



A Case of Deep Venous Thrombosis in the Third Trimester of Pregnancy Associated With Homozygote Factor V Leiden Mutation

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Abstract

Most deep venous thromboses occurs during the second or third weeks postpartum and is attributed to the hypercoagulability of pregnancy. The hypercoagulability of pregnancy has been attributed to increased plasma fibrinogen and clotting factors VII, VIII and IX and an increase in platelet adhesiveness. Recently, interest has turned to the naturally occurring inhibitors of coagulation, antithrombin III, plasminogen, protein C, and protein S, factor V Leiden mutation and the effect of these factors on blood coagulation. We report a patient with unilateral deep venous thrombosis at the lower extremities in the third trimester of pregnancy associated with homozygote factor V Leiden mutation. The evaluation of factor V Leiden mutation in patients with thrombotic events during pregnancy may reveal a specific cause for the thrombotic event and thereby influence patient management.

Key words: pregnancy, factor V Leiden mutation, thrombosis

Özet

Homozigot Faktör V Leiden Mutasyonuna Bağlı Gebeliğin Üçüncü Trimesterinde Gelişen Derin Venöz Tromboz Olgusu

Derin venöz trombozlarının çoğu postpartum iki ile üçüncü haftada ortaya çıkmakta ve gebeliğe bağlı hiperkoagülabilitéyle ilişkili olduğu düşünülmektedir. Gebeliğe bağlı hiperkoagülabilitenin nedeni olarak artmış plazma fibrinojen, factor VII, VI-II ve IX düzeyi ile artmış trombosit adhesivitesi gösterilmektedir. Yakın zamanda doğal koagülasyon inhibitörleri olan antitrombin III, plazminojen, protein C, protein S ile factor V Leiden mutasyonu ve tüm bu faktörlerin kan koagülasyonuna etkisi üzerinde durulmaktadır. Bu çalışmada gebeliğinin üçüncü trimesterinde homozigot factor V Leiden mutasyonuna bağlı tek taraflı derin ven trombozu bulunan olgu sunulmuştur. Gebelikte trombotik olay ile karşılaşılan olgularda factor V Leiden mutasyonu araştırılması ile trombotik olay hakkında spesifik bir neden ortaya çıkarılabilir ve hasta yönetimi daha iyi planlanabilir.

Anahtar sözcükler: gebelik, factor V Leiden mutasyonu, tromboz

Introduction

Most deep venous thromboses occurs during the second or third weeks postpartum and is attributed to the hypercoagulability of pregnancy. The hypercoagulability of pregnancy has been attributed to increased plasma fibrinogen and clotting factors VII, VIII and IX and an increase in platelet adhesiveness. Recently, interest has turned to the naturally occurring inhibitors of coagulation, antithrombin III, plasminogen, protein C, and protein S, factor V Leiden mutation and the effect of these factors on blood coagulation. Hypercoagulability and thrombosis is a well-recognized complication of pregnancy (1).

The clinical spectrum of deep venous thrombosis varies

greatly from no symptoms to severe pain and systemic signs of inflammation. Most patients complain of aching discomfort and tightness in the involved calf or thigh. The pain is aggravated by muscular exercise, and the involved leg may feel stiff. Swelling varies from minimal to massive. In some cases the onset is rapid and associated with tachycardia, anxiety and fever. The location of the thrombus determines the location of physical findings. The most frequent site is the calf, especially the venous sinuses of the soleus muscle and the posterior tibial and peroneal veins. Femoral vein thrombosis, which is frequently associated with calf thrombosis, produces pain and tenderness in distal thigh and popliteal region and prominent swelling than the calf thrombus alone. Thrombi involving the iliofemoral venous segment produce the most dramatic manifestations, often with massive swelling, pain, and tenderness of entire lower extremity.

Here, we report a patient with unilateral deep venous thrombosis at the lower extremities in the third trimester of pregnancy associated with homozygote factor V Leiden mutation.

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Table 1. The guidelines for the management of acute venous thromboemboli in patients with hereditary thrombophilia

- **Initial anticoagulation:** Unfractionated or low-molecular-weight heparin for a minimum of 5 d is followed in the non-pregnant by oral anticoagulation for 6 months at a target International Normalized Ratio (INR) of 2-5 (range 2.0-3.0).
- **Duration of anticoagulant therapy:** After a first venous thromboembolism, anticoagulant therapy is generally administered for 6 months. A shorter period of treatment may be acceptable when the thrombus is confined to distal veins and if there is evidence of a temporary risk factor that is no longer present.

Case

A 18-year-old gravida 1, para 0 woman was admitted to our clinic with the symptoms of left lower extremity swelling and pain at the 35th gestational week of pregnancy. Two days before the admission, she complained of swelling and pain originating from left lower extremity. The patient's past medical history was unremarkable including previous history of thrombosis. In cervical assessment dilatation was 2 cm, effacement was 30% and there were three contractions during the 20 minute observation period. Non-stress test trace was reactive and obstetric sonography was within normal limits. In physical examination there were bilateral pulses in all segments of lower extremity, circumference of the left lower extremity is longer than the right one and there was color change and heat elevation in the left lower extremity. Homan's test was positive. Body temperature was 37°C and arterial pressure and heart rate were 110/60 mm Hg and 96/min, respectively.

Color Doppler sonographic assessment of left lower extremity revealed acute phase of thrombosis beginning from the level of common iliac veins and down to the popliteal veins involving the cranial segments of deep crural veins. External iliac vein, common, deep and superficial femoral veins which were between these two segments and left greater saphenous veins were also included. Especially, there was collateral venous circulation around left common femoral veins forming cutaneous and subcutaneous edema involving the whole extremity. The activated partial thromboplastin time was 23.1 seconds (normal 18-23 seconds), prothrombin time was 10.75 seconds (normal 9.6-12.5 seconds), and fibrinogen was 852 mgr/dl (normal 181-514). Blood specimen was analyzed for the presence of factor V Leiden mutation and prothrombin mutation. As a result of DNA Molecular analysis by techniques of real time polymerase chain reaction and Fluorescence Resonance Energy Transfer, the patient was found to be homozygote for factor V Leiden Mutation (G 1691 A Mutation) and negative for prothrombin mutation (G-20210A Mutation). Patient was administered terbutaline intravenous infusion 250 mcg per hour for tocolysis and Betamethasone for fetal induction of pulmonary surfactant production.

For the deep venous thrombosis patient was consulted by vascular surgeons and advised leg elevation, antibiotic therapy and heparinization. Also they thought that uterine contractions during the labor may precipitate the detachment of thrombi that localized in pelvic veins and deep veins and may cause a pulmonary embolism. To avoid risk of pulmonary embolism a cesarean section was performed, with minimal pelvic hemorrhage and delivery time under the spinal anesthesia. She

delivered a 2550 g male fetus at the 37th gestational week by cesarean section. At the postoperative period she was administered low molecular weight heparin for a week and oral warfarin therapy for six months.

Discussion

Although the absolute numbers are small, thromboembolism during pregnancy and the puerperium is associated with higher rates of preterm delivery and perinatal mortality, and pulmonary embolism is second only to abortion as a cause of maternal mortality. Population based studies, often relying on clinical diagnosis have suggested that venous thromboembolism complicates 0.1% to 0.7% of pregnancies. However this incidence has been disputed with studies employing objective documentation of clinically suspected thromboembolism suggesting a lower incidence of 0.013% to 0.029%. Recurrent thromboembolism may complicate 4% to 15% of subsequent pregnancies (2). Although the third trimester has often been associated with the greatest thrombotic risk, some studies suggest that objectively documented thromboses are distributed among all three trimesters (7,8). The risk of thrombosis appears to be two to three times greater during the puerperium with a rate of 2.3 to 6.1 per 1000 delivery (3). The general guidelines for the management of acute venous thromboembolism in patients with hereditary thrombophilia were listed in Table 1.

The inherited thrombophilias constitute an additional risk for pregnancy-associated thromboembolism complicating 4% of pregnancies (3). Table 2 summarizes the investigation of pregnant patient for the presence of hereditary thrombophilia. Anticoagulant factor deficiencies, lupus anticoagulant, or fibrinolytic deficiencies have been reported in 20% of patients with pregnancy-related thrombosis. The factor V Leiden mutation may be particularly important in this regard, as resistance to activated protein C that is characterized by the failure of exogenous activated protein C to prolong the activated partial thromboplastin time has been identified in up to 59% of patients with pregnancy-related thromboembolism (4,5). It was first described in 1993 and now recognized that a single point mutation in the factor V gene, resulting in replacement of arginine 506 with glutamine (factor V Leiden; FV: R506Q), is presented in 94% of individuals with activated protein C resistance (6). Factor Va is activated by protein C-mediated cleavage at the Arg 306 and Arg 506 sites; this mutation thus renders factor Va less sensitive to degradation by activated protein C. The factor V Leiden mutation has an autosomal dominant mode of inheritance and is at least ten times more common than other inheritable defects (6).

**Table 2.** Investigation and tests for heritable thrombophilia (9).

- The **activated partial thromboplastin time** (APTT), prothrombin time and thrombin clotting time should be incorporated in the initial screening. The APTT may identify some patients with antiphospholipid antibodies (depending on the sensitivity of the APTT reagent used), but is not sufficient alone to exclude antiphospholipid antibodies.
- The **thrombin clotting time** will allow identification of dysfibrinogenaemia and heparin contamination.
- The **prothrombin time** is useful in the interpretation of low protein C or protein S results.
- Functional assays should be used to determine **antithrombin** and **protein C levels**. Chromogenic assays of protein C activity are less subject to interference than clotting assays and are preferable.
- **Immunoreactive assays of protein S antigen** are preferable to functional assays. If a protein S activity assay is used in the initial screen, low results should be further investigated with an immunoreactive assay of free protein S.
- **PCR-based testing for prothrombin G20210A** is required, as there is no screening test.
- Comprehensive assays for **antiphospholipid antibodies** (both lupus inhibitors and anticardiolipin antibodies) should be performed.
- **The modified activated protein C sensitivity ratio** (APC:SR) test (predilution of the test sample in factor V-deficient plasma), as opposed to the original APC:SR test, should be used as a phenotypic test for the factor V Leiden mutation. The exact detection of the factor V Leiden mutation relies on amplification of the nucleotide region close to the exon-intron boundary in exon 5 of the factor V gene from either genomic DNA or from mRNA followed by a mutation detection step.

The frequency of mutation shows significant geographic variability, with 8.8% of Europeans being carriers (7). Heterozygotes for factor V Leiden mutation carry a five fold to tenfold increased risk for thrombosis that is an additional ten times higher in homozygotes (6). Approximately 25% of individuals with the factor V Leiden mutation sustain a thrombosis by age 50 years and the prevalence of activated protein C resistance among deep venous thrombosis patients has varied from 10% to 65% (7). When factor V Leiden mutation is combined with the prothrombotic state of pregnancy, the result is an increased propensity to manifest a number of pregnancy complications. These include recurrent pregnancy loss and stillbirth, severe and early-onset preeclampsia, placental abruption and possibly, intrauterine growth restriction. Patients with factor V Leiden and a previous venous thromboembolism may, according to their level of risk, be offered either prophylactic or therapeutic heparin. The role of antithrombotic therapy in the prevention of severe pregnancy complications remains unclear. In a retrospective family study Middeldorp et al (8) found that the risk of pregnancy-related venous thromboemboli in women with a symptomatic first-degree relative was 17% per pregnancy. Anticoagulant prophylaxis during the postpartum period, either with low molecular weight heparin or warfarin is indicated in asymptomatic homozygous women with factor V Leiden who have a positive family history for venous thromboembolism. As the rate of deep vein thrombosis during pregnancy is distributed equally during all trimesters, low molecular weight heparin prophylaxis would have to be used during the entire pregnancy, which has been shown to be safe and effective.

As well as effective levels of dosage, patients with established deep venous thrombosis need an adequate duration of oral anticoagulation after the initial treatment with conventional or low molecular weight heparin. The optimum duration has been shown to depend on whether the episode is idiopathic or

secondary to a reversible clinical cause. Three months duration for proximal deep venous thrombosis is recommended as a minimum and at least 6 months in which deep venous thrombosis is idiopathic or recurrent.

In our patient, because of unknown diagnosis of factor V Leiden mutation until the occurrence of deep venous thrombosis we were not able to use thromboprophylaxis. Patient presented with the clinical picture of deep venous thrombosis and after the diagnostic evaluations she was initiated therapy for both deep venous thrombosis and preterm contractions. At 37th gestational week she has delivered a 2550 g male fetus by cesarean section and at postoperative period she was given low molecular heparin for a week and coumadin therapy for six months.

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