Factor V Leiden Mutation and Pregnancy

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Factor V Leiden mutation (FVL) is an autosomal dominant hemostatic disorder that predisposes affected persons to venous thromboembolic events (VTE). Although the mutation causing FVL is easily diagnosed using molecular DNA techniques,¹ patients who are heterozygous for this disorder often remain asymptomatic until they develop a concurrent prothrombotic condition. Pregnancy, which may increase an individual woman's risk of VTE by 5- to 6-fold,² represents such a condition. Because there are potentially serious effects of FVL for both the mother and the child, and because effective treatment strategies exist, early detection and treatment of this condition is warranted. An illustrative case is presented to highlight the importance of a good working knowledge of FVL for family physicians.

Case Presentation

The patient was a 25-year-old white woman, gravida 6, para 2, aborta 3, who presented for her initial obstetrical visit at the family practice clinic. Estimated gestational age was 12 weeks as measured from the patient's last menstrual period, which was confirmed by a first trimester crown-rump length. On the intake interview, the patient denied any significant past medical history or family medical history, including thromboembolic disease. The patient's social history was remarkable for current tobacco abuse, 1 pack of cigarettes per day, for 7 years. The patient was unable to tolerate prenatal vitamins because of nausea and was taking over-the-counter children's multivitamins. She denied taking any additional medications. The patient's past obstetrical history was significant for 3 early first trimester miscarriages, followed by 2 full-term spontaneous vaginal deliveries of healthy male children, all fathered by the same man. She denied having undergone any workup for the miscarriages

by her previous obstetrical provider. She denied any personal history of preeclampsia, placental abruption, or intrauterine growth retardation. The patient had normal blood pressure, and normal fetal heart tones were auscultated with a transabdominal Doppler. The results of the remainder of her physical examination were within normal limits, as were the results of her prenatal laboratory studies. The patient was encouraged to stop smoking, given miscarriage precautions, and told to return to the family practice clinic in 4 weeks.

The patient returned for her 16-week routine obstetrical visit. She reported no vaginal bleeding, no contractions, and no leakage of vaginal fluid. The patient had felt fetal movements a few days before her office visit. She was still smoking 1 pack of cigarettes per day. The patient was counseled about obtaining a maternal serum α -fetoprotein test, which she agreed to have done. She was again encouraged to stop smoking, given miscarriage precautions, and told to follow up in 4 weeks.

One week after the maternal serum α -fetoprotein test was ordered, the result was reported to the clinic as elevated, indicating an increased risk for fetal open neural tube defect (NTD). The patient was called by her physician and questioned about any family history of NTD, which she denied. She was referred to a maternal-fetal medicine specialist (MFM) for genetics counseling and level II ultrasound.

The family practice clinic was contacted by the MFM office 1 week later to discuss the results of the consultation. Results of the level II ultrasound were negative for NTD. On extensive questioning during the intake interview, however, the patient had revealed that she had a maternal aunt with a deep vein thrombosis, and another maternal aunt with deep vein thrombosis and pulmonary embolus. Both of the patient's aunts had developed VTE in their early 30s, without any known risk factors. The patient denied any personal history of VTE. Based on this, the MFM had tested the patient for FVL. The test revealed that the patient was heterozygous for FVL. The MFM recommended testing the father of the baby for the presence of the defect, which was subsequently performed and

Submitted, revised, 10 March 2004.

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found to be negative. The patient was started on 5000 units of subcutaneous, unfractionated heparin, twice a day, and she was strongly counseled by the MFM to stop smoking.

The patient returned to the family practice clinic for continued prenatal care. She received the unfractionated heparin for the remainder of her pregnancy. She was counseled numerous times about the risks of smoking during her pregnancy; despite this, she continued to smoke 1 pack per day throughout her pregnancy. Results of the patient's complete blood count and 1-hour Glucola test at 28 weeks were within normal limits.

The patient presented to Labor & Delivery in spontaneous labor at 37 + 0 weeks. She had not taken her heparin that morning. The patient quickly progressed to a spontaneous vaginal delivery of a 5-pound, 10-ounce viable female infant with Apgar scores of 9 at 1 minute and 9 at 5 minutes. There were no complications with the delivery. The patient's heparin was restarted on postpartum day 1. She was discharged from the hospital on postpartum day 2. She continued her heparin for 6 weeks. After having a normal postpartum examination, her heparin was discontinued. During her pregnancy and postpartum period, she had no evidence of a VTE.

Discussion

Activated protein C (APC) resistance represents the most common cause of inherited venous thrombosis.² FVL, in turn, is the most common cause of APC resistance, accounting for 95% of such disorders.³ It is an autosomal dominant genetic disorder characterized by a mutation at one of the factor V cleavage sites, making it difficult for APC to inactivate it.⁴ Although 5 to 9% of Europeans are heterozygous for FVL,⁵ it does not seem to be present in African Blacks, Chinese, or Japanese populations. Patients who are heterozygous for this condition are at 3- to 8-fold increased risk for VTE; those who are homozygous are at 50- to 80-fold increased risk.⁶

Protein C is a naturally occurring anticoagulant that selectively degrades coagulation factors Va and VIIIa through cleavage of these molecules to inactive forms, limiting the formation of clots. This requires both its activation by the binding of the thrombin-thrombomodulin complex to endothelial cells and the presence of protein S and ionized calcium.¹ Any disruption of this pathway will result in a predisposition to venous thrombus formation.

Pregnancy is also associated with a 5- to 6-fold increase in the risk of VTE. There are measurable increases in several clotting factors (I, II, VII, VIII, IX, and XII), decreases in protein S levels, and increased resistance to APC. It has been hypothesized that these maternal changes, producing a hypercoagulable state, may be important to minimize intrapartum blood loss.

Women who are pregnant and heterozygous for FVL have a 5- to 10-fold increase in the risk of VTE, whereas those who are homozygous have a 50- to 100-fold increased risk.¹ Other maternal complications of FVL include the hypertensive disorders of pregnancy and placental abruption. Fetal complications such as miscarriage,⁷ intrauterine fetal demise (IUFD), placental abruption, and intrauterine growth retardation (IUGR)¹ have also been associated with FVL. This review discusses maternal VTE.

Venous thromboembolism is the leading cause of morbidity and mortality in pregnancy and the postpartum period. VTE occurs in approximately 1 in 1500 pregnancies, and up to one fourth of untreated deep vein thromboses may lead to pulmonary embolism.¹ Women with a personal history of VTE in a previous pregnancy have a higher prevalence of FVL than those who have never had a VTE.⁸ A study of 119 women with pregnancy related VTE revealed that 44% of them had FVL, most of whom were heterozygous for the condition.⁹

Patients with a VTE during the current pregnancy or who are homozygous for FVL should be fully anticoagulated. Unfractionated heparin or low-molecular-weight heparin¹⁰ may be used. Patients on low-molecular-weight heparin should be changed to unfractionated heparin at 36 weeks to minimize the risk of epidural hematoma from regional anesthesia. Heparin should be discontinued immediately before delivery, and then both heparin and warfarin can be started postpartum. Once a target international normalized ratio of 2 to 3 is obtained, the heparin is discontinued. The warfarin is continued for 6 to 12 weeks postpartum. Long-term anticoagulation with warfarin should be considered for persons with FVL after one VTE. It is recommended if these persons have 2 or more VTE.¹¹

It is not known whether asymptomatic women who are heterozygous for FVL and have no history of a VTE should receive treatment.¹ Low-dose prophylactic heparin therapy has been recommended only if there is a strong family history of VTE or if another prothrombotic risk is present.¹²

Some European authors recommend only surveillance for these persons.¹³

Mass screening of women for FVL is not cost-effective and is limited by the lack of a safe, cost-effective, long-term method of prophylaxis. Screening should be recommended for women with a personal or family history of VTE, early onset or recurrent preeclampsia, recurrent IUGR, unexplained IUFD, and unexplained placental abruption.¹ Ideally, testing should be done remote from any thrombotic event, when the patient is not pregnant and not on any anticoagulation, because heparin may interfere with the assays. Such testing should also include studies for protein S, protein C, and plasma homocysteine concentration.¹⁴

There have been no randomized controlled trials of treatment for patients known to have FVL.¹⁵ It is also unknown whether prophylactic treatment of asymptomatic carriers, such as this patient, improves outcomes, although small observational studies do suggest a benefit.¹⁶ Current expert opinion recommends that management be based on the presence of a current VTE, the presence of a past VTE, and risk factors for a VTE during pregnancy. The American College of Obstetricians and Gynecologists recommends prophylactic doses of heparin during and after the pregnancy for women who are heterozygous for FVL and also have a history of one previous VTE.¹⁷ If these patients are currently taking long-term anticoagulation for a previous VTE, they should receive full anticoagulation with heparin as previously discussed.¹² Women who are heterozygous for FVL and also have a history of a previous pregnancy complication, such as preeclampsia, IUFD, IUGR, or placental abruption, are also candidates for heparin prophylaxis.

In conclusion, FVL is an inherited condition that predisposes persons to VTE. During pregnancy, persons with FVL are at increased risk for VTE, IUFD, IUGR, placental abruption, and preeclampsia. Although anticoagulation with heparin has not been demonstrated to improve pregnancy outcomes, most authors recommend treatment in persons with a personal or family history of VTE. It is important for family physicians to have a good knowledge of FVL and its potential impact on pregnancy.

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