A RARE CASE OF FACTOR V LEIDEN MUTATION COMPLICATING PREGNANCY IN INDIA

Chitra Kumbasubramaniyan1, Shanthi Chandran4, Vittal Shankreppa3

1Professor, Department of Obstetrics and Gynaecology, Madurai Medical College, Madurai.
2Professor & HOD, Department of Obstetrics and Gynaecology, Madurai Medical College, Madurai.
3Post Graduate, Department of Obstetrics and Gynaecology, Madurai Medical College, Madurai.

ABSTRACT

Factor V Leiden mutation (Factor V Leiden) is an autosomal dominant haemostatic 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 venous thromboembolic events by 5- to 6-fold,2 because there are potentially serious effects of FVL for both the mother and the child, and availability of effective treatment strategies, early detection and treatment of this condition is warranted.3 We are presenting this case in order to emphasise the existence of Factor V Leiden in Indian population and its approach during pregnancy.

KEYWORDS

Factor V Leiden, Deep Vein Thrombosis, Cerebral Venous Thrombosis, Anticoagulant Therapy, Thrombophilia Complicating Pregnancy.

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INTRODUCTION: Factor V Leiden is present in around 5% of Caucasians;4 it is rare or absent in people of black African, Far East Asian, native Australian, native American origin. Factor V Leiden (FVL) mutation (named after the Dutch university where it was discovered) is a point mutation in the gene for clotting Factor V. Pregnancy itself is a risk factor for venous thrombosis. It has autosomal dominant inheritance and is the most common cause of inherited thrombophilia. Factor V Leiden is the most prevalent thrombotic risk factor known in the Caucasian population (around 5%);5 Heterozygotes have a three to five times increased risk of thrombosis. Homozygotes are much less common but have a much higher thrombotic risk, around eighty times increased risk.

It leads to a hypercoagulable state. Heterozygous FVL mutation and the G20210A mutation in the prothrombin gene are the most frequent clotting abnormalities associated with venous thromboembolism (VTE). The two mutations may coexist.

An individual may be heterozygote or homozygote for the Factor V Leiden mutation. It is difficult to estimate the increased risk of thrombosis in given individuals, particularly heterozygotes, due to the variable penetrance of the thrombotic tendency (Interaction with rest of genotype) and variation in other risk factors. Heterozygous carriers have a 4- to 8-fold increased risk of venous thromboembolic events and homozygotes have an 80-fold increased risk.1

The risk of venous thromboembolic events of a FVL mutation is considerably lower than a deficiency of protein C, protein S, or antithrombin III;6

CASE HISTORY: A 27-year-old gravida-2, para-1, live-1, previous lower segment caesarean section, last child birth two and half years back. Last menstrual period and expected date of delivery was unknown in current pregnancy.

Previous Pregnancy History: There was no history of preeclampsia, placental abruption and intrauterine growth restriction in her previous pregnancy, she had no significant family history of any thrombophilic disorders. She underwent lower segment caesarean section in Taluka Hospital for foetal distress, delivered a live term male baby of weight 2.6 kg. She was discharged on eighth post-operative day after removal of sutures. On 12th post-operative day, patient was readmitted for calf muscle tenderness and diagnosed to have lower limb deep vein thrombosis and treated with injection heparin 5000 IU IV t.d.s. for 5 days and then overlapped with tab Acitrom 2 mg and discharged with tab Acitrom 2 mg 1 HS, and advised to follow up. Further investigations not done. After discharge, patient did not continue the anticoagulant agent.

In Present Pregnancy: Patient was referred from Taluka Hospital with complaints of altered sensorium and rightsided body weakness, at 3 months of amenorrhoea. She had normal blood pressure. After thorough investigations, ultrasonography of abdomen showed single live intrauterine gestation corresponding to 12 weeks of pregnancy. Her magnetic resonance imaging (PIC 1A and 1B) study of brain clinched the diagnosis of cerebral venous thrombosis and Thrombophilia profile (Table 1) suggested, Factor V Leiden mutation.

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Corresponding Author: Dr. ChitraKumbasubramaniyan, Professor, Department of Obstetrics and Gynaecology, Madurai Medical College, Madurai. E-mail: drchitraks@gmail.com DOI: 10.18410/jebmh/2016/469

MRV showing vein of Galen, transverse sinus and internal cerebral vein not visualised;

**Impression:** Deep cerebral vein and straight sinus thrombosis, causing secondary haemorrhage.

**Table 1: Thrombophilia Profile (Table 1)**

<table>
<thead>
<tr>
<th>TESTS</th>
<th>PATIENT VALUES</th>
<th>NORMAL VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>0.43</td>
<td>(&lt;0.8)</td>
</tr>
<tr>
<td>Anti ds-DNA antibody</td>
<td>63.75 IU</td>
<td>Negative(0-200)</td>
</tr>
<tr>
<td>Protein C</td>
<td>96.52%</td>
<td>70-150</td>
</tr>
<tr>
<td>Protein S</td>
<td>98.63%</td>
<td>70-150</td>
</tr>
<tr>
<td>Anti-thrombin III</td>
<td>27 mg/dl</td>
<td>17-30</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>DETECTED(PCR SEQUENCING)</td>
<td></td>
</tr>
<tr>
<td>VDRL</td>
<td>NEGATIVE</td>
<td></td>
</tr>
<tr>
<td>Anti-Phospholipid Ig M</td>
<td>5.24</td>
<td>NEGATIVE&lt;15</td>
</tr>
<tr>
<td>Anti-Phospholipid Ig G</td>
<td>6.25</td>
<td></td>
</tr>
</tbody>
</table>

Vascular surgeon and neurophysician opinion obtained and she was treated with heparin 5000 IU bolus and heparin 12500 in 250 mL NS over 12 hours infusion twice daily with aPTT monitoring and tab carbamazepine 100 mg-0-200 mg. After her recovery, she was kept on anticoagulant therapy, injection heparin 10,000 IU s.c. b.d. and tab carbamazepine with follow-up of aPTT, she was discharged after proper counselling and asked for routine follow-up. At fifth month of amenorrhoea, she was readmitted.

Vascular surgeon and neurophysician review obtained, she was switched over to low molecular weight heparin 0.4 mL subcutaneously OD and carbamazepine continued. She was monitored in hospital till term, confirmed by clinical examinations and abdominal ultrasonography and low molecular weight heparin stopped 12 hours before surgery. An elective repeat lower segment caesarean section done to deliver a live term male baby of weight 2.6 kg, with Apgar 6/10 at one minute and 8/10 at five minutes, there were no any placental lesions. Procedure was uneventful, then she was started with injection heparin 5000 IU IV q.i.d. after vascular surgeon’s opinion, 6 hours post-surgery.

Neurophysician review obtained and tab carbamazepine continued. Routine aPTT monitoring done and was in therapeutic range. Stockings provided to patient and encouraged for early mobilisation. On 6th post-operative day, vascular surgeon suggested to switch over to low molecular weight heparin 0.4 mL s.c. o.d. In spite of this, on the 18th post-operative day, patient developed left lower limb deep vein thrombosis. Confirmed by venous Doppler (PIC 2).

**DISCUSSION:** Pathophysiology: Blood coagulation is under the control of anticoagulant proteins present in the plasma or on the surface of the endothelial cells (Davie et al., 1991). Protein C, a vitamin K dependent plasma protein, plays a vital role in natural anticoagulation. Once activated on the endothelial cells by thrombin–thrombomodulin complex, protein C exerts a selective, proteolytic degeneration of Factor Va and VIIIa (Dahlback and Stenflo, 1994).

Protein S another vitamin K dependent protein present in the plasma as a both free protein and protein bound to compliment C4b-binding protein acts as a co-factor to APC (Dahlback 1991 ; Dahlback and Stenflo, 1994). The
replacement of the arginine with the glutamine at the position 506 in factor Va, protein molecule, encoded by the Leiden mutation, alters the cleavage site of this molecule by activated protein C. As a result, the mutated factor Va, while maintaining its physiological procoagulant properties, becomes resistant to proteolytic inactivation by APC (Bertina et al., 1994). In addition, co-factor activity to APC depends on factor V, becomes lost. These changes, in turn yield stabilisation of prothrombinase complex, rise in thrombin production and feedback activation of factor V and VIII resulting in a predisposition to thromboembolism (Dahlbäck 1994).⑳

Geographically: Factor V Leiden is present in around 5% of Caucasians,⑴ It is rare or absent in people of black African, Far East Asian, native Australian, native American origin.

Investigations: Mainly involves screening tests for hereditary thrombophilia, should only be carried out by physicians with a specialist knowledge who can explain the relevance of the findings to the patient and give any necessary therapy. Screening for thrombophilic disorders should not be undertaken routinely.⑸ Genetic testing can be performed. The polymerase chain reaction for the presence of the factor V Leiden mutation is 99% accurate.

Management: General: There is no evidence that the risk of venous thromboembolism is high enough to warrant long-term anticoagulation in carriers of the gene, even in the homozygous state.⑶ Guidelines published by the British Society of Haematology state that initiation and intensity of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia. Indiscriminate testing for heritable thrombophilia in unselected patients presenting with a first episode of venous thrombosis is not indicated.

Decisions regarding duration of anticoagulation (lifelong or not) in unselected patients should be made with reference to whether or not a first episode of venous thrombosis was provoked or not, other risk factors, and risk of anticoagulant therapy-related bleeding, regardless of whether a heritable thrombophilia is known. Case finding of asymptomatic relatives with low-risk thrombophilia such as Factor V Leiden is not indicated.

Decisions regarding the optimal duration of anticoagulation are based on an individualised assessment of the risks for venous thromboembolism recurrence and anticoagulant-related bleeding. In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for asymptomatic Factor V Leiden heterozygotes, although prophylactic anticoagulation may be considered in high-risk clinical settings.⑸

However, among individuals heterozygous for the Factor V Leiden mutation, while venous thromboembolism recurrence risk is greater, the risk for bleeding is recognised to be lower. Some specialists are now recommending considering longer duration anticoagulation.⑹

Factor V Leiden Mutation and Pregnancy: Venous thromboembolism and pregnancy.
Inherited thrombophilia is present in 30-50% of women with pregnancy-associated venous thromboembolism, with Factor V Leiden being the most frequently identified thrombophilia in the white population.⑸ Whether the administration of low molecular weight heparin (LMWH) during pregnancy is effective in preventing obstetric complications and pregnancy-related venous thromboembolism in women who are carriers of Factor V Leiden is controversial.⑹ Current opinion is often based on consensus and clinical judgement of the benefits and risks of antithrombotic therapy in individual cases. Joint opinion of haematologist, obstetrician and patient should decide the issue in non-straightforward cases.

Therapeutic decisions should be based on clinical circumstances and not on the results of thrombophilia testing. For example, in the case of the older woman (e.g., aged >35 years) with a poor obstetric history a decision to treat with low-dose heparin should not be determined by the results of testing for heritable thrombophilia.⑶

Antithrombotic therapy should not be given to pregnant women based on tests for heritable thrombophilia. Randomised controlled trials with a no treatment or placebo arm in women with a history of pregnancy complications are in progress.⑸ LMWH prophylaxis has been shown to reduce the risk of obstetric complications in carriers of Factor V Leiden, particularly in those with previous obstetric events. In addition, LMWH prophylaxis reduces the risk of pregnancy-related venous thromboembolism.⑷ The use of LMWH during pregnancy has been shown to be safe and effective in preventing venous thromboembolism in susceptible patients with Factor V Leiden.⑸

Heterozygotes are not routinely anticoagulated but a personal or family history of venous thromboembolism or other risk factors (e.g., obesity) may make them candidates for heparinisation. Once a woman is in labour or thinks she is in labour, she should discontinue her heparin and be reassessed, on admission to hospital, by medical staff. Local guidelines should be followed.⑸ Those considered to be in need of anticoagulation should usually receive warfarin or heparin for at least six weeks postpartum, when the risk of venous thromboembolism is high. It is safe to breast-feed whilst taking warfarin.

Factor V Leiden Mutation and Pregnancy Loss: Carriers of Factor V Leiden have double the risk of experiencing recurrent miscarriage compared with women without this thrombophilic mutation.⑹ One study clearly demonstrated a positive correlation between recurrent pregnancy loss and Factor V Leiden gene mutations.⑹ Current recommendations are that women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden.⑸ Mass screening of women for factor V Leiden 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 venous thromboembolism, early onset or recurrent preeclampsia, recurrent IUGR, unexplained intrauterine growth restriction, placental abruption, and preeclampsia. 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.\(^{(16)}\)

However, one recent study has shown that the frequency of Factor V Leiden mutation was not significantly different between patients with recurrent miscarriage and healthy women.\(^{(17)}\)

**CONCLUSION:** Pregnancy itself is a prothrombotic state, presence of Factor V Leiden mutation increases the risk. Factor V Leiden is an inherited condition that predisposes persons to venous thromboembolism. During pregnancy, persons with Factor V Leiden are at increased risk for venous thromboembolism, intrauterine foetal demise, intrauterine growth restriction, 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 venous thromboembolism. It is important to detect early and treat the condition with proper anticoagulant therapy. Our case depicts an early diagnosis and expert management, leading to prevention of complications antenatally and safe delivery with healthy baby and mother, discharged without any morbidity.

**REFERENCES**