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ORIGINAL ARTICLE

ADAMTS-3, -13, -16, and -19 levels in patients with habitual abortion



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Abstract A disintegrin-like and metalloproteinase domain with thrombospondin-type 1 motifs (ADAMTS) protein superfamily includes 19 secreted metalloproteases. Proteolytic substrates of ADAMTS enzymes have been linked to reproductive function. The aim of this study was to investigate serum ADAMTS-3, -13, -16, and -19 levels in women with habitual abortions compared with those in healthy controls. A total of 86 women were enrolled in this prospective case-control study. ADAMTS-3, -13, -16, and -19 values were recorded and analyzed in association with demographic and clinical parameters. There were no statistically significant differences between the two groups in terms of demographics. No statistically significant differences were observed between the groups with regard to ADAMTS-13 and -19 levels ($p > 0.05$). However, ADAMTS-3 and -16 were significantly higher in the study group than in the control group ($p = 0.004$ and $p = 0.005$, respectively). To estimate habitual abortions using an area under receiver operating characteristic curve analysis, the cutoff values for

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ADAMTS-3 and -16 were found to be 87.28 ng/mL (sensitivity, 64.44%; specificity 68.29%) and 15.75 ng/mL (sensitivity, 66.67%; specificity 68.29%), respectively. In conclusion, the pregnancy-loss rate seems to be affected by both ADAMTS-3 and -16.

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Introduction

Habitual abortion, also known as recurrent miscarriage, is a heterogeneous reproductive problem affecting 1–5% of couples [1]. There is a conceptual confusion regarding the definition of this disease; some define as two clinically recognized miscarriages and others define as three consecutive pregnancy losses [2]. The pathogenesis of habitual abortion has not yet been clarified in detail. It is acknowledged that the causes of habitual abortion are multiple and complex, including genetic factors, immunological factors, trauma, and viral/bacterial infection [3]. However, the cause cannot be determined in up to 50% of patients in whom the problem is defined as idiopathic recurrent miscarriage [4]. With the development of laboratory medicine and gene engineering, some progress has been made in exploring the relationship between gene expression and habitual abortion occurrence [3]. A correct understanding of the pathogenesis is essential for discovering potential effective methods of prevention and treatment, with the final aim of reducing the incidence of habitual abortion and improving the diagnostic and treatment standards.

A disintegrin-like and metalloprotease with thrombospondin type 1 motifs (ADAMTS) proteases were discovered in the late 1990s [5–7], and the first ADAMTS-like proteins (ADAMTSL) were cloned shortly thereafter [8,9]. There are 19 ADAMTS genes and 7 ADAMTSL proteins (ADAMTSL1–6 and papilin) in humans, mice, and other mammals [10]. ADAMTS proteinases, which are released outside the cell (soluble), play critical roles in the damage and repair of extracellular matrix (ECM) processes, such as remodeling [11].

The ADAMTS family, which degrades ECM structural substrates, such as collagen, aggrecan, and versican, has 19 members [12]. These enzymes, which are associated with a great number of vital physiological processes in the ECM, are inhibited by tissue inhibitors of metalloproteinases [13,14]. Family members of this group are divided into various subgroups according to their tasks in the ECM. There is an interest in these proteases, especially with regard to the physiology of ovulation. ADAMTS-1 also plays important roles in the processes of normal growth, fertility, and organogenesis [15]. ADAMTS-2, -3, and -14, also known as procollagen N-proteinases, play important roles in collagen synthesis in the ECM [16]. ADAMTS-1, -4, -5, -8, -9, -15, -16, and -18 degrade aggrecan, which is one of the main components of the ECM; therefore, they are called aggrecanases [11]. ADAMTS-5 and -6, expressed specifically in the placenta, are thought to be responsible for implantation [17]. Known as von Willebrand factor (VWF)-cleaving protease, ADAMTS-13 has effects on coagulation and

homeostasis. This protease degrades ultra-large VWF multimers that are localized in endothelial surfaces, thus preventing thrombus formation [16]. Thrombotic thrombocytopenic purpura, a serious problem during pregnancy, occurs in ADAMTS-13 deficiency [18]. Increased by follicle-stimulating hormone (FSH) and luteinizing hormone (LH), ADAMTS-16 degrades α -2 macroglobulin in the ECM [19]. ADAMTS-10 and -19, whose roles are presently unknown, are called orphan ADAMTS proteases [11].

The aim of this study was to evaluate ADAMTS-3, -13, -16, and -19 levels in patients with habitual abortion and to investigate the role of these molecules in the pathogenesis of this condition.

Material and methods

A total of 86 women (45 patients with habitual abortion and 41 healthy women) were enrolled in this prospective case-control study. The study group was selected from a population of women with two or more consecutive clinically diagnosed pregnancy losses prior to the 20th week of gestation who applied to the infertility outpatient clinic at Zekai Tahir Burak Women's Health Research and Education Hospital, Ankara, Turkey, between February 2015 and January 2016. The demographic characteristics and laboratory parameters of the habitual abortion patients and the controls were retrieved prospectively from the patients and their medical records. Patients with additional diseases (immunologic/rheumatologic/thrombophilic diseases, such as antiphospholipid syndrome; endocrine diseases, such as diabetes and thyroid disease; infectious diseases; and anatomical abnormalities) and who had genetic translocations were excluded from the study. The inclusion criteria for the control group were delivery of at least two healthy children, regular menstrual cycles, presentation to our hospital to request contraception on the 3rd day of the menstrual cycle, no use of hormonal contraceptive methods, no history of recurrent miscarriage, no acute or chronic illness, and no drug use. The local ethics committee approved the study, and written informed consent was obtained from all participants.

Laboratory assay

After at least 8 hours of fasting, venous blood samples were drawn from the antecubital vein of each participant. Hematologic parameters were investigated using the Coulter LH-780 hematology blood analyzer (Beckman Coulter Inc., Brea, CA, USA). Serum folate, vitamin B12, ferritin, and baseline hormone levels were measured by the

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