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Comparing of Pro-Inflammatory Cytokines in the Woman with Preterm and Term Labors

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Abstract

Background: Preterm birth is one of the most important issues in obstetrics medicine and yet, the leading cause of morbidity and long-term disabilities such as neuro developmental impairments. There have been many studies trying to recognize responsible factors and develop new methods to predict and cure the condition. One important factor in preterm birth is immune system and immune factors such as cytokines. In this regard, we aimed to measure different cytokines in sera of mothers experiencing preterm birth.

Methods and Materials: In this case control study, we measured serum levels of IL-2, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-10, IL-12(p70), IL-13, interferon gamma (IFN-g), granulocyte macrophage colony stimulating factor (GMC-SF) and TNF-alpha in women with preterm and term labors according to Enzyme-Linked Immune Sorbent Assay (ELISA).

Results: Serum levels of IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13 and TNF-α in preterm group were significantly higher than control group ($P < 0.05$, for all). Also, GMC-SF serum levels in the preterm group were significantly lower than control group ($P < 0.0001$).

Conclusion: here in this study we indicated that immune system and pro-inflammatory cytokine have been change in preterm birth and further examinations on more patients may create new insights in developing methods to predict and prevent the disease.

Keywords: Pro-inflammatory; Cytokines; Preterm; Term; Woman

Introduction

Preterm birth (PTB) is defined as giving birth to a child before 37 weeks of gestational age. Preterm birth is still one of the most important problems is obstetrics medicine and the leading cause of perinatal mortality and morbidity and long-term disability[1]. As Goldenberg et al.[2] report, the risk of neuro developmental impairments and respiratory and gastrointestinal complications are highly increased for children of mothers with preterm birth. Preterm birth has also many serious effects on parents and brings a heavy burden to the society and public health[3]. The global incidence of preterm birth has been estimated 9.6% in 2015 by Hamilton and colleagues[4] which indicated a mild decrease since 2006 (12.8%). But due to advanced maternal age, increased use of reproductive technology, and its concomitant increase in multiple gestations, the prevalence rates of preterm birth are reported to be increasing[5]. A personal history of spontaneous PTB and a short cervix on transvaginal ultrasound have been reported to be the two most important risk factors for a preterm birth[6]. The exact etiology of preterm birth is unknown in almost half of patients however multiple mechanisms have been accounted for initiation of preterm labor including infection or inflammation. Uterine infection and premature rupture of foetal membranes are reported to be responsible for preterm births. Although enormous lines of evidence have tried to evaluate a way to prevent or predict preterm labor, no proven method has been yet assigned[7].

A successful pregnancy requires a complex balance

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between all parts of the immune system and immune modulatory factors resulting in immune suppression or tolerance. Based on different lines of evidence, a preterm labor is resulted from early activation of inflammatory mediators which in turn, precede myometrial activation and contraction[8]. Pro-inflammatory cytokines are very impressive and important in immune modulation and an imbalance in the cytokines can also result in a preterm birth though, studying the role of cytokines in preterm birth has increasingly moved into the spotlight in obstetric medicine. As mentioned, Cytokines play a pivotal role in activation of either T helper 1 (cell-mediated immunity) or T helper 2 (humoral immunity)[9,10]. Luppi also declares that a shift in Th1/Th2 cytokines towards Th2 activity is essential for a term and normal pregnancy while an infection can change this balance towards Th1 activity and as a result, a preterm birth[9]. Pro-inflammatory cytokines are defined as those cytokines, responsible for promoting Th1 responses. Some evidence demonstrates the rise in inflammatory cytokines such as interleukin (IL) 6, IL-8 in amniotic fluid in women experiencing a preterm labor[11,12]. In order to predict a preterm birth, many clinical and paraclinical methods have been tried but it seems that evaluation of the presence of pro-inflammatory and inflammatory cytokines may be an easy and available method. In this setting, accumulating lines of evidence have tried to assess the presence and amount of such cytokines in sera of mothers presenting as a preterm birth but here in this paper, we aimed to compare the amount of pro-inflammatory cytokines in sera of women giving birth to preterm babies and term ones. This study might give us the insight in predicting or even preventing preterm births.

Methods and Materials

Subjects, sampling, and experimental setting

In this case-control study which was approved in Ethical committee of Isfahan University of Medical Sciences, 48 women with preterm labor (mean ages 23.39 ± 6.03 years) and 51 women without preterm labor (mean ages 30.14 ± 8.16 years) of Iranian population participated into the study, and subjects were matched in age and gestational age in both groups. The subjects as outpatients were referred to Beheshti Hospital of Isfahan Province-Iran between 2014 to 2017. All subjects had Complete Blood Count (CBC), C- reactive protein, imaging such as ultrasound (abdominal and vaginal) and cultures (vaginal and urine).Inclusion criteria for preterm labor women were defined as women with gestational ages between 24 to 34 weeks, regular and persistent uterine and cervix length less than 25 mm[13]. All subjects had informed consent to participate in study and inclusion criteria for the control group was woman with delivery in term gestational age. Also, patients with twice or multiple pregnancies, uterine malformation, cervical cerclage, rupture membrane, without last menstrual period data and severe pathology of uterine were excluded from the study. The blood samples were collected after delivery in cases group (before treatment) and in gestational aged, between 24 to 34 weeks in controls group, and also blood samples were stored in -30 ℃. After delivery in preterm labor women, patients were treated with a tosiban (intravenously bolus dose of 6.75 mg, continued for 3h by 300 mg/min and then followed within 48 h by 100 mg/min)[14]. All information of subjects were recorded in a checklist and this checklist was consisted of maternal data as age, weight, height, cervical length, body mass index, systolic and diastolic blood pressure, cigarette consumption in pregnancy, history of preterm labor or preeclampsia, and laboratory and culture finding and also obstetric and neonatal information such as type of delivery (cesarean or normal vaginal delivery), delivery age, onset weight of neonate, Apgar score in onset birth, and complications of delivery. After collected of sampling, the serum levels of IL-2, IL-4, IL-5, IL-6, IL-7, IL-8 (CXCL8), IL-10, IL-12(p70), IL-13, interferon gamma (IFN-gamma), granulocyte macrophage colony stimulating factor (GMC-SF) and TNF-alpha were measured with using enzyme-linked immune sorbent assay (ELISA) in accordance with the manufacturer's instructions (R&D Systems, Abingdon, USA).

Statistics

All data were analyzed with using SPSS version 24 (IBM, Chicago, IL), the Kolmogorov- Smirnov test was performed to assess normal distribution of data. Also, independent T-test, Man Whitney U test, Chi-Square were used to compare both groups as case and control. Data were showed according to the number (percent) and mean ± SD. In addition, P-Value less than 0.05 were performed as a significant threshold.

Results

In this study, the mean age in preterm group was significantly lower than control group (P = 0.02). Also, the means of WBC and CRP was in preterm group significantly higher than control group (P < 0.0001, for both). 31.3% of preterm group had preeclampsia and also 10.4% of this group had history of preterm, so these differences were significant (P = 0.01 for preeclampsia and history of preterm). There were no significant differences between two group regarding to BMI (P = 0.78), Systolic (P = 0.74) and Diastolic (P = 0.13) blood pressures, smoking (P = 0.27), history of uterine surgery (P = 0.27), vaginal culture positive (P = 0.06), urinary tract infection (P = 0.18), uterine cervical length (P = 0.46), delivery type (P = 0.15). According to neonatal information, there were no significant differences between groups according to gestational age (P = 0.52), gender of neonate (P = 0.24), Apgar in onset of delivery (P = 0.17) and other complication such as deaths (P = 0.07), acute respiratory distress syndrome (P = 0.14) and Necrotizing enterocolitis (P = 0.30). Also, the neonatal weight in the preterm group was significantly lower than control group (P < 0.001) (All data of demographics and clinical or para clinical were summarized in the table 1). The serum levels of pro inflammatory or inflammatory cytokines were measured, so serum levels of IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13 and TNF-α in preterm group were significantly higher than control group (P < 0.05, for all). Also, GMC-SF serum levels in the preterm group was significantly lower than control group (P < 0.0001). However, there were no significant differences between two groups regarding to serum levels of IL-2 (P = 0.67), IL-12 (P = 0.13), and IFN-gama (P = 0.37). All information summarized in the (table 2).

Table 1: Maternal and neonatal information of subjects in both group.

Characteristic		Preterm group	Control group	P-value
Number		49	51	-
Maternal information				
Age (Years) (mean ± SD)		23.39 ± 6.03	30.14 ± 8.16	0.02*
BMI (kg/m^2)(mean ± SD)		25.51 ± 3.58	25.23 ± 3.53	0.78*
Systolic blood pressure (mmHg)(mean ± SD)		125.45 ± 14.55	123.21 ± 13.89	0.74*
Diastolic blood pressure (mmHg)(mean ± SD)		78.20 ± 8.32	77.62 ± 10.56	0.13*
WBC(x10^6/mL)(mean ± SD)		11.93 ± 2.66	9.29 ± 1.49	0.0001 >*
CRP (mg/mL)(mean ± SD)		0.42 ± 0.30	0.15 ± 0.11	0.0001 >*
Smoking during of pregnancy		3(6.3%)	1(2%)	0.27**
History of preterm labor		5(10.4%)	0	0.01**
Urinary tract infection		15(31.3%)	10(19.6%)	0.18**
Preeclampsia		8(16.7%)	1(2%)	0.01**
Group B streptococcus positive (Vaginal culture)		7(14.6%)	2(3.9%)	0.06**
Uterine cervical length (mm)(mean ± SD)		16.52 ± 5.40	33.49 ± 4.70	0.46*
History of uterine surgery		3(6.3%)	1(2%)	0.27**
Delivery type	**NVD**	41(85.4%)	48(94.1%)	0.15**
	caesarean	7(14.6%)	3(5.9%)	
Neonatal information				
Gestational age (weeks)(mean ± SD)		30.06 ± 4.25	29.66 ± 3.97	0.52*
Gender (M/F)		18/30	25/26	0.24**
Weight (mean ± SD)		2625.16 ± 699.78	3128.60 ± 286.44	0.0001 >*
Apgar in onset of delivery (mean ± SD)		9.20 ± 0.79	9.74 ± 0.74	0.17*
Deaths		3(6.3%)	0	0.07**
Acute respiratory distress syndrome (ARDS)		2(4.2%)	0	0.14**
Necrotizing enterocolitis		1(2.1%)	0	0.30**

*independent t test, **Chi Square, WBC: white blood count, CRP: C-reactive protein, BMI: body mass index, NVD: normal vaginal delivery.

Table 2: The serum levels of IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IFN-g, GMC-SF and TNF-alpha in the groups.

Serum levels (mean ± SD) (Pg/mL)	Preterm group	Control group	P-value*
IL-2	708.33 ± 361.35	639.64 ± 312.18	0.67
IL-4	1291.50 ± 462.01	968.06 ± 208.12	0.0001 >
IL-5	123.30 ± 30.70	102.07 ± 22.68	0.01
IL-6	115.35 ± 40.64	90.65 ± 38.16	0.004
IL-7	9.75 ± 3.89	4.76 ± 2.66	0.003
IL-8	898.19 ± 167.66	343.74 ± 37.38	0.0001 >
IL-10	196.86 ± 59.90	132.20 ± 42.43	0.007
IL-12	238.27 ± 49.27	209.80 ± 58.80	0.13
IL-13	2942.01 ± 841.03	1982.37 ± 609.48	0.008
IFN-gama	437.50 ± 167.98	399.80 ± 151.21	0.37
GMC-SF	390.75 ± 175.02	237.12 ± 111.19	0.0001 >
TNF-α	583.75 ± 272.79	254.48 ± 77.14	0.0001 >

*Independent t test, IFN-g: interferon gamma, GMC-SF: granulocyte macrophage colony stimulating factor.

Discussion

Here in this study, we demonstrated that activation of maternal immune system by proinflammatory cytokines has an important role in the mechanisms that induce preterm labor. In this paper we showed higher number of inflammatory cytokines exist

in sera of mothers experiencing a preterm labor. Controversial results have been reported by different lines of studies accusing immune cells, cytokines, different hormones and other factors such as vitamins, responsible for a preterm labor[14,15]. In this study we also demonstrated that there were no significant differences between mothers experiencing a preterm labor and those with term labor regarding vital signs, uterine cervical length, vaginal culture and other factors. Our results were in line with a recent study, performed by Herrera-Munoz and colleagues[13]. There, they examine 61 preterm mothers and their measurements showed higher amount of IL- 5, IL-6, IL-7, IL-8, IL-10and TNF-a and lower amounts of GMC-SF which is suggested to be a sign of immune failure to maintain the mechanisms acting against inflammation[13]. But our results indicated that IL-4, IL-5 and IL-13 were also elevated in preterm labor. It should also be noted that their preterm cases had increased urinary tract infection rate than normal controls. Increase in inflammatory cytokines demonstrates the pivotal role of immune system in preterm labor as reported earlier by different studies[16,17]. Elevated IL-10 in preterm labor might cast doubt on Chatterjee et al.[18] findings that reported anti-inflammatory influences of IL-10 during pregnancy. Another study performed by Ito and colleagues[19], reports elevated amounts of IL-8, IL-17 and TNF-a. Elevated IL-8 was in line with our findings while as mentioned earlier; we found no significant difference between two groups regarding TNF-alpha measurements. Some studies suggest different factors to be measured in order to predict preterm labor such as GMC-SF[13] or amniotic fluid concentration of metalloproteases[1] or maternal serum concentration of these metalloproteases[20] and here we can suggest different inflammatory cytokines measurements for prediction of preterm labor such as IL-8 and IL-13. But there is much to discover and none of these factors could predict preterm labor accurately. Some studies suggest the possible role of intrauterine infections as inducer of intra-amniotic inflammatory response and activation of immune system resulting preterm labor[21]. Contrary to what they had reported, our cases and controls had no significant difference regarding vaginal culture for Group B streptococcus and Urinary tract infection meaning no active infectious sites were found and these findings cast doubt on their hypothesis.

As conclusion, immune system and pro-inflammatory cytokine have been change in preterm birth and further examinations on more patients may create new insights in developing methods to predict and prevent the disease.

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