Original Article

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Evaluation of Factor XII Activity in Women with Recurrent Miscarriages

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ABSTRACT

Objective: Our aim is to evaluate factor XII activity in women with recurrent miscarriages by active partial thromboplastin time (aPTT) measurement.

Methods: This study was conducted in 145 patients admitted to our clinic with recurrent miscarriages between 2014 and 2016. The inclusion criteria were two consecutive or three non-consecutive miscarriages in low-grade patients under the 12th gestational week. Factor XII activity was assessed by aPTT.

Results: The mean age of women with 145 recurrent miscarriages included in the study was 28.4 (±7.6) years and the mean number of abortions was 2. The mean factor XII activity was 106.19±33.62% (range, 90-200). Factor XII activity was found to be 60% in 93.2% (n=135) of the patients.

Conclusion: In the case of recurrent miscarriages, at least aPTT measurement during routine thrombophilic factors may be useful for diagnosis. Investigation of factor XII may be suggested to the patient have prolonged aPTT.

Keywords: Recurrent miscarriages, aPTT, Factor XII

Introduction

Recurrent miscarriage is one of the most important causes of infertility and affects 2 to 4% of women in reproductive period (1). Recurrent miscarriages are defined as 2 consecutive or 3 and more non-consecutive pregnancy losses before the 20th gestational week (2). Moreover, as the number of miscarriages occurring during the previous pregnancy increases, the likelihood of miscarriage in the subsequent pregnancy increases (3). Although there are many etiologic factors, a specific cause cannot be identified in 30% to 40% of the recurrent miscarriages (4, 5). Fibrinolytic system plays an important role during early trophoblastic invasion (6). Therefore, factors such as the deficiency of factor XII activity or increase in plasminogen activator inhibitor, which negatively affects the fibrinolytic system, may limit trophoblastic invasion (6). After the effects of thrombophilic factors on the etiology of recurrent miscarriages were first described in the 1990s, many studies were reported on the effects of hereditary thrombophilias (7, 8). Although the role of especially antiphospholipid syndrome, which is among the acquired thrombophilias, in the etiology of recurrent miscarriages has been well studied, it has been reported that acquired factor 12 deficiency, which is a rare issue, may also be a cause (9). However, some studies have pointed out that the acquired factor XII deficiency may be a subgroup of the patients who have recurrent miscarriages and whose antiphospholipid antibodies are positive (10, 11).

Factor XII deficiency may be a rare cause of hereditary-origin recurrent miscarriages in antiphospholipid syndrome subgroup (12). Many studies have been reported on the relationship

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between factor XII deficiency and recurrent miscarriages (6, 13, 14). In the light of this information, we planned to evaluate the aPTT measurement, which is an indirect indicator of factor XII activity in women with recurrent miscarriages.

Methods

This study was performed in 145 patients who were admitted to our clinic with recurrent miscarriage problems between the years of 2014 and 2016. Ethical approval before the study was obtained from Istanbul Medipol University, Non-Interventional Clinical Research Ethics Committee (10840098-604.01.01-E.9537), and informed consent was obtained from the patients. The definition criteria in the 2012 committee opinion of American Society of Fertility were accepted as the inclusion criteria, and the patients who had a history of 2 consecutive or 3 non-consecutive miscarriages in the 12th gestational week were included in the study. Paternal and maternal karyotype analysis of the patients, and prothrombin gene mutation and factor V leiden mutation analysis, which are the causes of hereditary thrombophilia, were homozygous normal. The patients without any problems of Protein C and protein S activity were included in the study. aPTT, which is an indirect indicator for evaluating the factor XII activity, was examined. At the same time; pregnancy, inflammation, age and autoantibodies, which are the conditions that may affect aPTT were evaluated through pregnancy test, CRP, anticardiolipin antibody IgM and IgG, lupus anticoagulant and antinuclear antibody. In our hospital, aPTT measurement was made using the Behring coagulation system (BCS; Dade Behring Inc., Liederbach, Germany). Plasma (George King Bio-Medical Inc., St. Overland Park, KS, USA) was incubated with pathromtin SL (Dade Behring Inc.) and 0.02 mol/L CaCl2 (Calcium Chloride) (Sysmex International Reagents Co., Ltd., Kobe, Japan). This mixture was incubated with patient or standard plasma and the clotting time was recorded. Activity was expressed as the percentage of standard human plasma reference and cut-off levels were evaluated as 10, 35, 60, and 150.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) 21.0 (IBM Corp.; Armonk, NY, USA) was used. Continuous variables were expressed as ± standard deviation (SD) and categorical variables as numbers.

Results

The characteristics of the 145 women who had recurrent miscarriages and were included in the study are summarized in Table-1. The mean age was 28.4 (± 7.6) and the mean number of miscarriages was found to be 2. In Table-2, the distribution of aPTT, an indirect indicator of factor XII deficiency, is shown as %. The mean PT percentage was found to be 106.19 ± 33.62 (90-200). The PT percentage was found to be less than 60% in 6.8% (n = 10) of the patients. There were 3 cases with PT percentage less than 35%. The percentage of PT was found greater than 60 in 93.2% (n = 135) of the patients.

Discussion

Since the fibrinolytic system has a very important role during placental invasion, recent studies have focused on investigating this issue in obstetric complications such as recurrent pregnancy losses. Although previous studies reported that factor XII deficiency was between 2.9% and 15% in patients with recurrent miscarriages (14-16), we found in our study that the aPTT activity, which is one of the indirect indicators of the factor XII deficiency, was 2.06%, which was not so different. It has been shown that factor XII activity significantly decreases in women with recurrent miscarriages along with known thrombophilia reasons (17, 18). Although factor XII has an impact on both the coagulation and fibrinolytic pathways, it is not clear yet through which mechanism it may cause recurrent miscarriages (19, 20). However, according to the general results of the studies, it is reported that factor XII deficiency may have a role in this pathology with thromboembolic effect rather than the increasing tendency to hemorrhage (14, 21). Probable placental microthrombi, which develop due to the factor XII deficiency especially in hemochoroendothelial vessels, lead to pregnancies resulting in miscarriages (14, 22). In many studies, it has been shown that through this mechanism, the defficiency of factor XII activity also plays a role in recurrent miscarriages as much as traditional thrombophilias (17). Interestingly, in spite of this pathophysiology which had been estimated; while some investigators found the correlation between recurrent miscarriages and reduced XII activity at a lower rate as in our study, others found this correlation to be higher. Similar to our study, Yamada et al. also found the correlation between factor XII activity and recurrent miscarriages at a rate of 2-4% (16). The possible cause of this inconsistency may be due to differences in the design of some studies or some phenotypic differences caused by various genetic factors (14). In a recent study, the effects developing in the factor XII gene locus or in the region close to this gene locus have been repoted to produce sensitivity to both factor XII activity and thrombotic disease (23).

Table 1: Demographic characteristics of the study group

	Mean	min-max
Age (mean ± SD) (years)	28.4±7.6	19-37
Gravida	4	2-9
Abortus	2	2-8
Previous live births	0	0-2

Table 2: Percentage of PT distribution used in the evaluation of Factor XII levels in women with habitual abortion

PT distribution	n=145	%	Mean±SD
<10%	1	0.3	0.9
10-35%	2	1.4	23.65±7.49
35-60%	7	5.1	49.71±6.71
60-150%	117	81.1	103.47±18.23
150-200%	18	12.1	179.61±15.41
Total	145	100	106.19±33.62

One of the reasons that lead to a decrease in factor XII activity may be antibodies developing against factor XII (11). The presence of antiphospholipid antibodies that reduce factor XII activity may also cause recurrent miscarriages (24). Moreover, some studies have also reported that recurrent miscarriages can also be caused by the antibodies that reduce factor XII activity and that develop against factor XII activity itself in patients with positive lupus anticoagulant and antiphospholipid antibodies (10). Although the decrease in factor XII activity was associated with recurrent miscarriages in most of the studies, some studies contrarily reported that they were not associated with pregnancy losses (25). There have been studies reporting that aPTT results can be within normal limits despite reduced factor XII activity (17).

The most important limitation of our study is that we had a small number of cases and that the factor XII levels were not measured in the patients whose aPTT times we thought were pathologic. In addition, since we did not have a control group, the data were not compared, which is another limitation of our study. Perhaps, the results we obtained may be interpreted differently in another study design in which patients with healthy children without recurrent miscarriages are compared.

Conclusion

Although there are contradictory data in patients with recurrent miscarriages, making the measurements of aPTT during the investigations of routine thrombophilic factors can be useful for diagnosis. If there is no explanatory cause in women with prolonged aPTT, it may be advisable to examine the factor XII, albeit rare.

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