WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 5, 1503-1514. Review Article ISSN 2277–7105

POLYMORPHISMS OF THE COMMON THROMBOPHILIC GENES AND THEIR CORRELATIONS WITH RECURRENT PREGNANCY LOSS

Tamara Reyadh Tahir*, Iman Yousif Abdulmalik

*MBCHB, Duhok Hospital of Obstetric and Gynecology, Kurdistan Region-Iraq.
Department of Obstetrics and Gynecology, College of Medicine, University of Duhok, Kurdistan Region-Iraq.

Article Received on
19 January. 2025,
Revised on 08 Feb. 2025,
Accepted on 27 Feb. 2025,
DOI: 10.20959/wjpr20255-35826

***Corresponding Author**
Tamara Reyadh Tahir
MBCHB, Duhok Hospital of Obstetric and Gynecology, Kurdistan Region-Iraq.

ABSTRACT

Two or more consecutive pregnancy failures, confirmed by ultrasound or histology, are referred to as recurrent pregnancy loss (RPL). Approximately 2% of pregnant women experience two consecutive miscarriages. The cause of RPL is unclear in up to 50% of individuals. RPL is one of the most complex and challenging situations in reproductive medicine. One recognized risk factor for RPL is polymorphisms of throm bophilic genes. This paper proposes an observational comparison of a group of 50 married women of reproductive age (20–40 years) with a history of two or more pregnancy losses during the first trimester, with a control group of 50 women of the same age who had at least one successful pregnancy without complications. Data were collected through questionnaires and blood tests for common clotting genes, including factor V Leiden, methylenetetrahydrofolate reductase, plasminogen activator inhibitor-1, beta-fibrinogen, and prothrombin. The results showed that the mean age of the cases (32.14 ± 6.474 years) was significantly higher than that of the controls (29.54 ± 5.588 years), and the mean weight of the cases was higher than that of the controls. 46% of the women had two recurrent pregnancy losses, and 44% had three recurrent pregnancy losses, while four or more pregnancy losses were less common. Genetically, heterozygous polymorphisms in the beta-fibrinogen gene were significantly higher in the cases, while homozygous beta-fibrinogen and heterozygous and homozygous methylenetetrahydrofolate reductase were significantly lower. The study also showed a weak

but statistically significant association between recurrent pregnancy loss and factor V Leiden only (r = 0.243, p = 0.015).

KEYWORDS: Polymorphisms, Recurrent Pregnancy Loss, Thrombophilic Genes.

1. INTRODUCTION

Recurrent pregnancy loss (RPL), which affects between 0.5 and 2% of couples, is characterized by two or more consecutive failed clinical pregnancies documented by B-HCG ultrasound and histopathology before the 20th week of pregnancy, after excluding molar and ectopic pregnancies. This disorder can be brought on by a variety of factors including chromosomal abnormalities, infections, anatomical, hormonal, and immunological abnormalities, and environmental factors.[1] In addition to all of these factors, the true causes of approximately half of RPLs are still being considered as idiopathic factors because they have not yet been adequately discovered.[2,3]

The RPL is one of the more complicated and difficult situations faced in reproductive medicine and it is upsetting for patients, their families, and medical professionals who are treating them. Patients may experience anxiety and ap The RPL is one of the more complicated and difficult situations faced in reproductive medicine and it is upsetting for patients, their families, and medical professionals who are treating them. Patients may experience anxiety and apprehension when the cause of RPL is unknown.[4]

There are two types of RPL: primary and secondary. Pregnancies lost in women who never gave birth to a living child are referred to as primary RPL. On the other hand, pregnancy loss in women who have previously given birth to a living child is known as secondary RPL.[1]

2. AIM OF THE STUDY

To analyzed the polymorphisms of five common genes in thrombophilia and their correlations with RPL in women of Duhok city.

3. Data Collection Tool

The data collected from the answers of patients to the checklist questionnaire during the interview with patients and reviewing their files by researcher, the questionnaire form include data about age, residence, educational levels, occupations, and the economical status. Gravidity, parity, and no. of RPL were assessed. The data was involved past medical history (PMH), past surgical history (PSH), family, social, and psychological history. Weight, height,

and BMI were asked about and determined. Types of supplemtations were evaluated.

To assess the relationship between these women's risk of RPL and the polymorphisms in MTHFR C677T, MTHFR A1298C, Prothrombin G20210A, FVL G1691A, and PAI-1 4G/5G, blood samples were obtained and submitted to a lab for genotyping analysis and DNA extraction.

Table (1): comparison of sociodemographic characteristics between cases and controls.

Sociodemographic characteristics		**Cases Mean ±SD**	**Controls Mean ±SD**	**p-value***
Age (years)		32.14±6.474	29.54±5.588	**0.034**
Study parameters		**Cases (n=50) No. (%)**	**Controls (n=50) No. (%)**	**p-value**
Residence	**Urban**	36(72.0)	47(94.0)	**0.003***
	Rural	14(28.0)	3(6.0)	
Education	**Read and write**	4(8.0)	1(2.0)	0.355**
	Primary	10(20.0)	9(18.0)	0.951*
	Secondary	21(42.0)	26(52.0)	0.550*
	Higher (ref.)	15(30.0)	14(28.0)	-----
Occupation	**Housewives (ref.)**	25(50.0)	11(22.0)	-----
	Government employee	19(38.0)	23(46.0)	**0.033***
	Non-government employee	6(12.0)	16(32.0)	**0.002***
Economical status	**Not enough**	9(18.0)	2(4.0)	**0.02****
	Enough (ref.)	30(60.0)	45(90.0)	-----
	More than enough	11(22.0)	3(6.0)	**0.008***
*Student t-test for independent two means; *Chi square test; **Fissure Exact test				

The study sample included 100 patients as cases and 100 healthy women as controls. The sociodemographic characteristics were demonstrated in table (3.1). The mean age among the cases (32.14±6.474 years) was significantly higher than that among the controls (29.54±5.588 years) at p=0.034. Concerning the residence, 72.0% of the cases and 94.0% of controls were lived in urban in comparison to 28.0% and 6.0% of cases and controls respectively were lived in rural; the difference was statistically significant at p=0.003. No statistically significant differences were found between the each levels of education. The study sample included 100 patients as cases and 100 healthy women as controls.

The sociodemographic characteristics were demonstrated in table (3.1). The mean age among the cases (32.14±6.474 years) was significantly higher than that among the controls (29.54±5.588 years) at p=0.034.

Concerning the residence, 72.0% of the cases and 94.0% of controls were lived in urban in comparison to 28.0% and 6.0% of cases and controls respectively were lived in rural; the difference was statistically significant at p=0.003.

No statistically significant differences were found between the each levels of education. Regarding the occupation, both government employee and non-government employee among the cases were significantly lower than those among controls at p=0.033 and p=0.002 respectively.

The economical status was not enough in 18.0% of cases and 4.0% of controls; the difference was statistically significant at p=0.02, furthermore the more than enough was found in 22.0% of cases and 6.0% of control with statistically significant difference at p=0.008.

Table (2): The comparison of anthropometric characteristics between cases and controls.

Anthropometric characteristics	Cases Mean ±SD	Controls Mean ±SD	P-value*
Weight (kg)	**76.78±13.453**	**71.98±10.172**	**0.047**
Height (cm)	**162.86±4.865**	**159.36±14.041**	**0.099**
BMI(kg/m^2)	**28.92±4.707**	**27.63±3.752**	**0.132**
*Student t-test for independent two means			

The comparison of anthropometric characteristics between cases and controls was demonstrated in table (3.2) and showed that mean weight among the cases was significantly higher than that among controls at p=0.047. The height and BMI showed no statistically significant difference.

Table (3): The distribution of obstetric characteristics between cases and controls.

Obstetric characteristics	Cases Mean±SD	Controls Mean±SD	p-value*
Gravida	4.24±1.672	1.52±0.677	0.000
Para	1.56±1.342	1.52±0.677	0.851
Investigation	**Cases No. (%)**	**Controls No. (%)**	**p-value****
Yes	11(22.0)	0(0.0)	0.000
No	39(78.0)	50(100.0)	
*t-test for independent two means; **Chi square test			

The comparison of obstetric characteristics between cases and controls was demonstrated in table.(3.3) The mean gravidity among cases was (4.24±1.672) which was significantly higher

than the mean gravidity among controls (1.52±0.677). The previous gene investigation was conducted among22.0% of cases but not the controls

Table (4): The comparison of thrombophilic genes between cases and controls.

Thrombophilic Genes		Cases No. (%)	Controls No. (%)	P-value
FV Leiden	**Heterozygotic**	2(4.0)	2(4.0)	1.000**
	Not detected	48(96.0)	48(96.0)	
Plasminogen	**Homozygotic**	4(8.0)	11(22.0)	0.063*
	Heterozygotic	38(76.0)	34(68.0)	0.560*
	Not detected (ref.)	8(16.0)	5(10.0)	------
Beta fibringen	**Heterozygotic**	42(84.0)	29(58.0)	**0.002***
	Homozygotic	0(0.0)	5(10.0)	**0.048****
	No mutation (ref.)	8(16.0)	16(32.0)	------
MTHFR	**Heterozygotic**	11(22.0)	29(58.0)	**0.000***
	Homozygotic	0(0.0)	16(32.0)	**0.000***
	No mutation (ref.)	44(88.0)	3(6.0)	------
Prothrombine	**Heterozygotic**	3(6.0)	2(4.0)	0.516*
	No mutation	47(94.0)	48(96.0)	
*Chi square test; **Fissure Exact test				

The comparison of thrombophilic genes between cases and controls was demonstrated in table (3.6) and showed that heterozygotic Beta fibrinogen was found in (84.0%) of cases which was significantly higher (p=0.002) than that among the controls (58.0%), the homozygotic Beta fibrinogen was not present among the cases and found in 10.0% among the controls with a statistically significant difference at (p=0.048). Heterozygotic MTHFR was found in 22.0% of cases and in 58.0% of controls while the homozygotic MTHFR was found in only the controls (32.0%); the differences of both heterozygotic and homozygotic MTHFR were statistically significant at p=0.000. FV Leiden, Plasminogen, and Prothrombine showed no statistically significant differences.

Table (5): The correlations of RPL with studied Thrombophilic Genes.

Spearman Correlation		Value	Asymp. Std. Error[a]	Approx. T[b]	p-value [c]
RPL	**VF Leiden**	0.243	0.075	2.475	**0.015**[c]
	PAI	-0.019	0.101	-0.185	0.853[c]
	Fibrinogen	-0.113	0.084	-1.125	0.263[c]
	MTHFR	0.081	0.096	0.809	0.421[c]
	Prothrombine	-0.116	0.085	-1.158	0.250[c]
N of Valid sample		200			
a. Not assuming the null hypothesis.					
b. Using the asymptotic standard error assuming the null hypothesis.					
c. Based on normal approximation.					

The correlations of RPL with studied thrombophilic Genes were displayed in table (3.7) and revealed that the RPL was weakly and directly (*r*= 0.243) correlated with VF Leiden in a statistically significant way (p=0.015). No significant correlations of RPL were found with PAI, Fibrinogen, MTHFR, and Prothrombine.

5. DISCUSSION

The multifactorial condition known as RPL appears to be exacerbated by thrombophilic gene polymorphisms. It was suggested that hereditary thrombophilia is linked to pregnancy loss.[10] Analysis of thrombophilia gene polymorphisms might be helpful given the significance of the condition in pregnant women and its link to recurrent pregnancy loss (RPL). FVL is one kind of thrombophilia.[11]

The mean age of the patients included in the present study is 32.14±6.474 years which is ranging from 20 to 40 years and among the controls, the mean age is 29.54±5.588 years. The study conducted by Incebiyik *et al.*[5] showed a lower mean age among the patients (24.69±2.48 years with range, 19-34 years). Also, Barut *et al.*,[12] study found that the mean age among the patient was 26.41±3.517 years (range 19-37 years).

Regarding the anthropometric characteristics, the present study showed that the cases had heavier weight (76.78±13.453 kg), taller height (162.86±4.865 cm), and higher BMI (28.92±4.707). These findings were much higher than the result of the Incebiyik *et al.*,[5] study, in which, the mean weight for the patients was (64.96±4.220 kg), the height was (170.82±1.942 cm) and BMI 22.3±3.01. In contrary, Bigdeli *et al.*,[13] results in Iran in a case-control study found that the BMI among their patient sample was (32.1 ± 2.9) and (31.9 ± 4.6) among the controls cases.

The gravidity and the parity were assessed in the present study and found that the mean gravidity was 4.24±1.672 which was significantly higher than among the controls while the difference of parity was not significant. Bigdeli *et al.*[13] study reported that among cases, gravidity was 2.59±1.99 and parity 1.05±1.29.

FVL mutation raises the incidence of venous thrombosis and recurrent RPL seven times in heterozygote carriers and eighty times in homozygote carriers, according to a research by Eslami et al.[7] According to a research by Sarig et al.[14] women who experienced fetal losses had a 25% incidence of factor V Leiden, compared to 7.6% for controls. According to a

research by Ezz Eldein et al.[6], a 39-year-old woman who had previously experienced spontaneous abortions and had given birth to one healthy kid on six separate occasions had the factor V Leiden mutation.

Consequently, pregnancy problems such pregnancy loss and RPL may result from an increase in the hypercoagulable condition.[15] Numerous surveys conducted in various countries have indicated wide differences in the heterozygous frequencies of FVL. The Mediterranean nations, including Lebanon (14.4%), Cyprus (12.1%), and Jordan (12.3%), were found to have the greatest prevalence rates. In certain groups, no mutations were found, including

Native Americans, Chinese, Japanese, and Africans.[16] A number of studies conducted in various parts of Turkey, a Mediterranean nation, have revealed wide variances in the frequency of FVL. In Turkey, the heterozygous frequency of the FVL mutation was 7.9%. The Thrace area had the lowest frequency (4.28%), whereas the cities of Ankara (9.8%) and Istanbul (10.3%) had the highest prevalence rates in Turkey (15,16). Diyarbakir, which is next to Sanliurfa, has a 4.6% incidence of the FV Leiden mutation.[7] Three patients (0.20%) were homozygous for the FVL (G1691T) change, whereas eighty-three patients (5.51%) were heterozygous.[5]

Regarding the polymorphism of PAI-1, the present study found that the homozygotic mutation detected in 8.0% of cases compared to 22.0% of controls while the heterozygotic mutation was found in 76.0% of cases and 68.0% of controls. Undetected mutation was reported in 16.0% of cases and 10.0% of controls. Gogu *et al.*,[8] According to the study, the case group consisted of 31 patients (31%) with heterozygous polymorphisms of the PAI-1 -675 4G/5G gene and 9 patients (9%) with its homozygous polymorphism, while the control group were composed of 27 women (27%) with heterozygous and 1 percent with homozygous polymorphisms of the gene.

In the present study, beta fibrinogen gene mutation among the cases was found as heterozygotic in 84.0% and 58.0% among controls while homozygotic mutation of the beta fibrinogen found among 10.0% of the controls only. Kamimoto *et al.*,[17] who studied beta-fibrinogen polymorphisms in an Italian population and found that frequencies of G/G, G/A and A/A genotypes of their control population were 62, 35 and 3%, respectively In a cohort of 36 women with pregnancy loss, Li *et al.*,[24] identified a surprisingly high number off the patients with reduced fibrinogen levels caused by genetic abnormalities. Al-Astal and Sharif

study[18] revealed that β–fibrinogen -455G/A minor allele frequency (allele A) and its homozygous genotype (AA) were not significantly different between the RPL and the control groups.

Heterozygotic of MTHFR mutation in the present study found in 22.0% of cases and 58.0% of the controls while the homozygotic mutation found in 32.0% of the controls. Undetected mutation found in 88.0% of cases and 6.0% of controls. It has been suggested that high levels of homocysteine could be one possible reason for RPL[19] In a healthy Turkish population, the rates of heterozygosity and homozygosity for MTHFR (C677T) were found to be 47.4% and 9.6%, respectively. According to a study by Yildiz et al.[20] the MTHFR C677T gene mutation was less common in RPL patients in Turkey than in the control group (36.9% heterozygous, 3.5% homozygous in PRL patients, whereas 42.6% heterozygous and 2.1% homozygous in the control group). The proportions of homozygous and heterozygous polymorphisms of MTHFR 677C/T were 15% and 42% in the case group and 9% and 25% in the control group, respectively, according to a research by Torabi et al.[16] In the case group, the rates of heterozygous and homozygous polymorphisms of MTHFR 1298A/C were 27% and 4%, respectively, whereas in the control group, there was no homozygosity and 6% heterozygosity.

The frequency of heterozygous prothrombin gene mutation in the current study showed that the heterozygotic found in 6.0% of cases and 4.0% of control with no significant difference, no homozygous mutation found in this study. Incebiyik *et al.*,[5]found that the homozygous mutation of the prothrombin gene (G20210A) was not found, while the frequency of heterozygous mutations was found to be 4.05%. There were 40.61% of patients with heterozygous MTHFR (C677T) and 8.29% of patients with homozygous mutation. 38 out of 86 patients had additional thromogenic gene variants in addition to FVL: 5 patients had prothrombin G20210A and heterozygous FVL (0.33%) mutations, and 33 patients had MTHFR and heterozygous FVL (2.19%) mutations. Serum prothrombin levels rise as a result of the prothrombin gene mutation, which is caused by a G-to-A change at position 20210 in the 3' untranslated region. RPL, vascular disease, and venous thrombosis may all be made more likely by this rise.[21]

In Turkey, 1.2% to 2.7% of individuals had the heterozygous prothrombin G20210A mutation. According to research, 1.7% of people in Sanliurfa, in the southeast region of Anatolia, have the heterozygous prothrombin gene mutation.[10] According to the current

study's evaluation of the correlations between RPL and the thrombophilic genes under investigation, VF Leiden and RPL had a poor relationship. There were no discernible relationships between RPL and prothrombine, fibrinogen, MTHFR, or PAI. The first investigation to concurrently examine the frequency and interrelations of the MTHFR 677 C/T, MTHFR 1298A/C, FV Leiden, factor II prothrombin 20210 G/A, ITGB3 1565T/C, and APO B R3500Q polymorphisms in a Caucasian population with a history of RPL was conducted by Hohlagschwandtner et al.[22]

They were unable to show any association between the examined polymorphisms and RPL, nor could they show that the interrelations of these polymorphisms had a significant impact on RPL. Sotiriadis et al., 23 assessed the prevalence of five prevalent thrombophilic polymorphisms (FV Leiden, FV 4070 A/G, Factor II prothrombin 20210 G/A, MTHFR 677C/T, and MTHFR 1298 A/C) and their combinations in women who had recurrent miscarriages compared to a control group. Combinations of all or part of the five thrombophilic SNPs were reported. were rare occurrences with varied patterns that did not substantially raise the chance of miscarriage. In addition, Hossain et al.[15] discovered that 66% of women who experienced idiopathic pregnancy loss also had thrombophilia. Additionally, they noted that women who experienced pregnancy loss frequently had mixed thrombophilia, and they came to the conclusion that thrombophilia was linked to a higher incidence of late

10 thrombophilic gene polymorphisms in 75 patients with a history of recurrent miscarriage with 14 fertile control women and found no differences between the two groups. However, compared to the controls, individuals who experienced repeated miscarriages had a considerably greater rate of total gene polymorphisms. Additionally, they observed that 68% of women with recurrent miscarriages had t hrombophilic gene variants, which were linked to more than three of the ten genes under study.[9]

CONCLUSION

Recurrent pregnancy loss is a challenging clinical problem for both patients and obstetricians. There are likely numerous factors that contribute to the tendency for a couple to have pregnancy loss. The present study concluded that there were no significant differences between the patients who had recurrent pregnancy loss and the healthy controls regarding the common thrombophilic genes apart from Beta fibrinogen and Methylenetetrahydrofolate Reductase.

REFERENCES

1. Pillarisetty LS and Mahdy H. Recurrent Pregnancy Loss. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
2. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and sterility., 2012 Nov 1; 98(5): 1103-1111.
3. El Hachem H, Crepaux V, May-Panloup P, et al. Recurrent pregnancy loss: current perspectives. Int. J. wom. Heal., 2017; 9: 331. https://doi.org/10.214 7/IJWH.S100817.1.
4. Kolte AM, Bernardi LA, Christiansen OB, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum. Reprod. 2015; 30: 495–498. https:// doi.org/10.1093/humrep/deu299.
5. Incebiyik A, Hilali NG, Camuzcuoglu A, et al. Prevalence of thromogenic genemutations inwomen with recurrent miscarriage: A retrospective study of 1,507 patients. Obstetrics & Gynecology Science. 2014; 57(6): 513-17. https://doi.org/10.5468/ogs.2014.57.6.5 13
6. Ezz Eldein AK, El Sharkawy EA, Salah KM, et al. Role of factor V leiden G1691A in women suffering frequent abortions Research Article Association of Factor V Leiden G1691A in Women Suffering Repeated Abortions, MJMR, 2020; 31(1): 36- 42.
7. Eslami MM, Khalili M, Soufizomorrod M, et al. Factor V Leiden1691G > A mutation and the risk of recurrent pregnancy loss (RPL): systematic review and meta-analysis. Thrombosis J. 2020; 18: 11. ttps://doi.org/10.1186 /s12959-020-00224-z
8. Gogu AE, Motoc AG, Stroe AZ, et al. Plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms associated with cardiovascular risk factors involved in cerebral venous sinusthrombosis. Metabolites. 2021; 11: 266-271.
9. Hamedi B, Feulefack J, Khan A, et al. Association between factor V Leiden mutation and recurrent pregnancy loss in the middle east countries: a Newcastle-Ottawa meta-analysis. Arch Gynecol Obstet, 2020; 302: 345-54. 10.1007/s00404-020-05610-6.
10. Hossain N, Shamsi T, Khan N, et al. Thrombophilia investigation in Pakistani women with recurrent pregnancy loss. J Obstet Gynaecol Res., 2013; 39: 121–125.
11. Udumudi A and Lava C. Genetic markers for inherited thrombophilia related pregnancy loss and implantation failure in Indian population – implications for diagnosis and clinical management. The Journal of Maternal-Fetal & Neonatal Medicine, 2022; 35(25): 9406-9414
12. Barut MU, Bozkurt M, Kahraman M, et al. Thrombophilia and Recurrent Pregnancy Loss: The Enigma Continues. Medical Science Monitor. International Medical Journal of

Experimental & Clinical Research. 2018; 24: 4288-4294. https://doi.org/10.12659/MSM.908832

13. Bigdeli R, Younesi MR, Panahnejad E, et al. Association between thrombophilia gene polymorphisms and recurrent pregnancy loss risk in the Iranian population. Systems Biology in Reproductive Medicine, 2018; 1080. DOI:10.1080/19396368.2018.1456576
14. Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. Fertil Steril, 2002; 77(2): 342-347. doi:10.1016/s0015-0282(01)02971-5
15. Hossain N, Shamsi T, Khan N, et al. Thrombophilia investigation in Pakistani women with recurrent pregnancy loss. J Obstet Gynaecol Res., 2013; 39: 121–125.
16. Torabi R, Zarei S, Zeraati H, et al. Combination of Thrombophilic Gene Polymorphisms as a Cause of Increased the Risk of Recurrent Pregnancy Loss. Journal of Reproduction & Infertility, 2012; 13(2): 89-94.
17. Kamimoto Y, Wada H, Ikejiri M. Hypo-fibrinogenemia and the α-Fibrinogen Thr 312 Ala Polymorphism may be Risk Factors for Early Pregnancy Loss. Clin Appl Thromb Hemost, 2017; 23: 52–57. doi:10.1177/1076029615594003.
18. Al-Astal MG and Sharif FA. Beta-fibrinogen (-455 G/A) and Integrin beta-3(PLA1/A2) polymorphisms and recurrent pregnancy loss in Gaza strip-Palestine. IntJ Reprod Contracept Obstet Gynecol, 2014; 3: 134-138.
19. Cao Y, Xu J, Zhang Z, et al. Association study between methylene tetra hydro folate reductase polymorphisms and unexplained recurrent pregnancy loss: a meta-analysis. Gene. 2013; 514: 105-111.
20. Yildiz G, Yavuzcan A, Yildiz P, et al. Inherited thrombophilia with recurrent pregnancy loss in Turkish women: a real phenomenon? Ginekol Pol. 2012; 83: 598–603.
21. Teremmahi AM, Nodushan HH, Aflatoonian A, et al. Case control study of the factor V Leiden and factor II G20210A mutation frequency in women with recurrent pregnancy loss. Iran J Reprod Med., 2013; 11: 61–64.
22. Hohlagschwandtner M, Unfried G, Heinze G, et al. Combined thrombophilic polymorphisms in women with idiopathic recurrent miscarriage. Fertil Steril., 2003; 79(5): 1141–1148.
23. Sotiriadis A, Vartholomatos G, Pavlou M, et al. Combined thrombophilic mutations in women with unexplained recurrent miscarriage. Am J Reprod Immunol, 2007; 57(2): 133–141.
24. Li J, Wu H, Chen Y, et al. Genetic association between FXIII and β-fibrinogen genes and

women with recurrent spontaneous abortion: A meta- analysis. Journal of Assisted Reproduction and Genetics, 2015; 32(5): 817-825. https://doi.org/10.1007/s10815-015-0471-9