First Korean case of factor V Leiden mutation in pregnant woman with a history of recurrent pregnancy loss

Sung Hee Han1*, Jung Jae Seo2, Eun Seol Kim3, Jae Song Ryu1, Seong Hyeon Hong1, and Seung Yong Hwang1

1Division of Biotechnology, Bio-Core Co. Ltd., Yongin, Korea
2Department of Obstetrics and Gynecology, Women’s I Hospital, Pohang, Korea

Case Report
https://doi.org/10.5734/JGM.2019.16.1.23
ISSN 1226-1769 (Print) 2383-8442 (Online)

Introduction
Recurrent pregnancy loss (RPL) has been public health concern, developed 1 in 300 pregnancies and 2-4% of reproductive-aged couples. RPL is defined as 2 or more spontaneous abortions before the 20th week of gestation [1]. An estimated 50% of RPL is idiopathic. Most couples with RPL should be evaluated for genetic and non-genetic causes. Thrombophilia has been suggested as one putative etiology of RPL [2]. Inherited thrombophilia is a genetic disorder of blood coagulation resulting in an unusual hypercoagulable state, which in turn can result in abnormal implantation and may manifest as spontaneous fetal loss [3]. The inherited predisposition to thrombophilia is most often associated with factor V Leiden (FVL) mutation (c.1601G>A), coagulation factor II (F2, also known as prothrombin) gene variant (c.20210G>A), and methylenetetrahydrofolate reductase (MTHFR) gene variants (c.677C>T and c.1298A>C) [4].

Activated protein C (APC) resistance is known to be the most frequent genetic cause of venous thrombosis, accounting for up to 40% of all thromboses. The FVL mutation, inherited as an autosomal dominant trait, is responsible for 95% of cases of APC resistance [5]. The FVL mutation is caused by a point mutation in the F5 (OMIM 612309, NM_000130.4), encoding a substitution of arginine for glutamine at position 534 of the factor V
molecule located on chromosome 1q24, the site at which APC cleaves factor Va. The FVL mutation renders factor Va resistant to the anticoagulant effects of APC, resulting in a genetic predisposition to thrombosis [5]. The distribution of FVL mutation varies greatly in ethnic groups. The FVL mutation is reported in 5% of the healthy white population, 1% of the healthy black population, reaching 10–15% in some European countries [6]. However, it appears that FVL mutation is extremely rare in Africans and Asian countries [7], and until now, there has been no report of FVL mutation positive detected in Korean population [8–11]. Here, we present the first Korean case of FVL mutation in pregnant woman with a history of RPL.

Case

The patient was a 36-year-old Korean woman, gravida 7, para 1, aborta 6, who presented with RPL at her initial obstetrical visit. Her past obstetrical history was significant for 1 ectopic pregnancy and 5 early first trimester miscarriages, followed by 1 full-term delivery by cesarean section. She had no previous history of preeclampsia, placental abruption, or intrauterine growth retardation (IUGR). The results of her physical examination were within normal limits. For evaluation of RPL, she was tested for complete blood count, coagulation profile, thyroid function test (T3/free T4/thyroid stimulating hormone [TSH]), prolactin, natural killer cell proportion, anticardiolipin antibodies immunoglobulin (Ig) M/IgG, lupus anticoagulant screening, anti-β2 glycoprotein-1 antibodies IgM/IgG, thyroid peroxidase antibody, protein C and S functional activity, antithrombin III activity, homocysteine, TSH receptor antibody, thyroglobulin antibody, chromosomal analysis, and genotype for FVL mutation (c.1601G>A), F2 gene variant (c.20210G>A), and MTHFR gene variants (c.677C>T and c.1298A>C).

Her baseline complete blood count, coagulation profile and thyroid function test were within normal limits. Serum prolactin was 10.6 ng/mL (normal range, 2.8 to 29.2 ng/mL). Serum homocysteine was 8.65 μmol/L (normal range, 6.72 to 15.16 μmol/L). Thrombophilia profile of this patient was evaluated by PCR-sequencing. In the F5 gene, heterozygous genotype c.1601G>A was detected (Fig. 1). The presence of the FVL mutation (c.1601G>A) was confirmed by direct PCR product sequencing (Fig. 2). The genotypes heterozygous wild type CT in position 677 and homozygous wild type AA in position 1298 of the MTHFR were determined. The F2 mutation (c.20210G>A) was not detected. Her karyotype showed normal female.

On 4 months later, she was presented with pregnancy at

<table>
<thead>
<tr>
<th>Restriction enzyme</th>
<th>Polymorphism</th>
<th>Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HinfI</td>
<td>MTHFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wild type allele 677C</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>Variant allele 677T</td>
<td>175, 23</td>
</tr>
<tr>
<td>MboII</td>
<td>MTHFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wild type allele 1298A</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>Variant allele 1298C</td>
<td>241</td>
</tr>
<tr>
<td>Mnl1</td>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wild type allele 1601G</td>
<td>164, 66, 36</td>
</tr>
<tr>
<td></td>
<td>Variant allele 1601A</td>
<td>200, 66</td>
</tr>
</tbody>
</table>

Table 1. Primer used to amplify variant polymorphisms of factor V Leiden (FVL) mutation, coagulation factor II, and MTHFR

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Primer sequences (5' to 3')</th>
<th>Size (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR (c.677C&gt;T)</td>
<td>TGAAGGAGAAGGGTCTGCGGGGA</td>
<td>AGGACGGTGCAGTGAGTGG</td>
</tr>
<tr>
<td>MTHFR (c.1298A&gt;C)</td>
<td>ATGGGGGGGAGGAGGTGAC</td>
<td>GTCCTCAGGTCTACAGTCC</td>
</tr>
<tr>
<td>F2 (c.20210G&gt;A)</td>
<td>CGCCTGGAAGAGTGATAC</td>
<td>CTTCTGGACCCAGAAGC</td>
</tr>
<tr>
<td>FVL (c.1601G&gt;A)</td>
<td>TCCCAGTGCTTAACAAAAAGCCA</td>
<td>TGTTATACACTTGCTAA</td>
</tr>
</tbody>
</table>

Table 2. Restriction enzymes used to digest polymerase chain reaction products, and related product size
her obstetrical visit. Estimated gestational age was 5 weeks as measured from the patient’s last menstrual period, which was confirmed by a first trimester crown-rump length. The couple was counseled about the autosomal dominant nature of FVL mutation. On the intake interview, the patient had no significant past medical history including thromboembolic disease. However, her father was diagnosed with a cerebral infarction and her grandmother died of myocardial infarction. The patient was advised folic acid supplementation and early antenatal registration with thromboprophylaxis in next pregnancy. In view of FVL mutation positive in pregnancy, the patient was started on low dose aspirin (100 mg) once daily and low-molecular-weight heparin (40 mg, Cnoxane; YOOYOUNG Pharm. Co. Ltd., Jincheon, Korea) subcutaneous injection once daily.

Discussion

In this report, we present the case of a Korean woman with a history of RPL that was complicated with the FVL mutation. In several studies, the potential clinical significance of hereditary thrombophilia factors, such as FVL mutation, F2 gene mutation, plasminogen activator inhibitor-1 gene polymorphism, protein S deficiency, protein C deficiency, and MTHFR gene polymorphism has been addressed [11,12]. A thrombophilia may result in impaired maternal fetal circulation by compromising the vascular system associated with significant fetal morbidity and mortality [13]. The FVL mutation has been significantly related to pregnancy complications associated with hypercoagulation, e.g., venous thromboembolism (VTE), hypertensive disorders of pregnancy, late pregnancy loss and stillbirth, placental abruption, and IUGR [14]. Recently, in meta-analysis, FVL mutation was associated with RPL (OR, 1.68; 95% CI, 1.16 to 2.44) [12]. VTE is the leading cause of morbidity and mortality in pregnancy and the postpartum period. VTE occurs in approximately 1 in 1,500 pregnancies, and up to one fourth of untreated deep vein thromboses may lead to pulmonary embolism [15]. Women with a personal history of VTE in a previous pregnancy have a higher prevalence of FVL mutation than those who have never had a VTE [15]. Patients who are heterozygous for this condition are at 3- to 8-fold increased risk for VTE; those who are homozygous are at 10- to 80-fold increased risk [16].

Current expert opinion recommends that management be based on the presence of current VTE, the presence of a past VTE, and risk factors for a VTE during pregnancy. High-risk thrombophilia, including FVL homozygosity, F2 mutation (c.20210G>A) homozygosity, heterozygosity for FVL mutation and F2 mutation (c.20210G>A), or antithrombin deficiency, recommend...
prophylactic anticoagulation therapy regardless of VTE history. Low-risk thrombophilia for women who are heterozygous for FVL mutation without previous VTE, such as the present case, the American College of Obstetricians and Gynecologists (2018) [17] recommends surveillance without anticoagulation therapy in pregnancy and postpartum period. However, even though low-risk thrombophilia without previous VTE, if the patient has additional risk factors, such as first-degree relative with a history of a thrombotic episode, or other thrombotic risk factors (e.g., obesity, prolonged immobility, cesarean delivery), postpartum prophylactic anticoagulation therapy is recommended.

Inherited thrombophilia has a different prevalence between various ethnic groups [6,7]. According to previous study of RPL in Korean women, FVL mutation was not found in any women and protein S deficiency was found 13.5% [11]. Another study for thrombophilia in Korean patients with VTE suggests that FVL mutation testing is unnecessary for Korean patients with VTE [10]. To our acknowledgment, this is the first case of FVL mutation in Korean. It is important to have a guideline for evaluation and management for Korean RPL women based on the evidence and our circumstances.

In conclusion, during pregnancy, patients with FVL mutation are at increased risk for VTE, intrauterine fetal death, IUGR, placental abruption, and preeclampsia. It is important to have a good knowledge of FVL mutation and its potential impact on pregnancy. Inherited thrombophilia has shown the ethnic difference signify the need for consideration in screening and interpretation. Appropriate counselling and clinical intervention should be considered during pregnancy to prevent adverse pregnancy outcomes.

References