The Role of the F2 Gene in the Occurrence of Obstetric Complications in the form of Hypertensive Conditions During Pregnancy

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Abstract: Antiphospholipid syndrome (APS) an autoimmune state of hypercoagulability caused by antiphospholipid antibodies. APS causes blood clots (thrombosis) in both arteries and veins, as well as pregnancy-related complications such as miscarriage, stillbirth, premature birth, and severe preeclampsia. [9,10]. Thrombosis is a pathophysiologic feature, but other factors such as complement activation may be important. Pregnant women with APS have an increased risk of recurrent miscarriage, intrauterine growth restriction, and premature birth. Placental infarction is often the cause of these complications. In addition, it can be the cause of preeclampsia, according to some authors, as it affects the bloodstream [1,5,6,8].

Key words: antiphospholipid syndrome, preeclampsia, thrombosis, F2 gene.

Relevance. Often, with undiagnosed recurrent miscarriage and complicated pregnancy, the therapy aimed at maintaining pregnancy contributes to the term of pregnancy, but despite this, it is not always possible to avoid perinatal losses in women of this category. Acquired risk factors such as surgery, immobilization, pregnancy, smoking, oral contraceptives and obesity, as well as hereditary risk factors, simultaneously contribute to the occurrence of venous thromboembolism in APS [7,8]. Antiphospholipid syndrome (APS) is an acquired autoimmune hypercoagulable syndrome characterized by venous and/or arterial thrombosis and/or pregnancy complications and the presence of antiphospholipid antibodies. Antiphospholipid antibodies (APA) are a heterogeneous group of autoantibodies directed against proteins associated with membrane phospholipids. The AFA group includes anticardiolipin antibodies (ACA); antibodies to beta-2-glycoprotein; lupus anticoagulant; antibodies to annexin V; antibodies to phosphatidylserine-prothrombin complex and others. Hereditary risk factors such as antithrombin deficiency, factor [F2] mutations are considered more frequently diagnosed, but rather moderate risk factors [1,2,3,4,5].

Antiphospholipid syndrome is an autoimmune disease in which antiphospholipid antibodies (anticardiolipin antibodies and lupus coagulant) interact with proteins that bind to anionic phospholipids on plasma membranes. Like many other autoimmune diseases, this syndrome is more...
common in women than in men. The exact cause of the disease is unknown, but it is clear that there is an activation of the blood clotting system. Clinically important antiphospholipid antibodies (those that arise from an autoimmune process) are associated with thrombosis and vascular disease. There are few case-control studies investigating the role of F2 in polymorphisms with thromboembolism [8, 9]. To study this gene for the occurrence of preeclampsia in APS, we decided to conduct this study.

**Purpose of the study:** the purpose of this study was to study the role of the F2 gene contributing to the development of obstetric complications in the form of hypertensive conditions during pregnancy.

**Materials and research methods.** This study included 107 pregnant women diagnosed with APS. They had a history of miscarriage more than 2 times before 24 weeks of pregnancy. The age of the patients varied from 20 to 35 years. In doing so, we take into account all these criteria: AFA (antiphospholipin antibodies) and the F2 gene. All these pregnant women were examined in the maternity complex of the city of Bukhara in the department of pathology of pregnant women. All patients gave written consent for the examination. The survey was conducted from January 2020 to May 10, 2021. Statistical significance was considered P<0.05.

The inclusion criteria for the study were: a history of miscarriage more than 2 times before 24 weeks of pregnancy, not receiving corrective therapy. Exclusion criteria: were pregnant women with a physiological course or pregnant women receiving therapy to prevent APS or anticoagulant therapy. Statistical processing was carried out by the Fisher-Student method.

After the start of the study (inpatients and outpatients) and at regular follow-up visits for 3–6 months, we reassessed the patient's medical history and possible risk factors that cause TE, such as oral contraceptive use, pregnancy, obesity, immobilization, surgery, and smoking. Clinical data collection also included laboratory test results, antithrombotic therapy including adherence to anticoagulation regimen, duration and family history of TE.

Mutations with written or verbal consent in F2 to rs3136516, as well as circulating antithrombin levels, blood coagulation inhibitors, d-dimer concentration, and lupus anticoagulants and antiphospholipid antibodies were investigated by standard laboratory methods at the beginning of TE and were repeated during routine follow-up.

**Research results and discussion.** In the present longitudinal study in German patients with TE, we have shown that the presence of an F2 mutation in rs3136516 in either its GG genotype or its GA genotype compared to the AA variant plays a modest but independent role in the first occurrence of VTE with an adjusted odds ratio of 1.48 (GG genotype) and 1.45 (GA genotype), respectively. In our study, in the last two cohorts, the F2 rs3136516 GG genotypes were compared with APA carriers [8,9]. Combining the results of four studies in 61 patients with TE and 65 population controls, we found a modest increase in association with TE in carriers of the F2 genotype (rs3136516) GG 1.3 (95% CI 1.2–1.4; p<0.0001; heterogeneity [I2] 0.0%). Interestingly, when examining the role of this F2 intron polymorphism in a genome-wide association study, risk association with TE was also modestly increased with an OR of 1.08 (1.06–1.11) [20].

Structure complications are presented in table. 1. Most common obstetric pathology were reproductive loss (regressive pregnancy, early and late spontaneous abortions). Share of women with habitual miscarriage was 43.0%. The number of losses per patient varied from 2 to 12. At the same time, patients with three consecutive losses up to 10 weeks of pregnancy, in accordance to the clinical criteria for a certain APS, there were only 16 people (5.0%). Late reproductive losses for periods of 10 or more weeks, also being an independent clinical APS criterion, 30.0% of the examined
Table 1. Structure of gestational complications in patients with aggravated obstetric history (n = 107)

<table>
<thead>
<tr>
<th>Complication</th>
<th>N=107</th>
<th>share %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 fetal loss before 10 weeks</td>
<td>9</td>
<td>8.4%</td>
</tr>
<tr>
<td>≥1 fetal loss at 10 weeks or more</td>
<td>10</td>
<td>9.3%</td>
</tr>
<tr>
<td>habitual miscarriage (≥2 reproductive losses)</td>
<td>8</td>
<td>7.4%</td>
</tr>
<tr>
<td>Fetal growth retardation syndrome</td>
<td>8</td>
<td>7.4%</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>12</td>
<td>11.2%</td>
</tr>
<tr>
<td>Primary detachment is normal located placenta</td>
<td>5</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

As can be seen from this table, which shows the complications associated with APS, 1 loss before 10 weeks of gestation history was 8.4%, more than 10 weeks 9.3%, more than 2 losses in history 7.4%, fetal growth retardation 7.4 %, severe preeclampsia in 11.2%, detachment of a normally located placenta in 4.6%.

In our cohort, combinations between the homozygous genotype F2 GG for rs3136516 and F5 for rs6025, additionally included in the statistical model in a multiplicative scale, did not have a significant effect on thrombotic risk at the onset of TE.

The results of our study, in which TE events were associated in most cases with provoking risk factors, are consistent with a higher risk of recurrence in pregnant women with spontaneous abortions due to APS after unprovoked TE. Carriers of the mutation carrying the F2 GG/GA variant (rs3136516) with an odds ratio of 3.34 compared to 1.86 found with only positive APA.

Bibliography
