Thrombophilias as risk factors for disorders of pregnancy and fetal damage

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Abstract

Inherited thrombophilias have been suggested as a possible condition of increased susceptibility to adverse pregnancy outcomes. Although there is no consensus on the association between the factor V Leiden mutation and early (less than 10 weeks) pregnancy loss, the evidence suggests an association between the mutation and second-, and third-trimester fetal loss and severe preeclampsia. At present the relationship between the prothrombin G20210A mutation and inherited thrombophilias and adverse pregnancy outcomes remains controversial. Due to the low prevalence, AT and PC deficiencies have been rarely found as the cause of complicated pregnancy, whereas increased risk for preeclampsia and fetal losses has been found in relation to PS deficiency. Concerning the association between pathological pregnancies and PAI-1 4G/5G deletion/insertion polymorphism, only few controversial data are available. A meta-analysis of ten case-control studies suggested an association between hyperhomocysteinemia, MTHFR C677T mutation and repeated

pregnancy losses before 16 weeks. Recently a role for Angiotensin Converting Enzyme I/D polymorphism in obstetrical complications has been suggested.

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In the recent years inherited thrombophilias, the principal risk factor of maternal thromboembolism, have been suggested as a possible condition of increased susceptibility to adverse pregnancy outcomes such as fetal loss, recurrent pregnancy loss, abruptio placentae, severe intrauterine growth restriction (IUGR) and early-onset, severe preeclampsia. All these outcomes complicate up to 0.2-3% of pregnancies and are the leading cause of perinatal morbidity and mortality. Histologic examination of uteroplacental vessels and intervillous architecture from such pathologic pregnancies typically display increased fibrin deposition, thrombosis hypoxia-associated endothelial and trophoblast changes. These findings suggest that thrombosis of the uteroplacental circulation underlies these obstetric conditions. During pregnancy, marked changes in hemostasis take place; pregnancy is associated with a 20-200% increase in levels of fibrinogen and factors II, VII, VIII, X and XII, whereas concentrations of factors V and IX are unchanged. In contrast, throughout pregnancy, endogenous anticoagulant levels increase minimally (tissue factor pathway inhibitor), remain constant (Antithrombin and Protein C), or significantly decrease (Protein S). Moreover, levels of immunoreactive and functionally active Plasminogen

Activator Inhibitor 1 (PAI-1) increase up to three-fold in pregnancy. Thus, the net effect of these pregnancy-induced changes is to promote clot formation, extension, and stability. The most common inherited thrombophilias are heterozygosity for the Factor V Leiden, prothrombin G20210A mutation, and the thermolabile variant of methylenetetrahydrofolate reductase (C677T MTHFR), the most common cause of hyperhomocysteinemia. Rarer thrombophilias include autosomal-dominant deficiencies of antithrombin (AT), protein C (PC) and protein S (PS). The principal acquired thrombophilia is the antiphospholipid antibody syndrome. In addition to these well-known conditions of thrombophilia abnormal pattern of fibrinolytic system and renin-angiotensin system may have a role as risk factor for pregnancy complications [1].

Factor V Leiden

The Factor V Leiden mutation (adenine to guanine at position 1691), which is resistant to inactivation by activated protein C, may be responsible for increased thrombin generation and a hypercoagulable state. The mutation is present in 5-9% of Caucasian populations, and heterozygosity is present in 20-40% of non pregnant patients with thromboembolic disease. Homozygosity for this mutation is very rare and confers a higher risk (more than 100-fold) of thromboembolism. Several studies show that the proportion of pregnant patients with thromboembolic events attributable to the factor V Leiden mutation is around 40% (11-78%). In the last five years more than twenty studies (table 1) of small and medium sample size (for a total of about 2000 patients) investigated the association between pathological pregnancies and factor V Leiden mutation; unfortunately, different inclusion criteria (any fetal loss, repeated fetal losses, first or second and third trimester fetal loss) have been used, so the results are not comparable. Although there is no consensus on the association between the factor V Leiden mutation and early (less than 10 weeks) pregnancy loss, the evidence suggests an association between the mutation and second-, and third-trimester fetal loss, severe preeclampsia [1-4]. Finally, the recent results of the study by Infante-Rivard et al.[5] do not confirm the reports from previous small studies of the association of IUGR with factor V Leiden mutation.

Activated protein C resistance

Transient activated protein C (APCR) resistance can be documented during normal gestations in women with normal factor V genotype. The APC-sensitivity ratio shows a progressive fall during normal pregnancy in correlation with changes in factor VII, factor V, and protein S levels. APC-sensitivity ratios may decrease further during gestations in women with

factor V Leiden mutation. Moreover, APC-sensitivity ratios were reported to be decreased in patient with recurrent pregnancy loss.

Prothrombin gene (G20210A) mutation

Prothrombin gene mutation (adenine to guanine at position 20210) is responsible of increased circulating prothrombin levels (150-200%). Heterozygosity for the mutation is present in 2-3% of Caucasian populations, and accounts for 17% of thromboembolism in pregnancy. Homozygosity confers a risk of thrombosis equivalent to that of Factor V Leiden homozygosity. In some studies, G20210A mutation has been found to be associated with II and III trimester fetal losses, IUGR or preeclampsia, but these results have not been confirmed in the largest studies (table 2). So, at present the relationship between the prothrombin G20210A mutation and inherited thrombophilias and adverse pregnancy outcomes remains controversial [1-4].

Antithrombin, Protein C and Protein S deficiencies

Antithrombin deficiency is the most thrombogenic of the inherited thrombophilias and results from numerous point mutations, deletions, and insertions. The frequency of the deficiencies of naturally occurring anticoagulant proteins in the general population is low being altogether less than 1%. Due to the low prevalence, AT deficiency has been rarely found as the cause of pregnancy complicated with fetal loss, severe preeclampsia, abruptio placenta and IUGR. No increase in pathological outcomes has been reported in PC deficiency, whereas increase risk for preeclampsia and fetal losses have been found in relation to PS deficiency (table 3, 4, 5). Some studies reported a modest increase of risk of stillbirth in patients when both deficiencies are present [2,6-8]

PAI-1 4G/5G deletion/insertion polymorphism

The PAI-1 4G/5G deletion/insertion polymorphism determines increased circulating levels of PAI-1 (3-5 fold). Homozygosity for the 4G/4G allele is relatively common and causes a modestly increased risk of thromboembolism. In relation to pathological pregnancies only few, controversial data are available: no significant association between 4G/4G PAI-1 mutation and preeclampsia was reported in the study by Morrison et al. 2002 (123 patients, 164 controls), whereas this polymorphism was found associated with pregnancy complications by Glueck et al. [9] in 122 patients.

Hyperhomocysteinemia and C677-T mutation MTHFR

Homocysteine is generated from the metabolism of the amino acid methionine and it is influenced by vitamins B6 and B12, and folic acid. The mild and moderate forms of hyperhomocysteinemia is associated with homozygosity for the C677T MTHFR thermolabile mutant and is present in 11% of Caucasian populations. Results of several studies showed that hyperhomocysteinemia is linked to severe preeclampsia, stillbirths, severe IUGR and placental abruption [10,11]. However, there are conflicting data on the link between hyperhomocysteinemia and recurrent spontaneous abortions (table VI). A meta-analysis of ten case-control studies on the association between hyperhomocysteinemia, MTHFR C677T mutation and repeated pregnancy losses before 16 weeks suggested an association with a pooled OR of 2.7 (95% CI 1.4-5.2) and 1.4 (95% CI 1.0-2.0) respectively, (OR 4.2 95% CI 2.0-8.8 after-load homocysteine) [12].

Angiotensin Converting Enzyme (ACE) I/D polymorphism

ACE is a key component of the Renin Angiotensin system (RAS), which represents one of the main factors regulating blood pressure, fluid and electrolyte balance. Placental and fetal membranes are important production sites of the RAS components. In vivo and in vitro studies suggest a role for the RAS in haemostasis regulation mechanisms and in modulating vascular fibrinolytic balance.

An insertion/deletion (I/D) polymorphism in the intron 16 of the ACE gene has been associated with serum ACE levels with a D allele dose dependent effect. ACE I/D polymorphism has a high prevalence in the general Caucasian population (D allele frequency 0.50); results from Fatini et al. [6], evaluating obstetrical complications, demonstrated that ACE D allele was significantly higher in women with first trimester fetal loss (D allele frequency 0.65), and ACE DD genotype accounts for more than 50% of fetal loss (OR 2.37 $p=0.03$). Recent data from these Authors provide a novel evidence that the ACE I/D polymorphism plays a role in preeclampsia and fetal growth restriction, which may stem from impaired placentation in early gestation and are associated with high impedance to flow in uteroplacental circulation. Results from this study demonstrated that the mean resistance indices of uterine and umbilical arteries were significantly higher in the ACE DD genotype women, underlying the modulatory role of the RAS on uteroplacental flow. Moreover, the documented significant association (OR 4.17 $p=0.0007$) between ACE DD genotype and the recurrence of adverse obstetric outcomes, as preeclampsia and fetal growth restriction in women with history of preeclampsia, defines its role as a new factor of susceptibility to negative pregnancy outcome.

Antiphospholipid antibodies

Antiphospholipid antibodies (lupus anticoagulant and anti-cardiolipin -ACA- antibodies) are heterogeneous antibodies directed against proteins that bind anionic phospholipids. Pregnancy morbidity represents a clinical criteria for antiphospholipid antibody syndrome. The conditions indicated at the International Consensus Workshop 1998 are 1) Three or more unexplained consecutive miscarriages with anatomic, genetic, or hormonal causes excluded, 2) One or more unexplained deaths of a morphologically normal fetus at or after the tenth week of gestation with fetal morphology documented by ultrasound or by direct examination of the fetus, 3) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation associated with severe preeclampsia or severe placental insufficiency. A systematic review by Alfirevic et al. [2] (including twenty-five studies) determined an association between antiphospholipid antibodies (ACA IgG) and pregnancy complications such as placental abruption (OR 20.8 95%CI 2.5-175.8), IUGR (OR 33.9 95%CI 1.6-735.8) and unexplained stillbirth (OR 5.8 95%CI 2.9-11.9). However, the search for an association between antiphospholipid antibodies and preeclampsia has resulted in conflicting results.

Lupus anticoagulant was found in association with unexplained stillbirth (OR 4.3 95%CI 1.7-10.6).

Therapeutic perspectives

In relation to the possible role of thrombophilia, the effectiveness of the antithrombotic therapy (heparin plus low-dose aspirin) for preventing negative gestational outcome in women at risk results in significant decrease in pregnancy complications in women with antiphospholipid syndrome. Very little research is now available on the prevention of adverse obstetrical outcomes in women with inherited thrombophilia. The potential advantage of low molecular weight heparin (LMWH) in ameliorating gestational outcomes in thrombophilic women at risk have been suggested by the results of small size studies, showing the beneficial role of LMWH. The results of ongoing prospective randomized studies hopefully may allow to obtain a clear confirm and indication of dosing and duration of antithrombotic therapy to be used in addition to the vitamin supplementation.

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