

Favorable Outcome Under Anticoagulant Therapy in a High Risk Pregnancy Case Report and Short Review of the (Recent) Literature

Irina VOICAN, MD^a; Prof. Ana Maria VLADAREANU, MD, PhD^a;
Minodora ONISAI, MD^a; Anca NICOLESCU, MD^a;
Prof. Radu VLADAREANU, MD, PhD^b

^aDepartment of Hematology, Emergency University Hospital, Bucharest, Romania

^bDepartement of Obstetrics-Gynecology, "Elias" Emergency University Hospital, Bucharest, Romania

ABSTRACT

The incidence of venous thromboembolism is significantly increased during pregnancy, recurrent venous thromboembolism being a serious complication because it is potentially life-threatening. According to recent ACCP guidelines, women with "high-risk" thrombophilias (e.g., homozygosity for factor V Leiden) who had a single prior episode of VTE treated with oral anticoagulants, should receive LMWH or UFH during pregnancy and puerperium, followed by resumption of long-term anticoagulants postpartum.

We present the case of a young woman with a history of severe deep vein thrombosis of the inferior vena cava, occurring during oral contraceptive use. Subsequent investigation revealed homozygosity for Leiden mutation. She was treated with enoxaparin throughout gestation and 6 weeks postpartum and no complications appeared.

Keywords: anticoagulant therapy, pregnancy, thromboembolism

Address for correspondence:

Voican Irina, MD. University Emergency Hospital, Bucharest, 169 Splaiul Independentei Street, Bucharest, Romania. Phone: +40 722 208 332
E-mail: voicanirina@yahoo.com

Received on the 27th of March 2012. Accepted on the 19th of September 2012.

INTRODUCTION

During pregnancy, several changes of the mother's coagulation system lead to hypercoagulability, which has likely evolved to protect women from bleeding during delivery or miscarriage. Pregnancy and puerperium raise the risk of thromboembolic events and the risk is further increased by previous venous thromboembolism (VTE) as well as by the association of additional risk factor such as hereditary or acquired thrombophilias (1). Thrombophilias increase not only the risk of maternal thrombosis but also the risk of poor pregnancy outcome (2,3). Up to 50% of Caucasian women who develop thrombosis during pregnancy and puerperium test positive for thrombophilia (4) and among hereditary thrombophilic mutations, FV Leiden is the most frequently encountered (5). The use of anticoagulant therapy during pregnancy is challenging for the clinicians but it is the single therapeutic option in high-risk situations that can provide a successful outcome both for the mother and the fetus. □

CASE REPORT

We present the case of a 24 year-old woman with a history of deep vein thrombosis, referred to us for a hematological opinion in view of a possible thrombophilia. The patient's medical history had started two years before presentation, with a deep vein thrombosis that developed after 2 months of hormonal contraception. At that time, the CT-scan revealed an extensive, completely obstructive thrombus involving the inferior vena cava (IVC), lying from above the right renal vein to the right iliac, femoral and popliteal veins and with partial extension into the left iliac vein (Figure 1). The subsequent venography revealed IVC hypoplasia, involving mainly the segment above the renal veins.

Anticoagulant therapy with continuous intravenous infusion of unfractionated heparin (UFH) was immediately started, with dose adjustment according to aPTT values for five days, and switched to oral therapy as soon as a therapeutic INR was obtained. Patient was discharged 8 days later being fully anticoagulated but after 1 week she experienced an episode of transient deafness in her left ear. Concomitant pain and progressive swelling of her right leg

reoccurred, so she returned to the hospital. The INR was 1.9 and the venous compression ultrasound showed extension of the thrombus in the popliteal vein. UFH was restarted, followed by oral anticoagulant when the clinical signs of thrombosis improved. Several investigations were performed in order to elucidate the etiology of the transitory unilateral hearing decrement, including cerebral CT-scan and MRI, audiometric tests as well as immunologic assays concerning vasculitis, but all failed to reveal any underlying pathology. Long-term oral anticoagulants with a two-weeks checking of the INR value and graduated compressive stockings were recommended upon discharge from the hospital. Oral contraceptives were firmly discouraged. The patient was warned about the risks of vitamin K antagonists (VKA) in case of a pregnancy. Subsequent evolution was favorable, with no other DVT episodes or hearing disturbances but she developed a post-thrombotic syndrome in her right leg. Six months later, the oral anticoagulation was stopped.

The current presentation was related to a new episode of hearing loss, two years apart from the first one, with no apparent triggering factors. A new complete set of investigations was performed in order to identify a potential causal factor for her previous and current disability, including imagistic re-evaluation of the brain as well as of the venous system. A complete repermeabilisation of the IVC and iliac vein and a residual thrombus in the right superficial femoral vein was observed. The cerebral MRI and Doppler ultrasound of the cerebral and cervical vessels were again, within normal limits. Audiometric examination revealed left ear sensorineural partial hear loss. The patient was referred to the hematologist with the suspicion of thrombophilia. The standard screening for hereditary thrombophilia was performed, including antithrombin activity (AT), protein C (PC) and protein S (PS) activity, activated protein C resistance, homocysteine as well as molecular tests for factor V Leiden (FVL) and prothrombin gene mutation G20210A. Screening for antiphospholipid syndrome and for autoimmune disorders (SLE, vasculitis) was done as well. The results are presented in Table 1.

Even though we hadn't had a clear evidence of a thrombotic cause, we decided anticoagulant therapy with LMWH (enoxaparin 60 mg sc bid) taking into account the homozygote status for FVL, the recurring episodes of hearing dis-

turbance and the favorable evolution of the first episode under anticoagulant therapy. The results were positive, the patient's hearing improved within a few days that made us to decide that permanent anticoagulation treatment would be beneficial. Accordingly, LMWH was switched to VKA after a short course of concomitant therapy and the patient was discharged from the hospital having an INR within therapeutic range. She was strongly advised against the use of VKA in case of pregnancy.

One year later, our patient became pregnant while using VKA, so she was advised to urgently switch to intermediate dose of LMWH, taking into account the ultrasound diagnosis of a 6 weeks pregnancy. Enoxaparin 40 mg bid was continued until the 26th week of gestation, when clinical examination revealed an important increase of 18 kg in the patient's body mass and ultrasound investigation showed abnormal Doppler velocimetry with elevated resistance index in both uterine and umbilical arteries. The level of anti Xa activity was 0.5 U/mL, so we increased the dose of enoxaparin to 60 mg twice a day (75% of the therapeutic dose) and continued with close surveillance. Four weeks later, the anti Xa level was 0.8 U/mL, the following monitoring visits showed no further significant changes in the patient's clinical condition and the results of the ultrasound examination improved. The patient's pregnancy evolved without any obstetric morbidity and a healthy baby of 3400 g was delivered at thirty-eighth week of gestation by elective cesarean section. The LMWH was stopped 24 hours prior to delivery and recommenced 12 hours after, according to the obstetric department's protocol. Two weeks later the patient was switched to oral anticoagulant while she was breastfeeding. □

COMMENTS

Leiden mutation is the most frequently encountered hereditary thrombophilia (6), with an incidence of 5-8% (7) in the European population and accounts for 20-30% of the thromboembolic events (6). The heterozygous state raises the thrombotic risk for 4 to 8 fold (6) whereas the homozygous state raises it for 80 fold (8). The addition of the acquired risk factors such as contraception pills or pregnancy further increases the thrombotic risk.

Pregnancy itself is an acquired prothrombotic condition. During pregnancy, the risk of

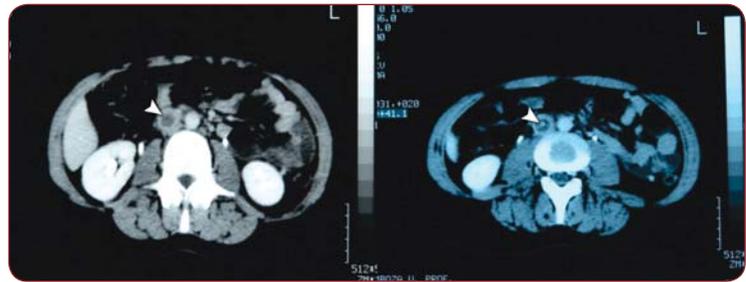


FIGURE 1. CT-scan showing extensive thrombosis of the inferior vena cava (arrow).

VTE is increased for 4- to 5-fold (9,10), for the entire duration of the pregnancy, with an even higher risk in postpartum. Between 20 to 50% of the thrombotic events during pregnancy and postpartum are related to thrombophilia (11). FVL is present in 44% of pregnant patients with VTE (12). Because in normal pregnancy there is an increased activated protein C resistance, the presence of the factor V Leiden abnormality worsens this phenomenon and likely accounts for the increased thrombotic diathesis (13). A systematic review of the risk of VTE and adverse pregnancy outcomes associated with thrombophilia in pregnancy, reports the highest odds ratio for VTE among factor V Leiden homozygous carriers (OR: 34.40; 95% CI: 9.86-120.05) while the homozygous prothrombin gene mutation G20210A has an OR of 26.36

| Parameter | Patient's value | Normal values |
|---|-----------------|---------------|
| AT | 106.9% | 80-120% |
| PC | 75% | 70-130% |
| Free PS | 60% | 65-145% |
| ProC global/FV | 0.38 | 0.7-2 |
| PCR for FVL | homozygous | negative |
| PCR for prothrombin gene mutation G20210A | negative | negative |
| Homocysteine | 8.3 µmol/L | 5-12 µmol/L |
| LA | negative | negative |
| a-CL | | |
| IgG | 6 GPL/mL | < 15 GPL/mL |
| IgM | 5 MPL/mL | < 15 MPL/mL |
| a-β2 GPI | | |
| IgG | 2.4 U/mL | < 5 U/mL |
| IgM | 1.1 U/mL | < 5 U/mL |
| IgA | 1.3 U/mL | <5 U/mL |
| a- ds DNA | 10.3 U/mL | < 50 U/mL |
| a-Sm antibodies | 3.57 EU/mL | < 20 EU/mL |
| a-SS-A antibodies | 7.65 EU/mL | < 20 EU/mL |
| a-proteinase 3 (c-ANCA) | 1.2 EU/mL | < 20 EU/mL |
| a-MPO (p-ANCA) | 1.8 EU/mL | < 20 EU/mL |

TABLE 1. Hematologic and immunologic parameters.

AT: antithrombin, PC: protein C, Free PS: free protein S, FVL: factor V Leiden, LA: lupus anticoagulant, aCL: anti-cardiolipin antibodies, a-β2GPI: anti-beta2glycoprotein I antibodies, a-ds DNA: anti-duble stranded DNA antibodies, c-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies, p-ANCA: classical antineutrophil cytoplasmic antibodies

(95% CI: 1.24-559.29) and heterozygous carriers of the Leiden mutation have an OR of 8.32 (95% CI: 5.44-12.70) for VTE (14). The most important individual risk factor for VTE in pregnancy is a history of thrombosis, as 15% to 25% of thromboembolic events in pregnancy are recurrent events (15). The type of thrombophilia is also important in assessing the thrombotic risk in pregnancy, and homozygosity for FVL is considered among the major risk factors (16). A recent study that compared the risk of VTE associated with oral contraceptive use versus pregnancy in carriers of the Leiden mutation found that pregnancy was associated with a 16-fold increase in risk, whereas OC use was associated with only a 2-fold increase (17).

Current expert opinion recommends that management of pregnant thrombophilic women should be based on the presence of a history of VTE and additionally risk factors for a VTE during pregnancy (18). According to the above mentioned data, homozygosity of FVL represents a "high risk" thrombophilia. Our patient had a history of a severe thrombotic event occurred while OC use (a temporary risk factor), that was probably favored by the anatomic anomaly of her IVC (a permanent risk factor). The two episodes of impaired hearing were also assumed as thrombotic events due to their occurrence concomitant with inadequate anticoagulant therapy. All these factors were taken into account when recommending long-term anticoagulation and the favorable subsequent evolution of the patient, with no other thrombotic events, demonstrate that it was an appropriate therapeutic approach.

Immediately after pregnancy was confirmed, the patient was switched from oral anticoagulants to LMWH. For women receiving anticoagulation who become pregnant, ACCP guidelines recommend LMWH use over VKA, during the entire pregnancy (18). VKA are contraindicated in all the three trimesters of pregnancy as they cross the placenta. When taken during the critical period of organogenesis (e.g.

4 to 8 week after conception), they are associated with a 15% to 56% risk of miscarriage (15) and up to 10% risk of congenital abnormalities (19). Placental transfer of VKA later in pregnancy can also result in fetal bleeding, stillbirth or CNS abnormalities with long-term squeals. In the beginning of the pregnancy we chose intermediate dose of enoxaparin but, as the placental vasculature seemed to have an impaired function and the body patient's weight increased, we switched to 75% of the therapeutic dose from the 26th week of gestation, having in mind that other maternal complications associated with FVL include intrauterine growth retardation, placental abruption, miscarriage, and the hypertensive disorders of pregnancy (14). As the subsequent ultrasound examination showed improvement, the same dose of LMWH was maintained until 24 hours prior to delivery and recommenced in postpartum. The oral anticoagulation was restarted two weeks later, while the parturient continued to breast-feed. □

CONCLUSION

We believe that the use of an effective antithrombotic treatment, primarily for the prevention of thromboembolism recurrence, may have secondarily contributed to the favorable outcome of pregnancy, by protecting against potential obstetrical complications associated to FVL homozygosity, as suggested by some reports on other cases in the literature (20).

Although homozygous FVL is a "high risk" thrombophilia, and pregnancy significantly increases both the thrombotic and the obstetrical risks, these risks are manageable. In our case, a special concern was due to the IVC hypoplasia that could represent an aggravating condition, as it was a permanent risk factor, but adequate antithrombotic therapy under close hematological and obstetrical surveillance provided the successful outcome of this pregnancy.



REFERENCES

1. Bourjeily G, Paidas M, Khalil H, et al. – Pulmonary embolism in pregnancy. *Lancet* 2010;375:500-512
2. Rodger MA, Paidas M, McLintock C, et al. – Inherited thrombophilia and pregnancy complications revisited. *Obstet Gynecol* 2008;112:320-324
3. Rodger MA, Paidas M – Do thrombophilias cause placenta-mediated pregnancy complications? *Semin Thromb Hemost* 2007;33:597-603
4. Marik PE, Plante LA – Venous Thromboembolic disease and pregnancy. *N Engl J Med* 2008;359:2025-2033
5. Franco RF, Reitsma PH – Genetic risk factors of venous thrombosis. *Hum Genet* 2001;109:369-384
6. Lee R – Factor V Leiden: a clinical review. *Am J Med Sci* 2001;322:88-102
7. Rees DC, Cox M, Clegg JB – World distribution of factor V Leiden. *Lancet* 1995;346:1133-1134
8. Kupferminc MJ – Thrombophilia and pregnancy. *Reprod Biol Endocrinol* 2003;1:111
9. Heit JA, Kobbervig CE, James AH, et al. – Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005;143:697-706
10. Pomp ER, Lenselink AM, Rosendaal FR, et al. – Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008;6:632-637
11. Dilley A, Austin H, El-Jamil M, et al. – Genetic factors associated with thrombosis in pregnancy in a United States population. *Am J Obstet Gynecol* 2000;183:1271-1277
12. Gerhardt A, Scharf RE, Beckmann MW, et al. – Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. *N Engl J Med* 2000;342:374-380
13. Battinelli EM, Bauer KA – Thrombophilias in pregnancy. *Hematol Oncol Clin North Am* 2011;25:323-333
14. Robertson L, Wu O, Langhorne P, et al. – Coagulation disorders in pregnancy: a systematic review. *Br J Haematol* 2006;132:171-196
15. James AH – Pregnancy-associated thrombosis. *Haematology Am Soc Hematol Educ Program* 2009;2009:277-285. Review
16. Jacobsen AF, Skjeldestad FE, Sandset PM – Ante- and postnatal risk factors of venous thrombosis: a hospital-based case-control study. *J Thromb Haemost* 2008;6:905-912
17. Van Vlijmen EF, Veeger NJ, Middeldorp S, et al. – Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutations: a rational approach to contraception. *Blood* 2011;118:2055-2061
18. Bates SM, Greer IA, Middeldorp S, et al. – VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e691S-736S
19. Middeldorp S – How I treat pregnancy-related venous thromboembolism. *Blood* 2011;118:5394-5400
20. Kupferminc HJ, Rimón E, Many A, et al. – Low molecular weight heparin treatment during subsequent pregnancies of women with inherited thrombophilia and previous severe complications. *J Matern Fetal Neonatal Med* 2011;24:1042-1045.