THROMBOPHILIA AND PREGNANCY

THROMBOPHILIA AND THROMBOSIS IN PREGNANCY

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The risk for venous thromboembolism (VTE) is increased 4-10 folds during pregnancy and in particular is high at the post-partum period. While the absolute risk of VTE is small 1/500–1/2000, in women at the reproductive age, pulmonary embolism is a major cause for maternal death. Thrombophilia is found in 50-70% of women with gestational VTE. The risk for VTE varies according to the thrombophilia subtype. The risk is especially high in women with homozygous factor V Leiden, antithrombin deficiency and combined thrombophilia. Women with antiphospholipid syndrome, PC and PS deficiency are also at an increased risk. Heterozygosity for factor V Leiden and prothrombin mutation confer 3-5 folds increase in the rate of VTE. Antenatal prophylactic anticoagulant therapy is advocated when the risk for clinical VTE is above 5%. In lower risk women, postpartum prophylaxis for 6 weeks is advocated. The dose of low molecular weight heparin is dependent on the VTE risk. A scoring system accounting for patient and family history of VTE, gestational complications and type of thrombophilia has been advocated to improve patient care. Monitoring of LMWH is debatable but measuring anti-factor Xa levels can be helpful especially in pregnant women who receive full dose anticoagulant therapy. Global coagulation assays are warranted for screening of women with pregnancy complications and before application of hormonal therapy.

THROMBOPHILIA AND PREGNANCY LOSS

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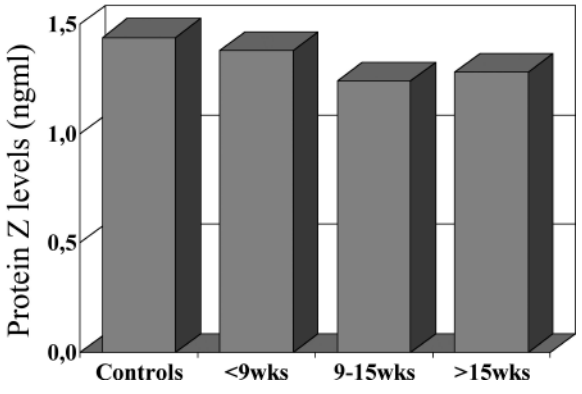
The outcome of previous pregnancy is relevant to a woman's overall risk of successful outcome of any pregnancy. In primigravidas and women with a history of successful pregnancies, the incidence of miscarriage is low (5 and 4% respectively). Women with histories only of unsuccessful pregnancy outcome have a much greater risk of miscarrying (24%). It has been estimated that when the outcome of the last pregnancy was a miscarriage, 19% of women miscarried compared to 5% when previous pregnancy was successful. For women with two successive miscarriages, the probability of a third is between 17 and 35%; for those who have had three or more, the probability of another is between 25 and 46%. Recurrent pregnancy loss (RPL), defined as the occurrence of three or more spontaneous consecutive pregnancy losses) is rather common (1-2% of fertile women). Although during the years many causes have been identified (karyotype, uterine abnormalities, autoimmune diseases and others), most of them remains unexplained. Acquired causes of thrombophilia, as the presence of antiphospholipid antibodies or essential thrombocythemia have been described to be associated with RPL.

A recent systematic review of the literature, in which 16 case-control studies for FV Leiden and 7 for the FII A20210 mutation were respectively considered, strongly suggested that inherited thrombophilias have a role in the occurrence of otherwise unexplained recurrent early fetal losses, in addition to otherwise unexplained fetal deaths. The authors recommend testing for those mutations in women with recurrent fetal losses. More recently, a possible role of Protein Z (PZ) in the occurrence of fetal losses has been invoked.

We carried out a study aimed at evaluating PZ levels in a group of women with early recurrent fetal losses or intrauterine fetal death (IUFD). Since March 1999 to February 2003, 453 women were consecutively referred to our Unit because of recurrent fetal losses or at least one IUFD. Women underwent a work-up for identifying known causes of fetal losses, as previously described (3). Only women having a history of recurrent (n=3) early unexplained fetal losses, defined as the occurrence of fetal loss until 14 weeks of gestational age, or at least one late fetal death (>20weeks) entered the study. At the end of the work-up, women with known causes of fetal losses were excluded (n=271). Moreover, women with inherited (FV Leiden or FII A20210 mutations, Protein C, Protein S or antithrombin deficiency) or acquired (antiphospholipid antibodies) thrombophilia (n=38), as well as those with previous thromboembolic disease, were excluded (n=3). Thus, 141 women were eligible, but blood samples were available only for 124 of them. Mean age (±SD) was 32+5.3 years.

Blood sample were obtained at least two months after the last fetal demise (mean 16.5±26.7 months). Blood samples were collected in 3.8% trisodium citrate and centrifuged at 2,000 g for 15 minutes to obtain platelet-poor plasma, that was immediately frozen and stored in small aliquots at –70°C until tested. PZ plasma levels were evaluated by means of an enzyme-linked immunosorbant assay (Asserachrom Protein Z, Diagnostica STAGO) and expressed in μg/mL as mean±1 SD. In the whole sample, 94 (75.8%) out of 124 women were primary (no previous live births) aborters with otherwise unexplained fetal losses and 30 secondary (24.2%). Fifty women (40.3%) had only events before 10 weeks of gestational age, 42 (33.9%) after the beginning of the 10th week, and 29 (25%) had events both before and after the gestational age of 10 weeks.

PZ values were 1.37±0.73 μg/mL in the whole group, 1.41±0.74 μg/mL in the group with primary recurrent miscarriages before 10 weeks, 1.34+0.82 μg/mL in the group with fetal losses after the beginning of the 10th week, and 1.32±0.59 μg/mL in women with events occurring in both periods (Figure 1).



These differences were not statistically significant (Kruskal-Wallis test). Moreover, no significant difference (Scheff's test) was observed comparing each group with a reference group from the same ethnic background, formed

by 60 women with uneventful pregnancies (mean age 29± 4.3 yrs, PZ values: 1.43±0.76 μg/mL). Twenty-nine women suffered from fetal losses at different periods of pregnancy. We also analyzed data on the basis of the contemporary presence in the obstetric history of fetal losses in different gestational age. No significant difference in protein Z values was observed among different groups.

We are not able to confirm data recently published by Gris and coll, although we employed similar selection criteria and have analyzed data using the same categories. However, our data are in agreement with a more recent report. At variance with study by Gris and coll, we excluded women with known inherited or acquired thrombophilias and also those with thrombotic antecedents. Moreover, mean values in our controls were different from those measured in some studies , but in agreement with others , including a different Italian setting. Genetic factors may be an important determinant of the wide normal range of PZ plasma concentrations and may justify inconcistencies. Further investigations are needed to shed light whether Protein Z deficiency is associated with a history of unexplained fetal losses in a specific subsetting of women. Observational studies have been carried out for testing antithrombotic prophylaxis or treatment in women with previous adverse obstetric outcomes and carriership of common causes of thrombophilia. These studies differ is some details (treatment of only inherited or inherited and acquired thrombophilias, use of different regimens and types of heparins, use of aspirin, enrollment of women with only previous fetal losses, or other gestational vascular complications), but in all cases outcomes of present pregnancies were compared with the previous ones in the same woman, with an objective drawback due to the fact that women were older when they underwent the treatment. Data are comparable, as in all the studies treated women obtained a significant higher percentage of successful pregnancies. Although we do not yet known factors that finally induce one woman to miscarriage and some others do not. These evidences indicate that women with a personal history of unexplained fetal losses, severe or recurrent intrauterine growth restriction and preeclampsia (in addition, obviously, to those with personal or family history of thromboembolism) should be screened for thrombophilia.

From a clinical point of view, the associations found in the majority of the studies between congenital causes of thrombophilia and gestational vascular complications open an important issue: the pharmacological treatment or prophylaxis during pregnancy in order to reduce the incidence or the recurrence of maternal and fetal complications.

Very recently Gris suggested to study women with one early fetal loss in the history. Although we strongly believe that inherited thrombophilia could play a role in well selected settings of women, nevertheless, we must keep in mind that it confers a susceptibility to spontaneous abortion and that the probability to carry out an uneventful pregnancy with one previous fetal loss according to epidemiological data by Stirrat is still about 78-86%; even after three or more consecutive losses the chance of a successful pregnancy is still at best 75% and at worst 54%. This information should allow all obstetricians to draw a practical implication: why should we test for thrombophilia a woman after the first fetal loss and eventually to treat those with a positive result in the following pregnancies, without the certainty (or the high probability) that thrombophilia is playing a role in spontaneous abortion in that woman?

THE ATIII EPAS STUDY

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A double blind, randomized, placebo-controlled study is currently underwaying in 15 Italian Centres evaluating the administration of an antithrombin concentrate (Kedrion S.p.A., Italy) at high doses for t days in patients with early-onset (<30 weeks of gestation) preeclampsia (Early Preeclampsia Antitrombin Study, ATIII-EPAS). The main aim of this study is the reduction in the combined endpoints of foetal-neonatal mortality and severe morbility with a sample size powered to detect a 30% difference between the placebo and the active treatment arm.

While ther're no reasons to prolong pregnancy in a severe preeclamptic woman beyond the 34th week, a conservative treatment of early-onset preeclampsia should be taken into account to reach an adequate foetal lung maturation. The more controversial issues are the role of the pharmacological treatment aimed at prolongation of pregnancy, the ability of such treatment to modify the course of the underlying disease and the effects on foetal and maternal outcomes. Antithrombin is a natural anticoagulant which at supra-normal concentrations may also exert anti-inflammatory activity, through an increase release of prostacyclin and the inhibition of white blood cells activation. Endothelial dysfunction or inappropriate endothelial cell activation are the most common clinical manifestations in preeclampsia, including enhanced endothelial-cell permeability and platelet aggregation. Such endothelial activation is part of a more general inflammatory reaction, including intravascular leucocytes as well as the clotting and complement systems. Rherefore it seems reasonable to evaluate the effects of ATIII on these pathophisiological pathways.

At present, 21 patients have been randomized in 12 months from the beginning of the study, with a combined perinatal mortality and severe morbility in about 50% of cases.