Highlow study: Low-molecular-weight heparin to prevent recurrent VTE in pregnancy: a randomized controlled trial of two doses

Published: 26-11-2012
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To evaluate the efficacy and safety of intermediate dose LMWH versus fixed low dose LMWH in pregnant women with a history of previous VTE.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pregnancy, labour, delivery and postpartum conditions
Study type	Interventional

Summary

ID

NL-OMON55412

Source
ToetsingOnline

Brief title
Highlow

Condition

- Pregnancy, labour, delivery and postpartum conditions
- Embolism and thrombosis

Synonym
deep vein thrombosis; pulmonary embolism

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: GlaxoSmithKline,Uit de onderzoeksmiddelen van de afdeling Vasculaire Geneeskunde van het AMC;waaraan ook industrieën bijdragen.

Intervention

Keyword: LMWH, pregnancy, prevention, VTE

Outcome measures

Primary outcome

Recurrence of VTE.

Secondary outcome

Safety (especially bleeding).

Study description

Background summary

Pregnancy-related venous thrombo-embolism (VTE), i.e. deep-vein thrombosis (DVT) and pulmonary embolism (PE), is one of the leading causes of maternal mortality in western countries. Women with a history of VTE have a 3 to 4 fold higher risk of recurrent VTE during subsequent pregnancies than outside of pregnancy, and the absolute risk without thrombosis prophylaxis is estimated between 2 and 10%. Thus, thrombosis prophylaxis with low-molecular-weight heparin (LMWH), that is safe for the fetus, is indicated in most women with a history episode of VTE throughout pregnancy and the 6 weeks postpartum period. However, the optimal dose of LMWH is unknown, since only two very small trials (n=40, n=16) with methodological limitations have been performed in this group of patients. Most centers use a prophylactic dose of LMWH in women who have an indication for thrombosis prophylaxis in pregnancy and the postpartum period. However, numerous treatment failures have been reported. Recent reports, have indicated that the risk of recurrent VTE despite the use of low-dose LMWH is as high as 5 to 6%, although another observational report suggests a high efficacy. Some centers use therapeutic dose LMWH to prevent recurrent VTE in pregnancy. A recent retrospective study showed no recurrences, whereas the risk of serious bleeding was not increased compared to women who had delivered in the same hospital without LMWH use. However, such an approach is not widely accepted, because of bleeding risks associated with delivery and neuraxial anesthesia, and the guidelines of the ACCP suggest either a prophylactic or an intermediate dose of LMWH to prevent recurrent VTE in pregnancy and the

postpartum period.

Study objective

To evaluate the efficacy and safety of intermediate dose LMWH versus fixed low dose LMWH in pregnant women with a history of previous VTE.

Study design

Multicenter randomized controlled phase IV parallel group study.
Randomisation (1:1) to:
3. Nadroparine intermediate dose qd
4. Nadroparine low dose qd.
Treatment from week de 4-14 of pregnancy until week 6 after delivery.
Follow-up until 3 months after devlivery.
Independent DSMB.
850-1100 patients.

Intervention

Treatment with LMWH in low or intermediate dose.

Study burden and risks

Risk: Adverse effects of study treatment.
Burden: Visits 2 after initiation of treatment and 20th and 30th week of pregnancy and 1, 6 weeks and 3 months after delivery. These visits wil coincide with the standard visits for pregnancy.
1-3 x safety blood tests (10 ml).
1x compression ultrasonography lower legs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age >= 18 years
- Pregnancy confirmed by urinary pregnancy test, gestational age < 14 weeks since first day of last menstrual period
- Previous objectively confirmed VTE, either unprovoked, in the presence of use of oral contraceptives or estrogen/progestagen use, or related to pregnancy or the postpartum period, or minor risk factors (e.g. long distance travel, minor trauma)

Exclusion criteria

- Previous VTE related to a major provoking risk factor (e.g. surgery, major trauma or plaster cast immobilisation in the 3 months prior to VTE) as the sole risk factor
- Indication for treatment with therapeutic dose anticoagulant therapy (e.g. treatment of acute VTE; permanent use of therapeutic anticoagulants outside of pregnancy)
- Inability to provide informed consent
- Any contraindication listed in the local labelling of LMWH.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-04-2013
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fraxiparine
Generic name:	nadroparin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23452
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-001505-24-NL
CCMO	NL40326.018.12
OMON	NL-OMON23452