Transient Focal Neurological Deficits During Pregnancy in Carriers of Inherited Thrombophilia

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Background and Purpose—The aim of our study was to investigate the association of transient ischemic cerebrovascular events during pregnancy and inherited thrombophilias.

Methods—The study group comprised previously healthy pregnant women who had their first ischemic event during pregnancy (n=12). The control group included 24 healthy women matched with the study women for age, ethnicity, and smoking status. All women were evaluated for factor V Leiden mutation, methylenetetrahydrofolate reductase C677T gene mutation, the G20210A mutation in the prothrombin gene, and deficiencies of plasma proteins C and S and antithrombin III.

Results—Inherited thrombophilia was detected in 83% of women with transient neurological manifestations compared with 17% of the control group (P<0.001).

Conclusions—Transient cerebrovascular ischemic events during pregnancy are associated with a high rate of inherited thrombophilias. Pregnant women with focal neurological symptoms should be evaluated for thrombophilia. (Stroke. 2000;31:892-895.)

Key Words: cerebrovascular disorders ● thrombophilia ● pregnancy ● stroke, acute

Ischemic cerebrovascular complications during pregnancy and puerperium are rare, with an estimated incidence of 8.1 per 100 000 pregnancies. However, it is estimated that the odds ratio for cerebral thromboembolism during pregnancy is 1.3 and that mortality is 3 times that of nonpregnant women. In only one third of cases could a predisposing factor, such as pregnancy-induced hypertension, chronic hypertension, or a hypotensive event, be demonstrated; in most cases, it occurred in seemingly healthy women and during an otherwise normal pregnancy.

Thrombophilias comprise a group of inherited and acquired coagulation disorders that predispose the carrier to vascular thrombosis. Previous studies have associated thrombophilia in both nonpregnant and pregnant patients with the occurrence of venous thromboembolisms (VTEs), including deep-vein thrombosis (DVT), pulmonary embolism, and cerebral vein thrombosis (CVT). Other reports did not support a role for thrombophilia in CVT or ischemic stroke.

In approximately 30% of cerebrovascular events, notably in previously healthy patients without identifiable risk factors, a decisive thrombotic cause could not be demonstrated radiologically. The etiology of these allegedly “idiopathic” ischemic neurological events, as well as their association with a predisposing factor for vascular thrombosis, such as thrombophilia, is unknown.

We conducted a prospective case-control study to investigate whether the development of transient neurological events during pregnancy is associated with inherited thrombophilia.

Subjects and Methods
The study group consisted of 12 pregnant women who were prospectively studied. These women had undergone neurological events during pregnancy (n=11) or labor (n=1) between 1996 to 1998 and were admitted to our institution (Table). All the women were otherwise healthy, and none had a history of a thromboembolic event or any signs or symptoms of venous thrombosis during pregnancy. Before the appearance of neurological events, none of the women had any identifiable risk factors (such as pregnancy-induced hypertension, chronic hypertension, peripheral vascular disease, small-artery disease, cardioembolism, large-artery atherosclerosis, hypotensive event, diabetes mellitus, or intracranial or extracranial vascular disease). Nine women were nulliparous. Three women smoked during pregnancy.

The neurological manifestations were transient and lasted <24 hours in 10 patients and between 2 to 3 days in 2 patients (patients 6 and 7 in the Table). All the women underwent a thorough physical and neurological examination, including neck auscultation to search for carotid bruits. The initial diagnostic workup, which included electrocardiography, echocardiography, complete blood count, pro-
thrombin and activated partial thromboplastin times, fibrinogen levels, antinuclear factor, anticardiolipin antibodies, and lupus anticoagulant, were normal for all the women. Each patient underwent CT and/or MRI of the brain after >24 hours of the acute event (Table 1), and without exception, the findings were normal. Each woman in the study group was matched for age, ethnicity, and smoking status with the consecutive normal 2 women who had 1 or more normal pregnancies. The healthy women were enrolled during their stay in the hospital after delivery. Informed consent was obtained from each subject according to the institutional review committee guidelines.

All the study women were investigated 2 to 3 months after delivery (mean 67.2 days, range 57 to 90 days) for the presence of a thrombophilic condition. The thrombophilic workup included molecular diagnosis for the guanine-1691-adenine (G1691A) mutation in factor V (factor V Leiden), as described by Brenner et al; the cytosine-677-thymine (C677T) mutation in methylenetetrahydrofolate reductase (MTHFR), as described by Frosst et al; and the guanine-20210-adenine (G20210A) mutation in the prothrombin gene, by use of a slight modification of the method of Poort et al.9 Plasma-free protein S was measured by a specific enzyme-linked immunosassay (Asserachrom free protein S assay, Diagnostica Stago). The normal value for free protein S in our laboratory is 65% to 130%.

Protein C antigen and antithrombin-III antigen were determined by rocket electroimmunoassay with rabbit anti-human protein C (Sigma) and rabbit anti-human antithrombin-III (Diagnostica Stago), respectively. The antithrombin III activity in plasma was determined by a chromogenic antithrombin III assay (Dade Diagnostica).

Normal values for protein-C antigen in our laboratory are 63% to 135%. Normal values for antithrombin-III antigen and antithrombin III activity in our laboratory are 82% to 126% and 74% to 114%, respectively.

Demographic and clinical data were compared using the Student t test and χ² test. Statistical significance was assumed at P<0.05.

Results
As expected from the recruitment criteria, there were no differences between the study and control groups in the mean age (25±6.9 years and 25±7.1 years, respectively), rates of Ashkenazi and non-Ashkenazi women (50% Ashkenazi and 50% non-Ashkenazi in each group), and number of smokers (25% of women in each group). There were 9 primiparous women in the study group, and all women in the control group were multiparous (P<0.001)

The mean gestational age at the time of the neurological manifestation was 24.9±9.8 weeks. Inherited thrombophilias were detected in 10 of 12 women with neurological symptoms (83%; Table), compared with 4 of 24 normal women (MTHFR mutation, n=2; factor V Leiden mutation, n=1; and prothrombin gene mutation, n=1; 17%, P<0.001).

The obstetric history of the study women is shown in the Table. Two primiparous women and 2 multiparous women (33%) developed obstetric complications during the current pregnancy. These 2 multiparous women also had had pregnancy complications in previous pregnancies.

Discussion
Thrombophilias are commonly associated with increased risk for VTE in both pregnant and nonpregnant patients. However, the evidence of the association of thrombophilia with both ischemic arterial and venous cerebrovascular events, such as cerebrovascular accident (CVA), transient ischemic attack (TIA) and CVT is inconsistent. Several studies reported that patients with the prothrombin gene variant (G20210A) and factor V Leiden mutation are at higher risk for developing CVT. In contrast, Bioussé et al10 found the prothrombin gene mutation (G20210A) in only 2 of 35 patients with CVT, and both had some other risk factors for thrombosis. Moreover, in several studies, the prothrombin gene mutation, the factor V Leiden mutation, and deficiencies of antithrombin III, protein S, or protein C were not associated with acute cerebral ischemic events, such as stroke and TIA. Finally, 2 recent studies reported that inherited thrombophilias are rarely associated with ischemic stroke or CVT in childhood.
sufficient, and they must interact with thrombosis-promoting factors. Pregnancy and puerperium are associated with hypercoagulability and increased rate of thrombosis. Thus, they may precipitate the first manifestation of inherited thrombophilia. Indeed, inherited thrombophilias were associated with an increased rate of VTE during pregnancy, and our group has recently reported a high rate of thrombophilias in women with severe preeclampsia, abruptio placentae, fetal growth retardation, and stillbirth, conditions known to be associated with inter villous and spiral artery thrombosis.

The association between pregnancy, thrombophilia, and cerebrovascular ischemic events has not yet been established. Hallak et al reported an increased prevalence of factor V Leiden mutation among pregnant women with thrombotic events, but found the mutation in only 1 woman in 7 with TIA or CVA. Similarly, Lidegaard et al found the factor V Leiden mutation in 2 of 8 women with nonvenous thrombosis (5 with stroke and 3 of the placenta) compared with 77% in women with VTE during pregnancy.

Of the 10 women with thrombophilia in the study group, 4 had the factor V Leiden mutation, 3 the prothrombin mutation, and 1 a combination of both. These 2 mutations, which are recognized risk factors for DVT and have also been associated with CVT, are relatively common in the general population but may interact with additional environmental factors to cause thrombosis. For example, the combination of these prothrombotic mutations and the use of oral contraceptives far exceeds and increases the separate relative risks associated with each mutation. It is therefore possible that the existence of 1 or both mutations in pregnant women may enhance the relative risk for stroke.

The present study is, to the best of our knowledge, the first to demonstrate a significant association between inherited thrombophilias and transient focal neurological events during pregnancy. Whereas previous works investigated only a few selected inherited thrombophilias, our patients underwent a comprehensive workup of all known inherited thrombophilias.

The prevalence of thrombophilia in our control group (17%) was similar to the rate previously reported by us in a cohort of Israeli women, however, inherited thrombophilia was found in 83% of pregnant women who had transient focal neurological deficits. The etiopathogenesis of TIA and minor ischemic strokes is related to small-artery disease, cardioembolism, and large-artery atherosclerosis. However, no identifiable cause could be found in about one third of the cases, and this rate is even higher in young patients. Our findings suggest that these idiopathic ischemic cerebrovascular events are associated with a high prevalence of inherited thrombophilias during pregnancy. The pathophysiological mechanism of these events is unknown, but their association with thrombophilia, pregnancy, and normal radiological finding in previously healthy women suggest that microvascular thrombus or microemboli may be the underlying cause. This is supported by a recent publication that established the importance of microemboli in the pathogenesis and prognosis of ischemic events.

Although women with stroke had higher prevalence of thrombophilia, this does not necessarily mean that the presence of a thrombophilic anomaly enhance the chance to develop for stroke. For example 17% of the women in the control group also were found to be carriers of thrombophilia. These women had 1 or more normal pregnancies without any thromboembolic complications. There may be specific subgroups or other as-yet-unidentified risk factors that enhance the risk of stroke development during pregnancy in women with thrombophilias.

The results we now present suggest that women with transient neurological events appearing during pregnancy should be investigated for inherited thrombophilias. Such a diagnosis may have important implications for both the mother and fetus. Moreover, because these patients may be at risk for recurrent vascular complications, antithrombotic treatment should be considered. The present study investigated a relatively small number of pregnant women with neurological complications; further studies are needed to confirm these preliminary findings.

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References


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