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# Factor V Leiden, the Use of Oral Contraceptives, and a Thrombophilic Event in a Perimenopausal Woman: A Case Report

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## Abstract

The following article outlines the case of a perimenopausal woman seeking relief from vasomotor symptoms, who had a previously undetected inherited coagulopathy disorder, is prescribed estrogen, and has a thrombotic event. The accompanying subspecialty consults surrounding the controversial follow-up care topics of anticoagulation therapy, menorrhagia management, migraine management, and genetic counseling and testing for the family members are explored. The clinical utility of Factor V Leiden testing, the recurrence risk of thrombotic events in such individuals, the familial risk, the future use of estrogen and/or progesterone, and a cost benefits analysis are discussed.

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## CASE STUDY

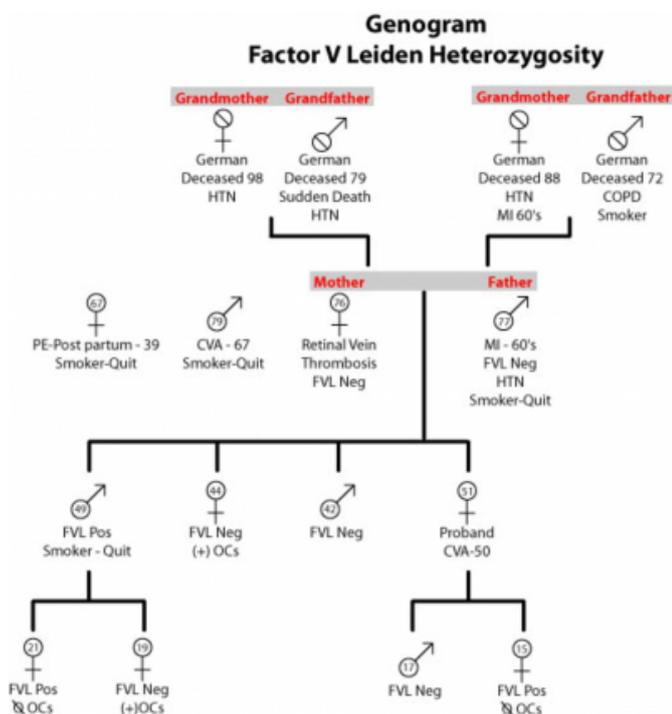
The patient was a fifty-year old female who presented to the emergency department (ED) accompanied by her son and father with a chief complaint of mental status change. She was late picking her daughter up from choir practice when the choir director followed her, and noticed her getting lost on a known route home. Her history of present illness is significant for taking oral contraceptives (OCs) for menopausal symptoms and dysfunctional uterine bleeding for the past six weeks prior to the presentation. Before that, she had been on the combined estrogen/progesterone patch. Additionally, she has been having increasing complaints of headache.

Her past medical/surgical history was significant for migraine headaches, hypothyroidism, and bilateral tubal ligation. She had traveled long distances and flown for 13-14 hours in the past without developing any adverse sequelae. She had a history of prior OC use in her twenties and experienced no problems at that time. She was a G2P1102 with one preterm breech Caesarian delivery at thirty-six weeks due to severe pre-eclampsia and one successful full term vaginal birth after Caesarian with her second

pregnancy. The patient's medications included Mircette, Cytomel, hydrochlorothiazide, and phentermine. Reportedly, she was under the care of a "diet doctor."

This patient's family history was significant for a myocardial infarction (MI) in her father in his early 60's and an MI in her paternal grandmother in her 50's. This same grandmother eventually died in her 80's from complications related to cerebrovascular accidents (CVAs). The maternal history is significant for a post-partum pulmonary embolus (PE) in an aunt (39) and a CVA in an uncle (65). A genogram can be viewed below.

**Figure 1**



Significant radiological findings included the following:

**Figure 2**

CT of the head without contrast: no evidence of acute intracranial abnormalities

MRI of the brain with and without IV gadolinium contrast: there were abnormal signal within the deep central veins within bilateral thalamostriate, bilateral internal cerebral, vein of Galen and proximal straight sinus. Areas of significant dark magnetic susceptibility signal were seen as hyperdense on the preceding CT study, confirming the venous thrombosis.

MR angiogram of the brain without contrast: on the source transverse arterial images dark signal consistent with thrombosis were seen in central veins and region of torula.

Her significant lab results included an undetectable TSH and the following hematology panel:

**Figure 3**

Prothrombin promoter mutation I negative (2210)  
 Dilute Russell viper venom time I negative (MTHFR)  
 Lupus anticoagulant I negative  
 Homocysteine 7.4 (within range)  
 Anticardiolipin antibody negative  
 Protein C, S, and anti-thrombin-3 were not drawn as she was currently on heparin (i.e., so these would have been artificially low and not interpretable)  
 Factor V Leiden (FVL) mutation I positive/heterozygous A

Her physical exam was unremarkable except for the following neurological findings: she was alert and oriented x 3 but with regurgitative answers and limited verbal output. Her family reported a personality change. As her time spent in the emergency department progressed, her confusion slowly progressed. She was admitted to the intensive care unit with the diagnoses of bilateral thalamic cerebrovascular accidents and cerebral vein thromboses and FVL heterozygosity. Her hospital course was uncomplicated, and she was discharged on day six after a complete neurocognitive and psychomotor recovery.

Just short of six months after the initial cerebral event, this patient again presented to the emergency department at the insistence of her family for subtle mental status changes. MRI of the brain with and without IV contrast at this time revealed no evidence of acute ischemia or venous thrombosis. MR angiography and venography revealed an improved appearance compared with prior MRV and MRA imaging.

After the second ED presentation, the patient and her spouse chose to seek secondary medical consultation due to conflicting opinions/advice of the different specialist physicians involved in her case. These opinions are listed below and demonstrate the confusion and frustration experienced by the patient.

**HEMATOLOGY**

The recommendation was that she should not take estrogen or progesterone unless anticoagulated with warfarin and that she receive increased prophylaxis for procedures and situations where thrombosis may be more likely, such as traveling long distances or having surgery. Currently, she was to receive 6-12 months of anticoagulation with warfarin to insure appropriate recanalization and development of collateral circulation secondary to the CVT.

## NEUROLOGY

Speculation was that the use of triptans might increase the risk of ischemic events through vasoconstriction; neither current nor recent triptan use was associated with risk of stroke (1). Regarding her migraines and headaches, when possible to discontinue warfarin, consideration of treatment with a triptan is a possibility.

## GYNECOLOGY

With FVL deficiency and a previous stroke, the patient should not have any estrogen or progesterone preparations ever.

## CLINICAL UTILITY OF FACTOR V LEIDEN TESTING

Most individuals with FVL mutation are heterozygous; only 0.02% are homozygous (2). As FVL is currently the most commonly recognized familial thrombophilia, expert consensus recommendations on methodology and diagnostic, prognostic, and management issues pertaining to clinical FVL testing were reviewed, edited, and ultimately approved by the majority of a panel of coagulation laboratory experts (3). Consensus recommendations were generated for topics of direct clinical relevance, including (one) defining those patients and family members who should and should not be tested for FVL; (two) defining the preferred FVL laboratory testing methods; and (three) defining the therapeutic, prophylactic, and management ramifications of FVL testing in affected individuals and their family members.

Factor V (FV) is a critical cofactor participating in the blood coagulation process that results in the formation of the fibrin clot at the site of a vascular injury (4). FV circulates in plasma as a single-chain procofactor that requires proteolytic cleavage for expression of its function in the procoagulant enzyme complex that activates prothrombin to thrombin; activated FV (FVa) is the substrate for activated protein C (APC), which destroys the clot-promoting properties of FVa following cleavage of the membrane-bound cofactor and is responsible for complete inactivation (5).

As described by de Ronde and Bertina (6), a point mutation in the coagulation FV gene (G 1691 → A, resulting in an Arg506 → Gln amino acid substitution in the FV molecule [FVL], leading to activated protein C resistance) is the most common genetic risk factor for familial thrombophilia. Cleavage at Arg 306 occurs only on the membrane-bound

cofactor and is responsible for complete inactivation (5). Individuals with a G → A substitution at nucleotide 1691 in the FV gene (resulting in an Arg 506 → Gln mutation in the factor V molecule; FVL) have a poor anticoagulant response to APC (APC resistance), which is associated with a significant increase in risk for venous thrombosis (7-fold for heterozygotes and 80-fold for homozygotes); APC resistance has been suggested to be the most common risk factor for developing deep venous thrombosis, most likely because FVaL is inactivated by APC at a slower rate than is normal FVa, thus leading to prolonged thrombin generation (5).

Screening for FVL mutation involves two tests; an initial screening test will identify individuals who are at high risk of having FVL mutation (2). The test currently used in the United States is a commercially available APC resistance test; the sensitivity and specificity as reported by the manufacturer are 76% and 98%, respectively (2). For those who screen positive for the FVL mutation, DNA mutation is confirmed by polymerase chain reaction (PCR); the cost of the APC resistance test ranges from \$75-\$94 and the cost of the confirmatory FVL PCR ranges from \$195-\$218 (2). A new mini-sequencing method using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry was developed for the screening of the 1692G → A substitution in FV; in this method a fragment of genomic DNA containing the 1691st base is first amplified, followed by mini-sequencing (4). This method is accurate, fast, and potentially allows for simultaneous multiplex genotyping of a number of mutation sites associated with thrombophilia and clot formation (4).

Mutations in the FV gene are associated with cerebral-vein thrombosis (CVT); CVT is a frightening event because of the severity of the clinical manifestations and the high mortality rate, estimated to be 5 to 30 percent (7). Clinically, CVT presents with a wide range of symptoms, including headache, focal deficits (motor or sensory), dysphasia, seizures, and impaired consciousness (7).

## RECURRENCE RISK

Patients with a first venous thromboembolism (VTE) event should receive oral anticoagulant treatment for at least 3 months after a deep vein thrombosis (DVT) and at least 6 months after a pulmonary embolism. Whether long-term continuation of anticoagulant treatment should be considered after a first venous event in carriers of a thrombophilic defect from thrombophilic families is still uncertain, as few

comprehensive data are available on whether inherited risk factors increase the risk of recurrence (8). In the absence of objective evidence of cerebral hemorrhage, Italian stroke specialists give oral anticoagulant therapy for at least three months after the occurrence of CVT to patients without coagulation defects; for up to one year to those with a coagulation defect and for life to those who have had more than one thrombotic episode (7).

For FVL, contradicting results have been published about the risk of recurrent VTE: the lowest recurrence rates were found in patients with FVL -3.5%/year without and 0.0%/yr with long-term treatment (8). A recent critical review of 4 studies (9) highlighted hazard ratios (HRs) ranging from 1.1 to 4.1 in carriers of FVL compared with noncarriers; Christiansen and colleagues found no evidence of an increased risk of recurrence for carriers of FVL (10). These findings have important implications for clinical strategies. Patients with an idiopathic first thrombotic event are often extensively tested for prothrombotic defects; however, a positive result of a defect does not predict the risk of thrombotic event recurrence and therefore has no clinical consequence (10).

Therefore, for most patients with familial thrombophilia, especially patients with FVL, long-term treatment after a first event does not seem to be justified, although the availability of anticoagulants with a better risk-benefit profile could change the balance (11). The hope is that a future agent would provide therapeutic anticoagulation without the risk of adverse hemorrhagic events.

Mayo Clinic analysis of 166 cases revealed that young, middle-aged women on oral contraceptives are the most typical cases of CVT. In general, this disease is associated with a good clinical outcome, low recurrence rate and good survival. deBruijn showed a prevalence of 85% of women with CVT used OCs, versus 45% of the control women, which corresponds to a threefold to fourfold increase in risk (12). In women who used OCs and also carried a prothrombotic defect, the odds ratio for CVT was about 30 relative to women who had neither risk factor; the use of OCs and being a carrier of a hereditary prothrombotic condition increases the risk of and interacts in a multiplicative way toward the development of CVT (12).

## **MEDICAL GENETICS**

Counseling points to consider include: family member screening, medical insurance implications for genetic testing,

type of prophylaxis for patient, family members found to be FVL carriers and not to be FVL carriers as well as those not wishing to be tested. In regard to testing the patient's son and daughter for this mutation, such testing is recommended and is especially important for the daughter since she might be on OCs, or should they (?) need stronger prophylaxis during periods of high risk thrombosis. Since the patient's diagnosis of FVL heterozygosity, her family was screened and her brother and his daughter were found to be also heterozygote for this disorder. The children, ages 17 and 15, were screened; the son was negative, and the daughter was positive.

## **FAMILIAL RISK**

Familial resistance to activated protein C is the most frequent genetic risk factor for thrombosis. In Caucasians, the ethnic group with the highest prevalence of FVL in the U.S., the mutation is present in about 5% of healthy individuals (13). Globally, the highest prevalence of FVL is among European populations, ranging from 2.0% to 7.0%. Prevalence is lower among Africans and Asians (14). In the U.S., the FVL mutation is carried in heterozygous form by about 5% of the white population and is less frequent among Hispanic-Americans (2.2%), African Americans (1.2%) and Asian-Americans (0.45%). Other thrombogenic mutations have been described, including prothrombin and deficiencies of protein S, protein C, and antithrombin (14).

FVL leads to a seven-fold increased risk of venous thrombosis. FVL is present in 20% of unselected consecutive patients with DVT, and in 50% of individuals from families referred because of unexplained familial thrombophilia (13). Reliable risk estimates for venous thrombosis (VT) in families with inherited thrombophilia are scarce but necessary for determining optimal screening and treatment policies (8). The lowest incidence for VT was found in those with the FVL mutation (1.5; 95% CI) (15).

In carriers of FVL, the annual incidences of total and spontaneous venous thromboembolism were 0.28% and 0.11%, respectively, as compared to 0.09% and 0.04% in non-carriers, respectively (relative risks 2.8 and 2.5). Oral contraceptive use and pregnancy/post-partum period increased the risk of thrombosis in carriers of FVL to 3.3-fold and 4.2-fold, respectively (16). Identification of carriers of FVL may be worthwhile in young symptomatic individuals and their relatives with a strong positive family history of VTE who may be at risk (e.g. pregnancy, use of

OCs) (13).

Lensen demonstrated an earlier age of onset in a series of selected patients from thrombophilic families with FVL than in a panel of unselected patients with a first VTE who turned out to be carriers of the FVL mutation. This finding suggests a higher thrombotic tendency in members from selected families than in consecutively diagnosed patients, even if both carry the same or a similar molecular defect (13). At the age of 50 years, 25% of carriers had experienced at least one VTE event (vs. 7% in non-carriers); important to clinicians is the question of what prophylactic measures are advisable for patients and their relatives in these selected thrombophilic families with FVL (13). In clinical practice special attention should be paid to young symptomatic individuals and their relatives with a strong positive family history of VTE or a history of recurrent VTE who are at risk, especially women who would like to use OCs or who intend to become pregnant. Identification of carriers of FVL may be worthwhile in these persons in order to discourage OC use among carriers and to protect carriers during pregnancies against VTE (13).

### **OCS AND THROMBOEMBOLISM IN WOMEN WITH THROMBOGENIC MUTATIONS**

Hypercoagulability can be inherited or acquired; the most common cause of acquired hypercoagulability in women of reproductive age in developed countries is the use of combination OCs (2). Although a greater risk for acquired hypercoagulability occurs during pregnancy, only 5.4 million women become pregnant annually in the U.S. compared with 10 million women who use OCs (2).

Withholding the most effective mode of contraception might lead to more pregnancies, which would also increase risk of VTE. For asymptomatic carriers, who are usually identified in family studies, counseling about alternative methods of contraception should be considered (7).

Because use of OCs confers some risk of VTE, concern exists that this effect may be greater among women with thrombogenic mutations. The Leiden Thrombophilia Case-Control Study (LETS) in the Netherlands was the first to reveal that the FVL mutation increased the risk of VTE among women of reproductive age (14). Furthermore, women using OCs who also had the FVL mutation had more than a 30-fold risk of VTE when compared with non-OC users without the mutation; translated, OC users with the mutation have a four-fold risk compared with nonusers with the

mutation (14).

Following the LETS study, seven other studies (7, 17, 18, 19, 20, 21, 22) plus a pooled analysis of three individual studies (23, 24, 25) have all shown an increased risk of VTE among women with FVL and further increased risk for OC users with the mutation, generally on a multiplicative scale. One of the studies found a smaller impact of FVL and OC use on VTE than in the LETS study and others (14). Spannagl and colleagues suspected that the true risk for women who are FVL carriers may be increased two- to four- fold rather than seven-fold or more, and that the risk for the combination of FVL and OC use may be increased in the order often to 15-fold rather than over 30-fold (20).

The above ten studies provided overall quality evidence that women with the FVL mutation who use OCs are at greater risk of developing VTE than nonusers without the mutation. Confidence intervals for thrombogenic mutation almost always overlapped with those for mutation plus use of OCs; the data overwhelmingly suggest that there is a multiplicative effect at work – the combination of factors produces greater risk than thrombogenic mutation alone (14). Based on the large increase in risk for women who have thrombogenic mutations and use OCs, perhaps women should be screened for thrombogenic mutations before using OCs. Based on these estimates, such a policy would deny oral contraceptives to at least 3%-6% of women, while preventing a small number of cases of thrombosis: 99.9% of women who are carriers of FVL mutation would not have thrombosis if they received OCs (14).

In 2003, the World Health Organization (WHO) reviewed this evidence during a meeting of the Expert Working Group for medical eligibility criteria (MEC) for contraceptive use; the Expert Working Group concluded that a new condition, “known thrombogenic mutations,” should be added to the MEC (14). The group also recommended that women with known thrombogenic mutations should not use combined hormonal contraceptive methods and issued a clarification with recommendation that, “Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.” (14).

### **COST EFFECTIVENESS ANALYSIS**

The number of women who would require FVL testing and the cost of identifying this cohort to prevent one death caused by VTE disease before prescribing OCs to prevent one VTE death attributable to the use of OCs in women with

FVL mutation is: >92,000 carriers would need to be identified and stopped from using these pills and the estimated charge to prevent this one death would exceed \$300 million. Interventions that cost \$50,000 or less per year of life saved are generally acceptable, whereas those that cost \$50,000-\$100,000 are borderline, and those that cost more than \$100,000 are not cost-effective. Screening for FVL mutation before prescribing OCs is not a cost-effective use of U.S. health care dollars. The best and most cost-effective screening tool we have is taking a thorough personal and family history related to VTE (2).

### **SUMMARY AND IMPLICATIONS FOR ADVANCED PRACTICE NURSING**

FVL is the most prevalent of the thrombophilic defects that advance practice nurses (APN) will encounter in the primary and acute care settings. One must have a high level of suspicion for this genetic disorder when assessing and diagnosing a patient who presents with a possible CVT. When performing a history prior to prescribing combined oral contraceptives, or estrogen in any form, the APN must be aware of the pertinent questions to ask related to this familial disorder. These include: personal or family history of first venous thrombosis episode before age 50 (some before age 30) whether involving pregnancy (placental infarction, prematurity, recurrent pregnancy loss), oral contraceptive use, estrogen therapy, malignancy, trauma, surgery or immobility (26). The use of a formal genogram may be helpful for genetic counseling purposes. APNs must take a more active role in identifying and assessing such patients in the future.

At the clinical research level, advanced practice nurses have many activities and roles. These include conducting health assessments, collecting medical and family histories, confirming family histories of genetic conditions, conducting physical assessments, educating and providing pre- and post-intervention genetic counseling, conducting clinical procedures and interventions, following and supporting individuals who are living with their particular condition, and overseeing follow-up in the clinical research center and as links to the primary care setting (26).

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