Clinical aspects of venous thromboembolism in special patient populations

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Citation for published version (APA):
Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy: rationale and design of the Highlow study, a randomized trial of two doses

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For the Highlow investigators
Abstract

**Background:** Women with a history of venous thromboembolism (VTE) have a 2% to 10% absolute risk of VTE recurrence during subsequent pregnancies. Therefore, current guidelines recommend that all pregnant women with a history of VTE receive pharmacologic thromboprophylaxis. The optimal dose of low-molecular-weight heparin (LMWH) for thromboprophylaxis is unknown. In the Highlow study (NCT 01828697; www.highlowstudy.org), we compare a fixed low dose of LMWH with an intermediate dose of LMWH for the prevention of pregnancy-associated recurrent VTE. We present the rationale and design features of this study.

**Methods:** The Highlow study is an investigator-initiated, multicenter, international, open-label, randomized trial. Pregnant women with a history of VTE and an indication for ante- and postpartum pharmacologic thromboprophylaxis are included before 14 weeks of gestation. The primary efficacy outcome is symptomatic recurrent VTE during pregnancy and 6 weeks postpartum. The primary safety outcomes are clinically relevant bleeding, blood transfusions before 6 weeks postpartum and mortality. Patients are closely monitored to detect cutaneous reactions to LMWH and are followed for 3 months after delivery. A central independent adjudication committee adjudicates all suspected outcome events.

**Conclusion:** The Highlow study is the first large randomized controlled trial in pregnancy that will provide high-quality evidence on the optimal dose of LMWH thromboprophylaxis for the prevention of recurrent VTE in pregnant women with a history of VTE.
Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of short and long term morbidity during pregnancy and postpartum periods. Moreover, PE is one of the leading causes of maternal mortality in developed countries. In the United Kingdom for instance, between 2006 and 2008, 0.79 deaths per 100,000 maternities (95%CI 0.49–1.25) were attributed to VTE (1–3). VTE occurs in 1 to 2 per 1000 pregnancies, and the risk is 5-fold higher in pregnant women compared to non-pregnant women of the same age (2). The antepartum and postpartum incidences of VTE are similar, but given the much longer duration of the antepartum period than the postpartum period, the daily absolute risk of VTE is highest postpartum (4,5). The majority of postpartum VTE occur in the first 6 weeks after delivery, with event rates decreasing sharply thereafter (6,7).

Women with a personal history of VTE have a 2% to 10% absolute risk of developing recurrent VTE during a subsequent pregnancy in the absence of pharmacologic thromboprophylaxis, with an odds ratio of 24.8 (95% CI 17.1 – 36.0) compared to pregnant women without previous VTE (2,8–10). Circumstances under which the first VTE occurred influence the risk of recurrence. In two retrospective studies, women whose first VTE was provoked by the use of oral hormonal contraceptives or was related to pregnancy had a higher risk of recurrent VTE during a subsequent pregnancy compared with women whose first VTE was unprovoked or provoked by a non-hormonal transient risk factor, although these differences did not reach statistical significance (9,10). Similarly, in a large retrospective cohort of women with prior VTE, those who had a history of pregnancy-associated VTE had a higher risk of recurrence during subsequent pregnancies compared to those with prior unprovoked VTE (4.5% versus 2.7% respectively; relative risk 1.7; 95% CI 1.0 – 2.8) (11).

The American College of Chest Physicians (ACCP) guideline recommends that all pregnant women with a history of VTE receive postpartum pharmacologic thromboprophylaxis (12). Low-molecular-weight heparin (LMWH) is the preferred anticoagulant for VTE prophylaxis in pregnant women, as it does not cross the placenta and is therefore safe for the fetus (13). The risk threshold for instituting antepartum thromboprophylaxis is higher than for postpartum thromboprophylaxis. The rational for this is the lower average daily risk of antepartum VTE and the need to self-inject LMWH for several months compared to 6 weeks postpartum. Therefore, in women with a low risk of recurrence (e.g. women with a single prior VTE associated with a major transient risk factor such as surgery, use of a plaster cast or trauma), close antepartum clinical surveillance rather than pharmacologic thromboprophylaxis is recommended. In contrast, women with a moderate or high risk of VTE recurrence (e.g. women with prior hormone/pregnancy-associated VTE or recurrent unprovoked VTE or VTE associ-
ated with a persistent risk factor such as paralysis) should receive thromboprophylaxis during the entire pregnancy (Table 3.1). Antepartum thromboprophylaxis should be commenced as early as possible, as the risk of VTE recurrence is increased from the beginning of pregnancy (14).

**Table 3.1.** Summary of the 9th American College of Chest Physicians (ACCP) recommendations to prevent pregnancy-related venous thromboembolism (VTE) in women with prior VTE (12).

<table>
<thead>
<tr>
<th>Antepartum and postpartum prophylaxis</th>
<th>Postpartum prophylaxis during 6 weeks</th>
<th>No pharmacological prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with a single unprovoked episode of VTE</td>
<td>Women with a history of a single episode of VTE related to a major nonhormonal transient risk factor³</td>
<td>General pregnant population</td>
</tr>
<tr>
<td>Women with a single episode of VTE provoked by use of hormonal contraceptives, pregnancy or the postpartum period</td>
<td>Women with a history of a single episode of VTE related to a major nonhormonal transient risk factor³</td>
<td>General pregnant population</td>
</tr>
<tr>
<td>Women with a single episode of VTE provoked by a minor nonhormonal transient risk factor³</td>
<td>Women with a history of multiple unprovoked episodes of VTE</td>
<td>General pregnant population</td>
</tr>
<tr>
<td>Women with a history of VTE and a persistent risk factor</td>
<td></td>
<td>General pregnant population</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; £ Long distance travel or minor trauma; # Surgery, major trauma or plaster cast immobilization in the 3 months prior to VTE.

The optimal LMWH dose for pharmacologic thromboprophylaxis of pregnancy-associated recurrent VTE is unknown, as no randomized controlled trials (RCTs) have been performed. Therefore the ACCP guideline suggests the use of either a prophylactic or intermediate (half therapeutic) dose of LMWH in this setting, without a preference for one dose over the other (12). Many centers prescribe a prophylactic dose. However, numerous treatment failures have been reported in retrospective studies and in the TIPPS trial, with an estimated recurrence risk of 5 to 8% using this strategy (9,10,15–18). Of note, compliance was not assessed in these studies and the results are inconsistent with those from another study (19). It has been postulated that an intermediate dose of LMWH could have superior efficacy compared to a prophylactic dose of LMWH, but potentially at the cost of a higher bleeding risk. Reassuringly, in a retrospective study in pregnant women receiving therapeutic doses of LMWH, there was no increased risk of clinically relevant or severe postpartum bleeding compared with women who had delivered in the same hospital without LMWH use (20). In another study, women receiving therapeutic LMWH during pregnancy were found to have an increased risk of
blood loss > 500mL and < 1000mL after vaginal delivery (21). The use of therapeutic-intensity LMWH for pharmacologic thromboprophylaxis during pregnancy is not widely accepted in view of the anticipated elevated bleeding risk in the peripartum period and because this strategy may preclude neuraxial anesthesia.

There is an urgent need for evidence regarding the optimal strategy in pregnant women who require pharmacologic thromboprophylaxis. To investigate the optimal LMWH dose for prevention of recurrent VTE in pregnant patients with a history of VTE, we are currently conducting the Highlow study (NCT 01828697). The results of this RCT are very likely to impact current clinical practice and modify consensus guidelines. We summarize herein the design of this study, and discuss the rationale for some of the unique study design features.

**Study objective and hypothesis**

We aim to compare a fixed low dose of LMWH with an intermediate dose of LMWH in the prevention of recurrent VTE in pregnant women with a history of VTE and an indication for ante- and postpartum thromboprophylaxis. We hypothesize that an intermediate dose is superior to a fixed low dose of LMWH in preventing recurrent VTE, with a comparable safety profile in terms of clinically relevant bleeding complications.

**Study design**

**Overview of study organization**

The Highlow study is an investigator-initiated, multicenter, international, randomized, open-label, superiority study for efficacy. Patients receive either a fixed low dose or an intermediate dose of LMWH during pregnancy and 6 weeks after delivery.

The protocol was reviewed and approved by the regulatory authority of the Netherlands and the ethics committee of the Academic Medical Center in Amsterdam. In each participating country, the protocol is or has been subsequently reviewed by the local regulatory authority and for each participating center by the local institutional review board or ethics committee. Informed consent is obtained from eligible patients prior to randomization. A central independent adjudication committee (CIAC) whose members are unaware of the treatment allocation will adjudicate all suspected episodes of recurrent VTE, major bleeding events, clinically relevant non-major bleeding events, cases of suspected type 1 allergy to LMWH injections, cases of suspected heparin-induced thrombocytopenia (HIT), and deaths. An independent data monitoring committee (DMC) monitors patient safety and outcomes at regular intervals during the study, and makes recommendations to the coordinating investigators. Monitoring is performed via an interdepartmental monitoring system.
Chapter 3

**Patient population and eligibility**

Pregnant women of 18 years or older with a history of VTE and an indication for ante- and postpartum thromboprophylaxis (Table 3.1) are eligible for the study. The inclusion- and exclusion criteria are listed in Table 3.2. Patients enter the study as soon as a home test confirms pregnancy, up to 14 weeks after the last menstrual period. Women previously enrolled in the Highlow study are allowed to participate during subsequent pregnancies, if the 6 weeks of postpartum thromboprophylaxis have been completed (after a full-term pregnancy, miscarriage, active termination or stillbirth).

**Table 3.2. Inclusion- and exclusion criteria of the Highlow study.**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥ 18 years</td>
</tr>
<tr>
<td>• Pregnancy confirmed by urinary pregnancy test, blood test or ultrasound examination</td>
</tr>
<tr>
<td>• Gestational age &lt; 14 weeks since the first day of the last menstrual period</td>
</tr>
<tr>
<td>• Previous objectively confirmed VTE*, either:</td>
</tr>
<tr>
<td>- Unprovoked, or</td>
</tr>
<tr>
<td>- In the presence of oral contraceptive or estrogen/progestogen use, or</td>
</tr>
<tr>
<td>- Related to pregnancy or the postpartum period, or</td>
</tr>
<tr>
<td>- In the presence of a minor provoking risk factor£</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Previous VTE related to a major provoking risk factor* as the sole risk factor</td>
</tr>
<tr>
<td>• Indication for treatment with a therapeutic dose of anticoagulant therapy (e.g. acute VTE, atrial fibrillation, a mechanical heart valve, recurrent VTE for which an indefinite duration of anticoagulant therapy is used prior to pregnancy)</td>
</tr>
<tr>
<td>• Inability to provide informed consent</td>
</tr>
<tr>
<td>• Any contraindication listed in the local labeling of LMWH</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; LMWH: low-molecular-weight heparin; £ Long distance travel or minor trauma; # Surgery, major trauma or plaster cast immobilization in the 3 months prior to VTE *Patient with a history of extensive superficial thrombophlebitis that was treated as deep vein thrombosis (i.e. if it was close to the deep venous system), are also eligible

**Stratification and randomization**

Once the patient has signed the informed consent form, the investigator provides information to a secure web-based randomization program (ALEA version 2.2), which randomly assigns the patient to either the fixed low dose or intermediate dose of LMWH. Randomly permuted blocks with maximum block size of 6 are applied, stratifying for center.

**LMWH regimen**

LMWH is injected subcutaneously once daily. Nadroparin is the preferred type of LMWH, but different types of LMWH are allowed in the study to reflect heterogeneity in
Low-molecular-weight heparin to prevent recurrent venous thromboembolism in pregnancy

current clinical practice. Table 3.3A depicts the dosing schemes for all available types of LMWH. The fixed low dose regimen is based on weight at randomization and will not be changed throughout pregnancy or the 6 weeks postpartum. In the intermediate dose regimen, the patient’s weight will be monitored at every follow-up visit and if necessary the dose will be changed accordingly.

Table 3.3.

A. Dosing schemes for all LMWH types in the Highlow study.

<table>
<thead>
<tr>
<th>Weight</th>
<th>nadroparin</th>
<th>enoxaparin</th>
<th>dalteparin</th>
<th>tinzaparin</th>
<th>Weight</th>
<th>nadroparin</th>
<th>enoxaparin</th>
<th>dalteparin</th>
<th>tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>In kg</td>
<td>In lbs</td>
<td>In kg</td>
<td>In lbs</td>
<td>In kg</td>
<td>In lbs</td>
<td>In kg</td>
<td>In lbs</td>
<td>In kg</td>
<td>In lbs</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 220</td>
<td>2,850 IU</td>
<td>4,000 IU</td>
<td>5,000 IU</td>
<td>&lt; 50</td>
<td>3,800 IU</td>
<td>6,000 IU</td>
<td>7,500 IU</td>
<td>4,500 IU</td>
</tr>
<tr>
<td>50 to</td>
<td>70 to</td>
<td>70 to</td>
<td>70 to</td>
<td>70 to</td>
<td>&lt; 110</td>
<td>5,700 IU</td>
<td>8,000 IU</td>
<td>10,000 IU</td>
<td>7,000 IU</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>&lt; 154</td>
<td>&lt; 110</td>
<td>&lt; 154</td>
<td>&lt; 110</td>
<td>&lt; 110</td>
<td>3,800 IU</td>
<td>6,000 IU</td>
<td>7,500 IU</td>
<td>4,500 IU</td>
</tr>
<tr>
<td>≥ 100</td>
<td>≥ 220</td>
<td>3,800 IU</td>
<td>6,000 IU</td>
<td>7,500 IU</td>
<td>4,500 IU</td>
<td>7,500 IU</td>
<td>10,000 IU</td>
<td>12,500 IU</td>
<td>10,000 IU</td>
</tr>
<tr>
<td>70 to</td>
<td>100 to</td>
<td>70 to</td>
<td>70 to</td>
<td>70 to</td>
<td>154 to</td>
<td>7,600 IU</td>
<td>10,000 IU</td>
<td>12,500 IU</td>
<td>10,000 IU</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>&lt; 220</td>
<td>3,800 IU</td>
<td>6,000 IU</td>
<td>7,500 IU</td>
<td>4,500 IU</td>
<td>7,500 IU</td>
<td>10,000 IU</td>
<td>12,500 IU</td>
<td>10,000 IU</td>
</tr>
<tr>
<td>≥ 100</td>
<td>≥ 220</td>
<td>3,800 IU</td>
<td>6,000 IU</td>
<td>7,500 IU</td>
<td>4,500 IU</td>
<td>9,500 IU</td>
<td>12,000 IU</td>
<td>15,000 IU</td>
<td>12,000 IU</td>
</tr>
</tbody>
</table>

All doses are administered once daily.
LMWH: low-molecular-weight heparin; kg: kilograms; lbs: pounds; IU: International Units; mg: milligrams.

B. Ratios of the intermediate dosages and the fixed low dosages

<table>
<thead>
<tr>
<th>Low dose group</th>
<th>nadroparin</th>
<th>enoxaparin</th>
<th>dalteparin</th>
<th>tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 kg / &lt; 220 lbs</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate dose group</th>
<th>nadroparin</th>
<th>enoxaparin</th>
<th>dalteparin</th>
<th>tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg / &lt; 110 lbs</td>
<td>x 1.3</td>
<td>x 1.5</td>
<td>x 1.5</td>
<td>x 1.3</td>
</tr>
<tr>
<td>50 to 70 kg / 110 to &lt; 154 lbs</td>
<td>x 2</td>
<td>x 2</td>
<td>x 2</td>
<td>x 2</td>
</tr>
<tr>
<td>70 to &lt; 100 kg / 154 to &lt; 220 lbs</td>
<td>x 2.7</td>
<td>x 2.5</td>
<td>x 2.5</td>
<td>x 2.9</td>
</tr>
<tr>
<td>≥ 100 kg / ≥ 220 lbs</td>
<td>x 3.3</td>
<td>x 3</td>
<td>x 3</td>
<td>x 4.3</td>
</tr>
</tbody>
</table>

Ref = reference category

C. Ratios of the low dosages for obese patients

<table>
<thead>
<tr>
<th>Low dose group</th>
<th>nadroparin</th>
<th>enoxaparin</th>
<th>dalteparin</th>
<th>tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 kg / 220 lbs</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
</tbody>
</table>

| ≥ 100 kg / ≥ 220 lbs | x 1.3 | x 1.5 | x 1.5 | x 1.3 |

Ref = reference category
Prior to delivery, women are instructed to stop LMWH when contractions start or when membranes rupture. If delivery is planned, the last dose of LMWH is given at least 24 hours prior to delivery. In the fixed low dose group, neuraxial anesthesia is allowed if the interval after the last LMWH dose is more than 12 hours. In the intermediate dose group, an interval of 24 hours between the last injection and neuraxial anesthesia is required. LMWH is restarted 12 to 24 hours after delivery at the discretion of the obstetrician.

The use of LMWH is open-label, and the medication is prescribed by the treating physician and supplied by pharmacies in the standard setting of patient care or in accordance with national regulatory requirements.

**Efficacy outcome variables**

The primary efficacy outcome is symptomatic confirmed recurrent VTE, defined as the composite of recurrent DVT and PE during pregnancy and 6 weeks postpartum (Table 3.4). The secondary efficacy outcomes are 1) symptomatic confirmed recurrent VTE, defined as the composite of recurrent DVT and PE up to 3 months postpartum and 2) symptomatic confirmed superficial thrombophlebitis up to 3 months postpartum.

**Table 3.4. Diagnostic criteria of confirmed symptomatic recurrent venous thromboembolism or superficial thrombophlebitis.**

<table>
<thead>
<tr>
<th>• Suspected (recurrent) DVT or superficial thrombophlebitis with one of the following findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>If there were no previous DVT investigations:</em></td>
</tr>
<tr>
<td>- Abnormal CUS</td>
</tr>
<tr>
<td>- An intraluminal filling defect on venography</td>
</tr>
<tr>
<td><em>If there was a previous DVT investigation:</em></td>
</tr>
<tr>
<td>- Abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression,</td>
</tr>
<tr>
<td>- An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• Suspected PE with one of the following findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A (new) intraluminal filling defect in subsegmental or more proximal branches on spiral CT scan</td>
</tr>
<tr>
<td>- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram</td>
</tr>
<tr>
<td>- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on VPLS</td>
</tr>
<tr>
<td>- Inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography</td>
</tr>
<tr>
<td>• Fatal PE is:</td>
</tr>
<tr>
<td>- PE based on objective diagnostic testing, autopsy, or</td>
</tr>
<tr>
<td>- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death)</td>
</tr>
</tbody>
</table>

DVT: deep vein thrombosis; CUS: compression ultrasonography; PE: pulmonary embolism; CT: computed tomography; VPLS: ventilation/perfusion lung scan
Safety outcomes

The primary safety outcomes are major bleeding, the composite of major bleeding and clinically relevant non-major bleeding, early postpartum hemorrhage (within 24 hours postpartum), late postpartum hemorrhage (within 6 weeks postpartum), blood transfusion within 24 hours postpartum, blood transfusion within 6 weeks postpartum, and mortality. The definitions of major bleeding and clinically relevant non-major bleeding are based on the criteria of the International Society of Thrombosis and Hemostasis (22) and are provided in Table 3.5. The CIAC will adjudicate major bleeding, clinically relevant non-major bleeding, and postpartum hemorrhage (defined as more than 500mL).

The secondary safety outcomes are minor bleeding, bruises, mild skin complications (e.g. itching, swelling, pain), severe skin complications (e.g. local erythema, edema, vesicles or bullae), type 1 allergic reactions to LMWH, the medical necessity to switch to another LMWH type, confirmed HIT and congenital anomalies or birth defects. The CIAC will adjudicate type 1 allergic reactions to LMWH and HIT.

**Table 3.5.** Definitions of major bleeding, clinically relevant non-major bleeding and postpartum hemorrhage in the Highlow study (34).

<table>
<thead>
<tr>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is defined as overt bleeding and</td>
</tr>
<tr>
<td>• Associated with a fall in hemoglobin of 2g/dL or more, or</td>
</tr>
<tr>
<td>• Leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or</td>
</tr>
<tr>
<td>• Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or</td>
</tr>
<tr>
<td>• Contributing to death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinically relevant non-major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, discomfort such as pain or impairment of activities of daily life</td>
</tr>
<tr>
<td>• Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract, or</td>
</tr>
<tr>
<td>• Macroscopic gastro-intestinal hemorrhage: at least one episode of melena/hematemesis, if clinically apparent, or</td>
</tr>
<tr>
<td>• Rectal blood loss, if more than a few spots, or</td>
</tr>
<tr>
<td>• Vaginal blood loss, if more than a few spots, or</td>
</tr>
<tr>
<td>• Hemoptysis, if more than a few speckles in the sputum, or</td>
</tr>
<tr>
<td>• Intramuscular hematoma, or</td>
</tr>
<tr>
<td>• Subcutaneous hematoma if the size is larger than 25 cm², or larger than 100cm² if provoked, or</td>
</tr>
<tr>
<td>• Multiple source bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postpartum hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss of more than 500 mL within 24 hours of delivery*</td>
</tr>
</tbody>
</table>

*According to the criteria of the World Health Organization
Chapter 3

Duration of study treatment and follow-up

All patients have specified scheduled contacts; 2 weeks after starting treatment (in the outpatient clinic or by telephone), at 20 weeks of pregnancy (in the outpatient clinic or by telephone), at 30 weeks of pregnancy (in the outpatient clinic or by telephone), 24 hours to 1 week after delivery (in the outpatient clinic or by telephone), 6 weeks after delivery (by telephone) and 3 months after delivery (by telephone). During these contacts efficacy and safety of LMWH will be evaluated. In parallel, patients are followed at the outpatient clinic by a midwife or gynecologist. In case of a suspected efficacy or safety outcome, appropriate physical examination, laboratory or diagnostic testing is performed. Figure 3.1 depicts the flowchart from randomization until end of follow-up.

In the event that a pregnancy results in a miscarriage or stillbirth, the patient will continue the use of LMWH until 6 weeks after termination, and will be followed up as usual.

Laboratory tests

At baseline, creatinine level, platelet count and D-dimer are collected. Two weeks after randomization, the platelet count is determined in order to detect a possible HIT. Anti-Xa peak levels (optional) and platelet count are determined 2 weeks after randomization, at 20 weeks and at 30 weeks of pregnancy.

Baseline ultrasonography

If the patient has a history of DVT, it is recommended that an ultrasound examination of the affected leg be performed at baseline, if this has not yet been performed after initial treatment of the prior DVT. Knowing whether there is any residual thrombosis in the leg, will be helpful in interpreting a new ultrasound examination in case the patient...
presents with a suspicion of a recurrent VTE during the study. However, a baseline ultrasound examination is not obligatory.

**Sample size and statistical analysis**

There is uncertainty about the actual incidence of recurrent VTE among pregnant women receiving pharmacologic thromboprophylaxis. Hence, an approach with a fixed sample size could lead to severe under-powering or undue lengthening of the study. The sample size calculation in this study is based on the required number of events. Assuming a 65% relative risk reduction with the intermediate dose, a total of 29 events would provide a power of 80% to demonstrate that an intermediate dose is superior to a low dose (two-sided $\alpha = 0.05$). Similar risk reductions have been achieved with current versus sub-standard anticoagulant treatment to prevent recurrent VTE in patients after elective hip arthroplasty (23). The efficacy analysis will be based on intention-to-treat (ITT) and the outcome is a symptomatic, objectively diagnosed recurrent VTE. The expected loss to follow-up is close to zero, hence no further sample size adjustment was made. Based on the available literature an incidence of recurrent VTE of 4 to 5% in the low dose group is expected, leading to a proposed sample size of 859 to 1074 women. However, this might be adjusted upward and downward based on the overall number of events observed during the primary analysis period in the study. The ITT population will consist of all patients who have been randomized. Patients will be analyzed in the treatment group to which they were assigned. The valid-for-safety-analysis population will consist of all patients who were randomized and received at least one dose of study treatment. The per-protocol (PP) population will consist of all randomized patients without any major deviation from the protocol. All efficacy analyses will be performed on the ITT population. Additionally, the primary efficacy outcome will be analyzed in the PP population.

**Rationale for some aspects of the Highlow study**

The Highlow study is the first large RCT in pregnancy that will provide high-quality evidence on the optimal prophylactic dose of LMWH in pregnancy in women with a history of VTE. At present, only two RCTs with major methodological weaknesses have evaluated the safety and efficacy of thromboprophylaxis (compared with placebo or no treatment) in pregnant women with a history of VTE, containing very small sample sizes of 40 and 16 patients respectively (24,25). Our study has several unique features that deserve explanation and that may help others design future studies on thromboprophylaxis in pregnant patients.
Rationale for open-label design

A double-blind design with labeling of the investigational medicinal product (IMP) would have been the ideal design for this study, but the associated costs make it impossible for investigator-initiated studies to implement such design. By law, IMPs should be available to subjects by the sponsor free of charge, but in several countries, including the Netherlands, an exception is made for registered medicines even if they are administered in a trial for another indication. Furthermore, in current practice LMWH is widely used in pregnant women in the dosages that are compared in the Highlow study, based on the ACCP guideline recommendations. Following these principles, the Highlow study uses a pragmatic open-label design, and we believe that our study will be representative of how LMWH is likely to be used in clinical practice. As the CIAC will adjudicate all primary outcome events blindly, we trust that the lack of blinded treatment will have little impact on the evaluation of efficacy and safety. Compliance will be assessed by history taking during follow-up visits and by collection of batch numbers and other details of used medication boxes.

Randomization < 14 weeks of gestation

Patients should be randomized before the 14th week of gestation in this study. We have carefully considered including patients at more advanced gestations, but as this would lead to the potential for selection of low risk patients with associated implications for generalizability, a decision was made to not include these patients. Furthermore, as the risk of VTE is already increased early in pregnancy, we believe that setting this cut-off enhances institution of prophylaxis as early as possible, following the recommendations of the current international guidelines.

Rationale for doses of LMWH in the ‘intermediate dose group’ and in obese patients in the ‘low dose group’

The ACCP guideline recommends the following daily doses of LMWH for prophylaxis in pregnancy: nadroparin 2,850 International Units (IU), enoxaparin 4,000 IU, dalteparin 5,000 IU or tinzaparin 4,500 IU (12). We use the same doses in the ‘fixed low dose’ group, except for tinzaparin for which we chose 3,500 IU instead of 4,500 IU, mainly based on availability of syringes. The doses in the ‘intermediate dose group’ are approximately half of a therapeutic dose, and were chosen based on 1) the examples given in the ACCP guideline, 2) the availability of pre-filled syringes and 3) similarity in ratios between the intermediate and low dose for all LMWH types. We chose a ratio between the most common intermediate dose group (70 – 100kg) and the fixed low dose group of 2.5 to 3.0 (Table 3.3B). It should be emphasized that no direct evidence is available to guide choosing a low dose or intermediate dose of LMWH in pregnancy, and that guideline recommendations are extrapolated from thromboprophylaxis studies in patients undergoing
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general surgery or hip arthroplasty. In the TIPPS trial, in which pregnant women with thrombophilia at increased risk of VTE or with previous placenta-mediated pregnancy complications were randomized to either antepartum thromboprophylaxis with dalteparin or to no dalteparin, the dose of dalteparin was increased from 5,000 IU to 10,000 IU at 20 weeks of gestation (18). This decision was based on results from pharmacokinetic studies, suggesting that at this point, the dose requirement increases (26).

No specific recommendations are given in the ACCP guideline regarding modification of prophylactic doses at extremes of body weight. Several studies on thromboprophylaxis in surgery or cancer patients have applied either dose elevations at cut-off values ranging from 70 to 100kg, or no dose elevation at all. In the FRUIT trial that evaluated the addition of LMWH to aspirin at less than 12 weeks gestation in women with inherited thrombophilia and prior delivery for hypertensive disorders and/or small-for-gestational age infants, the dalteparin dose was increased in women weighing above 80kg from 5,000 IU to 7,500 IU (27). The Royal College of Obstetricians and Gynecologists suggests a dose elevation above 90kg, and the product monograph of nadroparin recommends an increase of the prophylactic dose at a cut-off value of 100kg in patients undergoing hip arthroplasty (28). Thus, in the absence of consensus or evidence we pragmatically chose for a cut-off value of 100kg in the ‘fixed low dose’ group, above which the dose is elevated approximately 1.5-fold (Table 3.3C).

Prophylaxis following early termination of pregnancy

Limited data are available on the VTE recurrence risk after an induced abortion, miscarriage or stillbirth. In a study by Pabinger and colleagues, 2 of 83 patients (2.4%) with a terminated pregnancy had a recurrence, and this was the case in 1 of 53 patients (1.9%) after miscarriage and in 3 of 10 (30%) following stillbirth (9). Based on these observations, patients with early termination of pregnancy in the Highlow study should continue LMWH injections until 6 weeks after termination of pregnancy.

Debate on extended prophylaxis after 6 weeks postpartum

There has been some debate on the need of prolonging prophylaxis beyond the 6th week postpartum until the 12th week postpartum. The current ACCP guideline recommends prophylaxis until the 6th week postpartum, based on the fact that most pregnancy-related VTE episodes occur in the first 6 weeks postpartum (12,29,30). A recent study demonstrated that the risk of a primary VTE is 11-fold higher within 6 weeks after delivery than in the same period 1 year later. During the period of 7 to 12 weeks after delivery, the absolute VTE risk is low, with a 2-fold higher incidence as compared with the same period 1 year later (7). In the Highlow study patients are followed up until 12 weeks postpartum, which will allow us to assess the risk of recurrent VTE in the 6 weeks after cessation of LMWH.
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Cutaneous reactions to LMWH

Hypersensitivity skin reactions following LMWH injections are frequently seen, but are probably underreported in most observational studies. It is estimated that at least half of all pregnant women experience these side effects and switch to at least one alternative LMWH type (31–33). One unique feature of our study is the close monitoring of skin reactions such as redness, swelling, pain and itchiness, and the necessity to switch to other LMWH types. In addition, the occurrence of easy bruising is carefully recorded.

Therapeutic doses of LMWH

One may wonder why we chose not to compare an intermediate dose to a therapeutic dose of LMWH. In preparation of the Highlow study design, we found that most experts did not support the use of therapeutic doses of LMWH in the prevention of recurrent VTE, mostly based on concern of bleeding. Although in one study therapeutic doses of LMWH in pregnancy were found not to be associated with an increase in postpartum hemorrhage (20), a study with a therapeutic dose arm seems premature. If we find an unacceptably high incidence of recurrent VTE in the intermediate dose group in the Highlow study, a next step could be a randomized trial comparing an intermediate to a therapeutic dose of LMWH.

Challenges in setting up the study internationally

Setting up the study in different countries is challenging. Legislation has hampered approval of the study protocol in several countries; the waiver regarding supply of study medication by the sponsor is a frequent problem as not all countries have such waiver by law. Furthermore, the academic sponsor (Academic Medical Center, Amsterdam, the Netherlands) is only able to provide patient research insurance for Dutch patients, which cannot be extended to foreign patients. Consequently, local patient research insurance often needs to be arranged which may be costly. The institutional ethics committee unfortunately did not waive the need for patient research insurance, even though we believe that the risk for patients participating in this study is negligible, as there is a large body of evidence on the safety LMWH in pregnancy. LMWH is widely used in pregnant patients outside of a trial setting for the very indication and in the doses that are investigated in the Highlow study (12,13). A modest inclusion fee of €250 is available for every randomized patient with a completed case record form (CRF), to partly overcome the abovementioned expenses.
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Conclusion

In conclusion, this study is likely to greatly impact patient care and modify guideline recommendations. Although we have met several challenges, especially in setting up the study internationally, we are convinced that our goal of including approximately a 1000 patients will be reached within the foreseeable future.

Trial status

The Highlow study is registered on ClinicalTrials.gov (NCT01828697). An updated list of the number of included patients, participating centers and countries can be found at www.highlowstudy.org

Acknowledgments

We would like to acknowledge all Highlow investigators (Supplementary Appendix).

This study is supported by the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (NVOG Consortium 2.0), by two French gynecological networks (GO-CIC and CROG) and by the French network on thrombosis (INNOVTE).

Sponsorship and financial support

An unrestricted grant is provided by Aspen Pharma to the Academic Medical Center in Amsterdam (the Netherlands), who is the sponsor of the Highlow study (Principal Investigator: Prof. Dr. S. Middeldorp).

In France, where CHU de Saint Etienne is the sponsor, a grant was acquired from the French Ministry of Health (PHRC national 2014).

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