Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women


Summary

Women with a history of venous thromboembolism (VTE), thrombophilia or both may be at increased risk of thrombosis during pregnancy, but the optimal management strategy is not well defined in clinical guidelines because of limited trial data. A strategy of risk assessment and heparin prophylaxis was evaluated in pregnant women at increased risk of VTE. In a prospective trial (Efficacy of Thromboprophylaxis as an Intervention during Gravity [ETHIG]), 810 pregnant women were assigned to one of three management strategies according to pre-defined risk factors related to history of VTE and thrombophilic profile. Low-risk women (group I), received 50–100 IU dalteparin/kg body weight/day for 14 days postpartum, or earlier when additional risk factors occurred. Women at high (group II) or very high risk (group III) received dalteparin from enrolment until six weeks postpartum (50–100 IU and 100–200 IU/kg/day, respectively). Objectively confirmed, symptomatic VTE occurred in 5/810 women (0.6%; 95% confidence interval [CI], 0.2 to 1.5%) (group I, 0 of 225; II, 3/469; III, 2/116). The rate of serious bleeding was 3.0% (95% CI, 1.9 to 4.4%); 1.1% (95% CI, 0.5 to 2.2%) was possibly dalteparin-related. There was no evidence of heparin-induced thrombocytopenia, one case of osteoporosis, and rates of miscarriage and stillbirth were similar to previous, retrospective studies. Risk-stratified heparin prophylaxis was associated with a low incidence of symptomatic VTE and few clinically important adverse events. Antepartum heparin prophylaxis is, therefore, warranted in pregnant women with idiopathic thrombosis or symptomatic thrombophilia.

Keywords

Venous thromboembolism, pregnancy, risk assessment, low-molecular weight heparin, thromboprophylaxis

Introduction

Venous thromboembolism (VTE) remains an important cause of morbidity and mortality during pregnancy and the puerperium (1). Pregnancy and the early postpartum period carry an approximately five-fold increased risk of thrombosis that is further increased by acquired and inherited risk factors (2). Acquired risk determinants include age (over 35 years), obesity, delivery by caesarean section, and personal or family history of VTE. The risk of recurrence is increased in pregnant women who have a history of VTE (3, 4), and is higher in women with thrombophilia or following idiopathic events (4–8). A higher prevalence of...
combined and homozygous thrombophilic defects has been found in women with VTE during pregnancy compared with age-matched women without previous VTE (9). Data from the RIEPE registry, a database of consecutive patients with objectively confirmed symptomatic acute VTE, indicate that women with thrombophilia are at greatest risk of thrombosis during the first trimester of pregnancy (10). These data suggest that thromboprophylaxis should be started in the first trimester among at-risk women.

Despite recent data suggesting a steady (11) or rising rate (12) of pregnancy-associated deep-vein thrombosis (DVT) over time, the best prevention strategy in pregnant women at additional risk is unknown (13). Guidelines advise risk assessment of all pregnant women, and suggest heparin thromboprophylaxis at a dose and duration determined by the risk of thrombosis (13, 14), but do not offer strong recommendations (Evidence Grade 2C by the Seventh American College of Chest Physicians Conference) (13). This reflects the lack of prospective and comparative clinical trials (4, 14–16), and recent commentaries have highlighted the serious shortcomings of pregnancy-related thrombosis studies and the need for large, high-quality studies that address the management of thromboembolic risks in pregnant and postpartum women (17).

An expectant management strategy of antepartum surveillance, followed by postpartum thromboprophylaxis, has been recommended for women who have experienced a prior VTE as the risk of recurrence seems low (2.4%, 95% confidence interval [CI], 0.2 to 6.5%) (5). However, recent data have shown that the overall recurrence risk may be higher than previously thought (6.2%, 95% CI, 1.6 to 10.9%) (3), suggesting that further risk stratification for thromboprophylaxis may be beneficial to reduce the number of VTE. Postpartum thromboprophylaxis alone may be appropriate for those who have experienced thrombosis in the presence of a transient risk factor, but for women with prior idiopathic VTE, known thrombophilia, or both, the risk appears to be increased. For these women, the need for thromboprophylaxis is less clear, and further data are required. In a previous study, the risk of recurrence in this clinical setting was 5.9% (95% CI, 1.2 to 16.2%) when routine thromboprophylaxis was withheld (5). In a recent retrospective study of women with previous VTE who received no thromboprophylaxis during pregnancy, the overall risk of recurrence was 5.8% during pregnancy, and 8.3% during the puerperium (18). The risk was greatest among women with previous pregnancy-associated VTE. Cost-analysis has suggested that thromboprophylaxis for these women may be appropriate because of an acceptable cost-effectiveness ratio (19). In view of these considerations, we undertook a prospective study to evaluate a strategy of risk assessment and heparin prophylaxis for pregnant women at increased risk of VTE due to history of VTE and thrombophilia status. This study has a non-randomised design in view of the goals of the study and because we believe that it would be unethical to withhold thromboprophylaxis from pregnant women identified to be at high risk of VTE.

Materials and methods

Patients

Between March 1999 and December 2002, 810 pregnant women were enrolled at 55 centres in Germany (see Appendix) in the Efficacy of Thromboprophylaxis as an Intervention during Gravidity (ETHIG) study. Patients were already attending the investigators’ clinic or were recruited after referral by another physician. Pregnant women at increased risk of VTE because of their thrombophilic profile and history of VTE were eligible, as were pregnant women with acute VTE. In cases of multiple pregnancies during the study, only the first was considered. Exclusion criteria included: history of heparin-induced thrombocytopenia (HIT); allergy to dalteparin sodium or standard heparin; increased bleeding tendency including hemorrhagic diatheses, severe hepatic, renal or pancreatic diseases or severe thrombocytopenia; disorders suggestive of a vascular lesion, including gastric or intestinal ulcer, hypertension, hemorrhagic stroke, cerebral artery aneurysm, retinopathy, vitreous hemorrhage, and endocarditis.

The protocol was approved by all local ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice. Written informed consent was obtained from all patients.

Study design

Patients were assigned to one of three treatment groups (I, II and III) according to individual risk (Table 1) at the time of presentation. Criteria used to assess the level of risk are shown in Table 1. Known thrombophilic defects were recorded, and thrombophilia testing was requested for all patients (factor V Leiden mutation; prothrombin G20210A mutation; protein C; protein S measurement [no earlier than 6 weeks after discontinuation of oral contraceptives or 6 weeks after delivery]; antithrombin; antiphospholipid antibodies; lupus anticoagulant). Antiphospholipid syndrome was diagnosed according to defined criteria (20). Details of prior events (pulmonary embolism [PE], proximal or distal DVT, cerebral arterial ischemia, cerebral sinus venous thrombosis, thrombophlebitis), family history and previous thromboprophylaxis were recorded.

Patients received dalteparin sodium (Fragmin®, Pfizer GmbH, Karlsruhe, Germany) as once- or twice-daily subcutaneous injections in single-dose, pre-filled syringes (2,500, 5,000 or 7,500 IU) or single-dose vial (10,000 IU) according to body weight, measured at baseline and at monthly clinic visits.

Group I patients at low risk included women with prior secondary VTE, women with asymptomatic thrombophilia, including factor V Leiden, prothrombin G20210A, protein C or protein S deficiency, excluding antithrombin deficiency, and asymptomatic women with more than one current risk factor for thrombosis at enrolment (including obesity, age above 35 years, family history of VTE, varicosis or nicotine abuse) (Table 1). Patients in group I were monitored and received 50–100 IU dalteparin/kg body weight/day for 14 days postpartum, or earlier if additional risk factors occurred (immobilisation, surgery, hyperemesis/dehydration, thrombophlebitis).

Group II (high risk) and III (very high risk) patients received weight-adjusted dalteparin (50–100 IU and 100–150 IU/kg/day,
Table 1: Venous thromboembolic risk categorization and treatment strategy.

<table>
<thead>
<tr>
<th>Risk group and criteria for risk stratification</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I – Low-risk patients</strong></td>
<td></td>
</tr>
<tr>
<td>– Thrombophilia without prior VTE</td>
<td></td>
</tr>
<tr>
<td>– Prior secondary VTE (not associated with thrombophilia, pregnancy, oral contraception)</td>
<td></td>
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<tr>
<td>– Women with ≥2 risk factors</td>
<td></td>
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<tr>
<td>– Asymptomatic women with antiphospholipid antibodies</td>
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<tr>
<td><strong>Group II – High-risk patients</strong></td>
<td></td>
</tr>
<tr>
<td>– Prior VTE and thrombophilia</td>
<td></td>
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<tr>
<td>– Prior idiopathic VTE</td>
<td></td>
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<tr>
<td>– Prior VTE during pregnancy or oral contraception</td>
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<tr>
<td>– Recurrent secondary VTE</td>
<td></td>
</tr>
<tr>
<td>– Antithrombin deficiency type I and II (excluding type II heparin binding site) without prior VTE</td>
<td></td>
</tr>
<tr>
<td>– History of ≥2 pregnancy losses with antiphospholipid syndrome†</td>
<td></td>
</tr>
<tr>
<td><strong>Group III – Very high-risk patients</strong></td>
<td></td>
</tr>
<tr>
<td>– Antithrombin deficiency and prior VTE</td>
<td></td>
</tr>
<tr>
<td>– Antiphospholipid syndrome and prior venous or arterial thromboembolism†</td>
<td></td>
</tr>
<tr>
<td>– Women on long-term OAC</td>
<td></td>
</tr>
<tr>
<td>– Acute VTE in current pregnancy after day 11</td>
<td></td>
</tr>
<tr>
<td>– Dalteparin 50 – 100 IU/kg /day postpartum for 2 weeks; antenatal in the presence of additional risk factors</td>
<td></td>
</tr>
<tr>
<td>– Clinical surveillance and non-pharmacological thromboprophylaxis</td>
<td></td>
</tr>
</tbody>
</table>

1OAC = oral anticoagulant therapy. † In certain cases, (patients with acute VTE or mechanical heart valves) a dose of 200 IU/day was allowed. † Additional administration of aspirin, 100 mg in weeks 12–36 of pregnancy.

respectively), initiated at risk categorisation and continued until six weeks postpartum (Fig. 1). In certain cases (patients with acute VTE, mechanical heart valves), a dose of 200 IU/kg/day was allowed. Dose-adjustments were made using a dalteparin dosing schedule: for groups I and II, patients weighing <50 kg received 2,500 IU/day; 50–75 kg: 5,000 IU/day; 75–100 kg: 7,500 IU/day; >100 kg: 10,000 IU/day; for group III, patients weighing <50 kg received 5,000 – 7,500 IU/day; 50–75 kg: 7,500 – 10,000 IU/day; 75–100 kg: 10,000 – 15,000 IU/day. In group III, optional monitoring of anti-Xa activity was suggested, with a target range of 0.5 to 1.0 IU/ml (twice-daily dosing) and up to 1.5 IU/ml (once-daily dosing), 3–4 hours (h) after dosing. In women with a history of two or more pregnancy losses and antiphospholipid syndrome, concomitant aspirin (100 mg daily) between weeks 12–36 of pregnancy was recommended. Peripartum discontinuation of the dalteparin regimen was recommended, with a low dose of intravenous unfractionated heparin (e.g. 150–250 IU/kg body weight/24 h) or subcutaneous dalteparin (e.g. 2,500 IU twice daily). The prepartum regimen was re-started after three days, not earlier than 12 h postpartum, with dose adjustment for body weight, if necessary.

Assessments

The primary efficacy outcome was the incidence of symptomatic VTE, defined as DVT (proximal or distal), objectively confirmed by ultrasonography, or pulmonary embolism (PE), diagnosed by computed tomography (CT) scan or ventilation-perfusion scintigraphy. All outcomes were validated by an independent central Data Safety Monitoring Board.

The primary safety outcome was bleeding. Clinically relevant bleeding events were defined as any bleeding event that necessitated a dose reduction or an intervention. Clinically relevant bleeding that was fatal, life-threatening or warranted hospitalisation, transfusion or treatment cessation was classified as serious. All other bleeding events were classified as minor. Bleeding events were categorized by the investigators; clinically relevant bleeding events were assessed by the Data Safety Monitoring Board and were judged to be related or unrelated to dalteparin by assessment of the clinical circumstances.

Other adverse events were defined as serious if fatal, life-threatening, requiring unscheduled hospitalization, resulting in persistent or significant disability or incapacity, resulting in cancer, congenital abnormality, or were an important medical event. Thrombocytopenia was defined as >50% fall in platelet count. A diagnosis of HIT was based on testing for heparin-platlet factor 4 antibodies or by functional platelet aggregation tests. Osteoporosis was defined as the occurrence of symptoms of osteoporosis or of osteoporotic fractures.

Fetal and neonatal safety was described according to the incidences of miscarriage, intra-uterine fetal death, premature delivery, congenital abnormalities and birth of infants small for gestational age (birth weight below the tenth percentile for gestational age).

Statistical analysis

At study initiation, reported recurrence rates in pregnant women with prior VTE varied considerably (21). Excluding patients at very high risk of recurrence, such as in symptomatic antithrombin deficiency, a 5% rate of recurrence was expected without prophylaxis. In women with heparin prophylaxis we anticipated a recurrence rate below 2% (22). An exact binomial test with a nominal 0.05 two-sided significance level and 90% power to de-
tect the difference between the Null hypothesis proportion, $\pi_0$, of 0.02 and the Alternative proportion, $\pi_A$, of 0.05 would require a sample size of 400. Assuming that patients at high risk (group II) would represent 50% of the overall study population, a total of 800 patients was targeted. Data are expressed as means ± standard deviation, unless otherwise stated, and 95% CI were calculated for each point estimate of clinical events.

Results

Study patients and treatment
A total of 810 pregnant women were assigned to one of three treatment strategies according to risk: 225 (27.8%) to group I, 469 (57.9%) to group II and 116 (14.3%) to group III (Fig. 1). These patients comprised the population for the efficacy and safety analysis. Four patients withdrew consent, two switched to an alternative heparin, and one stopped treatment following an erroneous diagnosis of thrombocytopenia. Nineteen patients were lost to follow-up. Delivery information was unavailable for 26 women. The majority of women had a spontaneous vaginal delivery (61.0%), with 34.4% undergoing Caesarean section, and 4.6% having instrumental delivery. At enrolment, acute VTE was found in 66 (8.2%) women. In 56 (6.9%) women, long-term treatment with vitamin-K antagonist was replaced by dalteparin.

Patients’ demographic characteristics were similar, but there were between-group differences in risk factors (Table 2). There was no difference in mean age, weight or body mass index (BMI) between groups. The most common risk factors were inherited
thrombophilia (75.4%), previous history (60.1%), and family history (31.4%). Previous history was more prevalent in groups III (89.7%) and II (72.3%) than in group I (19.6%; p<0.0001). Incidences of thrombophilic defects were similar in each treatment group, but severe forms were more common in group III (p<0.0001). Protein S deficiency was found in 133 of 586 (22.7%), but a hormonal influence could not be discounted in some cases.

In all, 290 (35.8%) of 810 women had previously suffered 516 instances of pregnancy loss; 73% were early miscarriages, 15% late miscarriages and 12% were still births, respectively, with no difference between the treatment groups (Table 2).

Dalteparin was initiated prior to conception in 1.7% of patients, in 93.2% during pregnancy and in 5.0% postpartum. Median treatment initiation was at 17.0 weeks (range 4–41), at 24.0 weeks (range 4–41) in group I, 14.5 weeks (range 4–41), in group II and 16.0 weeks (range 4–38) for group III. In group I, dalteparin was initiated at first presentation in 74.2% due to the presence of risk factors, and in 11.1% during pregnancy. In groups II and III, dalteparin was given ante- and postpartum in all but six cases (study entry was postpartum). Mean daily dose was 66.2 ± 22.5 IU/kg (group I), 76.8 ± 24.1 IU/kg (group II) and 120.0 ± 49.1 IU/kg (group III). In total, 68.9% of group I and II received dalteparin 5,000 IU once daily, and 39.7% of group III received 5,000 IU twice daily. The majority of group III (85.3%) received a daily dalteparin dose of between 5,000 and 10,000 IU.

Treatment compliance, as judged by the investigators, was high or very high in 89.7% of cases.

### Table 2: Baseline characteristics and risk factors of the inception cohort.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 225)</th>
<th>Group II (n = 469)</th>
<th>Group III (n = 116)</th>
<th>Total (n = 810)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>30.9 ± 5.4</td>
<td>30.8 ± 5.4</td>
<td>30.8 ± 5.3</td>
<td>30.8 ± 5.4</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>75.0 ± 15.8</td>
<td>73.1 ± 16.7</td>
<td>73.2 ± 14.0</td>
<td>73.6 ± 16.1</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>167.9 ± 6.5</td>
<td>167.8 ± 6.6</td>
<td>167.9 ± 6.5</td>
<td>167.9 ± 6.5</td>
</tr>
<tr>
<td><strong>Body-mass index (kg/m²)</strong></td>
<td>26.6 ± 5.6</td>
<td>25.9 ± 5.6</td>
<td>26.0 ± 4.7</td>
<td>26.1 ± 5.4</td>
</tr>
<tr>
<td><strong>Inherited risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inherited thrombophilia (≥2)</td>
<td>17/225 (7.6)</td>
<td>47/469 (10.0)</td>
<td>7/116 (6.0)</td>
<td>71/810 (8.8)</td>
</tr>
<tr>
<td>Combined (≥2) thrombophilia</td>
<td>73/225 (32.4)</td>
<td>151/469 (32.2)</td>
<td>30/116 (25.9)</td>
<td>254/810 (31.4)</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or number (%). *Group I vs. group II, p=0.0001 (Fisher’s exact test). † Group I vs. group III, p=0.0001. ‡ Group II vs. group III, p=0.01. § Group I vs. group II, p=0.04. ¶ Group I vs. group III, p=0.04. ** Group I vs. group II, p=0.04.
### Primary outcomes
Symptomatic VTE occurred in five women (0.6%; 95% CI 0.2 to 1.5%; Table 3). There were no events in group I; three women in group II suffered an event (2 antepartum, 1 postpartum) and two in group III (both postpartum). The two antepartum DVT in group II occurred three and six days after enrolment, respectively, in women with initially suspected, but unconfirmed DVT at inclusion. As the DVT were confirmed a few days later, they had to be regarded as primary outcome events. There were one distal and three proximal cases of DVT and one PE. Four of the five cases had a thrombophilic abnormality, four women had suffered a previous event, and antiphospholipid syndrome had been diagnosed in both positive cases in the very high-risk group.

### Bleeding and adverse events
Bleeding was classified as serious in 24 episodes (3.0% 95% CI: 1.9 to 4.4%) in 22 women (2.7% 95% CI: 1.8 to 4.2%) (Table 4), and no cases of fatal bleeding occurred. Altogether 102 women

### Table 3: Symptomatic venous thromboembolic events.

<table>
<thead>
<tr>
<th>Group</th>
<th>Event (n)</th>
<th>Type of event</th>
<th>Risk factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>Calf vein DVT*†</td>
<td>Factor V Leiden mutation; previous DVT</td>
<td>Marked weight gain following enrolment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Femoral vein DVT‡</td>
<td>Obesity; previous DVT; smoking</td>
<td>Suspected DVT at inclusion; DVT after emergency caesarean 3 days after inclusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iliac vein DVT#†</td>
<td>Antithrombin deficiency; protein S deficiency</td>
<td>Suspected DVT at inclusion; confirmed 6 days after inclusion</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>Femoral vein DVT*†</td>
<td>APLS; previous PE on oral contraceptive; previous upper extremity DVT during pregnancy; history of miscarriage</td>
<td>DVT 7 days after normal delivery; no aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PE ‡§</td>
<td>APLS; previous PE following miscarriage</td>
<td>PE following caesarean; HELLP syndrome; no aspirin</td>
</tr>
</tbody>
</table>

*confirmed by ultrasonography. † antenatal event. ‡ post-partum event. † confirmed by CT scan. DVT denotes deep vein thrombosis, PE denotes pulmonary embolism, and APLS denotes antiphospholipid syndrome.

### Table 4: Maternal, clinically relevant bleeding events during study period.

<table>
<thead>
<tr>
<th>Clinically relevant bleeding events* n (%; 95% CI)</th>
<th>Serious bleeding events n (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum period</td>
<td>Related to treatment</td>
</tr>
<tr>
<td>Vaginal</td>
<td>10 (1.2; 0.6–2.3)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td>Peri-/postpartum</td>
<td>31 (3.8; 2.6–5.4)</td>
</tr>
<tr>
<td>Placental</td>
<td>12 (1.1; 0.5–2.2)</td>
</tr>
<tr>
<td>Uterine</td>
<td>3 (1.1; 0.5–2.2)</td>
</tr>
<tr>
<td>Laceration</td>
<td>5</td>
</tr>
<tr>
<td>Associated with caesarean section</td>
<td>4 (1.1; 0.5–2.2)</td>
</tr>
<tr>
<td>Uterine atony</td>
<td>6 (1.1; 0.5–2.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
<tr>
<td>Total – n (%; 95% CI)</td>
<td>41 (5.1; 3.7–6.9)</td>
</tr>
</tbody>
</table>

*Clinically relevant bleeding events include serious events.
(12.6%; 95% CI: 10.4 to 15.1%) suffered 126 episodes of bleeding, of which 41 episodes in 37 women (4.6%; 95% CI: 3.3 to 6.3%) were regarded as clinically relevant and 32 occurred postpartum (Table 4). Nine cases (1.1%; 95% CI: 0.5 to 2.2%), were judged to have a possible causal relationship with dalteparin. No correlation was observed between clinically relevant bleeding events and the available anti-factor Xa levels. Minor bleeding events (n=85) included injection site haematoma, gum bleeding, epistaxis, minor vaginal bleeding, sub-conjunctival haemorrhages and scleral haematoma.

Thrombocytopenia occurred in 18 women (2.2%; 95% CI: 1.4 to 3.6%), with no cases with clinical or laboratory features of HIT. Thirteen cases were associated with HELLP syndrome (haemolytic anaemia [HE], elevated liver enzymes [EL] and low platelet count [LP]), one case with sepsis, and one patient had systemic lupus erythematosus. Two women experienced a fall in platelet count during the peripartum period, but dalteparin was continued uneventfully. One splenectomised thrombocytopenic patient with falling platelet count was negative for heparin-platelet factor 4 antibodies, and dalteparin was restarted uneventfully. There was one case of osteoporosis (0.1%; 95% CI: 0.01 to 0.8%). In total, 335 (41.4%; 95% CI: 38.0 to 44.8%) patients experienced any adverse event (including study safety and efficacy endpoints) that included infections, gastrointestinal symptoms, neurological symptoms, and injection site reactions.

**Pregnancy outcome**

Overall, 784 pregnancies and 809 foetuses were included in the analysis of pregnancy outcome. There were 740 (94.4%) successful pregnancies resulting in 762 living neonates; 40 foetuses (4.9%; 95% CI: 3.6 to 6.7%) were lost due to miscarriage, seven due to elective termination. There were 125 premature births (15.9%; 95% CI: 13.5 to 18.7%) with similar rates in each treatment group. Twenty neonates (2.5%; 95% CI: 1.5 to 3.9%) were born with a physical malformation, and 11.2% (9.1 to 13.7%) were small for gestational age.

**Discussion**

This large, prospective study shows that using a risk-stratified prophylaxis strategy for pregnant women at increased risk of VTE resulted in low levels of symptomatic events. VTE occurred only in those patients at high or very high risk of thrombosis. The rate of VTE was similar to the overall findings of a systematic meta-analysis of mostly retrospective studies that employed low-molecular-weight heparin for the prevention and treatment of thrombosis (recurrence rate of 0.86%, 95% CI, 0.55 to 1.28%) (23). The proportion of women in our study who suffered clinically relevant bleeding was low (4.6%), and comparable with a previous, retrospective safety analysis of low-molecular-weight heparin thromboprophylaxis in pregnancy (22). These figures have to be viewed in context with the bleeding rate associated with normal pregnancy and delivery. However, prospective data on the frequency of postpartum hemorrhage and bleeding during normal pregnancy are sparse. Current data indicate that primary postpartum hemorrhage occurs in 4–6% of pregnancies (24), with the majority of cases (80%) occurring due to uterine atony (25). The risk of postpartum hemorrhage is particularly high in patients with complications of pregnancy such as pre-eclampsia, where the bleeding risk is increased by over five times (25).

In the very-high-risk group, postpartum VTE was recorded in two women. Both women suffered from antiphospholipid syndrome and had experienced previous pregnancy-related thrombosis. Current guidelines suggest these women should receive antenatal thromboprophylaxis continuing into the postnatal period (13, 14). The low event rate recorded in our study supports that view.

Management of patients in the low-risk group, which includes women with a single previous secondary episode of thrombosis or asymptomatic thrombophilia, has been controversial, with wide variations in risk reported (13). In a previous prospective study of 125 pregnant women with a single previous venous thromboembolic event in whom antenatal thromboprophylaxis was withheld (5), no thrombotic events were recorded in 44 women who had a temporary risk factor but no underlying thrombophilia. Similarly, in a subsequent retrospective analysis of 155 pregnancies in women with a history of VTE who did not receive thromboprophylaxis, there was no increase in the risk of recurrence if the first VTE was related to transient risk factors other than pregnancy, puerperium or oral contraceptive use (18). Smoking and obesity (defined as BMI>30) have recently been shown to be risk factors for VTE in pregnancy and the puerperium, and these were included in our criteria for evaluation of thrombotic risk (26).

The expectant management strategy adopted in our study, with prophylaxis provided if additional risk factors were present, followed by postpartum provision was also event free. This suggests the effectiveness of the approach taken and reflects recent modelling data that indicate that such a strategy is more effective and less costly than blanket prophylaxis provision (19). Furthermore, the provision of a short, two-week, period of postpartum thromboprophylaxis was shown to be sufficient in the low-risk group with zero events (95% CI 0.00 – 0.16). As the vast majority of the women in group I had at least one positive test for thrombophilia and/or a prior secondary venous thromboembolic event, the attending physicians initiated thromboprophylaxis according to protocol, as soon as these women presented additional risk factors. This accounts for the fact that most women in this group (85.3%) received thromboprophylaxis in the antepartum period.

In high-risk patients assigned to group II, which included women with idiopathic thrombosis or underlying thrombophilia, no randomized studies have yet been performed to specifically address the value of antepartum thromboprophylaxis. In our study, three cases of VTE were recorded in 469 women, with two events occurring in women with suspected, but unconfirmed, VTE on enrolment. This event rate is markedly lower than in previous studies in which no heparin prophylaxis was given (4, 5, 18). Our findings suggest that individualized risk assessment for this at-risk group reduces the risk of recurrent events, and are in line with the results of a recent cost-analysis (19) that was modeled on data described by Brill-Edwards (5). That analysis suggested that, for women at high risk of VTE, the benefits of antepartum prophylaxis outweigh the risks. In sensitivity analyses, thromboprophylaxis remained effective even if the true probabil-
ity of recurrent VTE was 1.8%. In summary, these findings confirm that high-risk pregnant women do benefit from routine, individualized risk assessment for antenatal heparin prophylaxis.

A major strength of our study is the relatively large number of patients prospectively enrolled, including 66 women with acute VTE. A recent retrospective population-based study identified 105 cases of VTE, but over a 30-year period (11). Other strengths include the independent adjudication of endpoints, in contrast with previous retrospective surveys. Furthermore, our study included an appropriate population of at-risk pregnant women, as shown by the high levels of previous history of thrombosis (60.1%), inherited thrombophilia (75.4%) and previous miscarriage, still birth and physical malformation (35.8%).

This study was non-randomized, but such a design would not have been possible, given the goals of the study and the at-risk patient population enrolled. Randomization ensures that well matched populations are used before attempting to establish the difference between interventions. This study actively set out to include a group of patients at risk of VTE and to assess the use of risk-stratified thromboprophylaxis. A randomized study in which prophylaxis was withheld from certain patients would have been difficult to justify on ethical terms and been difficult to conduct, a view confirmed by recent studies with poor recruitment (27, 28). Moreover, the current practice among German obstetricians of offering thromboprophylaxis precluded the feasibility of a placebo-controlled design. Thus, the design of this study reflects clinical practice, although we acknowledge that a non-randomised design cannot completely avoid the possibility of bias, and therefore our findings should be interpreted with this caveat in mind.

Important safety concerns with pregnant women receiving anticoagulant therapy include bleeding, HIT, osteoporosis and fetal safety. Clinically relevant bleeding was low (4.6% of women; nine events were judged to be related to dalteparin therapy) and comparable with previously reported rates (21). The majority (75%) of clinically relevant bleeding was postpartum hemorrhage, which is a frequent complication of pregnancy itself (29, 30). No cases of HIT were described. There was only one case of osteoporosis recorded; the woman suffered a fracture of the coccygeal bone during delivery. The rate of miscarriage or still birth of 4.9% was similar to the rate of 5.3% found by meta-analysis (23), and the rate of premature birth (15.9%) was lower than in a previous retrospective study (32). The rate of major congenital abnormalities (2.5%) was not different from the general population. These data suggest a satisfactory safety profile for the use of risk stratification and dalteparin therapy in pregnancy.

The regimen and the risk criteria used in this study are similar to those recommended in several reviews by Greer et al. (1, 16, 23) and by the American College of Chest Physicians (ACCP) (13). One difference, however, is that in the present study the initial treatment dose of dalteparin was reduced to an intermediate level from day 11. This regimen was effective in all patients with acute VTE. A similar dosing regimen has been evaluated in a trial of patients with VTE and cancer, a group of patients that also requires long-term thromboprophylaxis due to continuing thrombotic risk (31). This regimen, involving a dose reduction of dalteparin following a period of initial full-dose therapy, is recognised to be effective in preventing recurrence in patients with cancer and VTE (31).

ETHIG trial investigators (all investigators were based in Germany):
In this study, the classification of risk groups into low-, high-
and very high-risk groups is clinically relevant, given the import-
ance of routine thromboprophylaxis in the latter two groups. Our
criteria for distinguishing between low- and high-risk groups are
also consistent with those used in a recent review of the cost-
effectiveness of thromboprophylaxis in pregnant women with a
history of VTE (19).

In conclusion, a management strategy of risk assessment,
followed by heparin prophylaxis at an intensity and duration de-

cided by the level of perceived venous thromboembolic risk, was
an effective and safe means of preventing VTE in pregnant
women. Of particular note is the low event rate in the population
of pregnant women at risk of thrombosis because of prior idi-o-
pathic VTE, a known thrombophilia, or both.

Acknowledgements

We are indebted to Mrs. M. Merklin for her excellent help in the or-

ganisation and the logistics of the study, and valuable contributions in data man-
agement and analysis. For valuable statistical advice, we thank Dr. E. Herr-
mann, Dept. of Mathematics, Technische Universität Darmstadt, and Mrs.

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