The term thrombophilia is used to describe a heterogeneous group of coagulation abnormalities (acquired or inherited) that are generally associated with increased risk of arterial and venous thrombosis. Antiphospholipid antibodies (APA) is the most frequent acquired thrombophilic disorder during pregnancy. It is generally diagnosed in the presence of elevated levels of IgG and IgM (GpL or MpL values $\geq 20$) or the presence of lupus anticoagulant. The most common inherited thrombophilic disorders during pregnancy are mutations in factor V Leiden (FVL), prothrombin gene, and tetrahydrofolate reductase. During the past 2 decades, epidemiologic and case-control studies have evaluated the association between thrombophilias and adverse pregnancy outcome (APO), specifically, preeclampsia and intrauterine fetal growth restriction (IUGR).1,5

An association between severe preeclampsia at $<34$ weeks and APA was first reported by Branch et al in 1989.2 Based on this report, recommendations were made that women with severe preeclampsia at $<34$ weeks be screened for the presence of APA and be treated if positive in subsequent pregnancies. Since that publication, several studies were published supporting or refuting an association between these antibodies and preeclampsia.6,7 Indeed, a recent report concluded that data do not support routine testing for APA in women with early-onset preeclampsia.6

An association between preeclampsia and inherited thrombophilias was first reported by Dekker et al in 1995.8 Since then, a large number of retrospective and case-controlled studies have examined the association between carriage of thrombophilic mutations and preeclampsia. These studies were the subject of several reviews.1,3,4 Overall, the results of published reports have been inconsistent. However, meta-analysis of all case-control studies suggests that only FVL mutation is associated with an increased risk of preeclampsia (odds ratio, 1.18; 95% confidence interval, 1.14 to 2.87).4 The reasons for the differences in findings among various studies are attributable in part to a lack of well-designed prospective studies evaluating the risk of preeclampsia in unselected, asymptomatic pregnant women who are carriers for these thrombophilias, and in part to the heterogenous group of patients studied in case-control studies.4 Almost all studies evaluated the frequency of these thrombophilias in women with complicated cases of severe preeclampsia who were referred to tertiary care obstetric units. In addition, most studies used term-normal pregnancies as control group. Therefore, these studies are subject to bias by overestimating the rate of thrombophilias in the study group and underestimating the rate in the control group. In addition, there are major differences among reported studies regarding the severity of preeclampsia and the gestational age at delivery in the study group,4 as well as differences regarding race and ethnicity. For instance, most studies found an association between severe preeclampsia, particularly at $<34$ weeks and thrombophilias, but not for mild or term preeclampsia. In addition, a multicenter prospective observational study of 5168 pregnant women found a carrier rate for FVL mutation of 6% among white patients, 2.3% in Asians, 1.6% in Hispanics, and 0.8% in blacks.9 Thus, studies that included exclusively white women will have high association with genetic thrombophilia,8 whereas, studies that included mainly black or Hispanic women will have a low frequency of FVL or prothrombin gene mutations in study and control patients.

Mello et al10 report the results of a large, multicenter, case-control study comparing the frequency of thrombophilia between women with preeclampsia and those with normal-term pregnancy. The study populations were 808 white Italian women with preeclampsia and a matched control group (n=808) of women who had normal-term pregnancy. None of the women gave a history of thromboembolic disease, and all had a standardized thrombophilia work-up at 4 to 12 months after the index pregnancy. The authors also divided their study subjects according to the severity of preeclampsia (mild or severe). In addition, among those with severe preeclampsia, maternal and fetal complications were compared between those with and without thrombophilia.

The Italian study revealed that the prevalence of inherited or acquired thrombophilia was significantly higher in women with severe preeclampsia (50.7%) compared with control (17.2%) with an odds ratio of 4.9 (95% confidence interval, 3.5 to 6.9). In contrast, they found no association between thrombophilia and mild preeclampsia (16.7% versus 14.9% in control). A surprising finding of this study is that patients with severe preeclampsia and positive thrombophilia work-up had a significantly higher rate of maternal complications such as onset of disease before the 28th week of gestation, abruptio placentae, disseminated intravascular coagulopathy, and acute renal failure compared with preeclamptic women without thrombophilia. In addition, severe preeclamptic women with thrombophilia were more likely to deliver at $<28$ weeks and had higher perinatal mortality compared with those without thrombophilia.
This study has several strengths but also a few weaknesses. This is the largest case-control study to be conducted in a homogenous group of white women. In addition, it is the first to compare the results according to severity of preeclampsia. Moreover, case and control subjects were matched by age, parity, body mass index, and smoking history, all of which affect the rate of preeclampsia. Women with preexisting vascular disease were also excluded. Unlike previous studies, the authors required that all functional thrombophilia tests be positive on 2 separate occasions, and the values for anticardiolipin antibodies had to be in the moderate to high levels to be considered positive. A major weakness of the study relates to the selection of the control group (healthy-term pregnancy with delivery of normal-sized infants). The case and control groups should have been matched according to gestational age at delivery. In addition, the preeclamptic group was a select group of patients who were referred to tertiary care facilities because of complications and thus might not represent all women with severe preeclampsia in the region. This selection bias could have overestimated the strength of the association of thrombophilia with severe preeclampsia and maternal complications. Moreover, the results of this study might not be applicable to populations with diverse race and ethnicity similar to those seen in the United States.

Several questions remain unanswered by the current study. Should all women with severe preeclampsia be screened for thrombophilia? Screening is very expensive and most patients will have a negative screen. If the results are positive, what should the clinician do with this information? Several retrospective studies suggest that women with severe preeclampsia in association with thrombophilia are at increased risk for APO (preeclampsia, IUGR, fetal death) in subsequent pregnancies. In addition, some studies suggest that treatment with heparin and low-dose aspirin may improve outcome in subsequent pregnancies. Recently, low–molecular weight heparin was shown to improve pregnancy outcome in women with a history of 1 fetal loss and a constitutional thrombophilic disorder. Thus, there is an urgent need for a double-blind placebo controlled trial to evaluate the benefits of heparin during pregnancy in women with previous history of severe preeclampsia in association with thrombophilia. Until such a trial is conducted, screening of all women with severe preeclampsia for thrombophilia should remain experimental.

References
Thrombophilia and Severe Preeclampsia: Time to Screen and Treat in Future Pregnancies?
Baha M. Sibai

Hypertension. 2005;46:1252-1253; originally published online November 14, 2005;
doi: 10.1161/01.HYP.0000188904.47575.7e
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/46/6/1252

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/