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Original Article

Serum decorin measurement in prediction of the risk for preterm birth

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ABSTRACT

Objective: To define serum decorin (sDEC) levels in healthy pregnants and in patients with preterm labor (PTL), and to introduce possible role of sDEC in predicting the risk for preterm birth (PTB).
Materials and methods: Thirty-one women with diagnosis of PTL between 24th to 32nd weeks of pregnancy were compared with 44 healthy pregnants in this prospective case–control study. Maternal blood sDEC and uterine cervical length (CL) measurements were conducted at referral.
Results: Median sDEC level was significantly decreased in PTL group ($p = 0.013$). Median CL was significantly shorter in PTL group ($p < 0.001$). There was not any correlation between sDEC level and maternal age, BMI, and gestational age at blood sampling time within PTL ($p = 0.955$, $p = 0.609$, $p = 0.079$, respectively) and control groups ($p = 0.652$, $p = 0.131$, and $p = 0.921$, respectively). There was not any association between sDEC level and PTB within 7 days, before 34th weeks, but before 37th weeks there was ($p = 0.206$, 0.091, and $p = 0.026$, respectively). There was not any correlation between sDEC level and the CL in PTL group ($p = 0.056$).
Conclusions: sDEC has a limited effect in prediction of PTB within a week or before 34th weeks. Combination of sDEC with CL measurements predicted PTB before 37th weeks.conclusion

Introduction

Preterm birth (PTB) is a pathological process related to infection in a significant proportion of the cases [1]. It is also related with early maturation of physiological processes, which normally occur at term. Incidence of the PTB is as high as 12%–13% of all pregnancies [2]. In recent years, with the achieved advances in newborn facilities, prognosis of the low-birth weighted-premature infants has been recovered, but still the rate of prematurely delivered newborns has not been alleviated with the improved diagnostics. It is the leading cause of perinatal morbidity and mortality of the newborn [3]. As well, PTB is the major decision-making event in evolution of a healthy non-disabled fetus.

Tocolytic treatment is indicated in a patient with a diagnosis of preterm labor (PTL). Randomized controlled trials have indicated that tocolytic treatment could postpone PTB in patients with PTL for up to 7 days, however, a satisfactory reduction in the perinatal morbidity could not be demonstrated [3,4]. Therefore, determining the specific risk factors and introducing superb diagnostic modalities prior to the onset of PTB would be a more efficient strategy in decreasing the frequency of PTB and related morbidity.

Decorin is a short chained-proteoglycan, and one of the small leucine-rich proteoglycans (SLRPs), which is found in extracellular matrix [5]. It belongs to class I SLRPs. SLRPs are, like larger proteoglycans, comprised of a protein core and glycosaminoglycan side chains. The distinguishing feature of SLRPs is the presence of a central domain containing leucine-rich repeats in the protein core. This domain is responsible for most of the functional activity of these molecules. Decorin is located on the collagen fibrils. It was readily demonstrated that decorin regulates fibrillogenesis, cell organization and stabilization in connection with type I collagen *in vivo* [5,6]. The influence of transforming growth factor beta 1 reduces the synthesis and chain length of decorin [7,8]. Decorin is

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found in every tissue where proteoglycans exist. These include bone, cartilage, gum, vascular endothelium, endometrium, connective tissue of the cervix, placenta, and decidua [9–11]. Targeted deletion or alteration of any of the SLRPs lead to disruption in collagen fibrils in tissues.

To date, studies have concentrated on role of decorin in patients with preterm rupture of membranes [12–14]. The role of decorin in pathophysiology of PTL has not been investigated so far. As changes in collagen levels and the proteoglycan levels occur through the cervical ripening theoretically [15,16] we hypothesized that alterations in serum decorin (sDEC) levels could be found in women with the diagnosis of PTL prior to 32nd gestational weeks when compared to healthy pregnant women of the same gestational age.

Materials and methods

Study protocol and the participants

The study was conducted as prospective case–control study between May 2012 and August 2014 in a tertiary care university hospital. Pregnant women with 24–32 weeks of pregnancy who referred with a complaint of inguinal, abdominal or dorsal pain were defined as the target population. PTL was defined as presence of regular uterine contraction cycles frequent than once in 10 min together with a longitudinal cervical length (CL) measurement shorter than 25 mm. Among those candidates, women with preterm rupture of membranes, cervical insufficiency, multiple pregnancy, hypertensive disorders of pregnancy, pre-gestational or gestational diabetes mellitus, systemic disorders including connective tissue diseases and vasculitis, polyhydramnios, placenta previa, recent vaginal bleeding, placental abruption, and unfavorable fetal conditions including fetal growth restriction, congenital fetal anomalies, and fetal demise were excluded from the study. Patients between 24th and 32nd gestational ages who met the definition of PTL, with contractions and or shorter than 25 mm CL measurements designated the *PTL group*. Gestational age-matched healthy singleton pregnant women without uterine contractions and CL > 25 mm were assigned in the *control group*. Institutional Review Board approval was obtained (2012-9/14). All participants were fully informed and gave written informed consent.

Gestational age was calculated with respect to the last menstrual period or crown-rump length at first trimester ultrasonography, as appropriate. Frequency and amplitude of uterine contractions were recorded with external fetal monitor for at least 30 min. CL was evaluated by transvaginal ultrasonography. Following the obstetric evaluation, peripheric venous sampling from the participants was performed before any treatment has been started. All patients with PTL were administered 10 mg of oral nifedipine tablets 6 times daily or intravenous beta agonist (ritodrine hydrochloride) as the first-line tocolytic treatment. Betamethasone administration has been started to patients in PTL group.

Blood samples for serum decorin levels from healthy pregnants constituting the control group, were also taken between 24 and 32 weeks during their routine controls. All the patients included in the study were followed until birth.

Sample collection and analysis

3 mL of peripheric venous blood samples were drained into EDTA-containing test tubes. Materials were centrifuged at 1000 cycles for 15 min within 30 min after collection. Supernatants were isolated and stored in cryo tubes at −27 °C until being studied. sDEC levels were measured by enzyme linked-immunosorbent assay (ELISA) method. Human Decorin Elisa Kit (Adipo Bioscience, Santa Clara, CA, USA) was used for the sDEC measurements. Standard work-up for Elisa procedure was conducted according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using SPSS for Windows 20.0 statistical package program (SPSS Inc., Chicago, Ill). For the comparison of the continuous variables between the two groups, depending on the distribution of the sample group, Student's *t*-test or Mann–Whitney *U* test were carried out, as appropriate. Chi-square test was used in the comparison of categorical variables. Correlation analysis was performed with the Pearson's correlation coefficient or Spearman's rank correlation coefficient, as appropriate. ROC analysis was conducted to define cut-off values for predicting the risk of PTB within a week, before 34th, and 37th gestational weeks. $P < 0.05$ was considered as statistically significant.

Results

One hundred and sixteen patients were assigned in the study in order to constitute the PTL group. Fifty-two participants who meet the exclusion criteria subtracted from the study group. Among 64 remainders, 31 participants who obey the PTL criteria constituted the PTL group. Gestational aged matched 44 women were assigned in control group.

Table 1 demonstrates the characteristics of the study population. Mean maternal age and body mass index (BMI) and also median values of gravidity, parity, abortion, and gestational age at blood sampling between groups were not significantly different.

Median CL was significantly shorter in PTL group compared to control group (20 mm vs. 37 mm, $p < 0.001$) (Table 2). Median sDEC was significantly lower in PTL group compared to the controls (3026.2 pg/mL vs. 4021.2 pg/mL, $p = 0.013$). Median gestational age at delivery was significantly earlier in PTL group than the controls ($36^{2/7}$ vs. $38^{3/7}$, $p < 0.001$).

Six (19.4%) of the patients in PTL group and 9 of (20.5%) control participants were between 24th and 28th gestational weeks, whereas 25 (81.6%) of the patients in PTL group and 35 (79.5%) of the controls were between 28th and 32nd gestational weeks during the inclusion.

When pregnancies smaller than 28th weeks of gestation at diagnosis were analyzed, mean values of maternal age and BMI between groups were not significantly different. There was a significant difference in median gestational age at blood sampling between PTL and control groups ($p = 0.026$; $26^{1/7}$ vs. $26^{4/7}$). sDEC levels did not differ significantly between groups (Table 3).

When pregnancies greater than 28th weeks of gestation at diagnosis were considered, mean values of maternal age and BMI and median value of gestational age at blood sampling between groups did not differ significantly. Median sDEC level was significantly lower in PTL group compared to controls ($p = 0.043$) (Table 4).

We did not establish any correlation between sDEC level and maternal age, BMI, and gestational age at blood sampling within PTL ($p = 0.955$, $p = 0.609$, $p = 0.079$, respectively) and control groups ($p = 0.652$, $p = 0.131$, and $p = 0.921$, respectively).

In PTL group, there was an association between sDEC level and PTB before 37th gestational weeks ($p = 0.026$), but there was not between sDEC level and PTB within 7 days and before 34th gestational weeks ($p = 0.206$ and 0.091, respectively) (Table 5). We did not find any correlation between sDEC and the CL in PTL group ($p = 0.056$).

However, CL was associated with PTB within 7 days, before 34th and 37th weeks of gestation in PTL group ($p < 0.001$, $p < 0.001$, and