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Prevalence of Thrombophilia in Lebanese Women with Recurrent Miscarriages

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Abstract

Recurrent miscarriages can result from various causes, including thrombophilia. This study aims to determine the prevalence of thrombophilia among Lebanese women experiencing recurrent miscarriages. It includes 50 patients with a history of Recurrent Miscarriages (RM) who were suspected of having thrombophilia and underwent thrombotic risk assessment (CVD) between 2019 and 2023. Genetic testing using PCR-SSO was performed to identify mutations in factor V (Factor V Leiden and Factor V R2), prothrombin, factor XIII, fibrinogen, methylenetetrahydrofolate reductase (MTHFR C677T and A1298C), and thrombotic genotypes of PAI, ACE, and ApoE. All 50 patients were found to carry at least one mutation potentially associated with miscarriage. Mutation frequencies were 64% for MTHFR C677T, 52% for fibrinogen, 44% for MTHFR A1298C, 22% for FV R2, 14% for FXIII V34L, 6% for FV Leiden, and 4% for prothrombin G20210A. Genotypic analysis revealed 82% with the ACE D allele, 72% with the PAI 4G allele, and 8% with the ApoE E4 allele. These findings suggest that mutations in MTHFR, prothrombin, FV Leiden, and elevated PAI levels may increase the risk of recurrent miscarriage, with MTHFR mutations, the ACE D allele, and the PAI 4G allele being the most frequent in the Lebanese population studied.

Keywords: Thrombophilia; Miscarriages; Recurrent miscarriages; Genetic mutation; Thrombotic genotype

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Introduction

Recurrent Miscarriages (RM) are defined as at least two consecutive spontaneous pregnancy losses. In the general population, it is estimated that 15% - 20% [1]. Of pregnancies result in spontaneous miscarriage. RM can be caused by congenital or acquired factors. Uterine or cervical malformations, chromosomal abnormalities, hormonal disorders, thrombotic conditions, autoimmune diseases, and environmental or toxic factors can all contribute to recurrent miscarriages. However, despite thorough investigations, approximately 50% of spontaneous miscarriages remain unexplained [2]. In more than half of the women who experience RM, no specific cause can be identified. Given this high proportion of unexplained RM, congenital thrombophilia has attracted significant attention. Thrombophilia is defined as a predisposition to thrombosis and can be associated with various complications, including recurrent miscarriages, preeclampsia, intrauterine growth restriction, and others. Numerous studies have demonstrated a correlation between RM and thrombophilia. Several genetic abnormalities have been linked to recurrent miscarriages, including mutations in Factor V Leiden, prothrombin, and Methylenetetrahydrofolate Reductase (MTHFR). Other thrombotic genotypes such as platelet antigen mutations and PAI have also been implicated. In Lebanon, thrombophilia has a notable prevalence, especially considering the country is a genetic crossroad with a high incidence of congenital diseases and mutations.

Materials and Methods

In this study, we hypothesize that women with Recurrent Miscarriages (RM) have a high prevalence of genetic mutations associated with thrombophilia. The main objective is to assess the incidence of different types of thrombophilia in this population. We aim to compare these percentages with data reported in the literature for the general population.

Type of study and population

This is a retrospective study conducted at HDF, based on patient medical records available in the hospital's electronic system, DxCare, and the archives of the physicians in the Department of Gynecology and Obstetrics, in order to complete any missing information. The study was approved by the Ethics Committee of USJ and the Medical Affairs Directorate of HDF. The study participants were female patients aged between 20 and 50 years, with a history of miscarriage or Recurrent Miscarriage (RM), in whom thrombophilia was suspected and who underwent a thromboembolic risk screening test (CVD blood test) at HDF between 2019 and 2023.

Materials

CVD risk screening was performed in women after experiencing one or more miscarriages. The patients were tested for genetic mutations using PCR-SSO, including:

- Factor V (Factor V Leiden G1691A and Factor V R2 H1299R)
- Prothrombin (G20210A)
- Factor XIII (V34L)
- Fibrinogen (G455A)
- Methylenetetrahydrofolate reductase (MTHFR) (C677T and A1298C)
- Apo B (R3500Q)

In addition, they were tested for thrombotic genotypes by PCR-SSO, including:

- PAI (4G/4G, 4G/5G, 5G/5G)
- Platelet antigen (1a/1a, 1a/1b, 1b/1b)
- ACE (D/D, I/D, I/I)
- Apo E (E2/E2, E2/E3, E2/E4, E3/E3)

Methods

The study participants were identified based on the results of CVD risk screening tests performed at HDF. The women included in the study were between 20 and 50 years old. After obtaining approval from the heads of the Gynecology and Obstetrics Department, the medical records of these patients were reviewed to determine the reasons for conducting the CVD screening test. These reasons included a history of Miscarriage (MC) or Recurrent Miscarriage (RM), as well as suspected thrombophilia or other hematological abnormalities. From this group, patients with a history of MC or RM were selected. The collected data included the patients' clinical characteristics, as well as the results of genetic and biological tests. This information was extracted, organized into a secure database, and then statistically analyzed to assess the prevalence of various genetic mutations and their potential association with obstetric history.

Statistical analysis

The statistical analysis aimed to describe the incidence of each genetic mutation among patients with Recurrent Miscarriages (RM). The primary objective was to characterize the distribution of thrombophilia-associated mutations and determine their relative frequency within this population. Descriptive analyses were performed, and patient characteristics were expressed as percentages for quantitative variables. Data were entered, coded, and analyzed using Microsoft Excel. The resulting percentages were used to estimate the incidence of various genetic mutations (e.g., Factor V Leiden, prothrombin mutation, etc.) in the study population.

Results

Between 2019 and 2024, a total of 251 women aged between 20 and 50 years underwent CVD risk screening. Of these, 19.92% (n = 50) had a history of miscarriage. Therefore, 50 patients were included in the study. The average age of the participants was 34.76 years (± 4.99), with a median age of 36 years (Table 1).

The most frequent genetic mutation was MTHFR C677T, identified in 64% (n=32) of the patients, including 42% (n=21) in the heterozygous state and 22% (n=11) in the homozygous state. A mutation in the fibrinogen gene was found in 52% (n=26) of the patients, with 46% (n=23) being heterozygous and 6% (n=3) homozygous. MTHFR A1298C was mutated in 44% (n=22) of cases, including 30% (n=15) heterozygous and 14% (n=7) homozygous. Heterozygous mutations in the FV H1299R gene were identified in 22% (n=11) of patients. For Factor XIII, mutations were observed in 14% (n=7), including 12% (n=6) heterozygous and 2% (n=1)

Table 1: Frequencies of different genetic mutations in women with Recurrent Miscarriages (RM). Allele A represents the mutated allele, and allele G represents the wild-type allele.

Mutated gene	Genotype	Incidence (n=50)
MTHFR C677T	GG	36 % (n=18)
	AG	42 % (n=21)
	AA	22 % (n=11)
	Total of mutations	64 % (n=32)
Fibrinogene	GG	48 % (n=24)
	AG	46 % (n=23)
	AA	6 % (n=3)
	total of mutations	52 % (n=26)
MTHFR A1298C	GG	56 % (n=28)
	AG	30 % (n=15)
	AA	14 % (n=7)
	Total of mutations	44 % (n=22)
FV H1299R	GG	78 % (n=39)
	AG	22 % (n=11)
	AA	0 % (n=0)
	Total of mutations	22 % (n=11)
FXIII V34L	GG	86 % (n=43)
	AG	12 % (n=6)
	AA	2 % (n=1)
	Total of mutations	14 % (n=7)
FV Leiden	GG	94 % (n=47)
	AG	6 % (n=3)
	AA	0 % (n=0)
	Total of mutations	6 % (n=3)
Prothrombine	GG	96 % (n=48)
	AG	4 % (n=2)
	AA	0 % (n=0)
	Total of mutations	4 % (n=2)

Table 2: Frequencies of different thrombotic genotypes in women with Recurrent Miscarriages (RM).

Thrombotic genotype	Genotype	Incidence (n=50)
ECA	I/I	18 % (n=9)
	I/D	40 % (n=20)
	D/D	42 % (n=21)
	Total of mutations	82 % (n=41)
PAI	5G/5G	28 % (n=14)
	4G/5G	52 % (n=26)
	4G/4G	20 % (n=10)
	Total of mutations	72 % (n=36)
Apo E	E2/E3	12 % (n=6)
	E3/E3	76 % (n=38)
	E3/E4	8 % (n=4)
	Total of mutations	8 % (n=4)

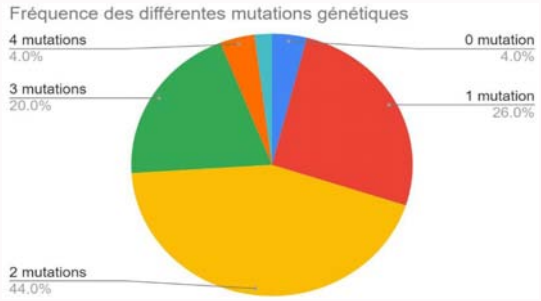

Figure 1: Diagram showing the frequencies of different genetic mutations in women with a history of recurrent miscarriages. FCR.

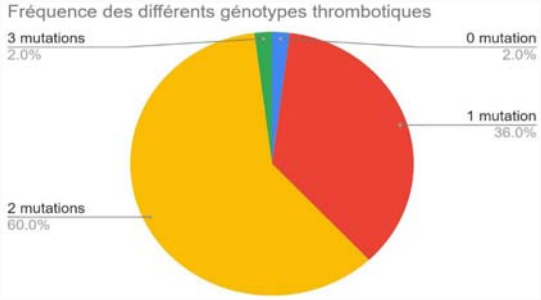

Figure 2: Diagram showing the frequencies of different thrombotic genotypes in women with a history of recurrent miscarriages.

homozygous. Heterozygous mutations in Factor V Leiden were found in 6% (n=3) of patients, and prothrombin gene mutations were detected in 4% (n=2) (Table 2).

Regarding thrombotic genotypes, the most prevalent was ACE, with an incidence of 82% (n=41), including 40% (n=20) in the heterozygous I/D form and 42% (n=21) in the homozygous D/D form. The second most frequent was PAI, found in 72% (n=36) of patients, with 52% (n=26) in the heterozygous form and 20% (n=10) in the homozygous form. Finally, Apo E was mutated in 8% (n=4) of cases, all presenting the E3/E4 genotype (Figure 1).

Four percent of the women showed no genetic mutations among the seven genes studied. Twenty-six percent had only one mutation, 44% had two mutations, 20% had three, and 4% had four mutations.

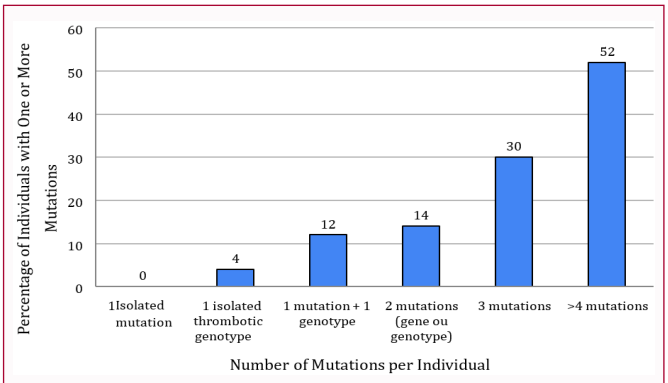

Figure 3: Histogram showing the percentage of individuals with one or more genetic mutations.

Only one woman was found to have five genetic mutations (Figure 2).

Regarding thrombotic genotypes, 2% of the women had normal genotypes. Thirty-six percent presented with one mutated genotype, 60% had two mutated genotypes, and 2% had all three thrombotic genotypes (PAI, ACE, and ApoE) mutated (Figure 3).

No woman presented with an isolated genetic mutation, but 4% had a single mutated thrombotic genotype. Twelve percent of the women had both a genetic mutation and a thrombotic genotype mutation. Among the 50 women, 14% had two mutations (either gene or genotype), 30% had three mutations in total, and 52% had more than four mutations.

Discussion

In this retrospective study, we examined the incidence of various thrombophilias in women with a history of Recurrent Pregnancy Loss (RPL). RPL is defined as the occurrence of two or more consecutive spontaneous abortions, affecting approximately 1% - 3% of women of reproductive age [3]. For a long time, a relationship between inherited thrombophilias and RPL has been suspected. While this hypothesis has been supported by several studies, the data remains inconsistent, and the evidence for such an association is still not definitively established. Some studies have reported a link between genetic mutations and RPL, while others have highlighted the absence of a significant correlation between the two entities.

In this study, 64% of women with a history of miscarriage carried the MTHFR C677T mutation, either in homozygous or heterozygous form. This result is consistent with findings in the Lebanese population [4], where 66.6% of women with RPL had this mutation. In the Syrian population, a rate of 59% was observed, with 18% homozygosity and 41% heterozygosity [5]. In Arab populations, the prevalence is around 66% [6], and 43% in Egypt [7].

The MTHFR C677T mutation leads to an increase in blood homocysteine levels, an important risk factor for thromboembolic events, which can impair placental vascularization. A recent meta-analysis confirms a high risk of RPL with the MTHFR C677T mutation [5,8]. A large number of studies suggest contradictory results to these conclusions [9-11]. This discrepancy may be due to the multifactorial nature of RPL, involving both genetic factors, including inherited thrombophilias, and environmental factors [1].

Like MTHFR C677T, the MTHFR A1298C mutation also results in elevated homocysteine levels. However, whether in homozygous or heterozygous form, this mutation alone is not sufficient to cause

a marked increase in homocysteine concentration. It is the presence of compound heterozygosity at C677T and A1298C that leads to the same manifestations observed in C677T homozygosity and thus to elevated homocysteine levels [12]. Therefore, its association with RPL is less consistent than the one established between MTHFR C677T and RPL. While some studies have observed an increased frequency of A1298C among women with RPL [5,13], others have not found a significant correlation [11,14].

In 2016, one study suggested that women homozygous for the mutations (C677T and A1298C), or compound heterozygotes (C677T and A1298C), are at higher risk for RPL [5]. In our study, about 14% of cases were homozygous for A1298C and 16% carried the compound heterozygous genotype.

The role of the β-fibrinogen gene mutation -455G/A in women with RPL remains controversial. Any dysregulation in fibrinogen levels, whether excess or deficiency, may result in obstetric complications, including RPL [15]. However, most studies in the literature suggest no significant correlation between this mutation and RPL [15-17].

The FV R2 (H1299R) mutation, whether isolated or combined with the FV Leiden mutation, has been associated with a significantly increased risk of venous thrombosis. Moreover, it impairs coagulation regulation by slightly increasing resistance to activated protein C and results in higher secretion of FV1, a more thrombogenic isoform of factor V [16,18]. The precise role of FV R2 in obstetric complications remains debated, but its presence, especially when combined with FV Leiden, may exacerbate coagulation dysfunction and lead to pregnancy complications. No significant correlation has been established between FV R2 and RPL in the literature to date [19].

The FXIII Val34Leu polymorphism alters the structure of fibrin, stabilizing it and making it more or less resistant to fibrinolysis. This variant has been associated with an increased risk of RPL, particularly in its homozygous form and in heterozygous form when combined with the hypofibrinolytic 4G variant of the common PAI-1 4G/5G polymorphism [20]. Furthermore, a 2017 meta-analysis suggests that the correlation between FXIII Val34Leu and RPL is strongly influenced by ethnicity. This association was observed only in Asian individuals, while no significant relationship was found in European or South American populations [21]. These ethnicity-dependent results suggest that this gene may act in combination with other factors to cause RPL. In our study, approximately 14% of women carried this mutation, which aligns with findings in Turkey [16].

Considered one of the major risk factors for RPL, the FV Leiden mutation is among the most prevalent worldwide, with a prevalence of approximately 14.4% [22]. The FV Leiden mutation contributes to a hypercoagulable state by making FV resistant to activated protein C. This can lead to the formation of microthrombi in placental blood vessels, thereby disrupting placental circulation and contributing to RPL. In our study, 6% of women were carriers of this mutation. This is significantly lower than the 21% reported in a 2022 Lebanese study where women with at least two consecutive miscarriages were included [4]. This difference can be attributed to the smaller sample size in our study and the broader inclusion criteria (including women with a single miscarriage). Nevertheless, many studies worldwide have shown a strong association between FV Leiden and RPL, particularly in the Middle East, Saudi Arabia, and Europe [4]. Despite numerous studies suggesting a link between FV Leiden and RPL, others highlight the lack of statistically significant evidence.

Like FV Leiden, the prothrombin G20210A mutation is among the most common thrombophilias. Its prevalence is estimated at about 2% in the Middle East [23]. This mutation increases prothrombin expression, leading to a hypercoagulable state and increased risk of thromboembolic complications. Among the 50 participants, 4% were identified as carriers of this mutation in the heterozygous form, consistent with data from the Lebanese population [4]. Similar results have been found in populations with shared ethnicity, such as Palestinians, Turks, Syrians, and others in the Middle East. As with FV Leiden, several studies have demonstrated an association between prothrombin G20210A and RPL, while others have not confirmed it [4].

In addition to these genetic mutations, thromboembolic genotypes have also been linked to RPL. In our study, we focused on three genotypes: ACE, PAI, and ApoE.

ACE and PAI have similar mechanisms. While their functions differ - ACE regulates blood pressure and PAI controls fibrinolytic activity - certain genotypes in both can lead to increased PAI, contributing to a thromboembolic state [24]. This hypercoagulability may be associated with RPL.

ACE presents three main genotypes: I/I, I/D, and D/D. Among these, two are associated with increased PAI-1 levels (I/D and D/D) [16,24]. In this study, about 82% of women with RPL carried the D allele, consistent with findings in the Egyptian population (86.2%) [25]. Interestingly, several studies have reported a strong association between ACE and RPL [24,26].

PAI also has three genotypes: 5G/5G, 4G/5G, and 4G/4G. The 4G allele is responsible for higher PAI concentrations in the blood. Increased PAI leads to reduced fibrinolysis, resulting in a hypercoagulable state that impairs blood circulation, especially placental. The combined total of heterozygous and homozygous genotypes was around 72% in our sample (52% and 20%, respectively), which aligns with data from Serbia [27]. Although studies report contradictory results - some deny a statistically significant correlation between PAI and RPL [27], others propose a close association between the two. A Serbian study in 2020, for instance, found no link between PAI and RPL or between FXIII and RPL, but observed an increased risk of RPL when both were present together [27]. Moreover, a recent meta-analysis highlights this association between PAI and RPL in both heterozygous and homozygous forms [28].

Apolipoprotein E (ApoE) is also implicated in RPL. It has been shown that two alleles, ApoE2 and ApoE4, are associated with a thromboembolic state. However, a 2022 meta-analysis indicates that ApoE4 confers a higher risk of RPL compared to ApoE2 and ApoE3 [29]. Furthermore, the role of ApoE4 in RPL varies depending on ethnicity. In the Asian population, a significant correlation is observed with a prevalence of 7.1% - 24%, consistent with our population (8%). In contrast, no relevant correlation has been found in Caucasian populations. Nevertheless, ApoE3 appears to confer a higher fertility potential compared to the other alleles [29].

The associations between most of the thrombophilias studied in this work and RPL remain unclear. Although some studies suggest a possible link, the mechanisms by which these coagulation disorders influence the occurrence of RPL are not clearly understood.

RPL has been significantly associated with several thrombophilias,

notably FV Leiden, prothrombin G20210A, both MTHFR mutations (C677T and A1298C), PAI, and ACE. Indeed, in our study, we found that all women with a history of miscarriage or RPL had at least one or more of these mutations.

Limitation and Biais

This study faces several limitations and biases. First, there is a selection bias. The sample size of this study was relatively small, limiting the generalizability of the results to the Lebanese population as a whole. A larger sample would strengthen the conclusions drawn from this work and yield results that are more representative of Lebanese women experiencing Recurrent Pregnancy Loss (RPL).

Furthermore, as a descriptive study without a control group, we were unable to establish a direct relationship between the various thrombophilias and RPL. We relied solely on comparisons with results from the literature. Therefore, case-control cohort studies would be beneficial to address this limitation.

Given the very low number of participants between 2019 and 2023, the inclusion criteria were broadened to include not only women with RPL but also those who had experienced a single miscarriage. In fact, many women undergo thrombophilia screening and Cardiovascular Disease (CVD) risk assessment after a first miscarriage, even though this does not necessarily meet the recommended indications for such testing.

Conclusion

In conclusion, the present study, which examined 50 patients with Recurrent Pregnancy Loss (RPL), highlights the prevalence of various thrombophilias within this population. Although certain forms of thrombophilia-such as MTHFR mutations (C677T and A1298C), Factor V Leiden, prothrombin mutation, and elevated PAI-1-appear to be the most plausible contributors in these patients, the relationship between these genetic abnormalities and the occurrence of RPL remains complex and multifactorial.

Given the wide range of factors involved in RPL, it is not possible to draw definitive conclusions about the direct role of thrombophilias in early fetal loss. In light of these findings and the significant frequency of certain mutations, thrombophilia screening through blood testing is recommended in cases of RPL, particularly when no obvious cause has been identified.

Future directions should be considered. Longitudinal case-control cohort studies could help to better understand the impact of these thrombophilias on RPL. Further research into the effectiveness of anticoagulant therapies and targeted treatments may also pave the way for new therapeutic approaches that could benefit this group of patients.

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