically significant.

Results

Baseline characteristics

In the present study, age and gestational age of study and control groups were not statistically different($p > 0.05$). In study group, CRP, IL-6, and procalcitonin levels were higher than control group ($p = 0.029$, $p < 0.01$, $p = 0.04$, respectively). Demographic characteristics of the study and control groups are shown in Table 1.

Preterm deliveries and laboratory results of participants in study group

In study group, the prevalence of delivery at < 37 weeks was 90% and 52.5% of participants delivered at < 34 weeks and 25% gave birth at < 32 weeks of gestation. In study group, 11 (27.5 %) patients delivered in 48 hours, 15 (37.5%) patients delivered before seven days, and 25 (62.5%) patients delivered after seven days. Mean cervical length was 3.53 ± 1.03 cm. The frequency of a cervical length < 1.5 cm was 5 %, < three cm was 17.5%, and > three cm was 82.5%. Mean IL-6 and procalcitonin levels were 0.43 ± 0.48 and 0.98 ± 0.35, respectively. Obstetric parameters and biochemical variables of study group are given in Table 1.

The value of CRP, IL-6, procalcitonin, and cervical length in prediction of PTD in study group

In present study, interval to delivery was positively correlated with cervical length (r = 0.415, $p = 0.008$), but there was no correlation with WBC, CRP, IL-6, and procalcitonin ($p > 0.05$) In study group, ROC analysis results of WBC, CRP, IL-6, and procalcitonin for prediction of PTD < 48 hours, < seven days, < 32 weeks, < 34 weeks, and < 37 weeks were not statistically significant ($p > 0.05$). It was shown through ROC analysis, that only cervical length had area under curve (AUC); 0.692 (0.511−0.873, $p = 0.044$) at cut off value ≤ 3.64 cm, AUC 0.758 (0.574−0.943, $p = 0.015$) at cut off value ≤ 3.50 cm, AUC 0.716 (0.553−0.879, $p = 0.032$) at cut off value < 3.80 cm, in predicting PTD within seven days, < 32 weeks, and < 37 weeks, respectively (Table 2).

The multivariate analysis by Cox regression using WBC, CRP, IL-6, procalcitonin, cervical length, and their interactions, showed a predictive significance of only cervical length

for the prediction of PTD < seven days, < 32 weeks, and < 37 weeks in cases with regular contractions (Table 3).

Discussion

For many years, clinicians have attempted to estimate the length of time they had for delivery after hospital admission. Of course, it is very important to be able to make this prediction as clinicians can perform treatment methods like cerclage, progesterone, tocolysis, and antenatal steroids so there is time for an in utero transfer to a tertiary health center and therefore appropriate management to optimize the care to both mother and delivered baby can be offered [16]. The main interest of the present research was to determine the efficacy of maternal WBC, CRP, IL-6, procalcitonin, and cervical length, as predictors of PTD among patients complaining of regular contractions before 34 weeks of gestation. The rate of PTD was 25% before deliveries at 32 weeks in the study population. This incidence was higher than the PTD rate in most countries of Europe [2]. The present authors that believe such a difference might be explained by occurrence of the present hospital as a reference center and hence the performance of the study on symptomatic women only.

In present study, it was determined that only cervical length had better predictive value for the admission-to-delivery interval especially within seven days, before 32 and 37 weeks of gestation pregnancies complicated with PTD. Nowadays, transvaginal cervical length measurement has been one of three tests, including fetal fibronectin and cervical pIGFBP-1 which have been introduced into routine obstetric care [17]. As determined in literature [18], in the present study, cervical assessment might help to distinguish patients likely to deliver with threatened preterm labor. However, better, more efficient, and more practical biological markers for predicting PTD and time to delivery were investigated in present study; cervical length measurement was performed transvaginally which may cause discomfort for pregnant women.

Many studies have discussed the efficacy of many other markers for the prediction of PTD. In present study, maternal blood IL-6 was investigated in preterm labour. In present study, IL-6 levels were higher in study group than control group. In preterm study group, ROC analysis results of IL-6 for prediction of PTD within 48 hours, seven days and before 32 weeks, 34 weeks, and 37 weeks were not statistically significant preterm labour. In literature, the majority of studies examining the correlation between interleukins including IL-6 and PTD relied on laboratory analysis of amniotic fluid, cervical fluid, or maternal blood. Firstly, interleukins in amniotic fluid was investigated for prediction of PTD [11]. It was determined that interleukins in amniotic fluid had important role as markers of infection in PTD [19]; however, amniocentesis to investigate these markers in amnion fluid was an invasive procedure and might sometimes have significant complications. Also, this procedure might lead to intrauterine infection and cannot be repeated as in CRP or WBC. Due to this, interleukins in cervical fluid has been investigated, which carries fewer risks to the patient [20]. In one of these studies, cervical IL-6, IL-8, and pIGFBP-1 combined with cervical length were used to predict PTD in symptomatic women with preterm labour. Similar to the present data, in preterm labour group, neither the sensitivity nor specificity of the tests used in that study were sufficient to predict preterm birth for clinical decision-making. [21]. In another study, cervicovaginal IL-6 was a good predictor of PTD. [22] In contrast to present study, another study determined that IL-6 in cervicovaginal secretions was a good predictor of preterm birth before 24, 28, and 37 weeks, and seven days in asymptomatic high risk population for PTD. Again in another study, Brik *et al.* [15] determined cervical IL-6 and cervical length in predicting PTD and time to delivery in patients threatened with preterm labour with intact membranes. However, in contrast to the present data in preterm group, they have concluded that, according to survival analysis, IL-6 added prognostic information to that provided by sonographic measurement of the cervical length. Lastly, there has been a limited number of studies regarding maternal blood IL-6 in preterm group for prediction of time to delivery. In contrast to the present study, it was determined that IL-6 had predictive value of birth of two and seven days [23]; however the control group included statistical analysis which could have affected the results. As a result, there have been no data regarding the prediction of time to delivery interval in only preterm group.

Procalcitonin is a recently determined biological marker used in the diagnosis of systemic infections. Up to now, there have been little data about procalcitonin levels in pregnancy. In present study, procalcitonin levels were higher in preterm study group than control group. ROC analysis results of procalcitonin for prediction of PTD within 48 hours, seven days and before 32 weeks, 34 weeks, and 37 weeks were not statistically significant in preterm labour. In literature, there have been researches assessing amniotic [19] or cervicovaginal procalcitonin and IL-6 [22]. It was determined that cervicovaginal concentrations of procalcitonin and serum concentration of CRP were higher in women who had preterm birth but only cervicovaginal concentration of IL-6 was a good predictor of PTD [22]. In another research, similar to the present data, it was shown that there was no association either between cervicovaginal procalcitonin concentration at hospital admission of patients and laboratory parameters of infection or interval between admission to hospital and birth [24]. In the literature, there is only one study investigating maternal circulating procalcitonin in preterm labour. It is concluded that there was no association either between maternal plasma procalcitonin concentration at hospital admission of patients and time between admission to hospital and birth

similar to results of the present study [14]. Consequently, controversies and different results of these studies regarding IL-6 and procalcitonin may be due to performance of these studies with cervicovaginal secretions which might be affected by any vaginal infection or some blood and amniotic fluid. There have been limited data about prediction of PTD using any biological marker in maternal circulation in preterm labour. These controversies may also be due to study populations as combination of both patients complicated with preterm birth and healthy pregnant women. The controversies may be overcome by multicentre researches including high number of cases complicated with preterm labour study group only.

Lastly, it is obligatory to emphasize the use of betamethasone which is important for fetal pulmonary maturation and is used mostly in combination with tocolytic agents in preterm labor, while discussing results of the present research about proinflammatory markers including IL-6 and procalcitonin as predictive value for the admission-to-delivery interval. There are many investigations regarding the effects of betamethasone on the inhibition of the inflammatory response [25]; however, in present study, blood samples were taken two hours before drug administration including steroids and tocolytics.

In conclusion, as IL-6 and procalcitonin levels were higher in preterm study group than in control group, inflammatory pathway was important in pathophysiology of preterm labour. However, although many markers in maternal circulation including WBC, CRP, IL-6, and procalcitonin have been investigated, cervical length appears to still be the most important valuable parameter with a predictive value for time to delivery interval in preterm labour.

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