Thrombosis during pregnancy and the postpartum period

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KEY WORDS
Deep vein thrombosis
Thrombosis in pregnancy
Postpartum thrombosis

Objective: To describe the circumstances surrounding deep vein thrombosis among pregnant or postpartum patients enrolled in a large multicenter registry.

Study design: Consecutive patients with ultrasound-confirmed deep vein thrombosis were enrolled at 183 institutions during a 6-month period from October 2001 to March 2002. Fifty-three who were either pregnant or within 6 weeks postpartum were analyzed.

Results: Thirty-four were pregnant and 19 were postpartum. Among those pregnant, 44% experienced deep vein thrombosis in the first trimester, 24% in the second, and 26% in the third. Deep vein thrombosis occurred in the left lower extremity in 76% of the pregnant and 47% of the postpartum women. Four pregnant and 2 postpartum women had pelvic vein thrombosis. Among those postpartum, 74% had undergone surgery within 3 months.

Conclusion: During pregnancy, the risk of deep vein thrombosis begins in the first trimester. Thus, we believe that when prophylaxis is indicated, it should be initiated early in gestation.

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Venous thromboembolism (VTE), which includes deep venous thrombosis and pulmonary embolism, occurs in approximately 1 in 1000 pregnancies.1 Women are 5 times more likely to develop VTE during pregnancy than when not pregnant.2 The hypercoagulable state of pregnancy has likely evolved to protect women from hemorrhage during miscarriage and childbirth. Indeed, the leading cause of maternal death in the developing world is hemorrhage,3 but in the United States, the leading cause of maternal death is embolic disease.4 In addition to the mortality and immediate morbidity resulting from VTE, there is long-term morbidity associated with the postthrombotic syndrome. The majority of women who suffer from VTE during pregnancy develop sequelae that range from edema and skin changes to recurrent thromboses and ulceration.5 Women who experience VTE in pregnancy may also be more likely to suffer poor pregnancy outcome. Those with inherited or acquired risk factors for thrombosis (thrombophilia) are more likely to experience manifestations of poor pregnancy outcome such as placental abruption, preeclampsia, fetal growth restriction, stillbirth, and possibly recurrent miscarriage.6,8 Prophylaxis and appropriate treatment of VTE in pregnancy may reduce maternal morbidity and mortality and improve the outcome of pregnancy.

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Despite a growing interest in the interaction between thrombophilia and pregnancy, there is little published information regarding the circumstances surrounding VTE in pregnancy or current practice with respect to its prevention and treatment. Data from a recently completed registry provided an opportunity to study VTE in pregnancy and postpartum. Five thousand four hundred fifty-one male and female patients with ultrasound-confirmed deep vein thrombosis (DVT) were prospectively enrolled at 183 medical centers around the United States during a 6-month period from October 2001 to March 2002. Of the 5451 patients, 53 were either pregnant or postpartum. The purpose of this largest ever, prospective registry was to explore the current epidemiology, prophylaxis, and initial management of VTE. The purpose of our study was to elucidate the circumstances surrounding VTE in the pregnant or postpartum women with DVT, including the demographics, comorbidities, clinical presentation, prophylaxis received, and initial treatment.

**Material and methods**

Institutional review board approval was obtained from each participating institution.

Consecutive patients with acute DVT confirmed by venous duplex ultrasound and who agreed to participate were enrolled. There were no exclusions. Data were obtained from medical records and recorded on case report forms by a study coordinator. Coexisting medical conditions or comorbidities were specified according to a prespecified list. Obesity was defined as a body mass index (BMI) greater than 30 kg/m². Gestational age was defined as the weeks gestation stated in the medical record. No additional testing was performed to confirm the diagnosis of pregnancy or gestational age. Postpartum was defined as the first 6 weeks after delivery. Thrombophilia testing was not performed as part of the study. Each site with more than 2 patients was monitored with at least 1 visit by an independent auditor to confirm the ultrasound diagnosis of DVT and review the medical records for accuracy. The diagnosis of pelvic vein thrombosis, suspected on the basis of alteration of venous flow at the level of the common femoral vein, was confirmed with computed tomography or magnetic resonance imaging at the discretion of the individual providers at their respective institutions.

To calculate descriptive statistics, each continuous and discrete variable was analyzed by Statistical Analysis System (SAS), version 6.12 (SAS Institute Inc, Cary, NC). For discrete variables with more than 1 level of response (eg, “check all that apply”), all responses for each patient were tallied. Therefore, the total number of responses for such variables may have exceeded the total number of patients in the study.

**Results**

Of the 5451 patients, 2559 were men and 2892 were women. Of the 2892 women, 53 (2%) were either pregnant or postpartum. Of these 53, 34 (64%) were pregnant and 19 (36%) were postpartum. Of the 45 women for whom information on age was available, the median age was 29 years. The racial distribution of the pregnant and postpartum patients was 27 (51%) Caucasian, 12 (23%) African American, 8 (15%) Hispanic, 3 (6%) other, and 3 (6%) unknown. Of the 41 women for whom BMI was recorded, 15 (37%) were overweight (BMI > 25 kg/m² and < 30 kg/m²) and 12 (29%) were obese (BMI > 30 kg/m²).

Of the pregnant patients whose previous delivery status was known, 16 (47%) were parous and 13 (38%) were nulliparous. Fifteen of the patients (44%) experienced DVT during the first trimester (less than 14 weeks); 8 patients (24%) during the second trimester (14 to 28 weeks) and 9 (26%) during the third trimester (> 28 weeks). The timing of DVT was unknown in two patients. Of the 10 postpartum patients for whom delivery status was known, 6 (60%) were delivered by cesarean, and 4 (40%) were delivered vaginally. The median number of days from delivery to diagnosis of DVT was 16.

The sites of DVT are elaborated in Table I. Among the pregnant women, the most common site of DVT was the proximal left leg without calf involvement, which occurred in 18 (53%). Overall, there were 26 DVTs (76%) located in the left lower extremity versus 4 (12%) in the right. Another 2 (6%) occurred in the right upper extremity. Four of the pregnant patients (12%) experienced a pelvic vein DVT. Among the postpartum women, the most common site of DVT was the proximal left leg with calf involvement, which occurred in 6 (32%). Overall, there were 9 DVTs (47%) in the left lower extremity versus 7 (37%) in the right. Another 3 (16%) occurred in the left upper extremity. Two of the postpartum patients (10%) experienced a pelvic vein DVT. None of the women experienced concomitant pulmonary embolus.

The median duration of time from onset of symptoms to diagnosis of DVT was 1 day (range 0-23) during pregnancy and 2 days (range 0-14) postpartum. The 2 most common presenting symptoms were swelling in 88% of the pregnant women and 79% of the postpartum women and extremity discomfort in 79% of the pregnant women and 95% of the postpartum women. Additional symptoms included difficulty walking, which occurred in 21% of the pregnant women and 32% of the postpartum women, and erythema, which was reported in 26% of both groups.

Although thrombophilia testing was not performed as part of the study, among the pregnant women, 8 (24%) carried a diagnosis of thrombophilia. Three (9%)
had protein S deficiency, 2 (6%) protein C deficiency, two (6%) factor V Leiden, and 1 (3%) antithrombin III deficiency. Among the postpartum women, 1 (5%) had the antiphospholipid antibody syndrome.

The distribution of thrombophilia and other conditions known to be associated with DVT is presented in Table II. Only 1 pregnant patient had either a history of surgery within the past 3 months or immobilization within 30 days prior to DVT. In contrast, 14 patients (74%) in the postpartum group had undergone surgery within the past 3 months. Although the reasons for surgery were not recorded, most operations were likely cesarean delivery. Seven patients (37%) had been immobilized within 30 days and, although the reasons were not recorded, presumably these were pregnancy-related conditions. None of the pregnant patients, but 3 (16%) of the postpartum patients had hypertension. None of the pregnant patients, but 3 (16%) of the postpartum patients stated that they were current cigarette smokers. For the majority of both the pregnant patients (85%) and the postpartum patients for whom previous DVT history was known (88%), this was the first DVT.

For treatment of DVT, most pregnant patients received either low-molecular-weight heparin (LMWH) as monotherapy (35%) or unfractionated heparin (UFH) prior to starting LMWH (32%) as treatment for DVT. Although 19 pregnant women were ultimately bridged to warfarin after delivery using either UFH (n = 12) or LMWH (n = 7), none was treated with warfarin initially. Among the postpartum patients, 47% were treated with UFH versus 32% with LMWH prior to beginning warfarin therapy. A smaller percentage of patients (21%) received LMWH as monotherapy. One of the pregnant women underwent inferior vena cava filter placement. Three of the postpartum women received thrombolytic therapy and 1 a catheter thrombectomy.

Among the pregnant patients, 8 were inpatients at the time of diagnosis and 26 were outpatients. Of these 26, 21 were admitted for initial therapy and 5 were managed exclusively as outpatients. Among the 19 postpartum patients, 7 were inpatients at the time of diagnosis and 12 were outpatients. Of these 12, all were then admitted to the hospital for initial therapy.

As a result of acute DVT, pregnant women required hospitalization for an average of 6.4 days (range 0 to 20 days). (Data on hospital stay were missing for 5 pregnant patients.) Postpartum patients were hospitalized for an average of 9.1 days (range 1-39 days).

Of the 34 pregnant patients, 28 (82%) had not received prior prophylaxis for VTE. Only 4 patients (12%) had received prior prophylaxis, whereas prophylaxis history was unknown in 2 patients (6%). Similarly, among the 17 postpartum patients for whom prophylaxis history was known, the majority, 14 (82%), had not received prophylaxis. Three postpartum patients (18%) had received prior prophylaxis. Two postpartum patients had a previous history of DVT, and 1 had a previous history of pulmonary embolism.

### Table I Sites of DVT

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left leg</td>
<td>26 (76%)</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>Proximal without calf involvement</td>
<td>18 (53%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Proximal with calf involvement</td>
<td>7 (21%)</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Calf only</td>
<td>1 (3%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Right leg</td>
<td>4 (12%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Proximal without calf involvement</td>
<td>3 (9%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Proximal with calf involvement</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Calf only</td>
<td>1 (3%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Left upper extremity</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Right upper extremity</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>4 (12%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

### Table II Distribution of comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Pregnant (n = 34)</th>
<th>Postpartum (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed thrombophilia</td>
<td>8 (24%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Surgery within last 3 months</td>
<td>1 (3%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>Immobilized within 30 d prior</td>
<td>1 (3%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (9%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>First DVT</td>
<td>29 (85%)</td>
<td>15 (88%), n = 17</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>5 (15%)</td>
<td>2 (12%), n = 17</td>
</tr>
<tr>
<td>DVT history unknown</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

### Comment

We found that approximately two-thirds of DVT occurred antepartum and one-third occurred postpartum, consistent with the findings of a meta-analysis. In this meta-analysis, 22% of antepartum DVT occurred during the first trimester, 34% in the second, and 48% in the third. In our study, no additional testing was performed to confirm the diagnosis of pregnancy, so it is possible that patients with undiagnosed or very early pregnancy may have been excluded. Nonetheless, we found that almost half of our cases occurred in the first trimester. Thus, we believe that when prophylaxis is indicated, it should be initiated early in pregnancy.

Among the pregnant women, the most common site of DVT was the left lower extremity. This predilection for the left leg and thigh has been reported previously. In a meta-analysis of leg of presentation during pregnancy and the puerperium, 82% of objectively diagnosed DVT occurred in the left lower extremity. Anatomic reasons have been postulated, but the real
reason is unknown. Pelvic vein thrombosis, a rare event outside of pregnancy or recovery from pelvic surgery, accounted for fewer than 1% of the cases in the registry as a whole but occurred in 6 or 11% of the pregnant or postpartum patients. Four were pregnant and 2 were postpartum. Whether the 2 who were postpartum had coexistent pelvic infection is unknown.

Because only those conditions identified at the time of enrollment were included in the analysis, and because testing for thrombophilia was not performed as a part of the study, thrombophilia was likely underreported. Nonetheless, 24% of the pregnant women carried the diagnosis.

Seven of 51 women (14%) for whom history was known had had a previous DVT. With a background risk of less than 1/1000 events per year and 1/1000 per pregnancy, the expected prevalence of a positive history in this group of women with a median age of 29 years would be less than 1%. A history of thrombosis appears to be an important risk factor for recurrent events in pregnancy or postpartum.

For treatment during pregnancy, LMWH was used more often than UFH but was not used exclusively. Among the postpartum women, UFH was used more often than LMWH for bridging to warfarin. These findings are surprising, considering LMWH is at least as safe and effective as UFH for the treatment of DVT in pregnancy but has a longer plasma half-life, a more predictable dose response, a lower risk of heparin-induced thrombocytopenia and probably a lower risk of osteoporosis. In a cost-effectiveness analysis, LMWH was superior to UFH for inpatient management of DVT. Compared with hospital administration of intravenous heparin, home administration of LMWH for treatment of DVT has been associated with a 67% reduction in length of hospital stay. In this study, the length of stay might have been reduced with greater use of LMWH.

Determining which patients should receive thromboprophylaxis remains a challenge. Risk factors such as hypertension, recent surgery, immobility, and cancer are unlikely to be present in pregnant patients, whereas thrombophilia and a history of previous DVT appear to be very important. Hypertension (probably in association with preeclampsia), immobility, and recent surgery (probably cesarean delivery) appear to be important risk factors for postpartum patients. There are published guidelines for thromboprophylaxis in pregnancy; however, there are no large, randomized trials of thromboprophylaxis in pregnancy and the puerperium. Optimal protocols for thromboprophylaxis have yet to be developed.

References