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SCIENCE DIRECT
Reproductive Toxicology 22 (2006) 227–233
Reproductive Toxicology
www.elsevier.com/locate/reprotox

Review

Inherited and acquired thrombophilia: Pregnancy outcome and treatment

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Received 1 March 2006; received in revised form 3 May 2006; accepted 3 May 2006
Available online 23 June 2006

Abstract

Maternal thrombophilias increases the risk of an adverse pregnancy outcome.

An extensive literature review highlights the role of inherited and acquired thombophilic disorders in spontaneous abortion, both early and late, recurrent or isolate, in intrauterine growth retardation, in placenta abruption, in pre-eclampsia and in venous thromboembolism. We have particularly focused attention on the following factors: antithrombin III (ATIII), proteins C (PC) and S (PS) deficiencies, genetic mutations particularly factor V Leiden (FVL), prothrombin gene G20210A (PTM) and the thermolabile variant of the methylene tetrahydrofolate reductase C677T (MTHFR) gene, lupus anticoagulant (LAC) and anticardiolipin antibodies, VIIIc factor, hyperhomocysteinemia and acquired activated protein C resistance.

Appropriate treatment can improve pregnancy outcome without teratogenic effects.

Keywords: Inherited thrombophilia; Acquired thrombophilia; Pregnancy outcome; Spontaneous abortion; Pre-eclampsia; IUGR; Placenta abruption; Anticoagulant therapy

Contents

1. Introduction

Complications which occur during pregnancy are the cause of morbility and mortality and necessitate medical intervention aimed at improving the fetal and maternal outcome. Coagulation anomalies, which play an important role in adverse pregnancy outcome, are the subject of this review.

Thrombophilia are hemostatic disorders, classified as inherited and acquired, which affect about 15% of the Caucasian population predisposed to thrombotic phenomenona [1]. Hereditary disorders include deficiencies of antithrombin III (ATIII), proteins C (PC) and S (PS) deficiencies, genetic mutations such as factor V Leiden (FVL), prothrombin gene G20210A (PTM) and the thermolabile variant of

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doi:10.1016/j.reprotox.2006.05.002

the methylene tetrahydrofolate reductase C677T (MTHFR) gene.

The most common acquired thrombophilias are due to antiphospholipid antibodies, which include lupus anticoagulant (LAC) and anticardiolipin antibodies. Thrombophilias derived from a combination of hereditary and acquired components, such as the VIIIc factor, hyperhomocysteinemia and acquired activated protein C resistance, are identified [1]. In addition, pregnancy itself leads to a thrombophilic state as a result of hemostatic and fibrinolitic changes. During pregnancy, procoagulant factors (such as VIII, XII, VII, V) and the von Willebrand factor and fibrinogen are increased, protein S and the activated protein C are reduced and fibrinolitic activity is diminished. All of these modifications, together with an enlarged plasmatic volume, prepare the mother to face the hemostatic state during delivery.

The risk of venous thrombosis in pregnancy is increased seven- to eight-fold, and even more after delivery, as a result of all these modifications or as the first feature of an hereditary thrombophilia [2].

Thrombophilias have been investigated in relation to the following obstetric complications: recurrent and non-recurrent miscarriages in early or late pregnancy, intrauterine death, intrauterine growth retardation (IUGR), placental abruption, hypertensive disorders of pregnancy and maternal or neonatal thrombosis. In recent years, the importance of the use of anticoagulant therapy during pregnancy in preventing an adverse fetal and maternal outcome due to thrombophilic disorders has been emphasized.

1.1. Pregnancy loss

Early and late abortion are defined on the basis of trimester (first or second) in which they occur; stillbirth is defined when pregnancy loss occurs after 24 weeks of gestation.

Since 1989, when Triplett and Harris identified a correlation between recurrent miscarriages and the antiphospholipid antibodies syndrome and 1996, when Sanson et al. correlated fetal loss with PC, PS and AT deficiencies, many studies have investigated the link between thrombophilias and spontaneous abortions [3,4]. Despite the substantial amount of data gathered, there is still a certain amount of controversy in the results.

In a retrospective cohort study, 228 FVL mutation carriers and 121 controls evaluating fetal loss before and after 20 weeks were analysed. The fetal loss was 31.6% versus 22.3% in the controls, with particular occurrence <20 weeks (29.4% versus 17.4%) with greater risk in FVL homozygous mutation [5], which was confirmed in further studies [6].

However, the evaluation of FVL mutation in 52 Japanese women with recurrent spontaneous abortions and 41 of their partners found no underlying differences when compared with 55 controls [7]. Evaluating for FVL and MTHFR genotypes in 584 patients in Ireland found a greater FVL in the patients who subsequently had a late spontaneous abortions but found no significant differences between case and control groups with regard to IUGR and pre-eclampsia [8].

In a total of over 3000 patients from two different studies, there were no statistical differences in late abortions regarding the FV Leiden [8,9].

No association was observed between recurrent abortions and factor V Leiden in a study conducted on 1111 Caucasian patients (904 with early recurrent miscarriages and 207 late miscarriages) compared with 150 controls. However, the same study noticed a correlation between protein C resistance and recurrent abortions [10].

A greater prevalence of the FV Leiden and prothrombin (FII) G20210A mutations in 150 patients with adverse pregnancy outcomes (99 with a positive history for recurrent abortion between 13 and 20 weeks of pregnancy and 51 with fetal loss after 20 weeks) was recently found when compared with 115 controls [11]. By focusing our attention on the most important studies carried out in the last 2 years, we have found a correlation between different thrombophilic factors.

In the studies published in 2005, an OR = 3.28 (95% CI 1.34–8.04; $P = 0.01$) was identified in relation to factor VIII and miscarriage in 92 cases compared to 380 controls and a clear association in Caucasian patients, but not in non-Caucasians (among whom the mutations were rare), was found when a case–control study of 3496 patients examined for the FVL and prothrombin G20210A mutations was carried out [12,13]. Both mutations were independent risk factors only in those who showed clinical features from the 10th week of pregnancy. In a study, which examined the association between activated protein C mutations and pregnancy complications such as abortion, fetal loss, IUGR, placental abruption and pre-eclampsia [14], it was confirmed that a greater thrombotic risk occurs after the 10th week. There was a similar association, in another study, between recurrent abortion, intrauterine death, placental abruption, pre-eclampsia and hereditary or acquired thrombophilia [15].

Behjati et al., in a study published on Iranian patients (36 with idiopathic infertility and 65 with recurrent spontaneous abortion, compared with 62 controls), found a greater frequency of mutations for the FVL in both infertility and abortion and a greater frequency of MTHRF mutations in patients with abortions but not idiomatic infertility. There was, however, no correlation with the factor II (FII) G20210A mutation and a reduction of the levels of APCR [16].

In the same period, no differences of allelic frequency between the cases and the controls with regard to FVL, PTG and MTHRF were reported, nor for multiple thrombophilic mutations analysing 357 couples with early recurrent abortion and 68 controls, all of Caucasian race [17]. However, among couples in which one or other partner had more than one thrombophilic mutation, the relative risk of abortion in the following pregnancy without therapeutic intervention was equal to 1.9 when compared to those couples who were not mutation carriers. It has been established that hereditary thrombophilia associated with positive histories for fetal loss, recurrent abortion, treatments for infertility and IUGR are not independent factors for the risk of perinatal mortality [18].

In a systematic review, also published in 2006, Robertson et al. evaluated the existing correlation between abortion and trom-