CEOG Clinical and Experimental Obstetrics & Gynecology

Detecting coagulability status by thromboelastography in women with the history of preeclampsia and inherited thrombophilia

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Summary

Objective: To assign tendency to thrombosis in patients with preeclampsia and inherited thrombophilia using thromboelastography (TEG), and therefore to evaluate possible relationship between thrombophilia and preeclampsia. *Materials and Methods:* Kinetics of clot formation was assessed with TEG analyzer in 49 patients with severe preeclampsia, 54 cases with previous diagnosis of inherited thrombophilia, and 31 controls. *Results: 'r', 'k',* TMA, coagulation index (CI) parameters were found statistically discrete between patients with inherited thrombophilia and controls. The difference between preeclampsia and control groups was not statistically significant. The difference in *α angle* was statistically significant between thrombophilics and preeclamptics ($p = 0.01$), and between thrombophilics and controls ($p = 0.004$). CI was found statistically lower in thrombophilia group than control group ($p = 0.006$). Particularly, c*lot lysis time* (CLT) was measured to shorten in preeclampsia when compared with controls and patients with thrombophilia ($p = 0.032$, $p = 0.028$, respectively). *Conclusions:* Not only the inherited thrombophilia group but also preeclampsia group demonstrated elongated clot initiation patterns when compared to the controls. Moreover, apart from the patients with inherited thrombophilia, preeclamptics exposed shorter CLT values indicating a possible increment in clot turn over, which eventually results in increased depletion of coagulation substrates, and thus, increased frequencies of oxidative cycle injury.

Key words: Blood; Coagulation; Thromboelastography; Preeclampsia; Thrombophilia.

Introduction

Hypertensive disorders which are seen in 5% to 15% of all pregnancies are one of the major causes of fetomaternal morbidity and mortality. It is of great importance to identify patients who are under risk of development of preeclampsia in order to gain advantage, if possible, from close follow-up together with convenient treatment [1].

The pathogenesis of preeclampsia is not yet fully evident. It is supposed that the development of preeclampsia is a consequence of alterations in placental microcirculation. Accordingly, a failure in achieving low resistant uteroplacental blood flow due to inadequate trophoblastic invasion of maternal spiral arteries gives rise to insufficient placentation [1, 2].

On the other hand, increased tendency to development of thrombosis is closely related with abnormal placentation. This condition is seen frequently in the presence of a hereditary or acquired risk factor [2]. This fact is more important for the women because of increased state of thrombosis already in pregnancy [3]. In the recent years, thrombophilia is indicated to be responsible from severe preeclampsia, eclampsia, HELLP syndrome, placental abruption, intrauterine growth restriction (IUGR), intrauterine fetal losses, and recurrent pregnancy losses (RPLs). Kupferminc *et al.* [4] demonstrated that hereditary and acquired thrombophilic factors are related with pregnancy complications. Correlation of thrombophilia and pregnancy complications could be thought to originate from insufficient fetoplacental circulation in this intuition.

Thromboelastography (TEG) which evaluates viscoelastic characteristics of the blood in vitro was first described by Hartert *et al.* [5] in 1948. It was used extensively in cardiac surgery and in renal and liver transplantation to monitorize coagulopathy closely and coordinate anticoagulant treatment [1]. Since vascular and endothelial injury accompany preeclampsia, and increased frequencies of coagulation disorders could be encountered in complicated pregnancy states, we aimed to investigate possible abnormal coagulability conditions in patients with inherited thrombophilia and history of severe preeclampsia using TEG, and thus to determine the relationship between thrombophilia and preeclampsia. As it is known, hemostasis is a dynamic, highly complex process which encloses vast interacting factors such as procoagulants, fibrinolytic proteins, activators, inhibitors, and cellular elements. Therefore, whole steps of coagulation cascade could be evaluated with TEG (Figure 1) [6].

Revised manuscript accepted for publication December 30, 2013

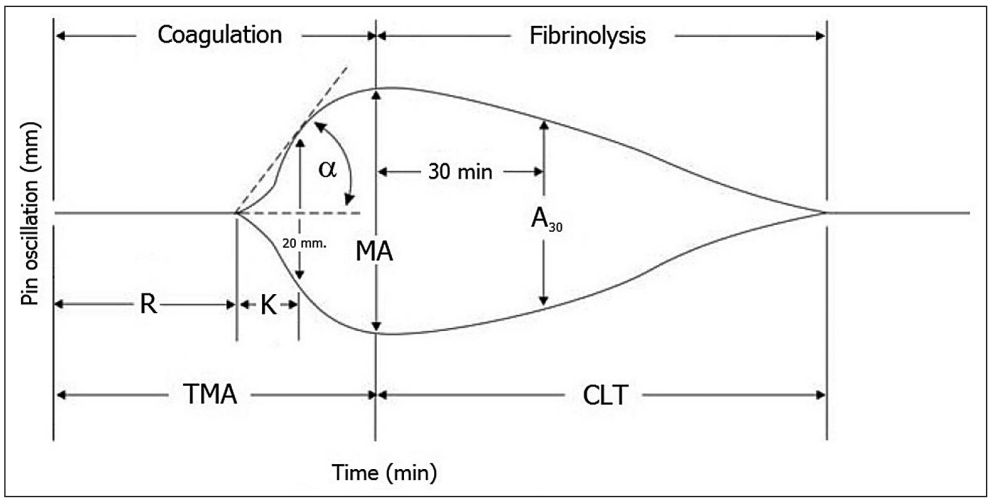

Figure 1. — Diagram outlining the relationship between coagulation cascade and TEG, together with the display of TEG parameters. Reaction time (r): The time elapsed from the beginning to the early clot formation. It is the distance from the beginning of the graph to the point where 2-mm deflection begins, and given in millimeters on the graph. k: The time length needed for a firm and steady clot formation. It is the time between 'r' and the point where 20-mm deflection exists. α angle: The parameter that shows the speed and the power of clot formation. It is calculated from the 20-mm deflection point on the graph, and directly related with 'k'. Maximum amplitude (MA): Represents the formation strength and rigidity of the coagulum. It is the value given in millimeters when the clot reaches its maximum width. Projection of MA (PMA): Gives an opinion about MA before the final measurement of MA itself. It begins on the screen when the amplitude reaches 5 mm and ceases when the clot formation slows down. Time for MA (TMA): Measures the time from the beginning of the survey until the most powerful state of the sample. Amplitude (A): It is the measurement of the extent of the studied sample in any time interval. It represents the function and elasticity of the clot, and its value is given in millimeters. Amplitude can be converted to the real measurement of the clot strength by SEMS (shear elastic modulus strength) which is given in dyn/cm^2. Absolute SEMS value gives G parameter. Calculation of G is formulated by G=5000A/ (100-A). Amplitude value of normal whole blood is 50 mm. Its SEMS value corresponds to 5000 dyn/cm^2. A rise in amplitude from 50 mm to 67 mm causes a two-fold increase in SEMS value. Therefore, G value is more convenient in reflecting any changes in clot formation besides measuring clot strength. E: Represents normalized value of G parameter, and it is thought as an elasticity constant. Thrombodynamic potential index (TPI): It is formulated by TPI = E_{max}/k. E at maximum amplitude (E_{max}) = (100xMA)/(100-MA). Coagulation index (CI): Consists of most of the TEG parameters including r, k, MA, and α angle. Normal values of CI are between -3.0 and +3.0. Values < -3.0 represent hypocoagulability, whereas > +3.0 indicates hypercoagulability. Reduction in length of amplitude after MA is represented by A30 (at 30 min) and A60 (at 60 min). Similarly, decreased area after MA is defined by LY30 and LY60 which stand for the course of fibrinolysis process, and given in percentages. Clot lysis time (CLT): Displays the time interval after MA until amplitude decreases to 2 mm.

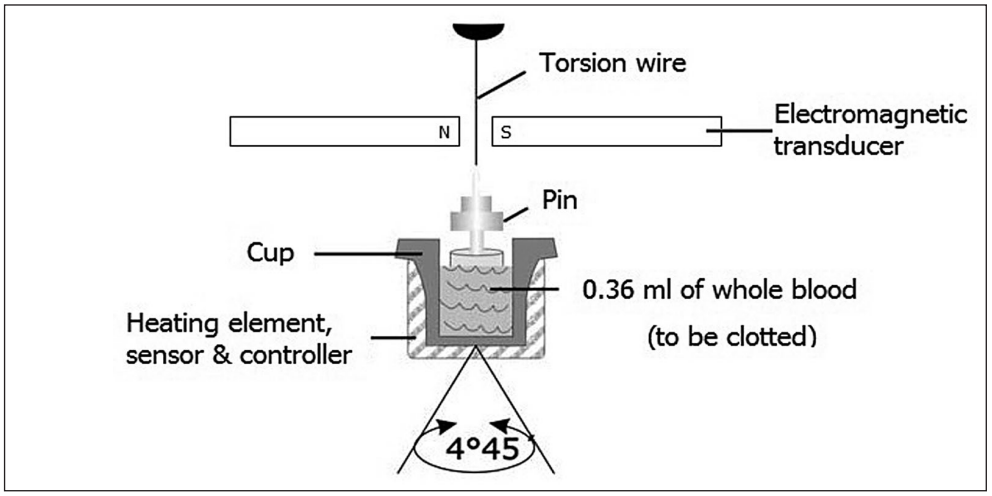

Figure 2. — Working principle of TEG.

Materials and Methods

The study was accomplished in our perinatology clinic between March 2003 and December 2009. Seventy-two patients with recent diagnosis of severe preeclampsia, 73 patients with previous diagnosis of inherited thrombophilia, and 31 healthy multiparous women were settled to participate in the study. Participants were evaluated at the earliest fourth month after delivery. All participants were Caucasians with average socio-economic status. Thrombophilia group was consisted of participants who experienced recurrent first-trimester pregnancy losses or unexplained second- or third-trimester fetal losses together with presence of at least one of the factors including deficiencies of antithrombin III, protein-S and protein-C, mutations of prothrombin, factor V Leiden and MTHFR genes, or positivity of lupus anticoagulant and antiphospholipid antibody. Eight patients out of 73 patients with thrombophilia rejected participating in the study, five patients were under low molecular weight heparin treatment and medical records of six patients were incomplete. Therefore, we enrolled 54 patients with inherited thrombophilia. Fourteen of 72 patients with severe preeclampsia refused to participate in the study, and nine of them were excluded from the study because of incomplete medical records and communication. Forty-nine women with severe preeclampsia were enrolled in the study. Severe preeclampsia was defined as presence of one of the following criteria in her previous pregnancy: systolic blood pressure measurement above 160 mm Hg or diastolic blood pressure measurement above 110 mm Hg on two occasions at least six hours apart, more than five grams urinary protein excretion in 24 hours or 3+ and greater random urine dipstick testing, less than 500 ml of urinary discharge in 24 hours, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain. Control participants were structured from 31 individuals without any history of medical disorders during pregnancy and after delivery. Local ethical committee approval was obtained. Written informed consent was taken from all participants. The patients were strictly questioned about any use of oral or parenteral medications for the past two months. Detailed medical history of the patients were collected including family history, previous pregnancies, systemic disorders, recently used medications, previous operations, and drug reactions.

Technique

Blood samples of two ml from all participants were taken. Subsequently, one ml of achieved sample was drawn into chaolin containing tubes within 30 seconds, and mixed up. 0.36 ml of the mixture was collected with a straw and was put inside the cup which was placed in the thromboelastography analyzer and processed with TEG analyzer which was calibrated before at 37^0C according to the instructions of the manufacturer. When coagulation begins, fibrin particles are formed in between a thermostatically controlled heated cup which turns in a $4^0$45' angle and a pin suspended on a torsion wire (Figure 2). Second phase, measures the speed at which the clot forms, and depends on the changes in distension of the clot when it begins to form. It is measured electromagnetically and recorded as graphs [7]. In addition to assessment of the beginning phase of the coagulation, it also evaluates speed and strength of clot formation as well as fibrinolysis of the clot. Therefore, disorders of both hypercoagulability and hypocoagulability could be detected as well [8].

Statistics

Statistics were performed using Statistical Package for the Social Sciences software version 13.0. Continuous variables were given in *means ± standard deviations*. Comparisons between two groups possessing normally distributed variables were performed with *independent samples t test.* Comparisons of more than two groups were fulfilled with *single factor analysis of variance (ANOVA) test*. The differences in two groups and more than two groups which do not show normal distribution were checked with *Mann-Whitney U* and *Kruskal-Wallis tests*, respectively. Groups comprising categoric variables were compared with *Pearson Chi-square test*. The level of statistical significance was defined as $p < 0.05$. ROC analysis was done among patients with inherited thrombophilia to determine cut of values for *r*, α angle, CI, TMA, CLT parameters.

Table 1. — *Demographic characteristics of all patients and healthy controls*.

	Patients with preeclampsia	Patients with thrombophilia	Control individuals	*p*
Age	28.9 ± 5.9	33.6 ± 5.8	33.6 ± 4.9	0.002*¥
Gravidity	1.9 ± 1.2	4.2 ± 1.6	2.0 ± 0.9	<0.001*§
Parity	1.4 ± 0.6	1.1 ± 0.5	1.6 ± 0.6	0.012§
Abortions	0.4 ± 0.8	2.9 ± 1.5	0.5 ± 0.7	<0.001*§
Number of living children	1.1 ± 0.6	1.0 ± 0.5	1.5 ± 0.6	<0.001¥§
Days after LMP	16.6 ± 15.1	14.9 ± 9.3	14.5 ± 7.7	0.985
Gestational age	33.4 ± 3.0	37.4 ± 2.6	38.9 ± 1.4	<0.001*¥§
Birth weight	1813 ± 749	2936 ± 870	3321 ± 440	<0.001*¥
1st min Apgar score	5.6 ± 0.6	7.3 ± 0.4	8.8 ± 0.4	<0.001*¥§
5th min Apgar score	7.1 ± 0.9	8.8 ± 0.2	9.6 ± 0.3	<0.001*¥§

LMP: Last menstrual period. Values are given in means ± standard deviations. Days after LMP: Days after last menstrual period which TEG was studied on. *Represents statistical significance between patients with inherited thrombophilia and history of preeclampsia; ¥Statistical significance between patients with history of preeclampsia and control individuals; §Statistical significance between patients with inherited thrombophilia and the controls.

Results

Demographic characteristics of the study participants are given in Table 1. There was a statistically significant difference between mean age of the patients with inherited thrombophilia and history of preeclampsia, and between preeclampsia and control groups (28.9 ± 5.9, 33.6 ± 5.8, and 33.6 ± 4.9, respectively; $p = 0.002$ for both). We thought that the differences in formerly mentioned variable did not influence the outcomes of this study. There was no difference between the groups when they considered the day after last menstrual period which TEG was conducted.

Dispersion of TEG parameters according to the groups are given in Table 2. The differences in mean values of MA, G, EPL, A, LY30, A30, CL30, A60, CL60, LY60, TPI, E, SP, and LTE between all three groups were not statistically significant.

The elongated "r" value which indicates a defect in the first fibrin formation and a deficit in the coagulation factors, inhibitors and/or activators, and thus, a delay in

Table 2. — *Demonstration of TEG parameters in study population.*

	Patients with preeclampsia	Patients with thrombophilia	Controls	*p*
r (min)	9.5 ± 3.0	10.7 ± 2.8	7.8 ± 3.7	0.003§
k (min)	2.9 ± 1.2	3.4 ± 1.4	2.6 ±1.1	0.025§
α angle	54.6 ± 9.7	49.8 ± 10.2	57.4 ± 9.2	0.01*, 0.004§
MA (mm)	66.5 ± 6.3	66.5 ± 6.2	66.1 ± 5.6	0.963
TMA (min)	31.4 ± 5.7	34.5 ± 4.4	29.4 ± 5.9	0.002§
G (dyn/cm²)	10.5 ± 3.1	10.3 ± 2.8	10.2 ± 2.6	0.993
EPL (%)	1.9 ± 2.4	4.3 ± 18.4	1.4 ± 1.9	0.311
A (mm)	61.5 ± 7.1	60.2 ± 8.2	60.7 ± 6.8	0.758
CI	-2.7 ± 3.6	-4.2 ± 3.4	-1.7 ± 3.7	0.006§
LY30 (%)	1.7 ± 2.3	2.7 ± 8.9	1.2 ± 1.6	0.421
A30 (mm)	63.8 ± 7.1	63.3 ± 8.2	63.7 ± 5.8	0.823
CL30 (%)	95.6 ± 4.1	95.4 ± 8.5	96.4 ± 3.5	0.441
LY60 (%)	3.5 ± 3.4	2.8 ± 2.4	3.1 ± 3.1	0.967
A60 (mm)	58.3 ±13.4	61.2 ± 6.6	60.4 ± 6.9	0.706
CL60 (%)	88.4 ± 18.1	92.0 ± 5.1	91.8 ± 6.4	0.836
CLT (min)	41.4 ± 14.8	49.3 ± 14.0	49.7 ± 14.3	0.028*, 0.032¥
TPI	44.6 ± 28.9	36.3 ± 20.6	45.9 ± 23.4	0.314
E (dyn/cm²)	210.7 ± 64.3	202.3 ± 56.4	199.5 ± 52.2	0.972
SP (min)	7.9 ± 2.5	8.2 ± 2.9	6.7 ± 3.3	0.128
LTE (min)	162.2 ± 32.5	164.1 ± 30.3	162.8 ± 33.9	0.997

Values are given in means ± standard deviations. min: minute.
*Represents statistical significance between patients with inherited thrombophilia and history of preeclampsia; ¥Statistical significance between patients with history of preeclampsia and control individuals; §Statistical significance between patients with inherited thrombophilia and the controls.

Table 3. — *Demonstration of the risk factors of the patient group.*

	Preeclampsia n (%)	Thrombophilia n (%)	Total n (%)
Individual history of			
Deep venous thrombosis (DVT)	2 (4.1%)	3 (5.5%)	5 (4.8%)
Abruptio placenta	3 (6.1%)	2 (3.7%)	5 (4.8%)
IUGR	27 (55.1%)	4 (25.9%)	41 (39.8%)
Oligohidroamnios	20 (40.8%)	2 (3.7%)	22 (21.3%)
HELLP syndrome	13 (26.5%)	—	13 (12.6%)
Eclampsia	6 (12.2%)	—	6 (5.8%)
Family history of			
Preeclampsia	5 (10.2%)	2 (3.7%)	7 (6.8%)
DVT	4 (8.2%)	9 (16.7%)	13 (12.6%)

IUGR: Intrauterine growth restriction;
HELLP: Hemolysis + elevated liver enzymes + thrombocytopenia;
DVT: Deep venous thrombosis.

thrombin formation, was found to be significantly higher in patients with thrombophilia compared to the control group in this series (10.7 ± 2.8 and 7.8 ± 3.7, respectively; $p = 0.003$). Although *r value* was established to lengthen in patients with preeclampsia (9.5 ± 3.0) compared to the controls, no statistically significant differences were found between preeclampsia group and the control group, and between preeclampsia and thrombophilia groups.

'k' value was found significantly higher in patients with thrombophilia when compared with control group in this series (3.4 ± 1.4 min and 2.6 ± 1.1 min, respectively; $p = 0.025$). Although we found a distinction between patients with preeclampsia (k = 2.9 ± 1.2 min) and the controls, and between preeclampsia and the thrombophilia groups with regard to *k value*, the differences did not reached expected statistical significance.

In patients with thrombophilia, *α angle* which measures the fibrin formation and cross-binding speed (kinetics of clot) was statistically smaller when compared with preeclampsia (49.8 ± 10.2 and 54.6 ± 9.7, respectively; $p = 0.01$) and control groups (57.4 ± 9.2; $p = 0.004$), However, the difference between preeclampsia and control groups was not statistically significant.

Mean value of TMA which measures the time period from the beginning of working the blood sample up to the most powerful state of the clot was found significantly longer in thrombophilia group when compared to control group (34.5 ± 4.4 min and 29.4 ± 5.9 min, respectively; $p = 0.002$). Although, there were differences between preeclampsia (31.4 ± 5.7 min) and the control groups, and preeclampsia and the thrombophilia groups, they did not reach statistical significance.

The coagulation index (CI), which is comprised of r, k, MA, alpha parameters, was significantly lower in the thrombophilia group when compared to the control group (-4.2 ± 3.4 and -1.7 ± 3.7; $p = 0.006$). However, the differences between preeclampsia group (-2.7 ± 3.6) and the control group, and preeclampsia and the thrombophilia groups did not reach statistical significance. Clot lysis time (CLT) was significantly shorter in the preeclampsia group when compared to the thrombophilia group (41.4 ± 14.8 min and 49.3 ± 14.0 min, respectively; $p = 0.028$), and the control group (49.7 ± 14.3 min; $p = 0.032$). There was not any statistical difference between thrombophilia and control groups.

When we investigated all patients (n=134) in terms of presence of IUGR, they could not find any significant relationship between a specific TEG parameter and IUGR. Similarly, there was not any established correlation between TEG parameters and presence of oligohydramnios.

To assess efficiency of TEG in demonstrating thrombophilia ROC analysis was used. For the *α angle*, sensitivity and specificity values were 54.8% and 86.2%, respectively, when cut off value was taken as 58.4. An *α angle* measured above 58.4 was found to increase thrombophilia risk 3.98 times (Figure 3).

For the *r value*, sensitivity and specificity values were 58.1% and 93.1% when cut off value was taken as 7.3, respectively. A *r value* value measured above 7.3 was found to increase thrombophilia risk 8.42 times (Figure 4).

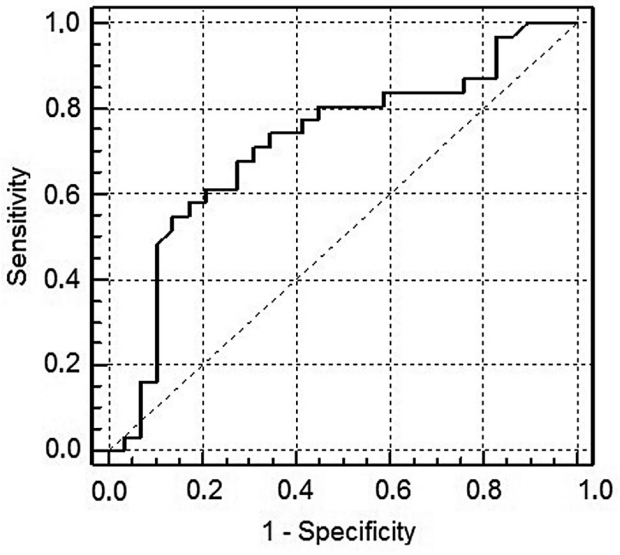

Figure 3. — ROC analysis of α angle in determining thrombophilia.

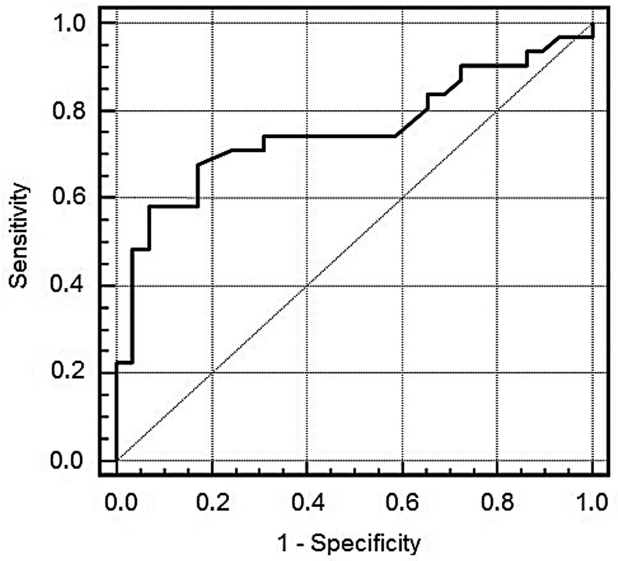

Figure 4. — ROC analysis of *r* value in determining thrombophilia.

Discussion

Preeclampsia, eclampsia, HELLP syndrome, abruptio placenta, and IUGR are serious obstetrical complications, and are main causes of perinatal morbidity and mortality. The results of studies on the etiology of these complications are yet equivocal to conclude in treatment methods . Hence, the treatment of pregnancy complications is usually directed to give up with the pregnancy. There are strong evidences suggesting that the uteroplacental insufficiency is the critical factor which provokes those complications. Accordingly, inadequate trophoblastic invasion causes the release of thrombin-antithrombin complexes in the uteroplacental bed, and thus, fibrin accumulates and inadequate degradation of fibrin results in formation of the thrombotic plugs. As a consequence, endothelial damage occurs and eventually uteroplacental insufficiency develops [9].

It is known that coagulation capability is increased in pregnancy. This increases risk of deep venous thrombosis (DVT) and pulmonary embolism in pregnancy. The reason for increased coagulation is increased thrombocyte aggregation, increased concentration of the coagulation factors, a decrease in the concentrations of coagulation inhibitors (antithrombin III, protein-C), a resistance to activated protein-C, and low fibrinolytic capacity [10]. Therefore, changes in the coagulation system in relation to pregnancy may call for the appearance of thrombotic context by increasing the concealed thrombogenic tendency that is already present in a patient with thrombophilia [11].

There are several studies evaluating the association between the inherited thrombophilia and pregnancy complications. This study analyzed the association between thrombophilia and severe preeclampsia, which is an important cause of fetal and maternal morbidity and mortality. TEG, which assesses the coagulation system as a whole, is used in this study instead of the tests that evaluate a single step of the coagulation system [12]. TEG measures the kinetics, integrity, and dissolution (stability) of the thrombus, and thus the functionality and sustainability of the thrombus as the ability of the thrombus to stop bleeding [13]. When compared to the routine coagulation tests, TEG has been used in the diagnosis of dilutional coagulopathy, DIC, and fibrinolysis in transplantations, during which major hemorrhages frequently occur. It can also be used in obstetrical hemorrhages in the same way. In addition, it can be used to define hypercoagulability states, although it has not been used much for this purpose.

Conventional coagulation tests end after the first fibrin formation. However, TEG continues to analyze and measure the kinetics of the thrombus (the rate of formation), and its durability, integrity, and dissolution. Thus, general information about the coagulation process is obtained by a single test [14-16]. TEG provides information about coagulation in general, from hypercoagulation to hypocoagulation and potential fibrinolysis, in addition to normal coagulation. Laboratory coagulation tests measure isolated specific points of the coagulation process. A wide variety of tests are needed to measure the whole cascade, which results in a waste of time, money, and labor.

Hypercoagulability in pregnancy can be demonstrated by TEG parameters [8, 17-19]. This fact is more evident in women in the course of active labor [20]. This hypercoagulable state returns to normal at sixth week after delivery [21]. The *'r'* and *'k' values* are decreased and the angle of α and MA are increased during pregnancy [18, 19]. Larger studies

are needed to identify the time in which these changes occur in terms of gestational weeks, which are already unknown.

When we evaluated TEG parameters in this series, the MA value which shows thrombocyte aggregation, the G value that shows the integrity of the thrombus, the A value which shows the function and elasticity of the thrombus, and the thrombodynamic potential index (TPI) that shows hypocoagulability and hypercoagulability states, were found to be similar in all three groups. No statistically significant differences were found between the three groups regarding clot lysis parameters, comprising the percentage of lysed clots in a time period after MA (LY30 and LY60), the values indicating decreased amplitude (A30 and A60), and the thrombus dissolving index in a specific time period after MA (CL30 and CL60).

A variety of reports are present in the literature evaluating the association of TEG and thrombophilia. It was suggested that TEG could be used in pregnant women to assess the risk of preeclampsia and thrombocytopenia [16], as well as, it could indicate the risk for recurrent pregnancy loss [14]. In another study, it has been postulated that TEG could contribute to treatment by identifying the recurrent pregnancy loss, IUGR, and congenital and acquired thrombophilia in preeclampsia [22].

Similar to our results, Sharma *et al.* [23] demonstrated that MA values were significantly higher in pregnant women who were diagnosed to have mild preeclampsia at birth when compared to healthy pregnant women. In addition, all TEG parameters were correlated with hypocoagulability in all pregnant women with severe preeclampsia and thrombocytopenia. The risks of abortus and abruptio placenta were found to be higher in another study when hypercoagulability was assigned with TEG [24].

Miall *et al.* [25] found significant correlations between PT, aPTT, plasma antithrombin levels, and TEG parameters including r, k, and MA. However, no correlations were identified between the TEG parameters and other thrombophilic factors (protein-C, protein-S, Factor V Leiden mutation, prothrombin G20210A mutation, MTHFR C677T mutation, and lupus anticoagulant). In their study, they established a significant correlation between TEG parameters and second trimester losses, nevertheless there was no correlation between TEG and other pregnancy complications.

Regan *et al.* [26] found MA value to be significantly higher in the patients with a history of recurrent pregnancy losses (RPLs), and the k value to be significantly higher in non-pregnant women with a history of second trimester losses. As Rai *et al.* [27] mentioned, pre-pregnancy MA value can be used to predict pregnancy complications. According to the serial TEG evaluations in the early weeks of pregnancy, the increments of MA in TGK were suggested to be associated with future pregnancy losses in the following weeks, while pregnancy resulted in live birth in cases with stable MA values with no change between fifth and 12th week of pregnancy [28].

A wide variety of results exist in the literature in studies performed with conventional laboratory tests to define the association of thrombophilia with preeclampsia, and its complications. These variations might be due to population differences, study design, and differences in the definition of preeclampsia. For example, factor V Leiden mutation is frequently seen in Caucasians, while it is extremely rare, almost non-existent in Asian and Japanese societies [29]. Since the rates of venous and arterial thrombosis and placental thrombosis in preeclampsia and other pregnancy complications are not affected from ethnic groups and races, other thrombophilic factors with undefined roles yet might have important influences on the clinical progress. Some thrombophilic women have not experienced thromboembolic complications during their pregnancies [30]. This observation demonstrates that additional factors are needed for the development of preeclampsia.

Management of a patient with a positive result for thrombophilia in thrombophilia survey is an actual clinical dilemma for future pregnancies and for the treatment in the time periods other than pregnancy. Today, there is no evidence to support women with thromboprophylaxis without a history of thromboembolus but with a positive thrombophilia screening test result [31]. However, there are sufficient evidences demonstrating that endothelial damage and activated mononuclear cell-derived tissue injury as the main concerns in pregnancies of them. Though, it is thought that low pressure intervillous blood flow and trophoblastic dysfunction in a maternal hypercoagulability state might trigger pathophysiological mechanisms of the disease through placental fibrin deposition and placental infarcts.

On the contrary, Mousa *et al.* [11] evaluated the association between thrombophilic state and placental histology in 79 women. They found that 70% of thrombophilia-positive women and 78% of thrombophilia-negative women had abnormal placental histology. Therefore, they concluded that there is a weak correlation existed between the pathological placental changes and thrombophilic state in women with severe pregnancy complications.

The reported recurrence rate of severe preeclampsia is 20% [32], and it is unknown that how high is the risk of recurrence in a thrombophilic woman. Kupferminc *et al.* [4, 33] demonstrated that 57% to 67% of multipara women with recurrent pregnancy complications had one thrombophilic factor. However, the type of complications might differ in one pregnancy to the other. On the other hand, the recurrence rate of severe preeclampsia is high, and even higher in thrombophilic women particularly with factor V Leiden and/or factor II mutations.

In the present series, *r*, *k*, and TMA values were found to be significantly higher in the thrombophilia group compared to the control group ($p < 0.01$), while no statistically significant differences were found between preeclampsia and control groups, and between preeclampsia and thrombophilia groups regarding these variables. CI and α angle were found to be significantly lower in the thrombophilia group compared to the control group ($p < 0.05$), while no statistically significant differences were found between preeclampsia and control groups, and between preeclampsia and throm-

bophilia groups. On the other hand, CLT was identified to be significantly lower in the preeclampsia group compared to both thrombophilia ($p = 0.028$) and control groups ($p = 0.032$). There was no statistically significant difference between thrombophilia group and the control group with regard to CLT. The r, k, angle, CI, and TMA parameters in TEG were significantly different in the thrombophilia group compared to the control group, while no difference was shown between the preeclampsia and control groups. Only CLT was statistically significantly lower in the preeclampsia group compared to the other two groups.

Thrombophilia emerges as a result of the deficiency of non-homogeneous factors responsible in different steps of the coagulation cascade. In each woman in whom a thrombophilia was identified in the laboratory, it is well known that the tendency to thrombosis differs according to the homozygosity/heterozygosity of the defect, to the factor activity, and to the type of the mutation. Randomized controlled studies in larger populations are needed, including the subgroups, since the defects in the different steps of the coagulation cascade might be reflected in TEG as various different results.

We esteem from this study that facts which provoke abnormal clot formation and fibrinolysis processes could be related with preeclampsia pathogenesis. This phenomenon could be due to presence of insensible consumption of coagulation parameters in preeclampsia, which is already experienced in the states of thrombophilia.

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