Anticoagulants for Living Fetuses in women with recurrent miscarriage and inherited thrombophilia; ALIFE2 study

Published: 31-08-2012
Last updated: 01-05-2024

To evaluate the efficacy of low molecular weight heparin (LMWH) in women with inherited thrombophilia and recurrent miscarriage on live birth.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON43583

Source
ToetsingOnline

Brief title
ALIFE2 study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Abortions and stillbirth

Synonym
habitual abortion, recurrent miscarriage

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,VIDI beurs toegekend aan prof. dr. S. Middeldorp

Intervention

Keyword: anticoagulants, inherited thrombophilia, recurrent miscarriage

Outcome measures

Primary outcome

The primary efficacy outcome is live birth in each treatment group.

Secondary outcome

Secondary efficacy outcome measures are prevalence of adverse pregnancy outcomes, such as miscarriage rates, pre-eclampsia, the syndrome of haemolysis, elevated liver enzymes en low platelets (HELLP-syndrome), intrauterine growth restriction, placental abruption, premature delivery and congenital malformations.

Safety outcomes are thrombocytopenia, hemorrhagic episodes and skin reactions to the prescribed study medication.

Study description

Background summary

In all clinically recognized pregnancies, a single spontaneous miscarriage occurs in 14-19% of patients, and 1-5% of women experience two or more miscarriages (recurrent miscarriage). In over 50% of cases of miscarriage the cause remains unexplained. Many studies have confirmed a relationship between inherited thrombophilia and miscarriage and other pregnancy complications. The role of thrombophilia in recurrent miscarriage can be explained partially by the concept of thrombosis of the (microvasculature of the) placenta, and partially because of inhibition of extravillous trophoblast differentiation. Therefore, anticoagulants are considered a possible therapy for women with recurrent miscarriage and inherited thrombophilia.
Beneficial effects of anticoagulants (low molecular weight heparin with or without aspirin) for women with unexplained recurrent miscarriage were reported in several studies. However, these studies were either not randomized, not placebo-controlled, or had other methodological limitations. Recently, the

results of three RCT's (ALIFE study, SPIN study and Habenox study) showed that treatment with low molecular weight heparin with or without aspirin does not improve the chance of live birth in women with unexplained recurrent miscarriage. Neither the ALIFE-study, nor the SPIN-study, nor the Habenox study was sufficiently powered to demonstrate an effect of pharmacological therapy in the subgroup of women with inherited thrombophilia. Pregnancy failure is severely distressing for couples who desire to have children. As can be concluded from the above written; there is an urgent need for randomized, adequately designed trials on the use of anticoagulants in women with recurrent miscarriage and inherited thrombophilia.

Study objective

To evaluate the efficacy of low molecular weight heparin (LMWH) in women with inherited thrombophilia and recurrent miscarriage on live birth.

Study design

Randomized intervention study of LMWH plus standard pregnancy surveillance vs. standard pregnancy surveillance alone.

Intervention

The subjects will be randomly assigned to receive LMWH plus standard pregnancy surveillance or standard pregnancy surveillance alone.

Study burden and risks

The administration of LMWH is considered to be safe in healthy human subjects, as well as in pregnant women. However, there are possible adverse effects. Potential risks include maternal or fetal bleeding, heparin induced thrombocytopenia and heparin induced osteoporosis. Subjects will receive standard surveillance care provided by their own obstetrician throughout pregnancy, including structural fetal ultrasonography.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific

Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Women with recurrent miscarriage (>= 2) and/or intra-uterine fetal deaths (i.e. >= 2 miscarriages of intra-uterine fetal deaths, irrespective of gestational age;
-Confirmed inherited thrombophilia; factor V Leiden mutation, prothrombin gene mutation (G20210A), protein S deficiency, protein C deficiency or antithrombin deficiency or a combination hereof. Protein S, -C and antithrombin deficiencies need to be confirmed by two independent tests, performed on two separate occasions and not during pregnancy or anticoagulant therapy;
-Pregnancy confirmed by urine pregnancy test;
-Age 18 - 42 years at randomisation;
-Willing and able to give informed consent;

Exclusion criteria

-Duration of current pregnancy >= 7 weeks; based on first day of last menstruation.
-Indication for anticoagulant treatment during pregnancy (for instance prosthetic heart valves, a history of venous thromboembolism or antiphospholipid syndrome);
-Contraindications to LMWH (previous heparin induced thrombocytopenia, active bleeds or renal insufficiency with creatinine clearance of less than 30ml/min);
-Known allergy to at least 3 different LMWH preparations;
-Previous inclusion in the ALIFE2 study (for another pregnancy);

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-01-2013
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	clexane
Generic name:	Enoxaparine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fragmin
Generic name:	Dalteparin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fraxiparin
Generic name:	Nadroparin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Innohep

Generic name:	Tinzaparin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2013
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:	05-03-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2016
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001447-43-NL
CCMO	NL40256.018.12