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The factor V Leiden mutation, high factor VIII, and high plasminogen activator inhibitor activity: etiologies for sporadic miscarriage☆,☆☆

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Abstract

We hypothesized that the thrombophilic G1691A factor V Leiden gene mutation was a common significant cause of sporadic first trimester miscarriage. We compared thrombophilia and hypofibrinolysis in 92 women (85 white, 5 black, 2 other) with 1 or more pregnancies and 1 miscarriage (143 live births, 92 miscarriages) (cases) and in 380 female controls (355 white, 21 black, 4 other) with 1 or more pregnancies and 0 miscarriages (964 live births). We used polymerase chain reaction techniques to characterize thrombophilic gene mutations (G1691A V Leiden [FV], G20210A prothrombin, C677T/A1298C MTHFR) and hypofibrinolytic gene mutations (plasminogen activator inhibitor [PAI-1] activity 4G4G). We carried out serologic measures of thrombophilia (homocysteine, anticardiolipin antibodies [ACLA] immunoglobulin G and immunoglobulin M, lupus anticoagulant, factor VIII, factor XI, protein C, total and free protein S, antithrombin III) and hypofibrinolysis (plasminogen activator inhibitor activity [PAI-Fx], lipoprotein[a]). Of the 380 controls, 6 (1.6%) had FV heterozygosity vs 12 heterozygous and 2 homozygous FV cases (15.2% [14/92]; $P < .0001$). Plasminogen activator inhibitor activity was high ($\geq$21.1 U/mL) in 21 (33%) of 63 cases vs 27 (18%) of 152 controls ($P = .013$). Factor VIII was high (>150%) in 15 (31%) of 48 cases vs 19 (18%) of 103 controls ($P = .079$). By logistic regression, with age and factor VIII (categorical [$\leq$150%, >150%]) as explanatory variables and group (cases, controls) as the dependent variable, after adjusting for age, high factor VIII was a significant predictor for miscarriage (odds ratio, 3.28; 95% confidence interval, 1.34-8.04; $P = .01$). There were no other group differences ($P > .05$) in measures of thrombophilia and hypofibrinolysis. After unexplained sporadic first trimester miscarriage, we suggest that measurements be done of the FV mutation, PAI-Fx, and factor VIII, etiologies for sporadic miscarriage.

1. Introduction

In most [1-11] but not all [12-14] studies of recurrent pregnancy loss (RPL) ($\geq$3 consecutive pregnancy losses <20 weeks of gestation), the factor V G1691A mutation (FV) has been identified as a major pathoetiology. Thromboprophylaxis with low-molecular-weight optimizes subsequent live birth outcomes in women with the factor V mutation [11,15-18]. Recently, Gris et al [18] prospectively studied 160 women with heterozygous factor V or prothrombin G20210A mutations or protein S deficiency who had one unexplained pregnancy loss, all given folic acid 5 mg/d. Half of the women were randomized to aspirin 100 mg/d and half to enoxaparin 40 mg/d. Twenty-three (29%) of the 80 women treated with aspirin and 69 (86%) of 80 on enoxaparin had a healthy live birth ($P < .0001$) [18]. Neonate weight was higher in women treated with enoxaparin, and small for gestational age neonates who were more frequent in women treated with aspirin [18]. No significant aspirin or enoxaparin side effects were observed in the women or newborn [18]. Gris et al [18] noted that "...our patients had the 3 constitutional thrombophilic disorders that have been validated by the available meta-analysis of the published studies [6] and mainly the 2 that are the most frequently diagnosed, namely the factor V and factor II mutations."

In the current study, we hypothesized that the thrombophilic G1691A factor V Leiden gene mutation was a common significant cause of sporadic first trimester miscarriage.

☆ This work was carried out with signed informed consent following a protocol approved by the Jewish Hospital Institutional Review Board.

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2. Materials and methods

2.1. Study design and subjects

This study followed a protocol approved by the Jewish Hospital Institutional Review Board, with written informed consent. At the initial outpatient visit, a detailed obstetrical history was obtained of number of pregnancies, spontaneous first trimester miscarriages, second and third trimester fetal loss, elective abortions, and live births. To reduce possible heterogeneity of thrombophilic-hypofibrinolytic etiologies for sporadic miscarriage cases, women with fetal loss in the second or third trimester were excluded.

Efforts were made to avoid selection bias by serially inviting all cases ($\geq$1 pregnancy and 1 first trimester miscarriage) and controls ($\geq$1 pregnancy, $\geq$1 live births, 0 miscarriages) to participate in the temporal order of their referral. Ninety-two cases and 380 controls were referred from a suburban Cincinnati obstetrics practice or had been referred for diagnosis and therapy of hyperlipidemia at the Jewish Hospital Cholesterol Center. No eligible women from the obstetrics practice and 4 from the Cholesterol Center declined participation. The 92 cases included 85 whites, 5 blacks, and 2 others. The 380 controls included 355 whites, 21 blacks, and 4 others. In the temporal order of their referral, a second case group included 72 women from suburban and urban Cincinnati obstetrics practices for evaluation of RPL ($\geq$3 consecutive pregnancy losses <20 weeks of gestation) [3,12-15]. No eligible RPL cases declined participation. Of the 72 women with RPL, 66 were white, 4 black, and 2 other.

To enter the study, women in the 1 miscarriage group and in the RPL group had to be free of the following known etiologies for spontaneous abortion: anatomic uterine abnormalities, cervical incompetence, poorly controlled diabetes, hypothyroidism, and previously known antiphospholipid antibody syndrome or familial thrombophilia (G1691A factor V Leiden, G20210A prothrombin gene mutations) [3,19]. No exclusions were made for parental karyotyping abnormalities [19], preferential X chromosome inactivation [20], or immunoglobulin A anti–beta2-glycoprotein antibodies [21], most of which had never been analyzed after previous pregnancy losses.

The current report is a consecutive case series of 92 women with 1 or more pregnancies and 1 first trimester miscarriage; 380 women with 1 or more pregnancies, 1 or more live births, and no miscarriages; and 72 women with RPL, free of the above exclusionary criteria.

2.2. Blood sampling and plasma preparation

Fasting blood was drawn from 8:30 to 10 AM from seated patients. Blood was collected in 3.2% buffered sodium citrate. The samples were immediately centrifuged at 2600*g* for 15 minutes to obtain platelet-poor plasma. Blood for polymerase chain reaction analysis was drawn in EDTA and the DNA extracted for subsequent analysis.

2.3. Coagulation assays

All coagulation measures were made in the nonpregnant state in both patients and controls, with subjects not taking hormones or corticosteroids that could affect serologic measures of coagulation. Polymerase chain reaction assays for 4 gene mutations (G1691A factor V Leiden, G20210A prothrombin, C677T/A1298C MTHFR, 4G/5G plasminogen activator inhibitor 1) were performed as previously described [3,11,22-25].

Non–polymerase chain reaction coagulation tests in plasma and serum were performed following previously published methodology [3,11,23-25]. The following tests were performed in plasma: dilute Russell's viper venom time, activated partial thromboplastin time, factor VIII, factor XI, plasminogen activator inhibitor activity (PAI-Fx), protein C antigenic, protein S total (antigenic), protein S free (antigenic), and antithrombin III (functional). The following tests were performed in serum: anticardiolipin antibodies, homocysteine, and lipoprotein(a).

2.4. Statistical methods

Categorical comparisons between cases, controls, and RPL cases were made by χ^2 analyses or Fisher exact test [26]. Spearman correlations were done between factor VIII or PAI-Fx with age, race, and body mass index (BMI) and between the factor V Leiden mutation and race. Logistic regression [26] was carried out with the dependent variables being group ($\geq$1 pregnancy, 1 miscarriage; $\geq$1 pregnancy, $\geq$1 live birth, 0 miscarriages) and explanatory variables in one model being factor VIII and age and, in the second model, PAI-Fx and BMI.

Sample size calculations [26] were done based on an estimated 2% Cincinnati area prevalence of the factor V Leiden mutation [24] and assuming a 15% factor V Leiden prevalence [3] in sporadic miscarriage cases, with α = .05 and power = .80.

3. Results

3.1. Thrombophilia and hypofibrinolysis in women with 1 miscarriage, 0 miscarriages, and RPL

The 92 cases had 143 live births and 92 miscarriages. The 380 controls had 964 live births and no miscarriages.

There were no racial differences (P = .84) among cases, controls, and RPL cases. Race did not correlate with presence of the factor V Leiden mutation in cases (r = 0.12, P = .25), in controls (r = 0.03, P = .51), or in RPL cases (r = 0.11, P = .37).

Race did not correlate with factor VIII in cases (r = 0.05, P = .74) or in controls (r = 0.12, P = .24) nor did it correlate with PAI-Fx in cases (r = 0.18, P = .15) and controls (r = 0.07, P = .43).

Of the 380 controls, 6 (1.6%) had FV heterozygosity vs 12 heterozygous and 2 homozygous FV cases (15.2% [14/92]) in women with 1 miscarriage (P < .0001, Fig. 1).

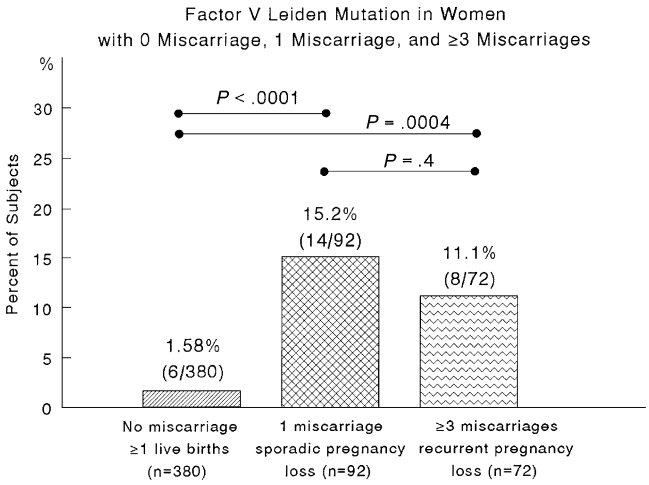

Fig. 1. Percentage of subjects with the factor V Leiden mutation in 92 women with 1 or more pregnancies and 1 miscarriage (sporadic miscarriage); in 380 women with 1 or more pregnancies, 1 or more live births, and 0 miscarriages; and in 72 women with RPL.

Our sample size of 92 cases and 380 controls was more than large enough than the 78 cases and 78 controls needed to declare a case-control difference in the factor V mutation with $\alpha = .05$ and power = .80. Of the 72 cases with RPL, 8 (11.1%) had FV heterozygosity, not different ($P = .4$) from the 1 miscarriage group but different from the live birth controls ($P = .0004$, Fig. 1).

Plasminogen activator inhibitor activity was high (≥21.1 U/mL) in 21 (33%) of 63 cases vs 27 (18%) of 152 controls ($P = .013$). Plasminogen activator inhibitor activity was correlated with BMI in cases ($r = 0.41$, $P = .0009$) and in controls ($r = 0.43$, $P < .0001$), but was not correlated with age ($P \geq .2$ for both). After adjusting for BMI, PAI-Fx (categorical) was marginally associated with the miscarriage group ($P = .07$).

Factor VIII was high (>150%) in 15 (31%) of 48 cases vs 19 (18%) of 103 controls ($P = .079$). Factor VIII was not correlated with age in cases ($r = 0.20$, $P = .16$), but was correlated with age in controls ($r = 0.36$, $P = .0002$). Factor VIII was not correlated with BMI ($P > .25$ for both groups). After adjusting for age, factor VIII (categorical [>150%, ≤150%]) was associated with the miscarriage group (odds ratio, 3.28; 95% confidence interval, 1.34-8.04; $P = .01$).

There were no other group differences ($P > .05$) in measures of thrombophilia and hypofibrinolysis.

4. Discussion

In the current report, women with a single first trimester miscarriage were more likely than women with 1 or more live births and 0 miscarriages to have the factor V Leiden mutation (15.2% vs 1.6%, $P < .0001$) and were comparable with women with RPL for the factor V Leiden mutation (15% vs 11%, $P = .4$).

Low-molecular-weight heparin optimizes live birth outcomes in women having had one unexplained "sporadic" pregnancy loss associated with familial thrombophilia (heterozygous factor V Leiden or prothrombin gene mutations or protein S deficiency) [18]. As reported by Gris et al [18], in women with familial thrombophilia who had one previous miscarriage, only 23 (29%) of 80 women treated with aspirin but 69 (86%) of 80 on enoxaparin in subsequent pregnancies had a healthy live birth ($P < .0001$) [18]. The G1691A factor V Leiden mutation is also a major pathoetiology for RPL, as in our current report and other studies [1-11]. Low-molecular-weight heparin optimizes live birth outcomes in subsequent pregnancies in women with RPL and the factor V Leiden mutation [11,15-18].

To a large extent, coagulation disorders that are associated with first trimester miscarriage are similarly associated with second and third trimester fetal loss [27-35]. As reported by Martinelli et al [27], in 67 women with a first episode of unexplained late fetal loss (fetal death after ≥20 weeks of gestation) compared with 232 women with 1 or more normal pregnancies and no late fetal losses, both the factor V and prothrombin mutations were associated with an approximate tripling of the risk of late fetal loss.

Because there were no racial differences ($P = .84$) among cases, controls, and RPL cases, race was not a confounding factor in comparisons of gene frequencies in cases vs controls. However, in population studies, the factor V Leiden mutation [36], the prothrombin gene [37], the MTHFR gene [38], and the PAI-1 gene [39] are all more common in whites than in blacks.

The current study revealed that women with 1 miscarriage were more likely than women having 1 or more live births with 0 miscarriages to have high levels of hypofibrinolytic PAI-Fx as well as high thrombophilic high factor VIII. High PAI-Fx has been previously associated with pregnancy loss [3,40-43]. Plasminogen activator inhibitor activity can safely be lowered during pregnancy with metformin [44]. Enoxaparin can promote conception and can optimize live birth outcomes in women whose hypofibrinolysis is associated with RPL [45]. High factor VIII has previously been associated with RPL [46,47].

After unexplained sporadic first trimester miscarriage, to provide the option of treatment to prospectively optimize subsequent live birth outcomes, we suggest that measurements be done of the factor V Leiden mutation [18], PAI-Fx, and factor VIII, etiologies for sporadic miscarriage.

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