

PRACE ORYGINALNE  
*położnictwo*

# Inherited thrombophilia with recurrent pregnancy loss in Turkish women – a real phenomenon?

Dziedziczna trombofilia a nawracające utraty ciąży u tureckich kobiet – prawdziwy fenomen?

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## Abstract

**Objectives:** To determine the prevalence and the role of hereditary thrombophilia caused by Factor V Leiden (G1691A), prothrombin G20210A or methylenetetrahydrofolate reductase (MTHFR) C677T gene mutations in recurrent pregnancy loss.

**Material and methods:** One hundred and nine patients, who were admitted to the 3rd Obstetrics and Gynecology Outpatient Clinic in Goztepe Training and Research Hospital between 2006 and 2008, were included into the study. The study group consisted of fifty-seven patients with a history of 3 miscarriages before 20 weeks of gestation and the control group consisted of forty-seven patients with at least one live birth without any history of miscarriage or pregnancy complications. The maternal blood was evaluated for Factor V Leiden (G1691A), prothrombin G20210A and MTHFR C677T gene mutations.

**Results:** No statistically significant difference was found between the study and the control groups in terms of the prevalence of Factor V Leiden (G1691A), prothrombin G20210A and MTHFR C677T gene mutations ( $p=0.534/p=0.452/p=0.656$ , respectively and  $p<0.05$ ). Furthermore, the prevalence of multiple gene mutations was not statistically different between the groups ( $p=0.375$  and  $p<0.05$ ) either.

**Conclusion:** Routine screening for Factor V Leiden (G1691A), prothrombin G20210A and MTHFR C677T gene mutations in patients with a history of recurrent pregnancy loss is not recommended in Turkish women.

Key words: **factor V Leiden / MTHFR / prothrombin / thrombophilia /**

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## Streszczenie

**Cel pracy:** Celem pracy była ocena częstości występowania i roli dziedzicznej trombofilii związanej z mutacją genu czynnika V Leiden (G1691A), protrombiny G20210A lub reduktazy metylenotetrahydrofolianowej (MTHFR) C677T u pacjentek z nawracającymi poronieniami.

**Materiał i metody:** Do badania włączono 109 pacjentek, które przyjęto do Poradni Położniczo-Ginekologicznej w Goztepe Training and Research Hospital w latach od 2006 do 2008. Grupa badana składała się z 57 pacjentek z 3 poronieniami w wywiadzie przed 20 tygodniem ciąży, grupę kontrolną stanowiło 47 pacjentek z przynajmniej jednym żywym urodzeniem i bez poronień czy innych komplikacji w wywiadzie. Zbadano krew matek pod kątem mutacji genu czynnika V Leiden (G1691A), protrombiny G20210A i MTHFR C677T.

**Wyniki:** Nie znaleziono istotnej różnicy pomiędzy grupą badaną a kontrolną w odniesieniu do częstości występowania mutacji genu czynnika V Leiden (G1691A), protrombiny G20210A i MTHFR C677T ( $p=0,534/p=0,452/p=0,656$  przy  $p<0,05$  istotnym statystycznie). Co więcej, częstość występowania wielokrotnych mutacji również nie różniła się pomiędzy grupami ( $p=0,375$  przy  $p<0,05$ ).

**Wnioski:** Nie powinno się rekomendować rutynowego skринingu mutacji genu czynnika V Leiden (G1691A), protrombiny G20210A i MTHFR C677T w populacji tureckich kobiet z nawracającymi poronieniami w wywiadzie.

Słowa kluczowe: **czynnik V Leiden / MTHFR / protrombina / trombofilia /**

## Introduction

About 50-70% of all conceptions end in miscarriage within the first trimester [1]. Up to 40% of the patients suffering pregnancy loss are not aware of their pregnancies and can be identified only with the beta hCG measurement [2]. Recurrent pregnancy loss is defined as 3 or more miscarriages within the first 20 weeks of gestation. Primary recurrent pregnancy loss refers to cases that never had a live birth and secondary recurrent pregnancy loss refers to those who did.

The frequency of recurrent pregnancy loss in fertile population is 1-2% when those with 3 or more pregnancy losses are taken into consideration and 5% when the cases with 2 or more pregnancy losses are taken into consideration [3]. Using current diagnostic methods, the underlying cause can be identified only in half of the cases with recurrent pregnancy loss [4].

Thrombophilia is defined as congenital or acquired conditions that overbalance the coagulation system in the direction of clot formation, thereby increasing the risk of thrombosis [5]. Hereditary thrombophilia is caused by gene mutations that are passed from parents to their offspring. Gene mutations that are involved in many factors which take part in the coagulation system and other factors that maintain the normal fluidity of the blood in the vessel may cause thrombophilia by increasing tendency to thrombosis.

## Objectives

In our study we evaluated the relationship between recurrent pregnancy loss and Factor V G1691A (Leiden), prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T gene mutations that are associated with maternal thrombophilia.

## Materials and Methods

One hundred and nine patients, admitted to the 3<sup>rd</sup> Obstetrics and Gynecology Outpatient Clinic in Goztepe Training and Research Hospital between 2006 and 2008, were included into the study. The study group consisted of fifty-seven patients with a history of 3 consecutive miscarriages before 20 weeks

of gestation. The control group consisted of forty-seven women with at least one live birth and without a history of miscarriage or pregnancy complications.

Patient age, age of the spouse, number of abortions, abortion week, consanguineous marriage, systemic disorders (diabetes mellitus, thyroid disease, chronic liver, kidney or heart disease), previous gynecological surgeries and history of venous thrombosis were recorded.

Glucose tolerance test was performed. All hormone tests including follicle stimulating, luteinizing, thyroid stimulating, prolactin and progesterone hormones were measured at the twenty first day. Pelvic physical exam was performed in all patients. Also pelvic structures were evaluated by transvaginal sonography for any other genital disorders. The karyotype analysis was performed in all patients. IgG and IgM anticardiolipin antibodies and lupus anticoagulant were measured in order to rule out the antiphospholipid antibody syndrome. We were not able to measure IgG antibodies to Beta-2 Glycoprotein 1 because of technical difficulties. Factor V Leiden (G1691A) mutation, prothrombin G20210A mutation and MTHFR C677T mutation were investigated in peripheral blood obtained from the patients. Follicular development as well as ultrasound evidence of spontaneous ovulation were confirmed in all patients.

Anticardiolipin IgG antibody returned positive in 2 patients who were excluded from the study. One patient was excluded due to diabetes mellitus, one patient due to hypothyroidism and one patient due to consanguineous marriage. Five cases altogether were excluded from the study. There were no patients with an impaired glucose tolerance in the study group. None of the cases in the study group has lupus anticoagulant and all of the patients had ovulatory cycles. The study group consisted solely of women with unexplained recurrent pregnancy loss.

## Molecular Diagnosis

From the patients in the study group, 2ml of blood was drawn into tubes (Vacuette, Austria) coated with K3 Ethylene Diamine Tetraacetic Acid (EDTA).

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Samples were processed in accordance with the following procedure using Genomic DNA from Blood (Macherey-nagel, Germany) kit for the isolation of genomic DNA:

- I. Red blood cell lysis.
- II. Setup of the DNA amplification.
- III. DNA binding.
- IV. Two-step procedure to wash silica-based membrane.
- V. Drying silica membrane.
- VI. Eluting purified DNA.

Isolated DNA was stored at -20°C. Mastermix was prepared using amplification mix, taq dilution buffer (ViennaLab GmbH, Austria) and taq DNA polymerase enzyme (Fermentas Canada Inc., Canada) in 0.2ml PCR tube (Greiner Bio-One, Germany). Mastermix was added into the PCR tubes and sample DNA was amplified in a thermal cycler (Applied Biosystems, USA). Finally, assay strips were placed in profiBlot device (Tecan, Switzerland) for hybridization. The developed lines on the strips were evaluated.

### Statistical Analysis

NCSS 2007&PASS 2008 Statistical Software (Utah, USA) package program was used for statistical analyses of the study results. Along with descriptive statistics (mean, standard deviation, frequency), Student's t test was used to compare quantitative parameters that show normal distribution. Chi-square test and Fisher's exact test were used for comparison of qualitative parameters. Statistical test results were evaluated by using an overall significance level of  $p < 0.05$  at 95% confidence interval.

### Results

All patients were below 35 years of age (mean age:  $26.89 \pm 7.32$  years). There was no statistically significant difference between the study and the control groups with respect to mean age ( $p = 0.665$  and  $p < 0.05$ ). Mean age was  $30.12 \pm 7.32$  years in the study group and  $27.80 \pm 6.36$  years in the control group.

Of the cases in the study group, 87.7% were found to be negative for Factor V Leiden (G1691A) gene mutation, whereas 10.5% had heterozygous and 1.8% had homozygous Factor V Leiden (G1691A) gene mutation. 59.6% was negative for MTHFR C677T gene mutation, and 36.9% had heterozygous and 3.5% had homozygous MTHFR C677T gene mutation. All cases in the study group were negative for prothrombin G20210A gene mutation. One case had both, homozygous Factor V Leiden and heterozygous MTHFR C677T gene mutations. Three cases had both heterozygous Factor V Leiden (G1691A) and heterozygous MTHFR C677T gene mutations (Table 1).

Of the cases in the control group, 91.5% were negative for Factor V Leiden (G1691A) gene mutation, whereas 8.5% had heterozygous gene mutation. 55.3% were negative for MTHFR C677T gene mutation, whereas 42.6% had heterozygous gene mutation and 2.1% had homozygous gene mutation. 97.9% were negative for prothrombin G20210A gene mutation whereas 2.1% had heterozygous gene mutation. One case in the control group had both heterozygous Factor V Leiden (G1691A) gene mutation and heterozygous MTHFR C677T gene mutations (Table II).

**Table I.** Distribution of the gene mutations in the study group.

	Factor V Leiden G1691A	MTHFR C677T	Prothrombin G20210A
	(n=57)	(n=57)	(n=57)
Negative	50 (87,7%)	34 (59,6%)	57 (100%)
Positive Heterozygote	6 (10,5%)	21 (36,9%)	-
Homozygote	1 (1,8%)	2 (3,5%)	-
TOTAL	57	57	57

**Table II.** Distribution of the gene mutations in the control group.

	Factor V Leiden G1691A	MTHFR C677T	Prothrombin G20210A
	(n=47)	(n=47)	(n=47)
Negative	43 (91,5%)	26 (55,3%)	46 (97,9%)
Positive Heterozygote	4 (8,5%)	20 (42,6%)	1 (2,1%)
Homozygote	-	1 (2,1%)	-
TOTAL	47	47	47

The prevalence of Factor V Leiden G1691A gene mutation was not significantly different between the groups ( $p = 0.534$  and  $p < 0.05$ ). The prevalence of Factor V Leiden gene mutation was 12.3% in the study group and 8.5% in the control group. Factor V Leiden gene mutation was associated with 1.505-fold higher risk in the study group. However, the risk was not statistically significant considering 95% CI being between 0.412-5.491 which also covers 1 (Table III).

**Table III.** Evaluation of Factor V Leiden gene mutations in the two groups.

Factor V Leiden G1691A	Study	Control	p	ODDS	95% CI
	(n=57)	(n=47)			
Positive	7 (12,3%)	4 (8,5%)	0,534	1,505	0,412-5,491
Negative	50 (87,7%)	43 (91,5%)			

(Chi-Square test was used)

The prevalence of prothrombin G20210A gene mutations was not statistically different between the study and control groups ( $p = 0.452$  and  $p < 0.05$ ). The risk related with this parameter could not be calculated since none of the cases in the study group had prothrombin gene mutation (Table IV).

**Table IV.** Evaluation of Prothrombin G20210A gene mutations in the two groups.

Prothrombin G20210A	Study	Control	p	ODDS	95% CI
	(n=57)	(n=47)			
Positive	0 (0,0%)	1 (2,1%)	0,452	-	-
Negative	57(100,0%)	46 (97,9%)			

(Fisher's Exact test was used)

The prevalence of MTHFR C677T gene mutation was not significantly different between the groups ( $p=0.656$  and  $p<0.05$ ) and was 40.4% in the study group and 44.7% in the control group. MTHFR C677T gene mutation was associated with 0.838-fold higher risk in the study group compared to the control group. However, the risk was not statistically significant considering 95% CI being between 0.383-1.830 which also covers 1 (Table V).

**Table V.** Evaluation of MTHFR C677T gene mutations in the two groups.

MTHFR C677T	Study	Control	p	ODDS	95% CI
	(n=57)	(n=47)			
Positive	23 (40,4%)	21 (44,7%)	0,656	0,838	0,383-1,830
Negative	34 (59,6%)	26 (55,3%)			

(Chi-Square test was used)

The prevalence of multiple gene mutations was not statistically different between the study and the control groups ( $p=0.375$  and  $p<0.05$ ) and was 7.0% in the study group and 2.1% in the control group. Multiple gene mutation was associated with 3,472-fold higher risk. However, the risk was not statistically significant considering 95% CI being between 0.375-32,17 which covers 1 (Table VI).

**Table VI.** Evaluation of multiple gene mutations in the two groups.

Multiple gene mutation	Study	Control	p	ODDS	95% CI
	n (%)	n (%)			
Positive	4 (7,0%)	1 (2,1%)	0,375	3,472	0,375-32,17
Negative	53 (93,0%)	46 (97,9%)			

(Fisher's Exact test was used)

## Discussion

Early spontaneous abortion is a serious epidemiological problem, which is one of the most common causes of referring married couples to genetic counseling [6]. The risk of miscarriage decreases as the pregnancy progresses. It is 11.5% when the gestational sac is observed but not the embryo; 5% when the embryo is measuring 5 mm and fetal heart beat is detectable and below 3% at 11 weeks of gestation [7]. The risk of spontaneous pregnancy loss increases with age, independent from the obstetric history of a patient. The patients in the study and control groups were below 35 years of age and no significant difference was found between the two groups in terms of age ( $p=0.665$  and  $p<0.05$ ). Among all factors studied until today, genetic, anatomic and immunological factors are regarded as the definitive causes of recurrent pregnancy loss. Alloimmunopathology, hereditary thrombophilia, endocrinopathies, infections and environmental factors are still under investigation. Even after a detailed investigation, definitive cause of recurrent pregnancy loss cannot be explained in about more than half of the cases.

Thrombophilia refers to a group of congenital or acquired coagulation disorders that is characterized by an increased tendency to thrombosis. Most genetic mutations predispose to thrombosis. Factor V Leiden G1691A, prothrombin G20210A and MTHFR C677T gene mutations are the most common hereditary abnormalities. Fetal loss related with hereditary thrombophilia could be caused by increased thrombosis in the placenta vessels, infarctions and utero-placental insufficiency. Fetal thrombophilia can also play a role in the etiology of fetal loss by causing thrombosis in the fetal part of the placenta. Apart from being involved in thrombosis, hereditary thrombophilia can also lead to fetal loss by interfering with implantation and trophoblastic differentiation [8].

There are studies that found no relationship between recurrent pregnancy loss and Factor V Leiden G1691A, prothrombin G20210A and MTHFR C667T gene mutations. However, there are also some studies that suggest a significant relation between thrombophilia and recurrent pregnancy loss.

In our study, the prevalence of Factor V Leiden G1691A gene mutation was not significantly different between the groups ( $p=0.534$  and  $p<0.05$ ) and was 12.3% in the study group and 8.5% in the control group (OR: 1.505 [0.412-5.491]). Balasch et al. compared 55 patients with more than 2 miscarriages with 50 patients with no past history of miscarriage. They reported no statistically significant difference between the group in terms of Factor V Leiden gene mutation [9]. Raziell et al. studied 36 patients with more than 2 miscarriages compared to 40 patients as the control group. They suggested no statistically significant difference between the two groups with respect to Factor V Leiden gene mutation (OR: 3.42 [0.14-86.71]) [10]. Finan et al. found Factor V Leiden G1691A gene mutation in 45 (40.91%) out of 110 patients who had a history of recurrent pregnancy loss. The prevalence of heterozygous Factor V Leiden gene mutation was 16.42% in the control group and they reported a statistically significant difference between the two groups [11]. Coutu et al. studied 88 cases with 3 or more miscarriages compared to 88 control cases and the prevalence of homozygous Factor V Leiden mutation was 3/88 (3.4%) in the study and 0/88 (0%) in the control groups (OR: 7.2 [0.3-142]). They suggested a statistically significant difference between the groups for this mutation [12].



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The prevalence of prothrombin G20210A gene mutation was not significantly different between the groups in our study ( $p=0.452$  and  $p<0.05$ ). The risk related with this parameter could not be calculated since none of the cases in the study group had prothrombin gene mutation. Pickering et al. evaluated three or more early ( $< \text{or} = 12$  weeks gestation;  $n=91$ ), late ( $> 12$  weeks gestation:  $n=2$ ), or mixed ( $n=29$ ) consecutive pregnancy losses. They compared them to 66 patients without a history of miscarriage. The prevalence of heterozygous prothrombin gene mutation was found to be similar in both groups (OR: 0.93 [0.16-5.26]) [13]. Altintas A et al. investigated the prevalence of Factor V Leiden (FV-Leiden) and prothrombin gene mutations (FII G20210A) in subjects with a history of early recurrent pregnancy loss. The authors found that 2 out of 114 (1.7%) patients in the study group (primary aborters) and 3 out of 185 (1.6%) patients in the control group were carriers of the FII G20210A mutation (1.7 vs. 1.6%,  $p=0.931$ ). They concluded that the prevalence of prothrombin G20210A mutation was not significantly different between patients with recurrent pregnancy loss and those in the control group [14]. On the other hand, Kupferminc et al. evaluated 27 patients with more than 2 miscarriages compared to 156 control patients and found higher prevalence of heterozygous prothrombin G20210A gene mutation in the study group (OR: 5.25 [1.31-21]) [15]. In another study, 102 patients with two or more consecutive abortions and 128 women without miscarriage were evaluated for prothrombin G20210A mutation. Heterozygous prothrombin G20210A gene mutation occurred more often in patients with recurrent spontaneous abortion. This effect was significant in the subgroup with abortions happening exclusively in the first trimester (6.7% vs. 0.8%,  $P = 0.027$ , OR 8.5) [16].

In our study, the prevalence of MTHFR C667T gene mutation was not significantly different between the two groups ( $p=0.656$  and  $p<0.05$ ). The prevalence of MTHFR C667T gene mutation was 40.4% in the study group and 44.7% in the control group (OR: 0.838 [0.383-1.830]). A study in Japanese women evaluated 85 patients with 2 or more miscarriages compared to 76 women without a history of miscarriage. No statistically significant difference was found between the two groups with respect to the prevalence of homozygous MTHFR C667T gene mutation [17]. Ren et al. reviewed 26 studies comprising a total of 2120 cases with recurrent pregnancy loss and 2949 control cases. They concluded that MTHFR C677T gene mutation was not a genetic risk factor for recurrent pregnancy loss [18]. One Indian study evaluated 24 cases with 2 or more miscarriages compared to 24 control cases. The prevalence of homozygous MTHFR C667T gene mutation was found to be 5/24 (13.4%) in the study group and 1/24 (4.2%) in the control group. This difference between the two groups was statistically significant ( $p<0.001$ ) [19]. In a study by Goodman et al., buccal swabs were obtained for DNA analysis from a total of 550 women with a history of recurrent pregnancy loss. They found that the prevalence of homozygous MTHFR C667T gene mutation was significantly higher in the study group as compared to 1956 control cases ( $p<0.0001$ ) [20]. In our study, the prevalence of multiple gene mutations was not significantly different between the groups ( $p=0.375$  and  $p<0.05$ ). The prevalence of multiple gene mutations was 7.0% in the study group and 2.1% in the control group (OR: 3.472 [0.375-32.17]). Sotiriadis et al. suggested that no difference existed in the distribution of Factor V Leiden ( $p=1.000$  and  $p<0.05$ ), FII G20210A ( $p=0.652$

and  $p<0.05$ ) and MTHFR C677T ( $p=0.869$  and  $p<0.05$ ) between patients with two and three or more miscarriages. Combinations of the thrombophilic mutations also did not significantly increase the risk of miscarriage [21]. In a study in 2002, Sarig et al. found the prevalence of multiple thrombophilic gene mutation to be 21% in patients with recurrent pregnancy loss and 5.5% in the control group. They reported a statistically significant difference between the two groups ( $p<0.05$ ) [22]. On the other hand, in a meta-analysis of 31 studies carried out between 1975 and 2002, Rey et al. recommended an investigation of Factor V Leiden and prothrombin gene mutations in patients suffering from recurrent early pregnancy loss [23]. In a systematic review of 25 studies carried out between 1991 and 2002, Robertson et al. evaluated the relationship between thrombophilia and early pregnancy loss. They found a statistically significant difference between recurrent pregnancy loss and homozygous Factor V Leiden gene mutation (OR: 2.71 [1.32-5.58]), heterozygous Factor V Leiden gene mutation (OR: 1.68 [1.09-2.58]) and heterozygous prothrombin gene mutation (OR: 2.49 [1.24-5.00]). They suggested that homozygous Factor V Leiden mutation and hyperhomocysteinemia have been associated with a higher risk of early pregnancy loss compared to other thrombophilia [24]. In another study which is similar to ours, however, it was suggested that neither Factor V Leiden nor prothrombin gene G20210A are associated with recurrent miscarriage before 10 weeks of gestation. Therefore, its screening is not recommended as an initial approach in Portuguese women with embryonic recurrent miscarriage and negative personal thromboembolic history [25].

## Conclusions

The ACOG Practice Bulletin in “*Inherited Thrombophilias in Pregnancy*” states that inherited thrombophilia testing in women who have experienced recurrent fetal loss is not recommended because it is unclear whether anticoagulation (blood thinning medication) reduces future losses [26].

Also, in the view of our results, routine screening for thrombophilia is not recommended considering the low incidence of hereditary thrombophilia among Turkish women. Randomized and controlled studies on larger patient population are needed in order to unravel the underlying etiology of recurrent pregnancy loss, including particularly hereditary thrombophilia and other genetic factors, and to propose standardized treatment protocols.

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## XI KONGRES

POLSKIEGO TOWARZYSTWA MENOPAUZY  
i ANDROPAUZY

8 – 9 lutego 2013 r.

Krynica-Zdrój, Hotel Prezydent\*\*\*\*\*

## I KOMUNIKAT

Szanowni Państwo, Koleżanki i Koledzy

*W dniach 8-9 lutego przyszłego roku odbędzie się w Krynicy Górskiej IX Kongres Polskiego Towarzystwa Menopauzy i Andropauzy. Kongres poświęcony będzie najnowszym trendom w diagnostyce i terapii problemów zdrowotnych okresu menopauzy i andropauzy.*

Tematy wiodące Zjazdu to:

- Standardy HTZ w 12 lat po WHI
- Najnowsze trendy w medycynie Anti-Aging – wskazówki dla praktyka
- Problemy uroginekologiczne okresu menopauzy
- Leczenie operacyjne pacjentki pomenopauzalnej – odrębności postępowania okołoperacyjnego
- Problemy psychosomatyczne po menopauzie (depresja, spadek libido, zaburzenia snu) – jak leczyć?
- Jak skutecznie zapobiegać zaburzeniom biocenozy pochwy po menopauzie?
- Antykoncepcja w okresie przejścia menopauzalnego – bezpieczeństwo, tolerancja, korzyści pozaantykonceptyjne
- Szkody jatrogenne hormonoterapii – jak zminimalizować ryzyko?
- Czy będziemy coraz rzadziej operować mięśniaki macicy?
- Suplementy diety po menopauzie – komu, co i w jakim celu?

*Ambicją organizatorów jest aby połączyć najwyższej próby walory naukowe i szkoleniowe Zjazdu z możliwością relaksu w pięknej Krynicy. Zaproszenie do udziału w Kongresie przyjęło liczne grono wybitnych wykładowców.*

Formularz zgłoszenia uczestnictwa i szczegóły dotyczące Kongresu znajdziecie Państwo na stronie

**www.konferencje.magan.pl**

*Do zobaczenia w lutym 2013 w Krynicy!*

Prof. zw. dr hab. Tomasz Paszkowski  
Prezes PTMA