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CLINICAL ARTICLE

Chitotriosidase and YKL-40 in normal and pre-eclamptic pregnancies

Riza Madazli [a,*], Mine Kucur [b], Altay Gezer [a], Ferruh Isman [c], Berk Bulut [a]

[a] *Department of Obstetrics and Gynecology, Cerrahpasa Medical Faculty, Istanbul, Turkey*
[b] *Fikret Biyal Central Biochemistry Laboratory, Cerrahpasa Medical Faculty, Istanbul, Turkey*
[c] *Taksim State Hospital, Istanbul, Turkey*

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Abstract

Objective: To compare macrophage activation in normal and pre-eclamptic pregnancies by determining YKL-40 concentration and chitotriosidase activity in maternal and cord serum. *Methods:* In this prospective case-control study samples of maternal peripheral blood and umbilical venous blood were collected from 28 pre-eclamptic and 24 normotensive pregnant women and their newborns. YKL-40 concentration and chitotriosidase activity were determined by enzyme-linked immunoassay and fluorometry, respectively. *Results:* Chitotriosidase activity in maternal and cord serum and YKL-40 concentration in cord serum were significantly higher in pre-eclamptic pregnancies ($P<0.001$), but there was no significant difference in maternal serum levels of YKL-40 between the case and control groups ($P>0.05$). There was a significant positive correlation between diastolic blood pressure and (1) chitotriosidase activity in both maternal and cord serum and (2) cord serum concentration of YKL-40 ($r=0.61$, $r=0.84$, and $r=0.58$, respectively). *Conclusion:* This study may be the first to demonstrate maternal and fetal macrophage activation in pre-eclampsia.

1. Introduction

Chitinases are enzymes that cleave chitin, the second most abundant polysaccharide on earth. Chitotriosidase is a human chitinase synthesized exclusively by activated macrophages [1]. The *Chit* gene is localized on chromosome 1 at bands q31–q32 and consists of 12 exons spanning about 20 kb of genomic DNA [2]. Chitotriosidase has been proposed as a biochemical marker of macrophage activation in several lysosomal diseases, and is a particularly valuable tool when monitoring treatment effect in patients with a β-glucocerebrosidase deficiency causing Gaucher disease. This disorder is characterized by the presence of large amounts of activated, lipid-laden macrophages in spleen, liver, and other tissues [3].

* Corresponding author. Department of Obstetrics and Gynecology Cerrahpasa Medical Faculty, 34301 Istanbul, Turkey. Tel.: +90 212 322 1919; fax: +90 212 291 6856.
E-mail address: madazli@superonline.com (R. Madazli).

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Moreover, serum chitotriosidase levels are increased in persons affected by hematologic disorders, including those due to malaria, when activated macrophages are involved [4,5]. Chitotriosidase activity has also been found to be significantly increased in persons who have atherosclerosis, and that this activity is related to the severity of the atherosclerotic lesion—which suggests a role for chitotriosidase as a marker of atherosclerotic extension [6,7].

YKL-40 is another glycoprotein of the chitinase family, and the *YKL-40* gene is located on chromosome 1 at band q32. The mammalian protein is a member of the 18-glycosyl-hydrolase family, a family that includes bacterial and fungal chitinases [8]. YKL-40 is expressed and secreted by activated neutrophils and macrophages, and serum elevations of YKL-40 have been noted in patients having conditions involving extracellular matrix degradation and angiogenesis, such as rheumatoid arthritis [9], hepatic fibrosis [10], and osteoarthritis [11], as well as several sorts of cancer [12,13].

Pre-eclampsia is a disease of pregnancy whose pathogenesis is not completely understood, and which is the major cause of maternal, fetal, and neonatal mortality and morbidity. Pre-eclampsia is characterized by a failure of transformation of the spiral arteries and a shallow trophoblast invasion, along with a dysfunctional maternal endothelium and a maternal inflammatory response [14,15].

Abnormal placentation is one of the initial events of pre-eclampsia. It is likely that successful implantation and placental development are both mediated by certain cytokines at the maternal/fetal interface. Macrophages are derived from blood monocytes and execute critical immunologic functions such as phagocytosis, antigen presentation, cytokine secretion, and the orchestration of innate and adaptive immune responses. Macrophages are thought to play important roles in the implantation and placentation processes and then in the development of the placenta. They promote cytotrophoblast invasion by mediating decidual remodeling through the phagocytosis of apoptotic cells, and are important for maternal tolerance of fetal antigens [16]. Macrophage-induced apoptosis has been shown to limit endovascular trophoblast invasion in pre-eclamptic women [17]. A link between activation of the innate immune system and pre-eclampsia has been proposed [18]. Granulocyte-macrophage colony-stimulating factor levels have been shown to be elevated in the placenta and blood of pre-eclamptic women [19].

The aim of this study was to assess chitotriosidase activity and YKL-40 levels in maternal and cord serum as markers of macrophage activation in healthy pregnant women and in women whose pregnancy is complicated by pre-eclampsia. Moreover, correlations between these markers and increased diastolic blood pressure would indicate a relationship between marker levels and disease severity.

2. Methods

2.1. Patient selection

The study was approved by the hospital's ethics committee and all participants gave informed consent for all investigations. The study was carried out between September 2006 and May 2007, and its population consisted of 24 healthy pregnant women and 28 women with pre-eclampsia who had been diagnosed and were treated at the Department of Obstetrics and Gynecology of Cerrahpasa Medical Faculty, Istanbul, Turkey. The women with pre-eclampsia did not receive steroids for fetal lung maturation, but some received magnesium sulphate or medications for acute hypertension; all underwent a cesarean delivery. In the control group the indication for cesarean delivery was a previous cesarean delivery.

Table 1 Characteristics of the study and control groups

Characteristic	Control group ($n=24$)	Pre-eclampsia group($n=28$)	P value
Age, years	31.6 ± 1.1	29.6 ± 0.8	0.131
Nulliparity	16 (66.6)	19 (67.8)	0.928
Diastolic blood pressure, mm Hg	73 ± 1.8	101 ± 1.9	0.001
Gestational age at maternal blood sampling, week	32.2 ± 0.4	31.6 ± 0.8	0.477
Gestational age at birth, week	37.1 ± 0.5	31.7 ± 0.8	0.001
Birth weight, g	2715 ± 154	1482 ± 135	0.001
Fetal growth restriction	0	14 (50)	0.001
Perinatal mortality	0	4 (14.3)	0.001

Values are given as mean ± SD or number (percentage) unless otherwise indicated.

Pre-eclampsia was defined as the onset of hypertension (2 blood pressure readings, at least 6 h apart, of a systolic blood pressure $\geq$140 mm Hg and a diastolic blood pressure $\geq$90 mm Hg), plus consistent proteinuria (300 mg/day or greater), during the second half of the pregnancy and the postpartum. The fourth Korotkoff sound obtained with a cuff sphygmomanometer was used to measure diastolic blood pressure, and the mean of repeated measurements was the value used in the analysis. The participants were screened for proteinuria using dipsticks, and the amount of protein excreted was measured in a 24-hour urine sample. Gestational age was based on the precise date of the last menstrual period and an ultrasound measurement of the crown-rump length in the first trimester. Intrauterine growth restriction was diagnosed when fetal abdominal circumference was found to be more than 2 standard deviations less than the mean for gestational age, and the finding was confirmed by a serial assessment of fetal growth. Multiple pregnancy, premature rupture of membrane, chorioamnionitis, or medical complications including autoimmune disorders, diabetes mellitus, chronic hypertension, and inflammatory conditions were criteria for exclusion. None of the controls had signs of elevated blood pressure or other pregnancy complications, and all gave birth to healthy infants.

2.2. Blood samples and biochemical analysis

At the same time in pregnancy, a single peripheral sample of venous blood was collected from each participant into vacutainer tubes. Immediately after delivery the umbilical cord was double-clamped and venous umbilical blood was collected. Serum was isolated by centrifugation at 2500*g* for 10 min at 4 °C and stored at −80 °C until the analyses were performed. Serum YKL-40 concentrations were determined by a commercial enzyme-linked immmunosorbent assay (Quidel, Santa Clara, CA, USA). The intra-assay and inter-assay variations were 3.6% and 5.3%, respectively. The sensitivity of the assay was