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Thrombophilia in Pregnancy Prophylaxis Study: a multicentre, multinational, randomised controlled trial of prophylactic low molecular weight heparin in high-risk pregnant thrombophilic women

Submission date
19/06/2003

Registration date
07/08/2003

Last Edited
28/04/2015

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Pregnancy and Childbirth

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT00967382

Protocol serial number
954E-CV9101-004; MCT-82205

Study information

Scientific Title
Thrombophilia in Pregnancy Prophylaxis Study: a multicentre, multinational, randomised controlled trial of prophylactic low molecular weight heparin in high-risk pregnant thrombophilic women

Acronym
TIPPS

Study objectives
Study rationale:
Thrombophilias are disorders that result in a predisposition to develop venous thromboembolic events (VTEs). Thrombophilias are common in the general population. Recent evidence indicates that women with thrombophilia not only have an increased risk of VTEs during pregnancy, but also increased risk of pre-eclampsia, intrauterine growth restriction (IUGR), abruptio placentae and foetal loss. The management of thrombophilic women in pregnancy is controversial and antithrombotic prophylaxis may reduce the rate of complications in pregnancy and the rate of VTEs.

Phase II studies with low molecular weight heparin (LMWH) in pregnant women, for a variety of indications, suggest that there may be a benefit to their use in this high-risk group. However, to date there have been no controlled clinical trials using LMWH to prevent pre-eclampsia, IUGR or foetal loss.

The purpose of this study is to determine the safety and efficacy of LMWH in preventing VTE, pre-eclampsia, IUGR and foetal loss in pregnant thrombophilic women.

Study design:
This study is a multi-centre, open-label, randomised controlled clinical trial based in a maximum of 30 centres. Two hundred and eighty-four (284) pregnant women with confirmed thrombophilia and at high risk for pregnancy complications will be randomised to prophylactic dose dalteparin or control (identical follow-up and care, but no drug intervention). Please note that as of 27/02/2007 the number of participants has been increased to three hundred and eighty-five (385).

The study will consist of five periods: a screening period, randomisation, antenatal follow-up, labour and delivery, and postpartum follow-up. Maximum time on study will vary between 26 and 46 weeks.

The primary objective of this study is to identify if LMWH prophylaxis in thrombophilic pregnant women results in a greater than 33% relative risk reduction in the composite outcome measure (VTE, pre-eclampsia, IUGR and foetal loss) compared to control.

Secondary objectives will be to:
1. Identify if prophylactic LMWH will reduce rates of pregnancy-induced hypertension (PIH), pre-term labour and abruptio placentae in pregnant thrombophilic women compared to control
2. Determine safety of LMWH use in pregnancy (specifically rates of bleeding, thrombocytopenia and fractures)
3. Identify whether prolonged LMWH use in pregnancy results in decreased BMD compared to control

On 01/10/2007 the overall trial end date was changed from 31/06/2007 to 31/07/2011.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ottawa Hospital Research Ethics Board (OHREB), 25/02/2000

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Thrombophilia

Interventions
Intervention group: 5000 IU dalteparin once daily (od) from randomisation until 20 weeks gestational age, then 5000 IU twice daily (bid) until the onset of labour. 5000 IU dalteparin od for 6 weeks postpartum.

Control group: 5000 IU dalteparin od for 6 weeks postpartum.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Dalteparin

Primary outcome(s)
The primary endpoint is a composite outcome that includes any of the following events (1 - 4):
1. Objectively documented VTEs including:
1.1. Deep vein thrombosis (DVT)
1.2. Pulmonary embolism (PE)
1.3. Sudden death
2. Severe or early onset pre-eclampsia:
2.1. Early onset defined as 32 weeks + 0 day using the time of diagnosis of pre-eclampsia as the index time
2.2. Severe being pre-eclampsia with any of the following:
2.2.1. Blood pressure (BP) greater than 180/110
2.2.2. Increased liver function tests (LFTs)
2.2.3. Thrombocytopenia
2.2.4. Oliguria (less than 30 cc/hr urine output)

2.2.5. Pulmonary oedema
2.2.6. Seizures
2.2.7. Coagulopathy
2.2.8. Proteinuria greater than 5 g/24 hours
3. Intrauterine growth restriction (IUGR), for which both of following criteria must be fulfilled:
3.1. Infant birth weight less than the 10th percentile in relation to normals for sex and gestational age and
3.2. One ultrasound (U/S) indicating two or more of the following criteria:
3.2.1. Oligohydroamnios
3.2.2. Cerebral redistribution (abnormal middle cerebral artery Doppler waveform with a pulsitility index less than the 5th percentile)
3.2.3. Increase in head circumference to abdominal circumference ratio over 1.1
3.2.4. Abnormal umbilical artery Doppler waveform
4. Foetal loss, either:
4.1. Miscarriage: foetal loss prior to 20 weeks gestation
4.2. Stillbirth: foetal loss at or greater than 20 weeks gestation

Key secondary outcome(s))
To achieve the secondary objectives the following outcomes will be determined:
1. Pregnancy induced hypertension (PIH), with or without proteinuria
2. Pre-term delivery (less than 37 weeks estimated gestational age)
3. Abruptio placentae
4. Major and minor haemorrhage
5. Thrombocytopenia (50% decrease from baseline)
6. Fractures
7. Bone mineral density (BMD) at six weeks postpartum
8. Non-compliance with study medication and/or follow up

Completion date
31/07/2011

Eligibility

Key inclusion criteria
1. High-risk pregnant women with a confirmed thrombophilia
2. Who have had any of the following pregnancy complications:
2.1. Recurrent miscarriages
2.2. Stillbirth
2.3. Pre-eclampsia (high blood pressure in pregnancy where protein leaks into the urine)
2.4. Very small birth weigh baby (called intrauterine growth restriction)
2.5. Bleeding in the placenta before delivery (called abruptio placenta)
2.6. Family history of blood clots in the legs or lungs
2.7. Personal history of phlebitis or blood clots in the legs or lungs
3. Confirmed thrombophilia
4. 18 years of age or older

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Greater than 19 weeks + 7 days gestational age at the time of randomisation
2. Contraindication to heparin therapy including:
2.1. History of heparin induced thrombocytopenia
2.2. Platelet count of less than 100,000 x 106/L
2.3. History of osteoporosis or steroid use (increased risk of osteoporosis and osteoporotic fracture with heparin therapy)
2.4. Actively bleeding
2.5. Documented peptic ulcer within 6 weeks (contraindication to anticoagulation)
2.6. Heparin, bisulfite or fish allergy
2.7. Severe hypertension (systolic blood pressure [SBP] greater than 200 and/or diastolic blood pressure [DBP] greater than 120 - contraindication to anticoagulation)
2.8. Severe hepatic failure (international normalised ratio [INR] greater than 1.8) (increased likelihood of bleeding)
3. Women with serum creatinines greater than 80 and an abnormal 24 hour creatinine clearance. Women with serum creatinines less than 80 do not require a normal 24 hour creatinine clearance to be eligible.
4. Geographic inaccessibility (less likely to comply with required follow-up visits and care)
5. Need for anticoagulants as judged by the local investigator such as but not limited to:
5.1. Women with recurrent foetal loss with antiphospholipid antibody syndrome
5.2. Women with prior idiopathic proximal VTE:
5.2.1. History of pulmonary embolism (PE) or DVT treated with anticoagulants (over one month of heparin or warfarin) or inferior vena cava (IVC) interruption
5.2.2. Idiopathic refers to a VTE that occurs outside all of the following periods: antepartum, postpartum, oral contraceptive use, surgery, immobilisation, cast, and/or malignancy
5.2.3. Proximal refers to a VTE that occurs above the bifurcation of the popliteal vein
5.3 Women with mechanical heart valves
6. Women less than 18 years of age
7. Women unable/unwilling to providing informed consent
8. Prior participation in TIPPS

Date of first enrolment
01/07/2000

Date of final enrolment
31/07/2011

Locations

Countries of recruitment
United Kingdom

Australia

Canada

United States of America

Study participating centre
The Ottawa Hospital
Ottawa
Canada
K1H 8L6

Sponsor information

Organisation
Ottawa Hospital Research Institute (OHRI) (Canada) - formerly Ottawa Health Research Institute

ROR
https://ror.org/03c62dg59

Funder(s)

Funder type
Charity

Funder Name
Heart and Stroke Foundation of Canada

Alternative Name(s)
Heart and Stroke Foundation, Heart & Stroke Foundation of Canada, Heart & Stroke, Fondation des maladies du cœur et de l'AVC, Fondation des Maladies du Cœur du Canada, Fondation des maladies du cœur et de l'AVC du Canada, HSFC, HSF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Canada

Funder Name
Canadian Institutes of Health Research

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR - Welcome to the Canadian Institutes of Health Research, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	08/11/2014		Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes