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Evaluation of Maternal Serum 25-Hydroxyvitamin D, Paraoxonase 1 Levels, and Neutrophil-to-Lymphocyte Ratio in Spontaneous Preterm Birth

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Background: The aim of this study was to evaluate the association of maternal serum 25-hydroxyvitamin D, paraoxonase 1, and neutrophil-to-lymphocyte ratio in women having early spontaneous preterm birth without clinical chorioamnionitis.

Material/Methods: This study was prospectively administered in women referred to our obstetrics service with preterm labor that resulted in preterm birth (n=35) and term labor that ended in term birth (n=44). The maternal serum levels of 25-hydroxyvitamin D and paraoxonase 1 were measured and neutrophil-to-lymphocyte ratio was calculated.

Results: The 25-hydroxyvitamin D and paraoxonase 1 levels of the preterm group were significantly lower than those of the term group ($p<0.05$). The neutrophil-to-lymphocyte ratio value of the preterm group was significantly higher than that of the term group ($p<0.05$). There was a significant but small positive correlation between the serum levels of 25-hydroxyvitamin D and paraoxonase 1 in the preterm group ($r=0.35$; $p=0.021$).

Conclusions: Decreased maternal serum 25-hydroxyvitamin D and paraoxonase 1 levels and increased neutrophil-to-lymphocyte ratio may have a role in the etiology of spontaneous preterm birth.

MeSH Keywords: 25-hydroxyvitamin D • Neutrophil to Lymphocyte Ratio • Paraoxonase 1 • Preterm Birth

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Background

Preterm birth remains the major cause of perinatal morbidity and mortality worldwide [1]. Spontaneous preterm birth has multifactorial etiologies, including premature activation of the fetal endocrine system, pathological distention, and inflammation/infection [2]. Intrauterine inflammation is strongly related to the onset of preterm birth. Inflammation and oxidative stress are coexisting situations, and there are potential mechanisms for the role of oxidative stress in the pathogenesis of preterm birth [3,4]. Preterm birth may result in many complications, such as necrotizing enterocolitis, respiratory distress syndrome, and retinopathy of prematurity [5,6]. Therefore, it is crucial to diagnose the inflammatory response or oxidative stress early in order to identify the strategies for treatment, thereby improving the prognosis [3,7]. However, there is at present no adequate diagnostic tool to use in recognizing the disease early.

Vitamin D is a prohormone that is either taken by food or produced by photochemical reactions in the skin. Therefore, vitamin D level is related to sunlight exposure and diet, and use of vitamin D in pregnancy cause little or no change in its serum levels in pregnancy [8,9]. Serum 25-hydroxyvitamin D levels shows the vitamin D storage in the body [10]. Vitamin D is associated with immune system function and inflammation, which may be a link between vitamin D and preterm birth. Decreased maternal serum levels of vitamin D have been reported to be involved in many complications, such as preterm birth, preeclampsia, small for gestational age, and gestational diabetes mellitus [10,11]. In case of systemic inflammation, neutrophil count increases and lymphocytes decrease in the circulation, resulting in high neutrophil-to-lymphocyte ratio, which is a simple marker of inflammation. Many studies have searched for the markers of intrauterine inflammation such as neutrophil to lymphocyte ratio, C-reactive protein, and 25-hydroxyvitamin D to find simple and less invasive methods to predict spontaneous preterm birth [7,9].

Pregnancy is a physiological condition that has a high susceptibility to oxidative stress, in which there is an imbalance between production of reactive oxygen species and ability of the anti-oxidative system to detoxify them. The high oxidative stress status in pregnancy may result in many complications, such as preterm birth, intrauterine fetal growth retardation, and preeclampsia [12]. Oxidative stress-related genes were reported to be involved in the physiopathology of preterm birth. Paraoxonase 1 is part of an enzyme with antioxidant properties that is related to high-density lipoprotein (HDL) particles. The major antioxidant role of HDL is through the metabolism of oxidative low-density lipoprotein by paraoxonase 1; thus, it can decrease the level of oxidative stress [13]. The relationship between the R alloenzyme of the paraoxonase 1 Q192R polymorphism and preterm birth was recently reported [14]. Paraoxonase 1 was also shown to have an anti-inflammatory role by decreasing chemotaxis and adhesion of monocytes to endothelial cells and inhibiting differentiation of monocytes to macrophages [15].

The factors involved in the etiology of spontaneous preterm birth are poorly known. The aim of this study was to evaluate the association between preterm birth and the maternal serum level of 25-hydroxyvitamin D and neutrophil-to-lymphocyte ratio as inflammatory markers and paraoxonase 1 as an oxidative marker.

Material and Methods

This prospective study was performed in the obstetrics service of our hospital over a period of 6 months. All patients provided written informed consent after approval of the study by the Human Research Ethics Committee of Cumhuriyet University. The patients with preterm labor and term labor who met the research criteria and consented to participate in this study were enrolled consecutively. All pregnancies resulted in birth inclusion criteria were: maternal age 18–45 years, pregnancy gestational age 22–37 for the preterm birth group and gestational age 37–42 for the term birth group, and singleton pregnancy without use of any drugs. Exclusion criteria for preterm and term birth groups were: maternal age less than 18 years or more than 45 years; multiple pregnancy; any evidence of chronic medical or infectious diseases; pregnancies with membrane rupture, presence of clinical or laboratory signs of chorioamnionitis, or placental disease; history of uterine or fetal anomaly; and pregnant women administered steroids, with fever of unknown origin, or fetal tachycardia.

Preterm and term labor were diagnosed by the spontaneous presence of persistent uterine contractions (4 every 20 min or 8 every 60 min) with documented cervical change or cervical effacement ≥80% or cervical dilation >2 cm [16]. Preterm birth is defined by gestational age by the U.S. Centers for Disease Control and Prevention (CDC) as preterm < 37 weeks, late preterm 34–36 weeks, and early preterm <34 weeks [17]. Term birth is the delivery of a fetus at 37–42 completed gestational weeks [18]. Gestational age data was based on the first day of last menstrual period of a pregnant woman with ultrasound confirmation at her first obstetrical visit [19]. The demographic and obstetrical information was obtained by interview with patients and by searching medical records. The major clinical parameters of the study population were: age, body mass index (BMI), socioeconomic status, gravidity, parity, miscarriage, gestational age, neonatal weight, and neonatal Apgar 1 and 5 scores.

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Table 1. Selected demographic, clinical and laboratory data of preterm birth and term birth groups.

	Preterm birth (n=35)	Term birth (n=44)	p
Age (year)	25.5±5.6	29.7±5.4	0.001
Body mass index (kg/m^2)	27±3.9	29±5.3	0.076
Socioeconomic status Low Intermediate High	 8 (23%) 19 (54%) 8 (23%)	 4 (9%) 29 (66%) 11 (25%)	0.153
Gravidity	2 (1–6)	3 (1–9)	0.002
Parity	1 (0–3)	2 (0–6)	0.001
Miscarriage	0 (0–3)	0 (0–4)	0.179
Gestational age (wk)	31.7±2.1	38.1±1.2	0.001
High density lipoprotein (mg/dL)	51.2±12.1	60.4±11.8	0.001
Low densitylipoprotein (mg/dL)	182±37.8	162.4±35.1	0.02
Monocyte (10^3/uL)	0.43±0.09	0.52±0.11	0.002
Neonatal weight (g)	2000±486	3249±339	0.001
Apgar 1st minute	7.7±1.1	8.7±0.6	0.001
Apgar 5th minute	9.0±0.7	9.8±0.4	0.001

Data were presented as percentage, median (min-max), and mean ±SD as appropriate.

Laboratory tests

Fasting venous blood samples were collected from all patients. The blood sera were separated by centrifugation and stored at –80°C until the time of study. Serum levels of high density lipoprotein and low density lipoprotein were measured. Serum 25-hydroxyvitamin D levels were detected by competitive immunoassay using Roche Diagnostic commercial kits and a multichannel automatic analyzer (Roche Cobas 6000-E 601, Rotkreuz, Switzerland). The evaluated assay of serum 25-hydroxyvitamin D was 3–70 ng/mL. Serum paraoxonase 1 levels were determined by kinetic method (RelAssay Diagnostics, Gyeonggi-do, Korea) as defined in the manufacturer's instructions. The coefficient value of paraoxonase 1 level was 5% and normal serum range was 200–400 U/L.

Blood samples were gathered in a hematological sample tube, and the neutrophil, lymphocyte, and monocyte counts were determined with the same hematology analyzer (Mindray BC-6800, Shenzhen, China) that was used for the calculation of the neutrophil-to-lymphocyte ratio.

Statistical analysis

Data are presented as mean ±SD, median (min–max), or percentage, as appropriate. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the data. For the analysis of parametric data, the *t* test was used. Data that were not normally distributed were analyzed with the Mann-Whitney U test for comparisons between groups. The association of serum 25-hydroxyvitamin D and paraoxonase 1 levels and neutrophil-to-lymphocyte ratio value in preterm and term groups was evaluated by using the Pearson correlation test. SPSS software (ver. 22.0 for Windows, IBM) was used for statistical analyses. A p value of less than 0.05 was accepted as significant.

Results

This study was conducted with 35 (44.3%) women with preterm birth and 44 (55.7%) women with term birth. None of the patients in the study groups was excluded during the study period.

Table 1 presents the selected demographic and laboratory data of preterm and term groups. The preterm group had significantly lower maternal age, gravidity, parity, gestational age, serum level of high-density lipoprotein, number of monocytes, neonatal weight, neonatal Apgar 1, and neonatal Apgar 5 than those of the term group ($p<0.05$). The BMI, socioeconomic status, and median number of miscarriages of the preterm and term groups were found to be comparable ($p>0.05$). The maternal

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Table 2. Association of serum 25-hydroxyvitamin D (25-OH Vit D) and paraoxonase 1 (PON1) levels and neutrophil-to-lymphocyte ratio (NLR) value in preterm birth and term birth groups.

	Preterm birth (n=35)		Term birth (n=44)	
	PON1	NLR	PON1	NLR
25-OH Vit D	r=0.35 p=0.021	r=0.281 p=0.065	r=–0.14 p=0.406	r=-0.27 p=0.113
PON1		r=0.16 p=0.289		r=–0.091 p=0.604

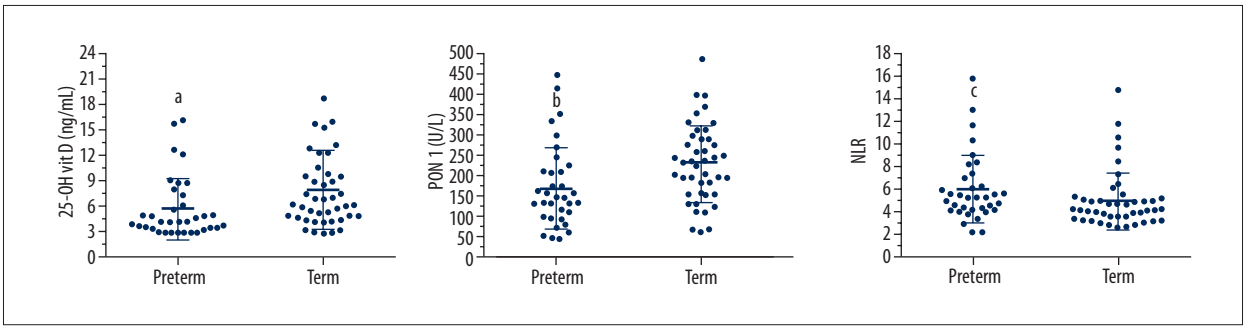

Figure 1. 25-hydroxyvitamin D (25-OH vit D) and paraoxonase 1 (PON 1) levels and neurophil-to-lymphocyte ratio (NLR) of preterm and term birth groups. Data were expressed as mean ±SD. a, b, c p<0.05, preterm *vs.* term.

serum level of low-density lipoprotein of the preterm group was significantly higher than that of the term group (p<0.05).

Table 2 shows the correlation coefficients of serum 25-hydroxyvitamin D and paraoxonase 1 levels and neutrophil-to-lymphocyte ratio value in the preterm and term groups. In the preterm group, regarding these parameters, there was a significant but weak positive correlation between the serum levels of 25-hydroxyvitamin D and paraoxonase 1 (r=0.35; p=0.021). In the term group, regarding these parameters, there was no significant correlation among these parameters (p>0.05).

Figure 1 presents 25-hydroxyvitamin D and paraoxonase levels and neutrophil-to-lymphocyte ratio of preterm and term groups. The 25-hydroxyvitamin D and paraoxonase 1 levels of the preterm group were significantly lower than those of the term group (p<0.05). The neutrophil-to-lymphocyte ratio of the preterm group was significantly higher than that of the term group (p<0.05).

Discussion

In this study we researched the relationship between preterm birth and the serum levels of 25-hydroxyvitamin D and paraoxonase 1 and neutrophil-to-lymphocyte ratio. As markers of inflammation and oxidative stress, the maternal serum levels of 25-hydroxyvitamin D and paraoxonase 1 were decreased and neutrophil-to-lymphocyte ratio was significantly increased in the preterm birth group. When we evaluated the correlation of these markers, a mild positive correlation was found between serum 25-hydroxyvitamin D and paraoxonase 1 levels in the preterm group.

25-hydroxyvitamin D is the primary storage form of vitamin D, so it may be detected in serum to determine vitamin D status [10]. Many studies have shown the association between vitamin D status and adverse pregnancy outcomes, including spontaneous preterm birth [11, 20]. Vitamin D has a role in inflammation and infection of the placenta. Vitamin D is known to prevent bacterial infections by stimulating cathelicidin in the cells in the placenta at both maternal and fetal sites [21]. Also, it arranges uterine natural killer cells and monocytes [22]. It was reported that in pregnancies with deficiency of vitamin D, there is increased production of tumor necrosis factor-α-like inflammatory cytokines [2]. Furthermore, vitamin D decreases inflammation in decidua by inhibiting the nuclear factor kappa B pathway. Women with deficient vitamin D levels might be at high risk for preterm birth because vitamin D deficiency can increase the inflammatory response to clinical and subclinical infections [23]. It has been reported that maternal vitamin D status in the gestational weeks close to delivery, but not in the early periods of pregnancy, is related to preterm birth [20]. The enzyme activating vitamin D and the vitamin D receptor are expressed in the human placenta and decidua. The maternal vitamin D receptor genotype was found

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to be related to deficient immune reaction at the placenta-decidua site that results in preterm birth [1]. In our study, we also found the decreased serum 25-hydroxyvitamin D levels in the preterm birth group. This may be the reason for spontaneous preterm birth without any clinical chorioamnionitis or any other detected infection.

The systemic response to intrauterine infection is arranged by the innate immune system, started by the recruitment of leukocyte types like neutrophils and lymphocytes [7]. An increase in white blood cell or neutrophil count is a sign of subclinical inflammation [24]. Since inflammation and infection are important mechanisms in the etiology of preterm birth, there is a much more need to use a noninvasive method rather than invasive methods such as amniocentesis. In spontaneous preterm delivery, neutrophil counts increase and lymphocyte counts decrease, resulting in an increase in neutrophil-to-lymphocyte ratio. Women experiencing high neutrophil-to-lymphocyte ratio when they are experiencing symptoms and signs of preterm labor might have a high probability of preterm birth. The cytokines released from the inflammatory region in the choriodecidua during the early phase of inflammation can result in a change in the number of leukocyte subsets. Therefore, an inflammatory condition in the placenta can be detected by measuring neutrophil-to-lymphocyte ratio, which is an inexpensive and noninvasive method [7]. The findings about neutrophil-to-lymphocyte ratio in our study was also compatible with the literature.

Paraoxonase is a hydrolytic enzyme associated with high-density lipoprotein protecting low-density lipoprotein from oxidative modification. Decreased lipid peroxidation and oxidative stress can protect against oxidative damage of DNA defect in signaling pathways [25]. The activity of paraoxonase was reported to be decreased in animal models of inflammatory diseases. Because of anti-inflammatory and antioxidant features of paraoxonase 1, decrease in its serum activity may worsen the inflammatory and oxidative stress condition [26]. In many studies, paraoxonase activity was found to be decreased in cases with preterm birth [13, 27]. Serum paraoxonase 1 levels were found to be decreased in the preterm group in our study that is compatible with the literature.

Decreased vitamin D activity was found to be associated with low levels of paraoxonase 1 activity, so the low serum vitamin D levels may result in a defective inflammatory and oxidative response. The acute-phase response due to low serum level of vitamin D results in decreased paraoxonase 1 activity and this condition causes the conversion of high-density lipoprotein from anti-inflammatory to proinflammatory molecules [26]. The low paraoxonase activity increases oxidative damage of DNA of lymphocytes [25], which explains the lower lymphocyte count increasing the neutrophil-to-lymphocyte ratio in preterm birth. These mechanisms may explain the decreased maternal serum 25-hydroxyvitamin D and paraoxonase 1 levels and increased neutrophil-to-lymphocyte ratio in spontaneous preterm birth.

There are some limitations of this study. We excluded many obstetric and medical situations with potential to influence the studied parameters, which reduced the sample size. Furthermore serum 25-hydroxyvitamin D and paraoxonase 1 levels and neutrophil-to-lymphocyte ratio could be evaluated only at a single state. We could not enroll a control group with the same gestational age as the preterm group, because our center is a tertiary one and only preterm pregnancies that will give birth are accepted in our service. Therefore, the cases of term birth were accepted as the control group.

Conclusions

The maternal serum 25-hydroxyvitamin D and paraoxonase 1 levels and neutrophil-to-lymphocyte ratio of preterm birth group are found to be significantly different when compared to term birth group in our study. These results may contribute to the etiology of spontaneous preterm birth. Further studies are needed to determine if these parameters can be used to predict if a preterm labor will result in preterm birth.

Conflict of interest

None.

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