Clinical and Experimental Health Sciences

The association of factor V Leiden mutation (G1691A) with pregnancy complications (miscarriage) in the Iran, East Azerbaijan

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ABSTRACT

Objective: The pathogenesis of human spontaneous abortion involves a complex interaction of several genetic and environmental factors. Resistance to anticoagulant activity of activated protein C (APC) is often due to point mutations in the Factor V gene. Leiden mutation is definitely associated with pregnancy complications. This study investigated the association of factor V Leiden with recurrent miscarriage in Iranian patients.

Methods: 200 women included in this study: 100 women as patients' group with two or more consecutive unexplained miscarriage and 100 women as controls group with at least one childbirth and without any abortion or pregnancy complications. Genomic DNA is extracted from the must be delete from peripheral blood of each person. Presence or absence of mutations in the factor V Leiden gene performed by factor V Leiden coagulation test, and to determine homozygous and heterozygous of the factor V Leiden mutation, used HRM techniques by PCR Factor V Leiden Kit.

Results: In this study, Chi-square analysis was a significant relationship between mutant G1691A and recurrent pregnancy loss, and other environmental variables in the statistical analysis, gestational age, and family history, statistically significant association with recurrent pregnancy loss.

Conclusion: The results of this study showed that Factor V Leiden mutation has an effective role in the risk of pregnancy complications and recurrent miscarriage. Factor V Leiden mutation frequency in various countries due to genetic differences and different geographic can prone to recurrent pregnancy loss, better management of patients, and adoption of effective preventive methods.

Keywords: Recurrent pregnancy loss, miscarriage, Factor V Leiden, mutation, pregnancy

1. INTRODUCTION

Aborsement is denominated as frequent spontaneous abortions and losing the pregnancy product. Frequent spontaneous abortions are classically defined as thrice spontaneous abortions in 20 weeks of gestation or less or the birth of fetuses less than 500 grams (1). Genetic abnormalities in recurrent miscarriages in the first quarterly are significantly low. Karyotype was normal in half of all recurrent miscarriages; this was only a quarter of the sporadic abortions. Since the timing of abortion can lead us to the cause of the miscarriage, it is observed that autoimmune or anatomical abnormalities generally cause miscarriage in the second quarterly (2). Additionally, the prevalence of recurrent miscarriage is one in every 300 births. Epidemiological studies have shown that 1-2% of women have experienced recurrent miscarriages (3). Recurrent miscarriage as a clinical problem requires diagnostic tests and therapeutic interposed to reduce the risk of the disease and then find a treatable cause for the disorder. Mutation of FVL in people is according to each record and leads to pregnancy complications such as miscarriage.

Generally, women who are getting frequent abortions have some problems in their blood coagulation system. During blood circulation, some clots erupt in capillaries, which may be hemophiliac to the fetus (4). It seems clot creation in blood vessels or thrombosis is probably caused due to disorder in blood circulation between mother, fetus and fetus and will lastly cause fetus abortion (5). One of the main genetic factors that have a role in thrombosis creation thrombosis is Factor V Leiden. The clot demonstration reason is a mutation in the factor V gene. Factor V acts as a helper agent in enzyme reaction, creates fibrin in a clot (6). According to the lack of studies in genetic variants prevalence of this factor in the Azerbaijan region, this research aims to evaluate the different alleles abundance of factor V in the G1691A situation among women in East Azerbaijan.

Resistance to active protein C is characterized by plasma resistance to the anticoagulant effects of active protein (7). Thrombin (factor IIa) converts fibrinogen to fibrin and active platelets, and this starter protein initiates the responsibility for fibrin inhibition activities (8). When thrombin binds to

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existing thrombomedulin at the level of endothelial cells, it is activated and can convert protein C to the active form. Protein C is only active when it binds to its cofactor (the S protein) is connected. Protein S is active when it is not bound to C4b. At baseline, about 40% of S protein is unconnected. The active C / S protein complex decomposes the Va and VIIa factor, reducing fibrin formation and ultimately reducing blood clotting. The role of these factors during pregnancy is vital; a successful pregnancy requires proper growth and development of placental circulation (9&10).

Factor V Leiden mutation inhibits APC's effects on factor V and is inherited in form of dominant autosome (11). This missense mutation replaces glutamine (CAA) instead of arginine (CGA) at position 506 of polypeptide factor V and 1691 position of gene F5, Exon 10. This case is due to omitting one of definition position factor V by APC. Finally, factor V is resistant to decomposition by activated protein C and facilitates the occurrence of thrombosis (20). This gene is cytogenetically located on the long arm of chromosome 1 at situations 23-24. And molecularly includes 169481191 to 169555768 pair bases. Factor V gene has 25 exon and 24 intron, and the size of this fragment is a 75-kilo base. Heterozygote form of active factor V is the most common hereditary thrombophilia (8). Factor V Leiden mutation can be found in about half of non-pregnant who, suffering from thrombophilia diseases. In heterozygote form, risk of thrombosis emergence increases ten times in pregnancy (12). The resistance of active protein C was measured in the biometric method. It should be noted that, anti-phospholipid antibody syndrome can cause the resistance of active protein C. the early pregnancy naturally increases the resistance due to changes in other coagulation proteins. During pregnancy, DNA analysis is used to confirm the mutation in the V factor gene (9). Studies have shown that, mutation of factor V Leiden increases the risk of the first episode of intravenous thromboembolism during pregnancy about 4 to 8 times. In addition to the aforementioned mutations, other single-nucleotide polymorphisms have been reported in the factor V gene, including the following: SNP in the promoter region (99930G> A), exon 16 nucleotides (42855A> G), intron 19 (37833T> G). (13) Coagulation Factor V plays a key role in regulating the homeostasis of coagulation pathways. GT691A point mutation in the coagulation factor V gene is called the Leiden thrombophilia factor (FVL), and it eliminates a breakdown position in coagulation factor 5; therefore, by affecting the function of the thrombinase complex, it induces resistance of coagulation factor V to activated protein C (APCR), which is associated with recurrent miscarriage (14). FVL polymorphism is due to increased risk of fetus abortion in people who carrying this polymorphism more than three times (6%-16%) in comparison with to healthy people. Many investigations approved the increasing risk of frequent abortion in women with this polymorphism. Coagulation V factor acts as a co-factor for factor X. Factor X converts prothrombin to thrombin, which plays an important role in the coagulation cascade. This factor analysis by active protein C. However, the V-factor Leiden is not inactivated by the action of protein C, which causes clots in the individual. As mentioned, the Leiden variant was caused by a G1691A point mutation in Exon 10. Because of this missense mutation, arginine amino acid converted to glutamine. FVL mutation prevents FV digestion, accordingly cause to blood clotting (15). May be deep vessels thrombosis (DVT) arising as a painful and protuberant and achy area (usually in the foot). If thrombosis is displaced, it might cause an obstruction of pulmonary bloodstream alongside dyspnea, tachycardia, arrhythmia, or sudden death. Insufficiency of C or S Proteins and presenting the FVL mutation are dangerous factors for causing effects on DVT (16). In 20% to 40% of people with signs of venous thrombosis, FVL mutation is observable, which is the most common factor of causing the effects on DVT. Heterozygotes with a copy of FVL mutation have a 7-fold increase in the risk of infection, and homozygotes with two copies of Leiden FV mutation have an 80-fold increased risk of DVT. It is expected that positive homozygote people have at least a thrombotic event during their age, while heterozygote people, according to thrombotic problems expression, are different (16).

Due to the deep relationship between thrombophilia and recurrent miscarriage, these polymorphisms were studied in various non-Iranian and Iranian populations (for a limited time) for many years, and contradictory results were obtained from these studies. For this reason, the study of these polymorphisms is recommended once again. If it is widespread in this area, it can be used as a diagnostic marker in women who have recurrent miscarriages. Undoubtedly there is a correlation between factor V mutation and pregnancy complications and the occurrence of recurrent miscarriage; Therefore, it was hypothesized that this relationship could be present in people with recurrent miscarriages in the East Azarbaijan region Tabriz city, which persuaded me to do this research. The purpose of this study is to investigate the relationship between mutation FVL in causing pregnancy complications and recurrent miscarriage in this region, which can consequently help us in the treatment process, prevention of such complications, and having healthy children.

2. METHODS

The research was done in Doctor Arami medical laboratory by evaluations accomplished and essential data obtained with a questionnaire. 100 patients and 100 healthy subjects (as a control group) with a mean age of 45 ± 1.28 in the age group of 18-45 years were selected randomly. The Control group were pregnant women who had no pregnancy complications and were healthy. The patient group was pregnant women who had a background of abortion. All health and patients took written subscriptions then registered their information about the number of children, occupation, place, and age of the pregnancy. Patient sampling does not require special preparations. 5 ml of blood took from people, 3 ml of which were transferred to the EDTA test tubes for PCR tests and 2

ml to the sodium citrate test tubes for the coagulation panel tests. Blood samples were stored in the freezer at a +2 /+ 8 degrees temperature for three days. For long-term storage, samples stored between – 85 and – 10 degrees.

Enter criteria to the study were pregnant women who had previous abortion affection and each complications kind of pregnancy because of thrombosis and exit criteria were existing anatomical raucousness, hormone disorders, autoimmune diseases, approved infection of genital and person who used heparin, aspirin or enoxaparin. Information obtained by a questionnaire was adjusted after reviewing texts and scientific articles and collected according to study aims, and blood sampling was directly from women.

Data collection tools included questionnaires and sampling of healthy pregnant women and pregnant women with miscarriages who were referred to gynecologists. At the request of the medicine, the patient was referred to the relevant laboratory and the pregnant women with abortion whose disease previously confirmed by the treating medicine and performed tests and the control group who did not have any evidence of any personal or family history of abortion with full consent examined with complete satisfaction.

This research was accepted with the Ethical standard code: IR.IAU.TABRIZ.REC.1395.63 in 06/17/2018 in Faculty of Medical of Islamic Azad University of Tabriz branch.

2.1 Clotting Panel test

In the possible shortest time (maximal 2 hours), the sample was centrifuged at 2500-3000 rpm for 20 minutes and separated plasma. Therefore, kept in – 20 degrees centigrade. HEMOCLOT Quanti.

V-L Ref CK065K done by coagulation, fully automatic method. The test does in 37 degrees centigrade. The device itself automatically adjusts this temperature during the test. The rack stand for the samples has a barcode reader system to detect the sample entered into the device. Regent solutions also placed in their own racks and identified by the device's barcode reader system. After placing the samples and solutions, we set the device, 1. from the main menu, press the start key, wait until the sample loading station lights change to green. Slide the sample tray into the sample loading station. 2. Press the ID entry area. Write and confirm the ID for each sample. 3. Confirm the test order. 4. Press the corresponding number field in the "POS" column. After these steps, we started the device and waited for the answers. After a few minutes, the answers were prepared on the device monitor. Results greater than two were reported as normal, and results less than 1.8 were positive (with V factor mutations). After confirming the results of the coagulation test, the HRM test was done with a Real-Time PCR device to detect the heterozygote and homozygote of the samples. Purification of nucleic acid should do according to the desired kit GeneProof Factor V Leiden lot No. P4101-16097 prepared for specific clinical materials. The nucleic acid separation must adjust to prepared intended kit for special clinical materials. Whole blood kit DNA for purification of DNA used health and purified blood. Using method in the present study was an ex-filled cartridge including salt for cells lysis and breaking proteins. DNA is surrounded by cellulose cover, which has magnet grains. After washing pollutants, purified DNA was washed with low salt washing buffer. Purified DNA was obtained about 20-30 kb long in this level proper of PCR. This method replied for all existing samples in the test and due to doing the polymerase chain reaction test with real-time device moved to the freezer, after ramp rate setting with real-time device samples placed in the device as the following progress: 1. Determine the RT-PCR approach. In performing RT-PCR, one-step and two-step methods are the two common approaches, each with advantages and disadvantages. 2. Prepare sample. 3. Design primers. 4. Remove genomic DNA. 5. Perform one-step RT-PCR. 6. Determine the RT-PCR approach. 7. Prepare sample. 8. Design primers. After samples, embedment, and program set up, we started the device and waited for results. The PCR Steps Explained: Step 1 – Denaturation. The solution contained in the tube is heated to at least 94°C (201.2°F) using a thermal cycler. Step 2 – Annealing. Step 3 – Extension. Step 4 – Analysis with Electrophoresis. Results got ready after one and a quarter-hour. Obtained results had some graphs.

2.2 Evaluating results of HRM

Results of HRM were obtained into graphs, in which FAM and HEX graphs reflect the kind of person genotype (homozygote and or heterozygote) (Figure 4).

In figure 5, there were both positive and negative results. FAM and hex graphs are both ascending, which present to be heterozygote of the sample. Ascending FAM and anticlimactic hex graphs indicate to being homozygote of the sample. GG genotype indicates the sample to be homozygote. Demonstrate AG genotype, which is show sample, be heterozygote and positive Factor V mutation (Figure 6).

2.3 Method of data analysis

After experimental techniques and collecting the genetic data, this information merged with another data outcome from questionnaires and after editing in excel software entered to SPSS software. On the device monitor were appearances some graphs adjust to 1, 2 and 3 figures that show the kind of gene and with the help of obtained graphs can diagnose the heterozygote or homozygote of the sample (Figure. 1, 2, 3). For accounting allele and genotypes abundance, chi-square statistical and Hardy-Weinberg balance test used pop gin s1 software and studied the relation of genotype kind and presence or absence of abortion in women used chi-square test in probability level of 95% and SPSS software version 24.

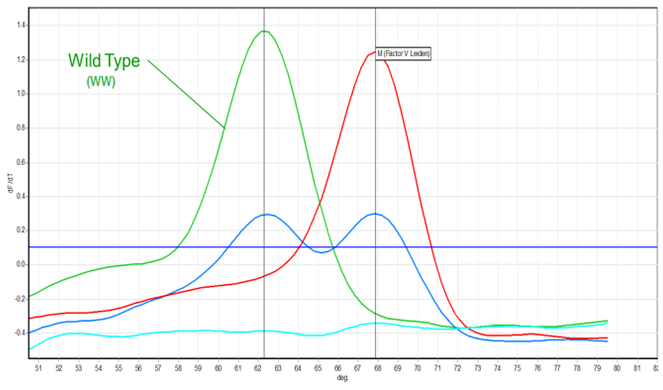

Figure 1. *Graph related to negative sample or WW genotype*

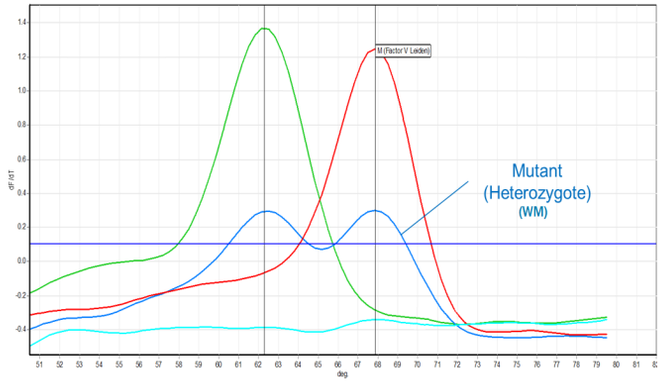

Figure 2. *Graph related to heterozygote positive sample or WM*

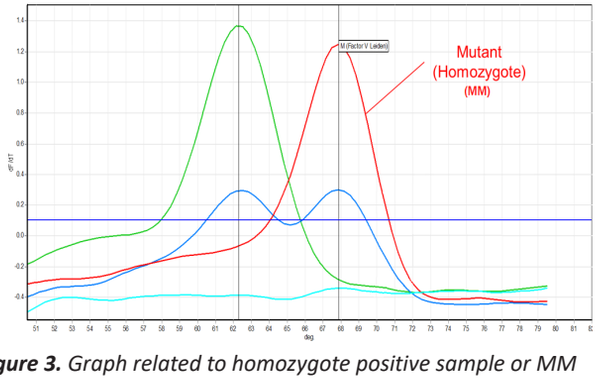

Figure 3. *Graph related to homozygote positive sample or MM*

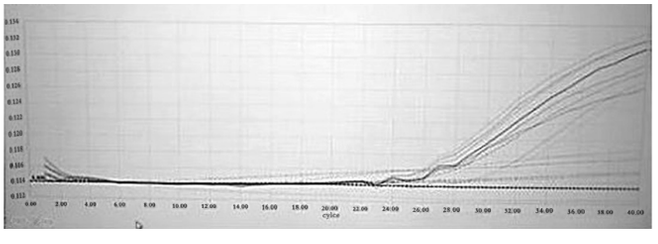

Figure 4. *Image of FAM and HEX graphs*

Figure 5. *GG genotype graph*

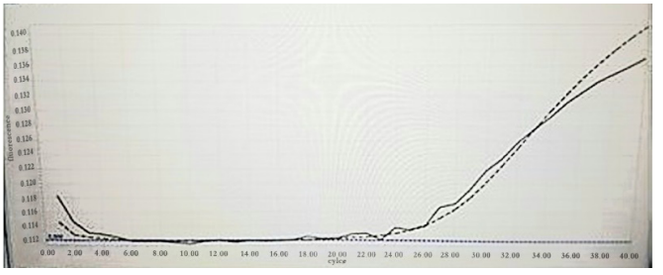

Figure 6. *Ag genotype graph*

3. RESULTS

3.1. Genotypic analysis of test groups

According to HRM obtained data, abundance genotypes from patient and control groups are like table 1 and table 2.

Table 1. *Abundance genotypic in-patient group*

Allele abundance	Number	Observed abundance	Expected abundance	Chi-square	Allele abundance
AA	0	25	0.029	3.95	A = 0.17 G = 0.83
AG	32	0.64	0.102		
GG	62	85	0.25		

Table 2. *Abundance genotypic in control group*

Control group	Number	Observed abundance	Expected abundance	Chi-square	Allele abundance
AA	0	0	0	0.003	A = 0 G = 1
AG	0	0	0.01		
GG	73	50	0.99		

3.2. Statistical analysis

Obtaining the expected frequency and using chi-square coefficient to obtain a value of p<0,05, it concluded that there is a significant relationship between the parameters like

pregnancy age (P=0.01), family history (P=0.01), and recurrent miscarriage with V-factor Leiden (P=0.02).

GG allele abundance is high in control and patient samples, which is reckon normal factor. Moreover, the AA allele was not observed in any of the samples. Also, AG allele was just observed in samples with high age and previous familial affected to frequent abortion. Generally, observed genotypes abundance in both groups is in table 3.

Table 3. *Genotypic abundance in both patient and control groups*

Total	Number	Observed abundance	Expected abundance	Chi-square	Allele abundance
AA	0	0	0.0092	1.87	A = 0.096 G = 0.904
AG	32	0.54	0.1733		
GG	135	0.12	0.8176		

3.3. Evaluating number of laborers with frequent abortion

Results of table 4 demonstrated the number of labors in studied samples that the most sample members are their first pregnancy. There is no significant relation between frequent abortion and numbers of labor.

Table 4. *Number of labors by tests*

Number of labors	Number	Percent
0	53	56.5
1	74	37
2	12	6
3	1	0.5

3.4. Studying relationship between previous familial with frequent abortion

Analyzing the last familial indicates the presence of significant relation between access abortion and previous familial diseases that 171 people of sample members had previous familial diseases and 29 people had no previous familial diseases (Table 5).

Table 5. *Previous familial diseases by tests*

Previous familial	Number	Percent
Had	158	85.5
Hadn't	29	14.5

3.5. Evaluating effective factors on results of coagulation test

Results of the correlation test indicate the effect of each three Leiden genotypes (P=0.02), previous familial (P=0.01), and age of a pregnancy (P=0.01). Factors are significant, and they significantly influence the coagulation test (Table 6).

Table 6. *Evaluating effective factors on result of coagulation test*

	MS	P value
Leiden genotype	1.03	0.027
Previous familial	3.91	0.01
Age of pregnancy	1.744	0.011
Error	0.262	-

3.6. Evaluating genotype effect

For surveying the effect of patient genotype on number of abortions, used Mann-Whitney test, which results indicate that genotype has a significant effect on abortion number (P=0.01) and heterozygote genotype is more than homozygote due to more abortion numbers (Table 7).

Table 7. *Evaluating effect of patient genotype on abortion numbers*

Genotype	Number	Average level	Mann-Whitney test	P value
AG	32	122.7	921.5	0.001>
GG	135	74.83		

3.7. Effect of the presence of previous familial

Also, due to indicating previous familial on frequent abortion, Mann-Whitney test and results of test demonstrated that previous familial has a significant effect on frequent fetus abortion (P=0.01) and samples with previous familial had more frequent fetus abortion than samples without previous familial (Table 8).

Table 8: *Studying effect of presence previous familial*

Previous familial	Number	Average level	Mann-Whitney test	P value
Presence	29	154.86	903.00	0.001>
Absence	171	91.28		

3.8. Compact people genotype

Due to compact health and patient people genotype, using chi-square test, which test results indicated genotype in health and patient people of samples are different with each other (P=0.01), and heterozygote genotype were more than homozygote genotype in patient samples, and health samples were more homozygote genotype (Table 9).

Table 9. *Compact genotype of health and patient samples*

	AG	G genotype	Chi-square
Patient	32	62	0.001>
Health	-	73	

4. DISCUSSION

According to the National Center for Health, pregnancies include 13 percent of births. Fertility under 19 and over 34 is considered high-risk pregnancies (17). Successful pregnancy is a pregnancy which the fetus grows and develops while maintaining mother's health, leading to the birth of a healthy baby (18). Bleeding, infection and bacterial shock (infection-induced shock) are complications of abortion. Patients who have had a previous miscarriage are about 20% more likely to have a miscarriage in their next pregnancy (19). In some women, fetal developmental defects in the fetus can lead to a bicornuate Uterus or bicornuate or various forms of uterine deformities, leading to miscarriage. Fibroma or uterine viscosity can also cause miscarriage in pregnant women (20). The risk of miscarriage is related to the mother's age, as studies show that abortion is more common in pregnant women under the age of 20 and over 40. Increasing abortions are observed in very young or old fathers. Abortion rates with women's pregnancy increase within three months of giving birth (20). How APS can cause recurrent miscarriage is not fully understood, but what is the evaluation of antibodies to anti-cardiolipin and lupus anticoagulants in these patients could be helpful. The recommended treatment for these people is a low dose of aspirin with heparin (21). Normal homeostasis requires balancing between pre-coagulation and anticoagulant factors. Factor V is one of the important pre-coagulation factors. Factor V glycoprotein acts as a prothrombinase complex and converts the protein to thrombin to form fibrinogen from the fibrin of the polymerized network and to form the primary clot (22). The A1691G variant is known as the FVL, which is the most common disorder of all three variants. It is associated with increased coagulation and increases the risk of thrombosis in the venous arteries of various tissues. FVL Polymorphism has a predominant autosomal recessive factor and occurs at the displacement of a nucleotide (23). The G>A mutation in nucleotide 1691 on Exon 10 of factor V altered arginine amino acid to glutamine, which eliminated the main site of failure at 506 and led to the resistance of factor V active to protein C function. In normal people, after the clot formation, the remnants of active factor V by protein C activated in arginine 506 site broke and inactive, but in people with factor V lead, factor V refracted to analysis, decompose, and remains active for a longer period. Increased risk of thrombosis associated. Fracture factor V was activated by protein C activation and protein S cofactor was performed. In these people, an increase in thrombin leads to the production of excess fibrin and more clots produced. 90 to 95% of mutations are heterozygous and other cases are homozygous (24). Pregnant women who have a FVL mutation are more likely to have recurrent miscarriages, preeclampsia, or even stillbirth. Thrombosis in placental capillaries disrupts the blood flow to the mother and fetus and eventually leads to miscarriage (25&26). FVL polymorphism is present in approximately 5% of the Caucasian population (whites), 3% – 8% of Europeans, and 4% – 7% of Americans, and is less common among Asian populations (27). The FVL allele of Europeans is 1 – 8.5 percent and is less common among Israelis, with large immigrant backgrounds, the allele frequency various, but, the highest rate reported among Turkish and Greek about 0.87.(13). In Iran, due to the existence of various ethnic groups and various indigenous groups, the Allele frequency for the FVL is somewhat different from the living area and ethnicity (27). In Tehran, the prevalence of FVL is 5.5% and the allele frequency is 2.7%. In southern Iran, the prevalence rate is 4.1% and the frequency of allylic for the V-factor varies is different from 0.207 to 0.209. The obtained allylic frequency in the present study in the northeast of the country is equal to 0.19% for the AG genotype and 0.808% for the GG genotype, and the prevalence of the V-factor is 1.8%. Which is more than the west and south of Iran and has a significant difference (1). The study of the Australian population in 2012, reported that heterozygosity related to intra-uterine death risk of the fetus, placenta separation, and clamps of preeclampsia for V Leiden factor mutations (28). A study in 2011, defined that hereditary thrombophilia is related to a high risk of thromboembolism and accompanied by undesirable pregnancy pages (29). In 2012 in Poland, defined Leiden Factor V mutation as a common disorder in patients with an abortion background, and clearly, it has a higher prevalence with frequent abortion and suggested that Leiden Factor V mutation was high in person with frequent abortion (27). A study in 2012 reported that Leiden Factor V mutation was observed in 4.5% of studied people who had frequent abortions (18). In a study in 2013, scientists reported that one of the effective reasons for increasing affliction risk to frequent abortion is Leiden Factor V mutation (29).

In our study, similar results were obtained and a significant correlation was found between heterozygous motility factor V Leiden and miscarriage risk. Chi-square analysis was a significant relationship between mutant G1691A and recurrent pregnancy loss, and other environmental variables in the statistical analysis, gestational age, and family history, statistically significant association with recurrent pregnancy loss.

5. CONCLUSION

In the present study, mutations in the factor V gene were investigated by using the HRM technique in 100 patients with recurrent miscarriage in northeastern Iran (Tabriz) whose disease was confirmed by relevant specialists and 100 healthy individuals treated as a control group. By examining and identifying mutations, genetic testing can diagnose recurrent miscarriages in people with the disease, and early detection of the disease can be a big step in treating these people and reducing fetal mortality from the disease. The frequency of allylic obtained in the present study is 0.19% for AG genotype

and 0.8% for GG genotype and the prevalence of factor V Leiden is 1.8%. In addition to studies, there is no relation to the situation of occupation, housekeeping and educational situation, and the number of labor and pregnancy with the rate of patient affect. The result of the correlation test demonstrates that in patient groups every three factors of Leiden genotype, previous familial, and age of pregnancy on coagulation test is more than to health group and has a significant effect on coagulation test. This means there is a significant and direct relationship between the age of the pregnancy, previous familial and frequent abortion.

In this research, we found a significant relation between heterozygosis of Leiden Factor V mutation and the risk of abortion. And it concluded that surveying Leiden Factor V as the main marker in patients affected by frequent abortion and pregnancy complications can avoid to next abortions and aggravation of pregnancy complications in the future. Some researchers suggested that a mutation in the factor V Leiden gene as a marker for recurrent miscarriage and thrombosis, due to its low frequency, could not affect the diagnosis, but in our study, it concluded that the factor V Leiden investigated. The title of an important marker in patients with recurrent miscarriages and pregnancy complications can prevent further miscarriages and exacerbation of future pregnancies. PCR testing is used only once to diagnose the type of mutation; therefore, patient control will only be possible by testing the low-cost V factor coagulation panel. In order to ensure the results, more studies proposed to confirm or reject the findings of this study. So that, investigate the relationship between recurrent miscarriage and other genetic factors, the causes of lack of factors in patients and better matching between the case group and the control in terms of other patients can examine.

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