

High frequency of thrombophilic disorders in women with recurrent fetal miscarriage

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Summary

Objectives: Our purpose was to examine whether genetic thrombophilias are etiological factors for recurrent fetal miscarriage or not.

Study Design: We compared the rate of thrombophilic anomalies in women with unexplained recurrent fetal miscarriages to the rate of age-matched women with successful pregnancies as a case-control study.

Results: A total of 101 consecutive patients with 102 age-matched controls were included in the study. The rate of Factor V (FV) Leiden mutation, Factor (F) II mutation, protein S, protein C, antithrombin III deficiencies and overall thrombophilia in patients with recurrent fetal loss was significantly higher than the frequencies in control patients.

Conclusion: Women with recurrent fetal miscarriages have an increased incidence of thrombophilia. Genetic thrombophilias may be one of the major etiological factors for recurrent abortion and fetal demise.

Key words: Genetic thrombophilias; Recurrent fetal miscarriage, Factor V Leiden.

Introduction

Recurrent fetal miscarriage is a major problem for obstetricians. Three or more losses affect 1%-2% women while two or more losses affect up to 5% during reproductive age [1, 2]. Although there are some well-known etiologic causes for this entity, 30%-40% of recurrent fetal miscarriages remains unexplained. Those patients who are free of hormonal, immunologic, microbial, anatomic or obstetric causes for recurrent fetal miscarriage need to be explained etiologically. Data accumulated in recent years suggest a possible association between thrombophilia and fetal miscarriage [3-6]. Morphological findings that are reported by pathological evaluations of aborted fetal placentas point to the thrombotic and antithrombotic cascade as the etiologic cause [7-10]. Minor disturbances in the antithrombotic cascade may cause problems in the microvascular circulation of the placenta. Inherited or acquired thrombophilias cause a tendency toward thrombosis by disturbing antithrombotic pathways. *These genomic* changes that predispose patients to thrombosis may be important risk factors for obstetrical complications that are related to inadequate fetal-maternal circulation. *Major entities of these genomic changes*, inherited or acquired, are known as Factor V (FV) Leiden mutation, Factor (F) II mutation, and deficiencies of protein C and S, and antithrombin III (ATIII) [3, 4]. It seems that the risk of recurrent fetal loss is increased by a deficiency of one of these proteins and those with combined defects [9]. FV Leiden mutation is known to be the most frequent genetic thrombophilia that

predisposes to thrombosis [3-6]. The carrier frequency for this mutation is reported to be between 3% and 12% in different populations [11].

In this study, we compared the rate of FV Leiden and F II mutations, proteins C and S, and ATIII deficiencies in caucasian women with the rate of those in a control group of parous women with successful pregnancies.

Materials and methods

A case-control study was carried out at Hacettepe University Hospital between 1998 and 2000. Consecutive patients with recurrent unexplained fetal loss attending to our obstetrics clinic and controls of aged-matched parous women attending to our gynaecology clinic were recruited prospectively into the study. The inclusion criteria were two or more spontaneous fetal miscarriages below 24 weeks or at least one intrauterine death beyond 24 weeks, and not more than one living child. Women who had a known thrombotic disorder, who were receiving any additional antithrombotic therapy for other causes, who had any other etiological disorders for recurrent fetal loss, and who were documented for first trimester preclinical and blighted ovum miscarriage were excluded from the study group. The study was approved by the institutional review board.

All patients were tested in order to define a recurrent fetal miscarriage by hormone profile, hysterosalpingogram, antibody screening for toxoplasmosis, cytomegalovirus, rubella, chlamydia and listeriosis, karyotype of the patient and her husband, and a screening for thyroid disease together with diabetes mellitus if not tested in the previous six months. Patients who were found to be positive for any of the factors above were excluded and the remaining women who had no known etiological factor for recurrent fetal loss were screened for familial thrombophilia. Familial thrombophilia screening was consisted of FV Leiden mutation analysis, F II mutation analysis, protein C

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activity and ATIII activity. The control group was screened to confirm the prevalence of a thrombophilic disorder in normal Turkish population, which was reported by our group previously [11].

Clinical data were collected at entry for the study and controls were enrolled the same day as their matched patients. Blood samples from the study and control groups were drawn on the day of enrollment. Plasma aliquots were frozen at -20°C . Genomic DNA was extracted from blood leucocytes by the standard techniques and was kept at -70°C .

Evaluation for thrombophilia

Antithrombin III and functional protein C activities in plasma were determined by chromogenic assays using Stachrom kits (Stago Diagnostica, France). Free protein S levels in plasma were measured with a specific enzyme linked immunosorbent assay using the Asserachrom free Protein S kit (Stago Diagnostica, France). FV G1691A (Factor V Leiden) was detected by polymerase chain reaction (PCR) and *Mnl I* digestion [12] and Factor II (FII) G20210A by PCR and *Hind III* digestion [13]. All digested fragments were electrophoresed on 10% polyacrylamide gels and visualized by ethidium bromide staining [14].

Statistical analysis

Results of hematological parameters for the two groups were compared with the Mann-Whitney U-test. Statistical analysis was performed with the Statistical Package for the Social Sciences for Windows, version 10.0 (SPSS, Chicago). The statistical significance of the ratios were evaluated by the chi-square test or Fisher's exact test.

Results

A total of 101 patients with 102 controls were included in the study. Patient characteristics of the study and control groups are shown Table 1. The mean age of the women with fetal loss was 29.7 ± 4.5 (range 19-44 years) and of controls 29.2 ± 4.3 years (range 19-44 years).

The prevalence of thrombophilic mutations and acquired thrombophilia types in women with recurrent fetal loss compared with women without recurrent fetal loss are shown in Table 2. Each of the thrombophilic abnormalities were found to be statistically frequent in the study group. Factor II mutation was observed only in the study group. FV Leiden mutation was found in 28.4% (29/101) of the study group compared to 6.9% (7/102) in the control group ($p < 0.001$). All patients, except one,

Table 1. — Patient characteristics.

	RFL Group*	Controls	p
Age (mean)	29.74 ± 4.57	29.24 ± 4.30	0.422
Gravida (mean)	3.49 ± 1.51	3.49 ± 1.28	0.294
Parity	0.61 ± 0.88	2.57 ± 0.91	0.000
Smoking	11 (10.8%)	10 (9.8%)	0.818
Fetal loss			
2	43 (42.2%)		
3	40 (39.2%)		
4+	19 (18.6%)		
1 st trimester losses	33 (32.4%)		
2 nd trimester losses	40 (39.2%)		
Stillbirth	29 (28.4%)		

*RFL: recurrent fetal loss.

Table 2. — Thrombophilic abnormalities in groups.

	RFL Group* (n = 102)	Controls (n = 102)	p
FV Leiden mutation	29 (28.4%)	7 (6.9%)	$p < 0.001$
F II G20210A mutation	2 (2%)	1 (1%)	$p < 0.001$
Pro S deficiency	23 (22.5%)	2 (2%)	$p < 0.001$
Pro C deficiency			
Antithrombin III	16 (15.7%)	1 (1%)	$p < 0.001$
def	3 (2.9%)		$p < 0.001$
Total	49 (49%)	11 (10.9)	$p < 0.001$

*RFL: recurrent fetal loss.

were heterozygote for Factor V in the study. The carrier frequency for the control group was found to be 6.9% and it was concordant with our previous study which determined the prevalence of FV Leiden mutation in a Turkish population as 7.1% [11]. Overall 49 of the women with recurrent loss (48%) had at least one of the two inherited thrombophilic disorders, as compared with 11 of 101 women with normal pregnancies (10.9%). In the study group 35 (12.7%) patients had one abnormality and 17 patients had multiple abnormalities in which 13 (12.7%) had two and four (3.9%) had three (Table 3). In the control group, multiple anomalies were not encountered.

In the study group, 43 (42.2%) women experienced two fetal losses, 40 (39.2%) women experienced three fetal losses, and 19 (18.6%) women experienced four or more fetal losses (Table 1). Overall thrombophilia rates did not differ with the number of fetal losses. However, we further analyzed data for each thrombophilia type. Only FV Leiden mutation rate had risen strongly with increased number of fetal losses (Table 4). With increased number of fetal losses, prevalence of protein S, protein C, and AT III rates did not differ statistically (data not shown). The number of cases with F II G20210A mutation rate was small which precluded statistical analysis.

Table 3. — Multiple thrombophilic abnormalities in the study group.

	No.
Pro S + Pro C	8 (7.8)
Pro C + FV Leiden	3 (2.9)
Pro S + FV Leiden	2 (1.9)
Pro C + Pro S + Antithrombin III	2 (1.9)
Pro S + FV Leiden + F II G20210A	2 (1.9)
Pro S + Pro C + FV Leiden	1 (0.9)

Table 4. — Thrombophilia frequency and fetal loss ($p < 0.001$)

	No. of fetal losses (%)			p
	2	3	+4	
FV Leiden mutation	8 (18.6)	10 (25.0)	11 (57.9)	0.006
Pro S deficiency	13 (30.2)	9 (22.5)	1 (5.3)	0.095
Pro C deficiency	10 (23.3)	4 (10.0)	2 (10.5)	0.2
Antithrombin III deficiency	1 (2.3)	2 (5.0)		0.6

Conclusion

In the last two decades, attention has been focused on thrombophilia for evaluation of the etiology of obstetric complications. Thrombophilias - acquired or inherited - have been found to be related to many of the problems complicating pregnancy. These pregnancy complications

include first and second trimester miscarriages, intrauterine growth restriction, intrauterine fetal death, placental abruption and preeclampsia [3]. The mechanisms responsible for the association of inherited thrombophilia with obstetric complications have not been clarified. However, it seems that thrombosis in the fetomaternal unit may cause recurrent fetal loss. Pregnancy itself is a thrombotic state and it may trigger thrombosis in patients who have genetic thrombophilia.

Factor V Leiden mutation is known to be the most frequent genetic thrombophilia that predisposes to thrombosis [3-6]. The carrier frequency for this mutation is reported to be between 3% and 12% in different populations [15-17]. This disorder is characterized by a lower sensitivity of activated Factor V to the anticoagulant action of activated protein C (APC). In most cases, the defect results from a single point mutation in the Factor V gene (G→A at nucleotide 1691) [18]. Glutamine replaces arginine at position 506, one of the two APC cleavage sites in activated Factor V. Family studies have demonstrated that the defect is an autosomal dominant trait and is associated with a 5- to 10-fold increased risk of venous thromboembolism in heterozygotes and this risk was reported to be 50-fold in homozygous patients [18].

Factor II mutation is a newly described mutation at nucleotide 20210 in the prothrombin gene and this mutation causes higher plasma concentrations of prothrombin and an increased risk of venous thromboembolism [13]. Protein C and S deficiencies are also thrombophilic disorders that hamper the antithrombotic pathway in vivo. Interestingly these thrombotic mutations and alterations are known to have a higher incidence in southern Europe and the Mediterranean [19].

In the studies of Brenner *et al.* thrombophilia was found to be related to major pregnancy complications, especially recurrent miscarriage [3, 5, 6, 14, 20-24]. They found thrombophilic polymorphism to be common in women with fetal loss without apparent causes and associated with late pregnancy wastage [24]. It was stated that APC resistance with or without FV Leiden mutation is the most common thrombophilic defect and combined thrombophilia - one or more thrombophilic defects - is a frequent finding in women with pregnancy loss [14]. In this recent study Brenner *et al.* concluded that combined thrombophilic defects were found in two-thirds of the patients with unexplained pregnancy loss and 21% of women with pregnancy wastage had at least two thrombophilic defects [14]. In a review by the same authors the relationships of each thrombophilic defect with different obstetric complications were pointed out [23]. New thrombophilias and screening methods are still being reported by the same center [22]. Many different authors have begun to report similar findings and conclusions as Brenner *et al.* Nearly all studies in the literature report high thrombophilic defects in women with recurrent miscarriage; the only point on which they differ from each other is the percentage of thrombophilic disorders and gestational weeks when pregnancy loss occurred. The NOHA study concluded that thrombophilic disorders are

common in late pregnancy wastages [9]. There are several studies supporting this finding [18, 25, 26] while some other authors concluded that thrombophilic disorders are associated with early pregnancy loss - recurrent abortion [21, 27-30]. A few authors like Carp *et al.* have found that thrombophilic causes are unrelated to recurrent abortion and other obstetric complications [31].

In the last five years a valuable number of reviews and meta-analyses regarding thrombophilia and recurrent pregnancy loss have been published [3-6, 20, 32-35]. In a very recent meta-analysis by Rey *et al.* [5] it was concluded that early and late fetal losses were clearly related to thrombophilic defects, and assessment of women with early recurrent pregnancy loss should include screening for FV Leiden, activated protein C resistance, prothrombin G20210 A mutation (PTm) and protein S deficiency whereas women with late fetal losses should be tested for FV Leiden, PTm, and protein S deficiency. Rey *et al.* reported that the association between FV Leiden and late recurrent fetal loss is stronger than for early pregnancy loss. The association between FV Leiden and recurrent fetal loss is stronger if other potential causes of fetal loss are excluded as is in the current study [5].

Our results show a clear association between thrombophilia and recurrent fetal miscarriage. Regarding FV Leiden as one of the leading thrombophilias, it is clear that this entity affects the pregnancies of women who are positive for this genomic mutation. FV Leiden mutation is known to be the most common thrombophilia in Caucasians and a founder effect has recently been suggested to explain its particular high prevalence in this population [12, 36]. The prevalence of 7% in the control group is representative of the population of Turkey - same as the was found in a previous study from our university [11]. Regarding these figures the prevalence of thrombophilias found in the study group shows that disturbance of the antithrombotic pathway may result in unsuccessful pregnancies, and women who have unexplained fetal losses should be evaluated for possible thrombotic abnormalities. This result is in agreement with those of recent studies, which compared findings from women with recurrent fetal miscarriages with women with successful pregnancies [21, 27-30, 37].

In the current study, we further analyzed data according to fetal loss time and no differences between fetal loss time (early abortion, late abortion or still birth) and the rate of FII mutation, protein S, protein C, antithrombin III deficiencies and overall thrombophilia were found. F II G20210A and antithrombin III rates were too low in this study to reach any conclusions. A statistically significant difference in rate of FV Leiden mutations between women with only early fetal miscarriages versus those with late events was observed ($p < 0.001$). Factor V Leiden can be tested easily using PCR tests and together with other inherited or acquired thrombophilias (Factor II mutation, deficiency of protein S and C, and Antithrombin III) these tests will greatly improve the management of unexplained fetal losses. Future studies must evaluate the treatment of these thrombophilic states for successful

pregnancy outcomes as a studies have demonstrated [3, 4, 6, 28, 32, 38-40]. Heparin and derivatives like low molecular weight heparin seem to be good treatment alternatives for this topic [41, 42]. Once diagnosed it is easier to help these patients because antithrombotic therapies like low molecular weight heparin prophylaxis during pregnancy will be successful.

These results should be viewed cautiously, because the current and past case-control studies deal with the retrospective nature of abortion data which limits conclusions. Notably, the classifying criteria for patients who have both early and late miscarriages were obscure in all studies. Moreover, the fetal thrombotic status can be as important as the maternal status and should be evaluated at the same time. It is assumed that fetal demise in carriers of thrombophilia is most likely explained by thrombosis in placental vessels [43]. The thrombotic tendency of these patients can appear as thrombotic areas in the fetomaternal unit causing placental insufficiency at different stages of pregnancy and can give a large clinical sequela. However, placental thrombosis seems to be caused by both maternal and fetal thromboses as other data have not been reported [3]. Studies addressing the benefit-to-risk ratio of routine thromboprophylactic applications in recurrent unexplained fetal miscarriages could investigate this issue. Different fetal thrombophilia rates in time and between patients and study groups can make differences insignificant by chance. Conceivably, only a few patients with FV Leiden may experience fetal loss. In addition we assume that the rate of thrombophilia-related abortion among unexplained early trimester abortions must be low naturally and could not be calculated with these confounding factors. We believe that this issue requires further investigation with prospective randomized studies.

In conclusion, our report supports the view that women with recurrent miscarriages or stillbirths have a statistically increased incidence of genetic thrombophilia. Thrombophilias such as Factor V Leiden, Factor II mutation, protein C and S, and antithrombin deficiencies must be part of routine screening tests in patients with unexplained recurrent fetal loss.

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