Thrombophilia and Preeclampsia: The Evidence So Far

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The Role of Thrombophilias

Pregnancy is a hypercoagulable state. The field of thrombophilia, the tendency to thrombosis, has been developed rapidly and has been linked to many aspects of pregnancy. Recently, it has been determined that severe pregnancy complications such as severe preeclampsia intrauterine growth retardation (IUGR), abruptio placentae, and intrauterine fetal death (IUFD) are associated with thrombophilia.

Thrombophilias are inherited or acquired conditions that predispose an individual to thromboembolism. Deficiencies of protein S, C, and antithrombin are rare and each of them is found in approximately 3% of patients with thrombosis. Three important inherited thrombophilias were discovered, which are responsible for the majority of thromboembolic events in patients with no otherwise apparent risk for thrombosis. Resistance to activated protein C caused by an adenine 506 guanine (A506G) mutation in factor V (factor V Leiden) has been linked with an increased risk for venous thromboembolism.1 Heterozygosity for the factor V (FV) Leiden mutation is found in approximately 5% of the population and the mutation is responsible for 20% to 30% of venous thromboembolism events. A recently described guanine 20210 adenine mutation in prothrombin is associated with higher plasma prothrombin concentrations and increased risk for venous thromboembolism1 and cerebral vein thrombosis.1 Homozygosity for the cytosine 677 thymine (C677T) mutation in methylenetetrahydrofolate reductase (MTHFR) results in decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of homocysteine to methionine, and the resulting increase in plasma homocysteine concentrations is a risk factor for thrombosis.1 The mutation is responsible for reduced MTHFR activity and is the most frequent cause of mild hyperhomocysteinemia and can be found in 5% to 15% of the population. Homocysteine is an independent risk
factor for atherosclerosis, stroke, peripheral vascular disease, and cardiovascular diseases. Homocysteine concentrations are affected by nutrition. A deficiency in folate, B-6, and/or B-12 causes elevation of homocysteine. Homocysteine concentrations are also affected by genetics such as cystathionine beta-synthase defect and C677T MTHFR gene mutation. Hyperhomocysteinemia promotes vascular damage by several mechanisms. Many of the endothelial vascular changes associated with hyperhomocysteinemia can be found in preeclampsia.

The antiphospholipid syndrome (APS), an acquired autoimmune condition, is characterized by the presence of certain features and circulating antibodies. The APS is associated with placental vascular thrombosis, decidual vasculopathy, intervillous fibrin deposition, and placental infarction. These pathologic changes in the placenta may result in miscarriage, IUGR, stillbirth, and early severe preeclampsia.

In this review, all aspects of preeclampsia and thrombophilia are discussed, and also all prophylactic and therapeutic implications.

**Thrombophilia and Adverse Pregnancy Outcome**

Preeclampsia, abruptio placentae, IUGR, and IUFD greatly contribute to maternal and fetal morbidity and mortality. Their causes are unknown, but all of them may be associated with abnormal placental vasculature and disturbances of hemostasis leading to inadequate maternal–fetal circulation.

The etiology of preeclampsia is unknown. It is associated with abnormal placental development and disturbances of hemostasis leading to inadequate fetomaternal circulation. Recent data suggest that endothelial dysfunction, vasoconstriction, placental ischemia, and enhanced coagulation are associated with abnormal placental development, which may lead to inadequate fetomaternal circulation and decreased placental perfusion. In normal pregnancy, the trophoblast invades the spiral arteries, which lose their muscular wall and become flaccid, allowing maximum blood flow to the placenta. The abnormal interaction between mother and fetal allograft in abnormal pregnancies leads to abnormal trophoblastic invasion of the spiral arteries, resulting in small, narrowed vessels. The subsequent vasculopathy and secondary thrombosis from hypercoagulability may result in inadequate perfusion of the intervillous space, preeclampsia, placental infarcts, IUGR, placental abruption, and IUFD. Placental pathologists use the term placental vasculopathy to describe pathologic placental changes characterized by superficial endovascular cytotrophoblast invasion in the spiral arteries, acute atherosclerosis, and thrombotic processes in the spiral arteries and/or the intervillous space. Clinically, placental vasculopathy is associated with preeclampsia, IUGR, placental abruption, and some cases of fetal loss and preterm labor.

The known thrombotic nature of the placental vascular lesions and the increased thrombotic risk associated with the existence of thrombophilias strongly suggest a cause-and-effect relationship between inherited and acquired thrombophilias and the listed severe obstetric complications.

**Placental Findings Associated With Thrombophilias and Pregnancy Complications**

Many et al described placental findings in women who had severe complications during pregnancy and were carriers of thrombophilias, and compared them with women with severe complications but who had no thrombophilias. Women who had severe preeclampsia, IUGR, abruptio placentae, or IUFD comprised the study population. Thirty-two women carried a thrombophilia and 36 women did not. The number of women with villous infarcts was significantly higher in women with thrombophilias (72% vs. 39%, P < 0.01) as was the number of women with multiple infarcts (P < 0.05). The incidence of placentas with fibrinoid necrosis of
decidual vessels was also significantly higher in women with thrombophilias \((P < 0.05)\). However, in a recent study with a very similar design and which also examined the relationship between placental histology and thrombophilia in women with severe complications, no specific histologic pattern could be identified when thrombophilia positive and thrombophilia negative groups were compared.\(^4\) Nevertheless, a high rate of placental infarcts (50%) and thrombosis was confirmed in both women with and without thrombophilia.\(^4\) Likewise, placental pathology in early-onset preeclampsia and FGR was similar in women with and without thrombophilia, although a high rate of placental abnormalities was found.\(^5\)

The high rate of placental lesions found in both thrombophilic women and nonthrombophilic women with severe complications in these studies may explain the difficulty in finding a difference between thrombophilic and nonthrombophilic women or may reflect an as-yet unknown state of thrombophilia. It should be noted, however, that all these reports evaluated mixed clinical conditions and not just severe preeclampsia.

### Severe Preeclampsia and Thrombophilia

The relation between APS and preeclampsia has been shown in several studies.\(^6\)–\(^8\) In a series of more than 300 patients with severe preeclampsia,\(^9\) an overall incidence of 21% was found related to detectable ACA (>10 GPL and/or MPL), with a 27.4% incidence in the group with delivery at less than 28 weeks’ gestation and a 19.3% incidence in the group with delivery more than 28 weeks’ gestation. However, after considering the nearly 20% low-positive IgG and/or IgM titers (<15 GPL and/or MPL) in their control population of healthy female volunteers, the authors concluded that 16% is a realistic estimate of the incidence of anticardiolipin (aCL)-positive patients in patients with a history of severe preeclampsia, which is concordant with other studies.\(^7\) It should be noted that several investigators found no correlation between APS and preeclampsia. Because in early-onset severe preeclampsia, most studies found an association with positive tests for aCL, testing in these patients may have therapeutic implications for future pregnancies.

Dekker et al\(^{10}\) tested women with severe preeclampsia at least 10 weeks postpartum for the presence of inherited and acquired thrombophilias. A high rate of protein S deficiency, APCR, hyperhomocystinemia, and aCL IgG or IgM was found. Dizon-Townson et al\(^{11}\) and Nagy et al\(^{12}\) described a higher prevalence of FV Leiden mutation in women with severe preeclampsia compared with controls. In the study of Dizon-Townson et al,\(^{11}\) 158 nulliparous women with severe preeclampsia at a mean gestational age of 33 weeks were compared with 403 normotensive women. Nagy et al\(^{12}\) in Hungary described a high prevalence of the FV Leiden mutation in 69 women with severe preeclampsia compared with 71 healthy controls. Rigo et al\(^{13}\) investigated 120 women with severe preeclampsia (72% nulliparous) and 101 healthy matched for age and parity. A total of 18.3% of preeclamptic women were carriers of the FV Leiden mutation compared with 3% in controls \((P < 0.001)\). However, there was no difference in homozygosity for MTHFR. Among FV Leiden positives, there was a statistically higher prevalence of HELLP syndrome compared with FV Leiden negatives. Perinatal outcomes were comparable in FV Leiden-positive and -negative women. Kupferminc et al\(^{14}\) conducted a study to determine whether obstetric complications are associated with thrombophilias. One hundred ten healthy women who had during pregnancy severe preeclampsia, IUGR (<5th percentile), severe abruptio placentae, and stillbirth were enrolled in the study. The control group comprised 110 healthy matched women with normal pregnancies. All 220 patients were tested for all known thrombophilias at least 2 months after delivery. Thirty-four of 110 patients had severe preeclampsia. All were nulliparous.
The FV and MTHFR mutations were significantly higher in women with preeclampsia (26% vs. 6.4% and 20.6% vs. 8.2%, respectively). The prothrombin mutation was not more prevalent in women with preeclampsia. Overall, 52.9% of patients with severe preeclampsia had a genetic thrombophilic mutation compared with 17.3% in the control group. In an additional 14.7% of the study group, other types of thrombophilia were found. Thus, the total prevalence of thrombophilias in the women with preeclampsia was 64.7% compared with 18% in controls. In women with IUGR, abruptio placentae, and stillbirth, the thrombophilia rate was 61.4%, 70%, and 50%, respectively. Of the 18 multiparous women in this group, 15 had had obstetric complications in a previous pregnancy. In 10 of these 15 multiparous women (67%), thrombophilia was found. This indicates a high rate of recurrence in multiparous women with thrombophilias.

van Pampus et al,9 in The Netherlands, described 345 women with a history of severe preeclampsia diagnosed before 34 weeks who were investigated postpartum for the presence of thrombophilias. The control group consisted of 67 healthy women with a history of uncomplicated pregnancies. The women with preeclampsia were further divided into those who had delivered at less than or more than 28 weeks’ gestation. In both subgroups and in all women study patients, a higher prevalence of APCR was found compared with controls, but the prevalence of the FV Leiden mutation was similar to controls. Hyperhomocystinemia was more prevalent in women with severe disease who had delivered at less than 28 weeks. Kupferminc et al,15 in another study, tested 63 healthy women with severe preeclampsia (54 nulliparous) and 126 matched controls for all thrombophilias. Again, FV Leiden mutation and MTHFR mutations were significantly more prevalent in women with severe preeclampsia but not the prothrombin mutation. Overall, 56% of women with severe preeclampsia had a genetic thrombophilic mutation compared with 19% in the control group, and the incidence of all thrombophilias was 67% in severe preeclampsia. Women with severe preeclampsia and thrombophilia delivered earlier and the neonates were of lower birth weight compared with preeclampsia and no thrombophilia (31 wks vs. 33 wks). The incidence of combined thrombophilias was also more prevalent in severe preeclampsia. Thrombophilia was found in 4 of the 7 multiparous women with preeclampsia (57%) who had had obstetric complications in a previous pregnancy, which indicates high rate of recurrence in these women. Von Tempelhof et al,16 in Germany, examined the FV Leiden mutation, PS, PC, AT III, aCL, and LAC in 61 women with severe preeclampsia (44 nulliparous) of whom 32 had HELLP syndrome. The FV Leiden mutation prevalence was higher in both severe preeclampsia and HELLP as were also aCL or LAC. Livingstone et al,17 in the United States, tested the genetic thrombophilic mutations in 110 women with severe preeclampsia and 97 controls. Most women were nulliparous and 60% of them were black. No difference was found in the prevalence of thrombophilias between the women with severe preeclampsia and control women groups or in fetal genetic thrombophilias. Laivuori et al, in Finland,18 tested 113 nulliparous women with preeclampsia—100 with severe disease, 13 with mild disease, and 103 controls—for the C677T polymorphism of the MTHFR gene. No difference in homozygosity for MTHFR was found between the 2 groups (3% preeclampsia 3% vs. 6% controls. Higgins et al19 tested the prothrombin mutation in 13 eclamptic and 74 preeclamptic women with severe disease coming from 34 families of mostly Anglo-Saxon origin. They were compared with 119 controls. The prothrombin mutation was found in only 1 family of the 34 tested and was similar in cases and controls. Kupferminc et al20 tested for the prothrombin mutation 222 patients with: severe preeclampsia (n = 55), mild preeclampsia (n = 25), and other complications and also 156 healthy women.
Twenty-eight (13%) were heterozygotes of the prothrombin mutation compared with 5 (3.2%) of the controls \( (P = 0.001) \). In women with severe preeclampsia, the prevalence of the mutation was 9% compared with 3.2% in controls \( (P = 0.07, \text{ odds ratio} 2.8 \ [0.9–9.4]) \). Abruptio placentae and IUGR were significantly associated with the mutation. Within the study group, of the 9 multiparous carriers of the mutation, 6 (66%) had had complications in previous pregnancies compared with 27 of 112 (24%) multiparous women in the study group without the mutation \( (P = 0.01) \). Krauss et al., in Germany, detected a higher incidence of APC resistance in 21 women who had HELLP syndrome, 6 months to 9 years after completion of pregnancy, compared with normal values obtained from 70 healthy nonpregnant females.

**Mild or Unknown Type of Preeclampsia and Inherited Thrombophilia**

Grandone et al., investigated the prevalence of prothrombin mutation and FV Leiden mutation in 140 women (62% nulliparous) with gestational hypertension with \( (n = 70) \) or without proteinuria \( (n = 70) \) and 216 controls. The FV and prothrombin mutations prevalence were higher in women with hypertension compared with controls, whereas MTHFR mutation prevalence was similar in preeclamptic and controls. In the 70 women with preeclampsia, the prothrombin and MTHFR mutations were more prevalent compared with the controls but not the FV Leiden mutation. Among nonproteinuric patients, a significant association with FV Leiden mutation was found. O’Shaughnessy et al., compared in a prospective study 283 women (230 primigravidas) with preeclampsia with 100 age-matched normal women and with another 100 normotensive women. There was no difference in the frequency of FV Leiden mutation or MTHFR mutations compared with the control group. A significant increase in homozygosity for the C677T MTHFR mutation in preeclampsia was reported by Shoda et al., in Japan, who tested 67 women and 98 pregnant controls. Mello et al., in Italy, investigated the prevalence of thrombophilias in 46 nulliparous women with preeclampsia and in women with a history of fetal loss in the second and third trimester. The frequency of APCR and FV Leiden mutation was significantly higher in women with preeclampsia and in the fetal loss group compared with the control group. Lindqvist et al., in a retrospective study, investigated the role of APCR and FV Leiden mutation in 2480 women enrolled in early pregnancy. The overall prevalence of APC resistance was 11% (270 of 2480). The APC-resistant subgroup \( (n = 270) \) did not differ significantly from the non-APC-resistant subgroup \( (n = 2210) \) in terms of preeclampsia or IUGR, but was characterized by an 8-fold risk of venous thromboembolism. De Groot et al., in The Netherlands, in a retrospective study examined 163 women who had preeclampsia in their first pregnancy and 163 controls matched for age gravidity and date of delivery. The prevalence of FV Leiden mutation and prothrombin mutations was similar in the groups. Morison et al., in Scotland, in a retrospective study examined nulliparous women with preeclampsia or gestational hypertension and healthy controls. They tested for genetic thrombophilias and plasminogen activator inhibitor (PAI-1) polymorphism. No difference was found in the prevalence of thrombophilias among women with preeclampsia, gestational hypertension, and controls. Kim et al., in a retrospective study in the United States, tested white women with preeclampsia and controls for C677T MTHFR and FV Leiden mutations and mutation of cystathionine beta synthase. There was no difference in the prevalence of these mutations either independently or in combination in women with mild or severe preeclampsia or HELLP syndrome. Among multiparous women with preeclampsia, the prevalence of MTHFR was 15.7% compared with 10.9% among nulliparous with
preeclampsia. This may indicate that women with this mutation are at high risk for developing recurrent preeclampsia. Lachmeijer et al. in The Netherlands, studied the MTHFR C677T and MTHFR A1298C mutations in association with preeclampsia.

One group consisted of 47 consecutive unrelated women with preeclampsia. Another group included 127 unrelated women with preeclampsia from affected sibpair families and a control group of 120 healthy women. Another 85 women with preeclampsia and known homocysteine status were tested for the relation between the C677T mutation and hyperhomocystinemia. Both MTHFR mutations were not more frequent in women with preeclampsia. Women with preeclampsia and hyperhomocystinemia had a higher prevalence of the C677T mutation compared with women with preeclampsia but without hyperhomocystinemia, but not the A1298C mutation.

Several studies described higher levels of homocysteine in preeclampsia. Rajkovic et al. reported that homocysteine levels were doubled in 20 women with preeclampsia compared with 20 healthy controls. Vollset, in the Hodarland homocysteine study, which is the largest performed to date, plasma homocysteine levels were evaluated in 5883 women with 14,492 pregnancies. It was shown that when comparing the upper with the lower quartile of plasma homocysteine, the adjusted risk for preeclampsia was 1.32 (95% confidence interval [CI] 0.98–1.77), for very low birth weight 2.01 (95% CI 1.23–3.27), and for stillbirth 2.03 (95% CI 0.98–4.21). Cotter et al. found that in 56 women who developed severe preeclampsia, homocysteine levels measured at 15.3 weeks were higher compared with those obtained from 112 healthy controls with normal pregnancy.

Glueck et al. investigated the hypofibrinolytic 4G/4G mutation of PAI-1 gene as a possible factor contributor to obstetric complications. They compared women who had obstetric complications, including 31 with severe preeclampsia, with matched control women with normal pregnancies. Women with obstetric complications were more likely than controls to be 4G/4G homozygotes.

**RECURRENT RATE OF ADVERSE PREGNANCY OUTCOME**

Several studies demonstrate a high recurrence rate in women with severe preeclampsia/HELLP syndrome (86%–88%). Several studies, albeit small, showed that in multiparous women with thrombophilies and severe pregnancy complications, there is a high (66%–83%) recurrence rate in subsequent pregnancies, whereas the type of complication may change from 1 pregnancy to the other; eg, severe preeclampsia to IUGR, 14–16,26,35–37 In 30 women with thrombophilia and pregnancy complications, the recurrence rate in women with severe preeclampsia was 52%, although the type of complication may change in subsequent pregnancy to IUGR stillbirth or placental abruption (Kupferminc et al, unpublished data).

**SUMMARY: PREECLAMPSIA AND THROMBOPHILIA**

The differences between reports may be related to different populations studied, study design, and different definitions of preeclampsia. Some studies deal with mild preeclampsia and others with severe disease. Several studies include only primigravidas and other both primigravidas and multiparous. Some include also women with recurrent preeclampsia. The fetus may also play a role: When the fetus has inherited thrombophilia from the mother, there may be an accelerated rate of thrombosis in the placenta with ensuing complications compared with a situation with an unaffected fetus. It is also possible that other presently undefined genes need to be activated to induce thrombophilic states with clinical significance in preeclampsia. Because the rate of venous and arterial thrombosis and of placental thrombosis in pregnancy complications is not essentially different between ethnic groups and races, it may be that other
thrombophilias presently play an unknown role. For example, the FV Leiden mutation is highly prevalent among the white population, the prevalence ranging from 10% to 15% in Sweden, 4% to 8% in central Europe, 2% in the south, and 5% in United States. The mutation is almost nonexistent in Asia, Japan, Africa, and South America. Preeclampsia is a multigenetic disease, and there are important differences in prognosis and management between late, mild preeclampsia and early-onset, severe disease.

Most studies and a recent metaanalysis suggest that there is an association between thrombophilias and the development of severe preeclampsia but not in mild preeclampsia. The low-pressure intervillous blood flow in the presence of a maternal hypercoagulable state may trigger fibrin deposition in the placenta and cause placental infarcts, which may incite development of early, severe disease.

The evidence in the literature and a recent metaanalysis suggest that severe preeclampsia but not mild preeclampsia is associated with thrombophilias. Mainly severe preeclampsia is associated with FV Leiden mutation, hyperhomocysteinemia, and deficiencies of protein S and AT III (Table 1). It is not clear as yet whether severe preeclampsia is associated with the prothrombin and MTHFR mutations.

### Management of Adverse Pregnancy Outcome Associated With Thrombophilia

Although at the moment, our knowledge about the optimal treatment during pregnancy is limited, the data suggest that certain risk groups such as pregnant women with severe preeclampsia should be screened for thrombophilia. Testing should also be performed on women with a history of recurrent first-trimester loss, late fetal loss, IUGR, or abruptio placentae. Are women with pregnancy complications and/or placental thrombosis and thrombophilias candidates for antithrombotic therapy as certainly are those with venous and arterial thrombosis? There are no controlled trials to guide us on how to manage women with thrombophilia and previous placental thrombosis and/or severe pregnancy complications. However, some data presented here suggest a high recurrence rate of complications in future pregnancies in women who had previously severe pregnancy complications and are carriers of thrombophilias.

The combination of aspirin and heparin or low-molecular-weight (LMW) heparin is effective in recurrent fetal loss in APS syndrome and could be considered for women with inherited thrombophilias and history of severe preeclampsia, IUGR, abruptio placentae, or fetal loss, although no controlled studies on the subject are currently available.

An interest in the potential therapeutic value of heparin to prevent and treat pregnancy complications has existed for many years. One of the larger retrospective cohort studies was performed by North et al., who reported on women with renal disease in pregnancy divided into a control group, patients treated by low-dose aspirin, and women receiving prophylactic heparin combined with aspirin and/or dipyridamole. Preeclampsia was less common in the heparin

### Table 1. Association of Preeclampsia and Thrombophilias

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<td>Antithrombin deficiency</td>
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<td>APC resistance</td>
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<td>MTHFR C677T</td>
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<td>Antiphospholipid syndrome</td>
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Degree of association: + possible association; ++ established association.
group compared with the no-treatment group and the aspirin group. Kupferminc et al. reported on the use of LMW heparin in prevention of recurrent adverse pregnancy outcome. Women with a history of severe preeclampsia, abruptio placentae, IUGR, or stillbirth and a known thrombophilia (n = 33) were treated with 40 mg/d enoxaparin and 100 mg aspirin beginning from 8 to 12 weeks’ gestation. The mean gestational age at delivery in the index pregnancies was 32.1 ± 5.0 weeks as compared with 37.6 ± 2.3 weeks’ gestation in the ensuing pregnancies treated with LMW heparin (P < 0.0001). The mean birth weight of the infants in the index pregnancies was 1175 ± 590 g compared with 2719 ± 526 g in the treated pregnancies (P < 0.0001). Pregnancy complications occurred in only 3 (9.1%) of the women and severe preeclampsia did not occur in the treated pregnancies. There were no perinatal deaths in the treated pregnancies. Ryazi et al. evaluated treatment with LMW heparin combined with aspirin in pregnant women with thrombophilia and a history of early-onset preeclampsia and/or IUGR. Twenty-six patients with thrombophilias had a subsequent pregnancy and were treated with LMW heparin plus aspirin. Their pregnancy outcome was compared with all patients having a subsequent pregnancy without thrombophilias receiving only aspirin (n = 19). There was no difference in the overall birth weight between the groups. However, when considering the 18 patients with single coagulation abnormalities (ie, excluding 8 patients with multiple thrombophilias), birth weights were significantly higher (P = 0.019) compared with the 19 with no abnormality. In addition, 2 perinatal deaths occurred in the aspirin group versus no perinatal death in the aspirin plus LMW heparin group. These preliminary studies suggest that LMW heparin may have an additional favorable effect on pregnancy outcome of women with a history of severe preeclampsia and/or IUGR and documented thrombophilia. Large randomized, controlled trials are urgently needed.

References


33. Cotter AM, Molloy AM, Scott JM, et al. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of


