Preeclampsia and Fetal Loss in Women With a History of Venous Thromboembolism

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Abstract—A higher prevalence of risk factors for venous thromboembolism (VTE) has been found in women with preeclampsia and fetal loss. We investigated whether women with a history of VTE have a higher prevalence of pregnancy-associated complications compared with control subjects. In 395 patients with a history of VTE and in 313 control women, the prevalence of complications during pregnancy and the mean birth weight of viable infants were evaluated. The prevalence of pregnancy-induced hypertension and preeclampsia was higher in patients (5.1% and 3.0%, respectively) compared with control subjects (1.3% each). The odds ratio was 4.13 for pregnancy-induced hypertension (95% CI 1.4 to 12.22, \(P = 0.0058\)) and 2.43 for preeclampsia (95% CI 0.78 to 7.6, \(P = 0.133\)). Stillbirth was slightly more frequent in patients (4.3%) than in control subjects (3.2%); the difference was not statistically significant. Miscarriage was equally frequent in patients (21.8%) and control subjects (21.3%). The birth weight of viable infants born to patients was, on average, 109 g lower than that of the infants born to the control subjects (\(P = 0.014\)) after adjustment for the mother’s body mass index. Our study demonstrates that women with a predisposition to VTE have, overall, a good chance for a successful pregnancy outcome. However, the findings from our study support the assumption that a predisposition to venous thrombosis is associated with a higher risk for complications during pregnancy and lower infant birth weight. (Arterioscler Thromb Vasc Biol. 2001;21:874-879.)

Key Words: venous thromboembolism ■ pregnancy ■ preeclampsia ■ fetal loss ■ birth weight

Complications of pregnancy, such as preeclampsia and fetal loss, are considered to result from underperfusion of the placenta due to structural and occlusive changes, including thrombosis of the placental vessels. Recently, a number of studies were published in which a higher prevalence of genetic or acquired risk factors for thrombosis was found in women with preeclampsia and/or fetal loss compared with control subjects. Among other causes, thrombophilia has gained major attention as a risk factor for preeclampsia in recent years. In several case-control studies, a higher prevalence of risk factors for thrombosis, especially the factor V Leiden mutation and the G20210A prothrombin gene variation, has been demonstrated in cases. Other authors do not confirm these data. If the pathogeneses of venous thromboembolism (VTE) and preeclampsia share similar mechanisms, it may be expected that women with a history of VTE are at an increased risk for these complications during pregnancy. Data on the risk of fetal death in patients with known risk factors for thrombosis are conflicting. An increased risk for stillbirth and/or miscarriage was found by several authors, whereas others could not demonstrate an association between markers of thrombophilia and fetal loss.

There are no systematic studies on the prevalence of preeclampsia, pregnancy-induced hypertension (PIH), and fetal loss in women who have experienced a venous thromboembolic event at a young age and can therefore be regarded as patients with clinically manifested thrombophilia. We studied whether women with a history of VTE have an increased risk for preeclampsia, PIH, or fetal death compared with age-matched women without a history of VTE. Furthermore, we investigated the birth weight of children born to patients with VTE compared with the weight of children born to the women in the control group.

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Methods

Patients and Controls
Nine hundred seventy-three consecutive women with a history of VTE that had occurred between the age of 13 to 45 years were investigated for risk factors of thrombosis between January 1985 and December 1998. In all these patients, the VTE was documented by antemortem criteria. Informed consent for collection of data was obtained from all control subjects. No laboratory investigations were performed in patients who were pregnant at least once and were included in the study. Of the 395 patients, 70 had been enrolled in the prospective Austrian recurrence (AUREC) study,17 and 159 individuals were taking oral anticoagulant treatment at the time of our investigation. The interval between current investigation and last VTE was at least 4 months.

Three hundred thirteen age-matched control women without a history of VTE, who were investigated or treated at the Department of Obstetrics and Gynecology (outpatients and inpatients with routine gynecological investigation, birth control counseling, or planned surgery because of nonmalignant disease), were invited for reinvestigation in 1999, and 507 women accepted our invitation. After informed consent was obtained, a blood sample was drawn, and the patients underwent a standardized interview on their history of thrombosis and pregnancy-associated complications, such as new onset of hypertension and proteinuria during pregnancy, miscarriage and stillbirth, duration of pregnancy, and infant weight. Of the 507 women, 112 had never been pregnant, and 395 women had been pregnant at least once and were included in the study. Of the 395 patients, 70 had been enrolled in the prospective Austrian recurrence (AUREC) study,17 and 159 individuals were taking oral anticoagulant treatment at the time of our investigation. The interval between current investigation and last VTE was at least 4 months.

Laboratory Analysis
Plasma samples were obtained from patients after overnight fasting and were centrifuged at 2000g for 20 minutes. Coagulation tests (lupus anticoagulant and factor VIII) were performed within 3 hours of sampling, snap-frozen, and stored at −20°C until analysis. For determination of homocysteine, samples were immediately cooled at 4°C and centrifuged within 30 minutes of sampling, snap-frozen, and stored at −70°C. Diagnosis of the lupus anticoagulant was made according to the criteria of the International Society of Thrombosis and Haemostasis18 by using 2 different screening tests (activated partial thromboplastin time and diluted Russell’s viper venom time) and confirmatory tests as previously described.19 Antithrombin activity (STA antithrombin III, Diagnostica Stago; normal range 75% to 125%) and protein C activity (COAMATIC protein C, Chromogenix AB; 65% to 130%) were determined by the STA analyzer (Stago Diagnostica). Free protein S antigen was determined by ELISA according to the manufacturer’s instructions (Asserachrom protein S, Diagnostica Stago, 50% to 160%). Factor VIII clotting activity (95th percentile of 307 healthy individuals was 248%) was determined by 1-step clotting assay on a KC 10 coagulometer (Amelung) by mixing 100 µL of a 1:10, 1:20, 1:40, and 1:80 plasma dilution (Owen’s diluted buffer, Immuno AG) with 100 µL factor VIII–deficient plasma (Immuno AG) and 100 µL activated partial thromboplastin time reagent (Dade Acti-FS, Dade Diagnostics AG). After an incubation for 240 seconds at 37°C, coagulation was started by the addition of 100 µL of 0.025 mol/L CaCl₂. For the calibration of factor VIII activity determination, dilutions of Cal N (Dade Diagnostics AG) with the respective factor-deficient plasma were used. Total homocysteine (normal range <13.6 µmol/L for women and <16.3 µmol/L for men) was determined by using a high-performance liquid chromatographic kit by Immunodiagnostics, as previously described.20 Analysis of the FV:R506Q and the FII:A20210G genotypes was performed by multiplex polymerase chain reaction (PCR) according to the general principle of mutagenically separated PCR. The reaction mixture contained wild-type and mutant-specific forward primers of different lengths and 2 common reverse primers. PCR products were generated in 50-µL volumes containing 1.25 U AmpTag Gold (Perkin Elmer Cetus), 1.5 mmol/L MgCl₂, 200 µmol/L of each dNTP (Amersham Pharma-
Clinical Features of VTE and Risk Factors for Thrombosis in the Patient Group

The mean age at first VTE in the 395 patients was 31.6 ± 8.4 years. The site of the first VTE was deep vein thrombosis of the lower extremity in 230 (58.2%) of the patients, pulmonary embolism in 61 (15.4%), deep vein thrombosis combined with pulmonary embolism in 78 (19.8%), caval vein thrombosis in 2 (0.5%), arm vein thrombosis in 16 (4.1%), and other events in 2 (0.5%). One hundred forty-five (37%) of the patients had experienced a recurrent VTE.

In 186 (47.1%) of the women, the first thrombotic event had occurred in the absence of a high-risk situation. At that time, 122 (65.6%) of the women were taking oral contraceptives. Twenty (5.1%) of the women had their first VTE event during pregnancy; 31 (7.8%), after vaginal delivery; 13 (3.3%), after delivery by cesarean section; and 2 (0.5%), after miscarriage. Further triggering events were surgery in 58 (14.7%) of the women, trauma in 38 (9.6%), immobilization in 29 (7.3%), and other events in 18 (4.6%). In 75 women, VTE preceded the first pregnancy; in 197, the first VTE occurred after the last pregnancy. One hundred twenty-three women experienced the thrombotic event between 2 pregnancies. Forty-seven women had taken anticoagulant drugs (heparin or oral anticoagulants) during 1 of their pregnancies.

Hereditary and acquired risk factors of VTE in the patient group are listed in Table 2, and 39.9% of the patients had no detectable risk factor. As expected, the factor V: R506Q (factor V Leiden) mutation was the most frequently found abnormality; 114 (28.9%) of the women were heterozygous, and 14 (3.5%) were homozygous. Thirty-nine (10%) of the women carried the prothrombin variation, and 1 of them was homozygous. A natural inhibitor deficiency was found in 8.8% of the women. Factor VIII:C was determined in 373 women; of these, 37 (9.9%) had levels above the 95th percentile of normal individuals. Of the patients, 18.4% had elevated homocysteine levels. A lupus anticoagulant was detected in 1.8% of the patients. The combination of 2 risk factors was detected in 12.1% of the patients, and the combination of 3 risk factors was detected in 3.9% of the patients.

Prevalence of PIH, Preeclampsia, and Fetal Loss in Patients and Control Subjects

There was an ~3-fold increase in the prevalence of PIH, preeclampsia, or eclampsia in patients (7.6%) compared with control subjects (2.6%), with an OR of 3.1 and a 95% CI of 1.4 to 7.0 (P = 0.003, Table 3). Two of these women had PIH and preeclampsia in 2 different pregnancies, respectively. PIH was statistically significantly more frequent in women with a history of VTE (OR 4.1, 95% CI 1.4 to 12.2; P = 0.006). Preeclampsia (including 2 patients with eclampsia in the patient group) was more prevalent in the patient group (OR 2.4, 95% CI 0.8 to 7.6); however, the difference was not statistically significant. An increased risk for PIH/preeclampsia was associated with an increased BMI in our population of patients and control subjects (OR 1.16, 95% CI 1.1 to 1.2; P = 0.0001). The higher risk for PIH/preeclampsia in patients remained statistically significant after adjustment for BMI (OR 2.8, 95% CI 1.2 to 6.3; P = 0.014).

The prevalence of stillbirth was slightly higher in patients (4.3%) compared with control subjects (3.2%), as seen in Table 3.
Six of these 22 women were on oral anticoagulant treatment when they became pregnant. Patients who had an induced abortion because of personal or medical reasons were not included in this analysis.

**Birth Weight in Infants Born to Patients and Control Subjects**

The mean birth weight of 617 viable infants born to the patients was 3281±617 g; the mean birth weight of 486 viable infants born to the control women was 3335±582 g. The duration of pregnancy ending with delivery of a viable infant was equal in patients (39.3±2.2 weeks) and control subjects (39.3±2.3 weeks).

When the median birth weight for each mother was calculated as a summary measure, the unadjusted difference between patients (3247±570 g) and control subjects (3307±507 g) was not statistically significant (P=0.16). Because the birth weight of the infant is dependent on the mother’s BMI and height, these covariates were considered in the ANCOVA model. The height- and BMI-adjusted difference between the median birth weight of patients and control subjects was statistically significant (P=0.014). The birth weight of viable infants born to patients was, on average, 109 g lower than the birth weight of infants born to the control subjects (95% CI 22 to 195 g). The mean birth weight was 3190±667 g in infants born to women with a hereditary abnormality and 3295±486 g in those born to women without a hereditary abnormality; thus, there was no statistically significant difference between these 2 groups (P=0.1).

**Discussion**

Our large retrospective study provides evidence that the chance for a woman with a predisposition to VTE to have a successful pregnancy outcome is high and close to that of women without previous VTE.

A significantly higher prevalence of PIH was found in women with a history of VTE compared with control subjects (OR 4.13). Preeclampsia (PIH and proteinuria) was more frequent in women with VTE than in control subjects (OR 2.43); however, the difference did not reach statistical significance. We cannot exclude the possibility that part of the women who had PIH indeed had preeclampsia, because if it was not definitely known by the women or stated in medical

**Table 4. Complications of Pregnancy in Patients With and Without Risk Factors for Thrombosis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Present* (N=214), n (%)</th>
<th>Absent (N=142), n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIH/preeclampsia†</td>
<td>12 (5.6)</td>
<td>13 (9.2)</td>
<td>0.59 (0.26–1.33)</td>
<td>0.20</td>
</tr>
<tr>
<td>PIH</td>
<td>9 (4.2)</td>
<td>8 (5.6)</td>
<td>0.74 (0.28–1.96)</td>
<td>0.54</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>5 (2.3)</td>
<td>5 (3.5)</td>
<td>0.65 (0.19–2.33)</td>
<td>0.53</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>47 (22.1)</td>
<td>32 (22.5)</td>
<td>0.97 (0.58–1.61)</td>
<td>0.92</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>5 (2.4)</td>
<td>7 (4.9)</td>
<td>0.46 (0.14–1.49)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

In 356 women, all risk factors were determined.

*Risk factors for thrombosis are antithrombin protein C, and protein S deficiency, factor V;R506Q, prothrombin variation, lupus anticoagulant, hyperhomocysteinemia, and elevated factor VIII.

†Two women had PIH and preeclampsia in 2 different pregnancies, respectively.

**Table 5. Complications of Pregnancy in Patients With First VTE Before and After Their Pregnancies**

<table>
<thead>
<tr>
<th>First VTE</th>
<th>Before First Pregnancy (N=75), n (%)</th>
<th>After Last Pregnancy (N=197), n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIH/preeclampsia</td>
<td>3 (4.0)</td>
<td>15 (7.6)</td>
<td>0.5 (0.14–1.80)</td>
<td>0.3</td>
</tr>
<tr>
<td>PIH</td>
<td>2 (2.7)</td>
<td>12 (6.1)</td>
<td>0.4 (0.09–1.93)</td>
<td>0.3</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1 (1.3)</td>
<td>3 (1.5)</td>
<td>0.9 (0.08–8.50)</td>
<td>0.9</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>22 (29.3)</td>
<td>35 (17.8)</td>
<td>1.9 (1.04–3.56)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>3 (4.0)</td>
<td>8 (4.1)</td>
<td>1.0 (0.2–3.8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3. However, the difference was statistically not significant. The prevalence of miscarriage was similar in patients (21.8%) and control subjects (21.3%).

The group of women with a history of VTE was separately evaluated according to their risk factor profile and pregnancy-associated complications. In 214 patients, at least 1 known risk factor for VTE (antithrombin protein C, or protein S deficiency, factor V;R506Q mutation, prothrombin variation, lupus anticoagulant, hyperhomocysteinemia, or elevated factor VIII:C levels) was detected; in 142 patients, none of these risk factors was present. Pregnancy-associated complications were not more frequent in women with a known risk factor compared with those without a known risk factor (Table 4). A separate analysis of women with classic heritable risk factors did not reveal different results. In the 176 women with antithrombin, protein C, or protein S deficiency, factor V:R506Q or prothrombin variation preeclampsia occurred in 6 (3.4%), PIH occurred in 7 (4.0%), stillbirth occurred in 8 (4.6%), and miscarriage occurred in 37 (21.1%); thus, the percentages were comparable to those in the group of patients without a detectable risk factor for thrombosis.

The frequency of complications of pregnancy was separately evaluated in patients who had experienced the first VTE before the first pregnancy and in those who had experienced the first VTE after the last pregnancy (Table 5). The percentage of women with PIH or preeclampsia was not definitely known by the women or stated in medical...
records that proteinuria was present, the women were classified into the group of patients with PIH only. Preeclampsia is still a major health problem for mothers and infants. Abnormal implantation and reduced placental perfusion together with maternal constitutional factors are regarded as important mechanisms for the development of preeclampsia.22 Hereditary and acquired risk factors for VTE have been found more frequently in women with preeclampsia than in women with normal pregnancies.2-3 However, in a prospective study on 2480 women,24 factor V:R506Q was not identified as a risk factor for preeclampsia, and De Groot et al31 found a similar prevalence of thrombotic risk factors in patients with severe preeclampsia and in control subjects. It may well be that the factor V:R506Q mutation or other markers of thrombophilia itself are not a major risk factor for pregnancy complications, unless additional predisposing conditions are present. Interestingly, in the study of the World Health Organization on the impact of oral contraceptives on the VTE risk,25 a history of PIH during a previous pregnancy was identified as an important risk factor for VTE later in life. Hereditary and acquired risk factors for VTE, such as antithrombin, protein C, or protein S deficiency, factor V:R506Q mutation, prothrombin G20210A variation, hyperhomocysteinemia, an increased factor VIII level, or lupus anticoagulant, are found in up to 50% of patients with clinically manifested thrombosis. Such abnormalities may predispose women to preeclampsia under specific circumstances. In the present study, PH and preeclampsia were not associated with specific laboratory abnormalities of patients and were independent of the presence of all analyzed abnormalities. However, yet-unknown risk factors for VTE may be present in women with a history of thrombosis, and they may contribute to the development of PIH and preeclampsia. Our data indicate that the increased risk for PIH and preeclampsia is not linked to any specific abnormality but rather to a general predisposition for thrombosis. This assumption is supported by the observation that the number of women with PIH and preeclampsia was similar among patients who suffered from thrombosis before their first pregnancy and those who had experienced thrombosis after their last pregnancy.

An increased BMI is an important and generally accepted risk factor for preeclampsia26 and is also a well-known risk factor for VTE. However, the higher BMI in our patient group does not account for the higher prevalence of preeclampsia and PIH, inasmuch as the risk in patients remained higher after adjustment for BMI.

In the present study, the frequency of miscarriage was similar in patients and control subjects and comparable to data from the literature.27 A direct comparison of the present study with data from the literature is not possible, because the design of the studies is different. In a large retrospective study of carriers and noncarriers of the factor V:R506Q, Meinardi et al28 found a higher risk, whereas Tormene et al29 and Balasch et al30 did not find a higher rate of early miscarriage in carriers. Dizon-Townson et al31 found a similarly low prevalence of factor V:R506Q mutation in couples with and without a history of recurrent miscarriage. In the European Prospective Cohort on Thrombophilia (EPCOT) study,14 only women with antithrombin deficiency had a significantly increased risk of miscarriage. A detailed analysis of our patients revealed that miscarriage was statistically significantly more frequent in patients who had VTE before the first pregnancy than in those with VTE after the last pregnancy. A quarter of these miscarriages occurred in women who were on oral anticoagulant treatment during early pregnancy. Oral anticoagulants taken during the first trimester might influence the miscarriage rate.

Stillbirth was not a major problem in women with a history of venous thrombosis. Intrauterine death after the 24th week of gestation occurred only slightly more often in women with a history of thrombosis compared with the control subjects; however, the difference was not statistically significant. Data in the literature are conflicting. Although in a number of publications,2-4,29 late fetal loss has been attributed to maternal risk factors for thrombophilia, contrasting data have also been published. In the prospective study of Lindqvist et al,24 the factor V:R506Q mutation was not associated with fetal loss. In a recent study from our group on females with homozygous factor V:R506Q, the risk of stillbirth was not significantly increased compared with risk in a control group.16 Meinardi et al,28 on the other hand, found a significantly increased risk of stillbirth in homozygous carriers of the factor V:R506Q mutation but not in heterozygous individuals.

Because data on complications of pregnancy were collected retrospectively and were mainly based on information given by the patient, a recall bias cannot be excluded. However, this bias is expected to be similarly distributed in the patients and control subjects, because both groups were evaluated the same way. An evaluation of the influence of anticoagulants, especially heparin, on the prevalence of pregnancy-associated complications has not been performed because this was a retrospective study and because treatment regimens were not uniform regarding dosage and duration of treatment. Furthermore, to avoid bias, our analysis was based on patients and not on pregnancies, because a woman’s pregnancies cannot be assumed to be independent of each other.

The adjusted median birth weight of infants born to women with a history of VTE was significantly lower. Apart from gestational age, maternal BMI is an important predictor of the infant’s birth weight.31 Infants born to the VTE patients weighed, on average, 109 g less weight than did infants born to the control subjects. It is improbable that the difference between birth weights in both groups is due to a recall bias, because the patient group and the control group were studied similarly, and it is known that a mother’s recall of birth weight is sufficiently accurate for clinical and epidemiological use.32 The significantly lower birth weight of children born to mothers with VTE may be due to a higher frequency of placental thrombi, resulting in placental infarction and deterioration of the fetal blood supply.

The findings of the present study indicate that predisposition to thrombosis may be relevant in the development of complications during pregnancy. Patients with a history of thrombosis must be monitored closely for the development of hypertensive disorders during pregnancy. Anticoagulant therapy to inhibit procoagulatory mechanisms may be considered but cannot generally be recommended. At present, such a treatment modality is usually performed in women with a history of thrombosis and in women with certain abnormalities known to dramatically increase the risk of
thrombosis during pregnancy, such as antithrombin deficiency, or the antiphospholipid syndrome. Whether anticoagulant treatment is beneficial in the prevention of preeclampsia can be assessed only in properly designed clinical trials.

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References


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