

Theme Issue Article

Thrombophilia and pregnancy complications

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Summary

The implications of currently available data on the association of gestational vascular complications with thrombophilia are presented in this consensus report. Screening is recommended for women with the following previous complications: fetal loss including three or more first trimester loss, two or more sec-

ond trimester loss, or any stillbirth; early, severe or recurrent preeclampsia and severe intrauterine growth restriction. Maternal antithrombotic therapy is currently evaluated in women with thrombophilia and previous complications.

Keywords

Thrombophilia, pregnancy, antithrombotic therapy, fetal loss

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Introduction

An acquired hypercoagulable state with an increased thrombotic risk, which is also high during the first few months postpartum, exists during pregnancy. This situation may result from an increase in procoagulants, such as factor VIII, and a decrease in physiological anticoagulants, such as protein S. Moreover, acquired APC resistance increases and fibrinolytic activity is reduced as the pregnancy progresses and the mother proceeds into the postpartum period. Obstetric complications such as placental abruption, preeclampsia, fetal loss and stillbirth are associated with intervillous or spiral-artery thrombosis, and placental infarction is frequently observed in low birth weight neonates. Gestational vascular complications (GVC) are a major cause of maternal and fetal morbidity and mortality. A growing body of evidence supports the association of thrombophilia with GVC.

Recurrent fetal loss

Recurrent fetal loss (RFL) is a common problem. Of women in the reproductive age group, 1% to 2% experience 3 or more losses, and 5% experience 2 or more losses. Recurrent fetal loss has a well-established association with certain acquired thrombophilic disorders, such as the antiphospholipid syndrome (1). A number of observations suggest an association between RFL and uncommon inherited thrombophilic states such as dysfibrinogenemia, protein C, protein S and antithrombin deficiencies (2, 3).

The association of RFL with the main thrombophilic polymorphisms factor V Leiden (FVL) and factor II G20210A mutation is now well established. At least 16 case-control studies (4) found a high prevalence of FVL in women with unexplained RFL (up to 30%) compared to 1% to 10% of control subjects (odds ratios ranging from 2 to 5) (4). Despite differences in

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study populations and selection criteria, the results were consistent. No association between FVL and RFL was found by six other case-control studies. These latter studies were smaller and most included women with common first trimester fetal losses (often due to non-thrombophilia-related factors). Three retrospective cohort studies found that FVL carriers have a significantly increased risk of RFL. A recent meta-analysis documented an association of FVL with early and late fetal loss (5).

The risk for RFL is greater in homozygotes than in heterozygotes with FVL (6) and in female siblings of thrombophilic women with FVL (7). Women with thrombophilia have an increased percentage of losses at later stages of gestation (8). However, APC resistance and the FVL can also be associated with recurrent first trimester pregnancy loss (9). Activated protein C resistance in the absence of the FVL has also been associated with pregnancy loss (10). A number of recent meta-analyses have demonstrated an association of factor II G20210A with RFL. Factor II G20210A mutation is associated, mostly with second and third trimester losses, but also with early fetal loss (5, 11, 12). In contrast, a meta-analysis of 10 case control studies evaluated the role of the MTHFR T/T genotype and hyperhomocysteinemia in women with pregnancy loss. In 5 of the 6 case-control studies, the MTHFR T/T genotype was not found to be a significant risk factor for recurrent early pregnancy loss (5, 12). However, elevated fasting and post-methionine-loading homocysteine levels were found to be associated with recurrent early pregnancy loss (pooled OR = 2.7; 95% CI = 1.4–5.2 and OR = 4.2; 95% CI = 2.0–8.8, respectively) (13). Thus hyperhomocysteinemia but not MTHFR is associated with RFL. Combinations of thrombophilic states may further increase the risk for RFL, as demonstrated by the European Prospective Cohort on Thrombophilia (EPCOT) study which documented the highest OR for stillbirth (OR = 14.3; 95% CI = 2.4–86) in women with combined thrombophilic defects (14).

Recently, increased levels of factor VIII (15) and antibodies to endothelial protein C receptor (16) have been suggested to be associated with RFL.

Gestational vascular complications

Although preeclampsia, fetal growth restriction, and placental abruption are also thought to involve impaired placental perfusion, their association with FVL remains controversial, with conflicting results from different studies. In one recent study, FVL was found in 20% of the women with preeclampsia, placental abruption, fetal growth retardation, or stillbirth compared to only 6% of control women without these complications (odds ratio 3.7) (17). Six other case-control studies found a significantly higher prevalence of FVL in women with preeclampsia (up to 26%) compared to women with normal pregnancies

(2%–6%; odds ratios ranging from 2 to 5). However, 5 other case-control studies (4) and 1 prospective cohort study did not find a significant association of FVL with preeclampsia (4).

The association with FVL is stronger in women with severe early onset preeclampsia (18). Likewise, FVL is associated with severe but not with mild IUGR (19, 20). Placental abruption has also been associated with FVL (21).

Hyperhomocysteinemia was documented in 26% of women with placental abruption, in 11% of the cases with intrauterine fetal death, and in 38% of women delivering babies whose birth weight was below the fifth percentile, compared with an estimated 2% to 3% in the general control population (22). Likewise, hyperhomocysteinemia was documented in 26 (31%) of 84 women with previous placental infarcts or abruption, compared to 4 (9%) of 46 control subjects (23). In the Hordaland Homocysteine Study, plasma homocysteine levels were evaluated in 5883 women with 14492 gestations. The study reported an increased risk in these subjects with elevated plasma homocysteine for preeclampsia (OR = 1.33), stillbirth (OR = 2.11), early labor (OR = 1.41), and placental abruption (OR = 3.03) (24).

As hyperhomocysteinemia is associated with gestational vascular complications, this may imply ample maternal intake of folate and vitamins B₆ and B₁₂.

Recommendations regarding screening for thrombophilia in pregnancy

The available data suggest that inherited thrombophilia is a mild risk factor for RFL primarily in the second and third trimesters, and possibly other serious obstetric complications. Because the probability of a successful pregnancy outcome is still high, and most carriers will not develop these obstetric complications, routine screening of all pregnant women for thrombophilia is currently not recommended. Screening is recommended for women with the following previous complications: fetal loss including three or more first trimester, two or more second trimester, or any stillbirth, early, severe or recurrent pre-eclampsia or severe intrauterine growth restriction.

The role of screening for thrombophilia in women with placental abruption has not been established yet.

Antithrombotic therapy

The high prevalence of genetic thrombophilias (8, 17), and the thrombotic changes in the placentae of the majority of women with pregnancy complications (25) suggest that antithrombotic drugs will potentially have a therapeutic benefit to preserve pregnancy in women with gestational vascular complications.

Early suggestions, that aspirin may prevent pregnancy complications, were later refuted. Vitamin K antagonists cross the placenta, and should not be used in pregnancy at large.

Data on treatment of women with inherited thrombophilia and pregnancy loss are predominantly uncontrolled and include a small series of patients treated mostly with low-molecular-weight heparin. A recent collaborative study demonstrated the safety of using low-molecular-weight heparin during 486 gestations. A successful outcome was reported in 83 (89%) of 93 gestations in women with a history of recurrent pregnancy loss and in all 28 gestations in women who experienced preeclampsia during a previous pregnancy (26). In women with thrombophilia, 46 (75%) of 61 pregnancies treated with a low-molecular-weight heparin (LMWH) resulted in a live birth, compared to a success rate of only 20% in these same 50 women in prior gestations without antithrombotic therapy (27). However, the optimal dosage of low-molecular-weight heparin is unknown and should be optimized by prospective randomized trials, which are currently underway (28).

Issues concerning the potential therapeutic benefit of LMWH for women with pregnancy complications and thrombophilia were presented in a recent debate (29, 30), and await confirmation by prospective randomized trials. Recently, a

number of prospective studies have demonstrated the benefit of LMWH in pregnant women with thrombophilia (31-34).

Maternal thrombophilia and neonatal outcome

In addition to the potential involvement of genetic or acquired maternal thrombophilic risk factors in fetal wastage, neonatal prematurity and intrauterine growth restriction, fetal thrombophilic polymorphisms such as factor V Leiden were reported in association with cerebral palsy, neonatal stroke and placental and neonatal thrombosis (35-40). While the relationship of neonatal thromboembolism with neonatal thrombophilia has been explored, it is possible that maternal and fetal thrombophilic genes may interact in the production of placental and fetal thrombi; the combined contribution of maternal and fetal thrombophilia to fetal and neonatal thromboembolism requires further study. Maternal thrombophilia may play a role in early delivery resulting in a proportion of neonatal prematurity.

References

- Triplet DA, Harris EN. Antiphospholipid antibodies and reproduction. *Am J Reprod Immunol* 1989; 21: 123-31.
- Sanson BJ, Friederich PW, Simioni P et al. The risk of abortion and stillbirth in anti-thrombin, protein C, and protein S-deficient women. *Thromb Haemost* 1996; 75: 387-8.
- Haverkate F, Samama M. Familial dysfibrinogenemia and thrombophilia: report on a study of the SSC Subcommittee of Fibrinogen. *Thromb Haemost* 1995; 73: 151-61.
- Press RD, Bauer KA, Kujovich JL, et al. Clinical utility of Factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. *Arch Path Lab Med* 2002; 126: 1304-18.
- Rey E, Kahn SR, David M, et al. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003; 361: 901-8.
- Meinardi JR, Middeldorp S, de Kam PJ, et al. Increased risk for fetal loss in carriers of the factor V Leiden mutation. *Ann Intern Med* 1999; 130: 736-9.
- Tormene D, Simioni P, Prandoni P, et al. The risk of fetal loss in family members of probands with factor V Leiden mutation. *Thromb Haemost* 1999; 82: 1237-9.
- Brenner B, Sarig G, Weiner Z, et al. Thrombophilic polymorphisms are common in women with fetal loss without apparent cause. *Thromb Haemost* 1999; 82: 6-9.
- Younis JS, Brenner B, Ohel G et al. Activated protein C resistance and factor V Leiden mutation can be associated with first- as well as second-trimester recurrent pregnancy loss. *Am J Reprod Immunol* 2000; 43: 31-5.
- Sarig G, Younis JS, Hoffman R, et al. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. *Fertil Steril* 2002; 77: 342-7.
- Martinelli I, Taioli E, Cetin I, et al. Mutations in coagulation factors in women with unexplained late fetal loss. *N Engl J Med* 2000; 343: 1015-18.
- Kovalevsky G, Gracia CR, Berlin JA, et al. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. *Arch Intern Med* 2004; 164: 558-63.
- Nelen WL, Blom HJ, Steegers EAP, et al. Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. *Fertil Steril* 2000; 74: 1196-9.
- Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996; 348: 913-6.
- Marietta M, Fachinetti F, Sgarbi L, et al. Elevated plasma levels of factor VIII in women with early recurrent miscarriage. *J Thromb Haemost* 2003; 1: 2536-9.
- Hutado V, Montes R, Gris JC, et al. Autoantibodies against EPCR are found in antiphospholipid syndrome and are a risk factor for foetal death. *Blood* 2004; May 18 [Epub ahead of print].
- Kupfermanc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 1999; 340: 9-13.
- Morrison ER, Miedzybrodzka ZH, Campbell DM, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. *Thromb Haemost* 2002; 87: 779-85.
- Kupfermanc MJ, Many A, Bar-Am A, et al. Mid-trimester severe intrauterine growth restriction is associated with a high prevalence of thrombophilia. *BJOG*. 2002; 109: 1373-6.
- Infante-Rivard C, Rivard GE, Yotov WV, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med* 2002; 347: 19-25.
- Weiner-Megnagi Z, Ben-Shlomo I, Goldberg Y, et al. Resistance to activated protein C and the Leiden mutation: high prevalence in patients with abruptio placentae. *Am J Obstet Gynecol* 1998; 179: 1565-7.
- de Vries JJP, Dekker GA, Huijgens PC, et al. Hyperhomocysteinemia and protein S deficiency in complicated pregnancies. *Br J Obstet Gynaecol* 1997; 104: 1248-54.
- Goddijn-Wessel TA, Wouters MG, van de Molen EF, et al. Hyperhomocysteinemia: a risk factor for placental abruption or infarction. *Eur J Obstet Gynecol Reprod Biol* 1996; 66: 23-9.
- Vollset SE, Refsum H, Irgens LM, et al. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine study. *Am J Clin Nutr* 2000; 71: 962-8.
- Gris JC, Quere I, Monpeyroux F, et al. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent: the Nimes Obstetricians and Haematologists Study 5 (NOHA5). *Thromb Haemost* 1999; 81: 891-9.

26. Sanson BJ, Lensing AWA, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999; 81: 668-72.
27. Brenner B, Hoffman R, Blumenfeld Z, et al. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. *Thromb Haemost* 2000; 83: 693-7.
28. Brenner B. Clinical management of thrombophilia-related placental vascular complications. *Blood* 2004; 103: 4003-9.
29. Brenner B. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications – Yes. *J Thromb Haemost* 2003; 1: 2070-2.
30. Middeldorp S. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications – No. *J Thromb Haemost* 2003; 110: 2073-4.
31. Brenner B, Hoffman R, Carp H, et al. Enoxaparin treatment improves the gestational outcome of pregnant women with thrombophilia and recurrent pregnancy loss: The LIVE-ENOX study. *Blood* 2003; 104: abstr. 43, P16a.
32. Gris JC, Mercier E, Quere I, et al. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood* 2004; 103: 3695-9.
33. Vossen CY, Preston FE, Conard J, et al. Hereditary thrombophilia and fetal loss: a prospective following study. *J Thromb Haemost* 2004; 2: 592-6.
34. Hoke M, Kyrle PA, Philipp K, et al. Prospective evaluation of coagulation activation in pregnant women receiving low-molecular weight heparin. *Thromb Haemost* 2004; 91: 935-40.
35. Verspyck E, Le Camp-Duchez V, Gravier A, et al. Small for gestational age infant in association with maternal prothrombin gene variant (nt 20210A). *Eur J Obstet Gynecol Reprod Biol* 1999; 83: 143-4.
36. Kries von R, Junker R, Oberle D, et al. Foetal growth restriction in children with prothrombotic risk factors. *Thromb Haemost* 2001; 86: 1012-6.
37. Vries de LS, Eken P, Groenendaal F, et al. Antenatal onset of haemorrhagic and/or ischaemic lesions in preterm infants: prevalence and associated obstetric variables. *Arch Dis Child* 1998; 78: F51-F56.
38. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol* 1999; 30: 759-69.
39. Debus O, Koch HG, Kurlemann G, et al. Factor V Leiden and genetic defects of thrombophilia in childhood porencephaly. *Arch Dis Child* 1998; 78: F121-F124.
40. Thorarensen O, Ryan S, Hunter J, et al. Factor V Leiden mutation: an unrecognized cause of hemiplegic cerebral palsy, neonatal stroke, and placental thrombosis. *Ann Neurol* 1997; 42: 372-5.