Thrombosis Research 135, Suppl. 1 (2015) S26–S29

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

New studies of low-molecular-weight heparin in pregnancy

Saskia Middeldorp *

Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Venous thrombosis
Low-molecular-weight heparin (LMWH)
Pregnancy
Randomized controlled trials

ABSTRACT

Several aspects of the diagnostic and therapeutic management of women with venous thrombosis are uncertain, because of the absence of adequately sized observational or intervention studies. Here, I will discuss the rationale and design of two currently ongoing investigator-initiated, international, randomized controlled trials of LMWH in pregnancy. The Highlow study (www.highlowstudy.org; NCT Clinicaltrials.gov) 01828697) investigates two doses of low-molecular-weight heparin to prevent recurrent venous thromboembolism (VTE) in pregnant women with a history of VTE. The ALIFE2 study (www.alife2study.org; www.trialregister.nl, NTR 3361) investigates the effect of LMWH on live birth in women with inherited thrombophilia and two or more miscarriages.

Introduction

Heparins, both unfractionated and low-molecular-weight (LMWH), are parenteral anticoagulants that are widely used for various thrombotic diseases. Importantly, heparins do not to cross the placenta and can be safely used in pregnant women [1]. Established indications are treatment of acute venous and arterial thrombotic episodes, as well as prevention of venous thromboembolism (VTE) and prevention of stroke and systemic embolism in women with mechanical heart valves [1]. More controversial indications are prevention of placenta-mediated complications and recurrent miscarriage [2–4].

In pregnant women, LMWH is preferred over unfractionated heparin, because of the lower risk of heparin-induced thrombocytopenia and symptomatic osteoporosis [1]. The use of LMWH is burdensome and requires daily subcutaneous injections for a long time if required in pregnancy and/or the postpartum period. Furthermore, a quarter to one-third of pregnant women experience delayed type IV hypersensitivity reactions [5,6], a side effect that is often underreported in cohort studies and systematic reviews that have not prospectively recorded this [7]. Finally, the use of LMWH in pregnancy leads to specific issues with regard to delivery and neuraxial anesthesia, and should hence not be prescribed without good indication [8].

There is a paucity of high-level evidence in the field of women's issues in thrombosis and haemostasis, and many conclusions on the efficacy and safety, and hence the risk–benefit ratio, of anticoagulant drugs have been extrapolated from the non-pregnant population. Here, I will discuss two ongoing investigator-initiated randomized controlled trials investigating LMWH in pregnancy. These trials are dedicated to two frequently asked clinical questions in relation to pregnancy, VTE and thrombophilia.

Prevention of recurrent VTE in pregnancy: the Highlow study

Pulmonary embolism (PE) is a leading cause of maternal mortality in the Western world and deep vein thrombosis (DVT) in pregnancy is an important cause of short term and long term maternal morbidity [9,10]. During pregnancy, the risk of VTE is increased approximately 5-fold compared to age-matched non-pregnant women and occurs in approximately 1 to 2 of 1,000 pregnancies [9,11]. The risk increases with age, mode of delivery, and presence of comorbid conditions [12]. In the postpartum period the relative risk has been found as high as 60-fold during the first 3 months after delivery [13], with small risk increases identifiable up to one year [14]. Approximately two-thirds of DVT of the leg occur antepartum, and are distributed more or less equally over all trimesters [15]. Given the much longer duration of the antepartum period than the postpartum period, the daily absolute risk of VTE is highest postpartum.

Despite these strong risk increases, a strong evidence base for preventive measures for VTE in pregnant and postpartum women is missing. The identification of women in whom the risks and burden of preventive strategies outweigh the risk of VTE requires good quality observational studies of the natural course of untreated pregnancies in women at risk. The optimal efficacious and safe dose of LMWH, once a decision has been made that prevention is indicated, should be based on randomized intervention studies, but these are virtually absent in the pregnant population. The Highlow study (www.highlowstudy.org; NCT Clinicaltrials.gov) 01828697) focuses on the latter issue.

* Correspondence to: Saskia Middeldorp, MD, Professor of Medicine, Academic Medical Center, Department of Vascular Medicine, F4-276, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Tel.: +31 20 5665976; fax +31 20 6968833.
E-mail address: s.middeldorp@amc.uva.nl (S. Middeldorp).

0049-3848/$ – see front matter

Women with a history of VTE have a three- to four-fold higher risk of VTE during subsequent pregnancies than outside of pregnancy [16]. In studies investigating the absolute risk of recurrent VTE during pregnancy without use of pharmacological prophylaxis, estimates ranged from 2.4 and 10% [17–19]. All women with a history of VTE should receive prophylaxis with LMWH for 6 weeks postpartum. In women at moderate (hormone or pregnancy-related or unprovoked VTE) to high (multiple prior unprovoked VTE or persistent risk factors such as paralysis) risk of recurrence who are not on long-term anticoagulant therapy, prophylaxis with LMWH is also recommended during the entire pregnancy. The recommendations, also for women who have not had previous VTE but have an increased risk based on thrombophilia, are summarized in Table 1.

The optimal dose of LMWH to be used for prevention of (recurrent) pregnancy-related VTE is controversial, since no evidence from adequately sized randomized controlled trials is available. Either a prophylactic or an intermediate dose of LMWH to prevent recurrent VTE in pregnancy and the postpartum period is suggested, without preference for one over the other. As can be expected with any prophylactic anticoagulant, treatment failures have been reported in observational, mainly retrospective studies [18,20,21], with an estimated risk of recurrent VTE despite the use of low-dose LMWH as high as 5 to 6% [18,22,23]. However, these studies did not assess compliance and are inconsistent with another study [24]. Potential benefits of intermediate dose of LMWH consist of superior efficacy as compared to low-dose LMWH. Harms consist of an increased risk of bleeding, mostly associated with delivery and neuraxial anesthesia, but few data are available. In a retrospective study of 95 women who used therapeutic dose LMWH, we did not observe recurrent VTE whereas the risk of serious postpartum bleeding was not increased compared to 524 women who had delivered in the same hospital without LMWH use [25]. However, another study with a similar design found an increased risk of postpartum bleeding over 500 mL after vaginal delivery, without a difference in postpartum bleeds exceeding 1000 mL [26].

The Highlow study (www.highlowstudy.org; NCT Clinicaltrials.gov 01828697) is an investigator-initiated, randomized-controlled open-label trial comparing two different doses of LMWH in pregnant patients with a history of previous VTE. Patients enter the study as soon as a home test confirms pregnancy. LWMH will be administered until 6 weeks postpartum, and follow-up will continue until 3 months postpartum. The intervention is intermediate dose LMWH (nadroparin or alternative first choice LMWH), adjusted to actual body weight during pregnancy. The comparator treatment is fixed low-dose LMWH (nadroparin 2850 IE if the patient weighs less than 100 kg or 3800IE if the patient weighs 100 kg or more, or alternative first choice LMWH). Postpartum doses are similar to the last dose given antepartum, but will be decreased according to weight loss. LMWH will be discontinued 6 weeks after delivery. Outcome measures consist of primary and secondary efficacy outcomes (symptomatic VTE during pregnancy and 6 weeks and 3 months postpartum respectively), and primary safety outcomes (major bleeding, composite of major bleeding and clinically relevant non-major bleeding, postpartum haemorrhage, blood transfusion in the first 24 hours postpartum and within 6 weeks after delivery, median peripartum blood loss and mortality, and secondary safety outcomes including minor bleeding, skin complications (e.g., itching, swelling, pain), bruises, necessity to switch to another LMWH, heparin-induced thrombocytopenia and congenital anomalies or birth defects). An event-driven sample size has been chosen because of the uncertainty about the event rate, in which we assume a 65% relative risk reduction with the intermediate dose. A total of 29 events would provide a power of 80% to demonstrate that intermediate dose is superior to low dose (two-sided alpha = 0.05). Based on the available literature an incidence of 4 to 5% in the Low group is expected, leading to a proposed sample size of 859 to 1074 women. Between April 2013 and December 2014, 57 patients have been randomized in 15 Dutch hospitals; half of all patients have been recruited in our own center, and more Dutch hospitals are still in the process of starting. At present, we are in the process of getting the study started in other countries, including France, Ireland, Austria and Belgium. Hence, we are confident that the Highlow study will be the first large randomized controlled trial in pregnancy that will provide high-quality evidence on the optimal prophylactic dose of LMWH in pregnancy in women with a history of VTE.

Prevention of recurrent miscarriage with LMWH: the ALIFE2 study

Whether women with placenta-mediated pregnancy complications including recurrent miscarriage, late pregnancy loss, preeclampsia, intra-uterine growth restriction and placental abruption, benefit from anticoagulant or antithrombotic agents, e.g. aspirin or heparin is a frequently occurring clinical question [2,23]. Pregnancy failure is extremely distressing for couples who desire to have children, and preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) are leading causes of maternal and perinatal mortality and morbidity. A presumed benefit of antithrombotic therapy, in the perceived absence of harm, has led many clinicians to prescribe LMWH, aspirin, or both to women with placenta-mediated pregnancy complications, sometimes but not exclusively, based on the presence of thrombophilia. However, the absence of high-quality evidence, even in areas that are not subject to intense debate, for instance in women with obstetric antiphospholipid syndrome (APS) is striking and distressing given the impact of treatment with LMWH during the entire pregnancy. Different recommendations regarding antithrombotic drugs in women with various clinical manifestations of obstetric APS are given by

Table 1
Summary of recommendations to prevent a first or recurrent pregnancy-related VTE[a].

Antepartum and postpartum prophylaxis	Postpartum prophylaxis during 6 weeks[b]	No pharmacological prophylaxis[b]
Women with a single unprovoked episode of VTE, or provoked by use of oral contraceptives, pregnancy or postpartum	Women with a history of a single episode of VTE related to a major non-hormonal transient risk factor	General population
Women with a history of recurrent VTE	Women with hereditary thrombophilia and a positive family history[c] of VTE	Women with a positive family history[c] for VTE
Women who are homozygous for factor V Leiden or prothrombin mutation who have a positive family history[c] of VTE	Women who are homozygous for factor V Leiden or prothrombin mutation who do *not* have a positive family history[c] of VTE	Women who are heterozygous for factor V Leiden of prothrombin mutation who do *not* have a positive family history[c] of VTE

VTE, venous thromboembolism.
[a] Recommendations are weak, based on a low level of evidence leaving room to individualize prophylactic strategies based on patient's preferences.
[b] Unless women can be categorized into one of the more aggressive prophylactic strategies in this table.
[c] A positive family history is defined as having a first degree relative with VTE.