Genetic Predispositions to Thrombophilia Associated with Recurrent Pregnancy Loss

Bogdanova N, Markoff A

J. Reproduktionsmed. Endokrinol 2008; 5 (2), 101-105

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Indexed in EMBASE/Excerpta Medica/Scopus
Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz
Ab sofort in unserem Verlag

Thomas Staudinger
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2. Auflage Jänner 2019
ISBN 978-3-901299-65-0
78 Seiten, div. Abbildungen
19.80 EUR

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Fetal loss is a common and considerable problem during pregnancy. About 20% of women worldwide have at least one abortion and 5% have two or more spontaneous pregnancy losses [1]. The most common reason for adverse pregnancy outcome in the first trimester consists in fetal chromosomal abnormalities which are not compatible with survival. However, 30–40% of recurrent fetal losses remain unexplained after standard gynaecological, hormonal and cytogenetic investigations [1].

Prime candidates forming molecular basis of fetal loss are various acquired or inherited hypercoagulation disorders promoting thrombosis, collectively termed ‘thrombophilias’ [2]. Related evidence comes from histological studies reporting microthrombi to be a common finding in the placental vessels amongst women with recurrent miscarriage [3, 4]. Changes in blood coagulation and fibrinolysis during normal pregnancy induce a state of hypercoagulability, which predisposes to development of thrombosis [5, 6]. In combination with the physiological changes during pregnancy, hereditary thrombophilic defects may increase the risk of uteroplacental thrombosis and hence the risk of fetal loss [7].

Up to 70% of the patients prone to thrombophilia will be found to have one or several of the five major inherited defects listed in Table 1. Two of these genetic defects – the factor V Leiden (FVL) mutation and the prothrombin G20210A mutation (PTm) – found together in more than half of all cases of inherited thrombophilia are well conserved single nucleotide substitutions for which direct DNA-based assays are available.

The factor V Leiden mutation results from a guanine substitution for adenine at position 1691 of the gene encoding the coagulation factor V [8–10]. The resulting amino-acid substitution, namely, arginine (R) to glutamine (Q) at amino-acid position 506, occurs precisely at one of the three sites where activated protein C (APC) normally cleaves and inactivates the procoagulant factor Va. Because of this single amino-acid substitution activated factor V Leiden is partially resistant to the anticoagulant action of APC and is inactivated at an approximately ten-fold slower rate than normal, resulting in increased thrombin generation and a prothrombotic state.

Activated protein C resistance not due to factor V Leiden has also been identified as an independent risk factor for deep vein thrombosis [11]. These states may correspond to acquired conditions as reported for pregnancy [12] and oral contraceptive use [13]. Some laboratory phenotypes, such as lupus anticoagulant and high factor VIII levels, are also associated with a reduced sensitivity for APC. It may also be due to other inherited traits. For example, two mutations involving the Arg205 APC cleavage site of factor V were described [14, 15]. One mutation (Arg306Thr, factor V Cambridge) was indeed associated with APC resistance. The other mutation (Arg306Gly) found in a Hong Kong Chinese, was reported not to be associated with APC resistance. In some
patients no obvious reason can be found for the APC-resistant phenotype without the factor V mutation.

The 20210G>A mutation (PTm) in the 3’ untranslated region of the Factor II gene encoding prothrombin causes a gain of function due to increased recognition of the 3’ end cleavage signal and increased 3’ end processing. The net result is accumulation of messenger RNA and increased protein synthesis of prothrombin [16].

Homozgyous and heterozygous forms of factor V Leiden and PTm increase the risk of thrombosis (Tab. 1). Factor V Leiden is the most common inherited cause of thrombophilia, being present in heterozygous form in about 12–20 % of the patients with venous thrombosis and in 40–50 % of those with recurrent venous thrombosis. This mutation is very common in the white population: about 3–7 % of the normal white population of northern European or Scandinavian ancestry are heterozygous FVL carriers. Heterozygous carriers of FVL have been shown to have an overall 3- to 7-fold increased risk of venous thrombosis, while homozygous individuals have a 50- to 100-fold increased risk [17–19].

The prevalence of the prothrombin mutation in Europe is about 2 % overall, with a range of 1–3 %. The highest prevalence appears to be in southern European regions (approximately 3 %) and the lowest prevalence in the northern parts of the continent (approximately 1.7 %). Heterozygous carriers of the 20210A allele have a 2- to 8-fold increased risk for venous thrombosis [20]. There are very few cases of homozygosity for this mutation. Although more severe thrombotic risk may be expected in the homozygous state, there is a broad clinical spectrum with striking heterogeneity, because of the very small number of cases [21].

Patients carrying both the FVL and prothrombin G20210A mutations have an odds ratio for venous thrombosis of 20, i.e. higher risk as compared to heterozygous for FVL or prothrombin G20210A only. Analysis for both mutations is therefore recommended in patients with personal or family history of thrombosis [22, 23]. Hereditary deficiencies of the anticoagulant proteins antithrombin, protein C and protein S are heterogeneous in nature and caused by several different genetic mutations [24]. Although these deficiencies have been more frequent targets for clinical thrombophilia research, together they are found in less than 10 % of the patients with thrombophilia [25].

It has been suggested that elevated total plasma homocysteine level (hyperhomocysteinemia) could predispose to thrombophilia. Homocysteine is a non-protein-forming sulphydryl amino-acid formed from the intracellular demethylation of methionine. In hepatocytes, homocysteine is remethylated to methionine by donation of a methyl group from methyltetrahydrofolate, derived in a reaction catalyzed by methylene-tetrahydrofolate reductase (MTHFR). A quite common variant in the MTHFR gene, a C to T substitution at cDNA position 677 leading to a change from alanine to valine, may lead to an increased level of plasma homocysteine. This variant demonstrates reduced activity at 37 °C and increased thermolability at 46 °C. About 12 % of the white population is homozygous for this mutation, and moderate hyperhomocysteinemia is typically manifest when folate levels are in the lower end of the normal range [26]. Although initial studies have suggested an association between homozygosity for MTHFR C677T and venous thrombosis, prospective studies could not confirm such an association [27, 28]. However, the risk for thrombosis may be more closely linked to a combined defect of homozygosity for MTHFR C677T and for another unequivocal risk factor such as factor V Leiden [19, 29, 30].

A second common polymorphism in the MTHFR gene, A1298C, has been described by van der Put [31]. The prevalence of individuals homozygous for this variant in the white population is approximately 10 % and 23 % are combined heterozygous for C677T and A1298C [32]. It has been shown that combined heterozygosity for C677T and A1298C, but not homozygosity for A1298C, is associated with increased fasting and post-methionine load homocysteine plasma levels [32].

In the last years a large number of studies on the association between inherited thrombophilia and pregnancy loss has been published [33–42]. Because of the conflicting results of these studies regarding the presence and magnitude of the associations, and because of the increasingly widespread availability of screening tests for thrombophilia, a meta-analysis on 31 association studies published in literature has been put together [43] in order to estimate the strength and precision of the association between individual inherited thrombophilia and fetal loss and to examine whether these associations vary according to the timing or definition of fetal loss (Tab. 2). From this analysis factor V Leiden is associated with early and late recurrent fetal loss (OR 2.01; 95 % CI: 1.13–3.58) and late non-recurrent fetal loss (7.83; 2.83–21.67). Exclusion of women with other pathologies that could explain fetal loss strengthened the association between factor V Leiden and recurrent abortions. Furthermore, there is a significant association between PTm and recurrent abortions before 13 weeks of pregnancy (2.56; 1.04–6.29) as well as non-recurrent fetal loss after 20 weeks. While protein S deficiency is related to non-recurrent pregnancy loss occurring after 22 weeks, activated protein C resistance not due to factor V Leiden is associated with recurrent early pregnancy loss. In contrast, there is no signifi-

<table>
<thead>
<tr>
<th>Thrombophilic effect</th>
<th>Recurrent pregnancy loss before 13 weeks</th>
<th>Non-recurrent pregnancy loss</th>
<th>Non-recurrent pregnancy loss after 19 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>0.88</td>
<td>1.54</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>1.57</td>
<td>1.41</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>14.72</td>
<td>7.39</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>2.01</td>
<td>1.73</td>
<td>3.26</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>2.05</td>
<td>2.32</td>
<td>2.30</td>
</tr>
</tbody>
</table>
Based upon these observations and patients with preeclampsia [55], annexin A5 expression in placental trophoblasts has also been documented immunohistochemically in the presence of aPL [54]. Reduced annexin A5 expression in placental trophoblasts has also been documented immunohistochemically in patients with preeclampsia [55]. Based upon these observations and the reported anticoagulation activity of annexin A5 [56], it has been suggested that annexin A5 molecules form an antithrombotic shield on the apical surface of placental syncytiotrophoblasts, which may then be disrupted by antiphospholipid antibodies [57]. This hypothesis has recently received additional support from in vitro studies employing atomic force microscopy and functional assays [58].

Recently, we found that a sequence variation in the promoter of the placental anticoagulant protein annexin A5 (ANXA5) gene represents a risk factor for recurrent pregnancy loss [59]. Sequence analysis of 70 German RPL patients, all known to carry neither factor V Leiden nor a prothrombin mutation, revealed four consecutive nucleotide substitutions in the ANXA5 promoter that were transmitted as a joint haplotype (M2). Reporter gene assays revealed that M2 reduces the in vitro activity of the ANXA5 promoter to 37–42% of the normal level. The possible relationship between M2 and RPL was evaluated by comparing RPL patients (n = 70) with two independent control groups recruited from the registries of the Institute of Human Genetics in Münster (n = 500) and the PopGen biobank in Kiel (n = 500), respectively. Carriers of M2 were found to exhibit a more than two-fold higher RPL risk than non-carriers (OR 2.42; 95% CI: 1.27–4.58) when using unselected controls (PopGen), and an almost four-fold higher risk when using the Münster ‘super-controls’, i.e. women with successful pregnancies and no previous history of pregnancy losses (OR 3.88; 95% CI: 1.98–7.54).

However, the distribution of ANXA5 promoter haplotypes in other populations and their impact on RPL and other prothrombotic pathological conditions requires further evaluation. Analyses of the presence of RPL-associated aPL in conjunction with ANXA5 promoter haplotypes is also an important subject for future investigation. Another interesting avenue of further studies would be to clarify the possibility of interaction of the M2 haplotype with the other known RPL genetic factors. All these issues will be addressed in a research project planned to start in the next future. Nevertheless, the ANXA5 promoter M2 haplotype is a strong candidate for predisposition to fetal loss and will be probably included in the analytical panel in the near future after the results of this initial study are proved in large patient groups from different populations. This should facilitate the development of improved prognostic algorithms for RPL, involving a more precise assessment of individual disease risks, and provide a guide to offering adequate therapies where relevant.

**Advice for the Clinical Practice**

Based on the present knowledge some forms of hereditary thrombophilia are associated with recurrent fetal loss. Genetic testing for the factor V Leiden mutation and for the Prothrombin G20210A variation is indicated in women with recurrent fetal loss (two or more miscarriages) as well as non-recurrent late miscarriage. Since homozygosity for the MTHFR C677T variant combined with another thrombophilic factor increases the risk for pregnancy wastage, it is advisable to include this variant in the analytical panel. Optionally the MTHFR A1298C variant could be also tested, but the interpretation of its’ relevance should be done with precautions and exclusively in conjunction with C677T. Evaluation of the activated protein C resistance not due to factor V Leiden and protein S deficiency when using unselected controls (PopGen), and an almost four-fold higher risk when using the Münster ‘super-controls’, i.e. women with successful pregnancies and no previous history of pregnancy losses (OR 3.88; 95% CI: 1.98–7.54).

It is advisable to refer women, tested positive for one or more mutations, to a specialised centre for monitoring a future pregnancy and for eventually considering heparin or aspirin prophylaxis during and/or after pregnancy. Women who are homozygous for MTHFR C677T or are C677T/A1298C combined heterozygous for MTHFR C677T variant and protein S deficiency should be strongly advised to ensure the regular folate intake before a pregnancy has occurred.

**References:**


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