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Factor V Leiden Mutation in Women with Recurrent Pregnancy Loss: A Single-center Study

Aslı Odabaşı Giden[1], Çağrı Doğan[2]

[1]*Ordu State Hospital, Clinic of Hematology, Ordu, Türkiye*
[2]*Ordu University Training and Research Hospital, Department of Medical Genetics, Ordu, Türkiye*

ABSTRACT

Aim: Recurrent pregnancy loss (RPL) affects approximately 1-2% of women of reproductive age and remains a clinically challenging condition with diverse underlying causes. Inherited thrombophilic abnormalities, particularly Factor V Leiden mutation, have been proposed as potential contributors to its pathogenesis; however, the available evidence remains inconclusive. This study aimed to determine the frequency of the Factor V Leiden mutation in women with RPL and to evaluate whether mutation carrier status was associated with the number of previous pregnancy losses within this cohort. The relationships of maternal age, hemoglobin concentration, and fasting blood glucose levels with the number of previous pregnancy losses were investigated.

Methods: This retrospective cross-sectional study included 103 women aged 18-45 years who had experienced RPL. Demographic, clinical, laboratory, and genetic data were retrieved from hospital records. Associations between thrombophilia mutations and pregnancy loss were assessed using comparative and correlational analyses, followed by multivariate linear regression to determine independent predictors.

Results: Factor V Leiden mutation was identified in 10 patients (9.7%), whereas the Prothrombin G20210A mutation was detected in 5 patients (4.85%). Neither mutation was significantly associated with the number of previous pregnancy losses ($p>0.05$). Maternal age was significantly positively correlated with the number of previous pregnancy losses ($r=0.51$, $p<0.001$). Although fasting blood glucose and hemoglobin levels were associated with the number of previous pregnancy losses in univariate analyses, only hemoglobin and maternal age remained independently associated with the number of previous pregnancy losses after multivariate adjustment (maternal age: $B=0.033$, standardized $\beta=0.459$, $p<0.001$; hemoglobin: $B=0.112$, standardized $\beta=0.293$, $p=0.016$).

Conclusion: Within this cohort of women with RPL, no statistically significant association was observed between Factor V Leiden mutation carrier status and the number of previous pregnancy losses. Maternal age was independently associated with the number of previous pregnancy losses. Larger controlled prospective studies are needed to further clarify the role of inherited thrombophilia in RPL.

Keywords: Recurrent pregnancy loss, Factor V Leiden, prothrombin mutation, thrombophilia, maternal age

Introduction

Recurrent pregnancy loss (RPL) is a complex reproductive disorder that is generally defined as two or more consecutive pregnancy losses before fetal viability. Affecting approximately 1-2% of women of reproductive age, RPL remains an important clinical problem because of its multifactorial etiology and considerable emotional and reproductive consequences. Although advances in reproductive medicine have improved the understanding of this condition, no specific cause can be identified in a substantial proportion of affected women. Current evidence indicates that genetic, anatomical, endocrine, immunological, and hematological abnormalities may all contribute to the development of RPL [1-4].

Inherited thrombophilia has been extensively investigated as one of the possible mechanisms underlying RPL. Pregnancy itself is associated with a physiological hypercoagulable state, and inherited thrombophilic disorders may further increase the tendency toward thrombosis. Consequently, placental

Address for Correspondence: Aslı Odabaşı Giden MD, Ordu State Hospital, Clinic of Hematology, Ordu, Türkiye
E-mail: asli.odabasi@saglik.gov.tr **ORCID ID:** orcid.org/0000-0001-7375-4485
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microvascular thrombosis, impaired uteroplacental perfusion, and placental insufficiency have been proposed as potential mechanisms linking thrombophilia to pregnancy failure [5,6].

Among inherited thrombophilic disorders, Factor V Leiden mutation is the most prevalent genetic abnormality associated with an increased risk of venous thromboembolism [7,8]. Likewise, the Prothrombin G20210A mutation represents another inherited prothrombotic condition that has been investigated as a possible contributor to adverse pregnancy outcomes [9]. Although numerous observational studies have explored the association between these mutations and RPL, the available evidence remains inconsistent. While some reports have demonstrated a significant relationship, others have failed to confirm a clinically meaningful association, leaving the role of routine thrombophilia screening in women with RPL a matter of ongoing debate [10,11].

Increasing maternal age is consistently recognized as one of the strongest predictors of pregnancy loss. This association is primarily explained by the age-related rise in embryonic chromosomal abnormalities and the progressive decline in oocyte quality. In addition, maternal metabolic disturbances and hematological factors have been suggested to influence reproductive outcomes and pregnancy maintenance [12-15].

Accordingly, the present study was undertaken to determine the frequency of the Factor V Leiden mutation in women with RPL and to evaluate whether carrier status for the Factor V Leiden mutation was associated with the number of previous pregnancy losses in this cohort. The Prothrombin G20210A mutation was evaluated as a secondary inherited thrombophilic variant, and the potential influence of maternal age, hemoglobin concentration, and fasting blood glucose levels was investigated.

Methods

Study Design and Setting

This retrospective cross-sectional study was conducted at the Clinic of Hematology, Ordu State Hospital. Medical records of eligible patients evaluated between January 2023 and December 2025 were retrospectively reviewed to investigate the association between inherited thrombophilic mutations and RPL.

Study Population

A total of 103 women aged between 18 and 45 years with a history of RPL were included in the study. RPL was defined as two or more failed clinical pregnancies, in accordance with the recommendations of the American Society for Reproductive Medicine [3]. Patients with documented uterine anatomical abnormalities, chromosomal abnormalities, uncontrolled endocrine disorders (including diabetes mellitus and thyroid disease), or infectious causes of pregnancy loss, identified in the available medical records, were excluded from the study. Patients with incomplete medical records or lacking thrombophilia test results were also excluded.

Data Collection

Demographic, clinical, laboratory, and genetic information was retrospectively retrieved from the hospital electronic medical record system. The collected variables included maternal age, number of pregnancy losses, hemoglobin concentration, fasting blood glucose level, Factor V Leiden mutation status, and Prothrombin G20210A mutation status. Hemoglobin concentration and fasting blood glucose were obtained from routine laboratory evaluations conducted during the same clinical assessment in which genetic testing for inherited thrombophilia was requested. These laboratory values represented the patients' baseline clinical status at the time of evaluation, rather than reflecting measurements obtained during pregnancy. Hemoglobin and fasting blood glucose were included in the regression analysis because maternal hematologic and metabolic status has previously been associated with adverse pregnancy outcomes, and these measures were therefore considered clinically relevant covariates.

All patient information was anonymized before analysis, and confidentiality was maintained throughout the study.

Genetic Evaluation

The presence of the Factor V Leiden (F5 c.1601G>A, p.(Arg534Gln)) and *Prothrombin *G20210A (*F2 c.97G>A)* variants was determined by previously performed molecular genetic analyses that were recorded in the hospital laboratory information system. All genetic analyses had been performed in the same molecular genetics laboratory as part of routine clinical care, using standardized laboratory protocols and internal quality-control procedures. Mutation status was interpreted according to the official laboratory reports and recorded as negative, heterozygous, or homozygous. Zygosity information was available for all mutation-positive patients. Because of the retrospective nature of the study, detailed information regarding the specimen type, deoxyribonucleic acid extraction method, molecular assay platform, and assay manufacturer was not consistently available in the medical records.

Ethical Approval

Ethical approval for this study was granted by the Ordu University Non-Interventional Clinical Research Ethics Committee (approval no: 82, date: 11.03.2026). Because of the retrospective design of the study, the requirement for informed consent was waived by the Ethics Committee. All study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were carried out using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as frequencies and percentages. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test.

Comparisons between independent groups were performed using the Independent Samples t-test. Pearson correlation analysis was used to evaluate the relationships between continuous variables. Participants were additionally categorized according to fasting blood glucose levels (<100 mg/dL and ≥100 mg/dL), and comparisons between these groups were conducted accordingly.

To identify variables independently associated with the number of pregnancy losses, multivariate linear regression analysis was performed, including maternal age, hemoglobin concentration, fasting blood glucose level, Factor V Leiden mutation status, and Prothrombin G20210A mutation status. A two-sided p value of <0.05 was considered statistically significant. Regression coefficients are reported as unstandardized coefficients (B). Binary mutation variables were coded as 1=present and 2=absent.

Results

During the study period, the medical records of 103 women who were evaluated for RPL and met the study eligibility criteria were retrospectively reviewed. Complete demographic, clinical, laboratory, and genetic data were available for all eligible patients; therefore, all 103 women were included in the final analysis. The mean age of the participants was 34.15±5.74 years. The mean number of previous pregnancy losses was 2.10±0.44. The mean hemoglobin level was 11.91±0.99 g/dL. The demographic and clinical characteristics of the study population are presented in Table 1.

Factor V Leiden mutation was detected in 10 (9.7%) patients, all of whom were heterozygous. The Prothrombin G20210A mutation was identified in five (4.85%) patients, of whom four were heterozygous and one was homozygous (Table 1).

The mean number of pregnancy losses was 2.20 among patients with the Factor V Leiden mutation and 2.09 among those without the mutation. There was no statistically significant difference between the groups (p=0.479). Similarly, no significant difference was observed between patients with and without the Prothrombin mutation (p=0.655) (Table 2).

A moderate positive correlation was found between age and the number of pregnancy losses (r=0.51, p<0.001). Weak but statistically significant positive correlations were observed between hemoglobin levels and pregnancy loss (r=0.21, p=0.037) and between fasting blood glucose levels and pregnancy loss (r=0.25, p=0.010) (Table 3).

When patients were grouped according to fasting blood glucose levels, those with elevated glucose levels (≥100 mg/dL) had a significantly higher mean number of pregnancy losses compared to those with normal glucose levels (<100 mg/dL) (2.29 vs. 2.03, p=0.016) (Table 4).

Multivariate linear regression analysis demonstrated that

Table 1. Demographic and clinical characteristics of the study population

Variable	Mean ± SD or n (%)
Age (years)	34.15±5.74
Pregnancy losses (n)	2.10±0.44
Hemoglobin (g/dL)	11.91±0.99
Factor V Leiden heterozygous	10 (9.7%)
Factor V Leiden homozygous	0
Factor V Leiden negative	93 (90.3%)
Prothrombin G20210A heterozygous	4 (3.9%)
Prothrombin G20210A homozygous	1 (0.97%)
Prothrombin G20210A negative	98 (95.15%)
SD: Standard deviation	

Table 2. Comparison of mean number of pregnancy losses according to mutation status

Variable	Mean (mutation$^+$)	Mean (mutation$^-$)	p value
Factor V Leiden	2.20	2.09	0.479
Prothrombin G20210A	2.20	2.10	0.655
Statistical test: Independent Samples t-test			

Table 3. Correlation between clinical variables and number of pregnancy losses

Variables	r	p value
Age vs pregnancy losses	0.51	<0.001
Hemoglobin vs pregnancy losses	0.21	0.037
Blood glucose vs pregnancy losses	0.25	0.010
Statistical test: Pearson correlation analysis		

Table 4. Comparison of pregnancy losses according to blood glucose levels

Glucose level	Mean pregnancy losses	p value
<100 mg/dL	2.03	-
≥100 mg/dL	2.29	0.016
Statistical test: Independent Samples t-test		

maternal age was independently associated with the number of previous pregnancy losses within this cohort (B=0.033, standardized β=0.459, p<0.001). Hemoglobin level was also independently associated with the number of previous pregnancy losses (B=0.112, standardized β=0.293, p=0.016). In contrast, fasting blood glucose level, Factor V Leiden mutation, and Prothrombin G20210A mutation were not independently associated with the outcome (Table 5).

No missing data were identified for the variables included in the final statistical analyses.

Because the number of previous pregnancy losses was not normally distributed, additional non-parametric sensitivity analyses were performed. Spearman correlation analysis confirmed a significant positive correlation between maternal age and the number of previous pregn+ancy losses (ρ=0.475, p<0.001). No significant correlation was observed for fasting blood glucose levels (p=0.180, p=0.069), whereas hemoglobin levels were weakly correlated with the number of previous pregnancy losses (p=0.316, p=0.021). Furthermore, Mann-Whitney U tests demonstrated no significant differences in the number of previous pregnancy losses with respect to Factor V Leiden mutation status (p=0.495) or Prothrombin G20210A mutation status (p=0.638).

Discussion

The present study investigated the relationship between inherited thrombophilic mutations and RPL while simultaneously evaluating maternal demographic and metabolic characteristics. The principal finding was that neither Factor V Leiden nor Prothrombin G20210A mutation showed an independent association with pregnancy loss. In contrast, maternal age and hemoglobin concentration remained independently associated with the number of previous pregnancy losses after multivariate adjustment.

The prevalence of the Factor V Leiden mutation in our cohort was 9.7%, whereas that of the Prothrombin G20210A mutation was 4.85%. These frequencies are comparable with those reported in previous studies involving women with RPL, indicating that our study population is broadly representative of similar cohorts described in the literature [5,10].

Although inherited thrombophilia has long been proposed as a potential contributor to RPL, its exact role remains controversial. Several investigators have suggested that thrombophilic mutations may impair placental circulation through thrombotic mechanisms, thereby increasing the likelihood of miscarriage [9,11]. In addition, an association between Factor V Leiden mutation and unexplained recurrent fetal loss has been reported [16]. Nevertheless, systematic reviews and meta-analyses have produced inconsistent findings, and a definitive relationship between inherited thrombophilia and RPL has not been established [10,17]. Our findings are consistent with the latter reports, as neither of the investigated mutations was independently associated with pregnancy loss.

The clinical relevance of the Prothrombin G20210A mutation remains uncertain. While some studies have linked this mutation to adverse pregnancy outcomes [9], others have failed to demonstrate a significant association with recurrent miscarriage [10]. Consistent with these observations, the Prothrombin G20210A mutation was not identified as an independent predictor of pregnancy loss in the present study.

Among all evaluated variables, maternal age and hemoglobin concentration remained independently associated with the number of previous pregnancy losses in this cohort of women with RPL. The association with maternal age is consistent with previous studies showing that increasing maternal age is associated with a greater cumulative number of pregnancy losses, partly because of increasing embryonic chromosomal abnormalities and reduced oocyte quality [12,13]. However, because the present study included only women with RPL and lacked a control group, this association

Table 5. Multivariate linear regression analysis of factors associated with pregnancy loss

Variable	B	SE	Standardized β	p value
Age	0.033	0.008	0.459	<0.001
Hemoglobin	0.112	0.045	0.293	0.016
Fasting blood glucose	0.002	0.003	0.112	0.352
Factor V Leiden mutation	-0.163	0.148	-0.123	0.277
Prothrombin G20210A mutation	-0.190	0.174	-0.119	0.282

Model: Multivariate linear regression analysis including age, hemoglobin level, fasting blood glucose level, Factor V Leiden mutation, and Prothrombin G20210A mutation
Dependent variable: Number of previous pregnancy losses. Mutation variables were coded as 1=present and 2=absent
B: Unstandardized regression coefficient, β: Standardized regression coefficient, SE: Standard error

should not be interpreted as demonstrating that maternal age is an independent determinant of RPL. Older women have a longer reproductive lifespan and therefore greater cumulative opportunities to experience pregnancy losses, which may also have contributed to the observed association.

Although both fasting blood glucose and hemoglobin levels were associated with the number of previous pregnancy losses in the univariate analyses, only hemoglobin remained independently associated after multivariate adjustment, whereas the association with fasting blood glucose was no longer significant. The observed association between hemoglobin concentration and the number of previous pregnancy losses should be interpreted cautiously because laboratory measurements were obtained during routine clinical evaluation rather than during pregnancy, and because residual confounding cannot be excluded. Previous investigations have shown that impaired glucose metabolism may adversely influence pregnancy outcomes [14]. Furthermore, a recent systematic review and meta-analysis suggested that women with RPL exhibit abnormalities in several markers of glucose metabolism, particularly those reflecting insulin resistance, whereas fasting blood glucose alone is not consistently different between affected women and controls [18]. Accordingly, these findings should be interpreted cautiously because of the retrospective design, the timing of laboratory measurements, and the potential for residual confounding.

The findings of the present study should be interpreted within the context of its limitations, including its retrospective design and the absence of a control group. Although no statistically significant association was observed between Factor V Leiden mutation carrier status and the number of previous pregnancy losses within this cohort, these findings should not be interpreted as evidence against a possible role of inherited thrombophilia in RPL in general. Current recommendations regarding thrombophilia testing are based on the broader body of evidence rather than on the findings of the present study alone [3].

It should also be emphasized that inherited thrombophilia and antiphospholipid syndrome are distinct clinical entities with different levels of evidence and different clinical implications in RPL. Unlike antiphospholipid syndrome, which is an established and treatable cause of RPL, the contribution of inherited thrombophilic variants remains uncertain and is debated in the current literature.

Study Limitations

Several limitations should be acknowledged. First, the retrospective design may have introduced selection bias. Second, the relatively small number of patients carrying thrombophilic mutations may have reduced the statistical power to detect significant associations. Third, because of the retrospective design, several clinically relevant reproductive variables, including gravidity, parity, live birth history, reproductive duration, gestational age at pregnancy loss, and the interval between the first pregnancy and inclusion in the study, were not consistently available in the medical records, and, therefore, could not be included in the analyses. Consequently, residual confounding cannot be completely excluded. In addition, the limited variability of the outcome variable and the small number of mutation-positive patients should be considered when interpreting the statistical findings. Although additional non-parametric sensitivity analyses supported the primary results, these analyses should be regarded as exploratory, and a type II error cannot be excluded. Furthermore, because genetic testing for inherited thrombophilia was performed according to routine clinical practice, indication bias cannot be completely excluded. T he single-center design of the study may limit the generalizability of the findings to other populations.

Conclusions

Despite these limitations, this study provides additional evidence regarding the relationship between inherited thrombophilia and RPL by evaluating genetic, maternal, and metabolic characteristics within the same cohort. Moreover, the application of multivariate regression analysis strengthens the interpretation and reliability of the present findings.

Within this single-center retrospective cohort of women with RPL, maternal age was independently associated with the number of previous pregnancy losses, whereas neither Factor V Leiden nor the Prothrombin G20210A mutation was significantly associated with the number of previous pregnancy losses. Because this study did not include a control group, these findings should not be interpreted as evidence of a role for inherited thrombophilic variants in RPL. Larger prospective controlled studies are warranted to further clarify these associations.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by the Ordu University Non-Interventional Clinical Research Ethics Committee (approval no: 82, date: 11.03.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.O.G., Design: A.O.G., Data Collection or Processing: A.O.G., Ç.D., Analysis or Interpretation: A.O.G., Ç.D., Literature Search: A.O.G., Writing: A.O.G.

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