The EPPI Trial - Enoxaparin for the Prevention of Preeclampsia and Intrauterine growth restriction - a open-label randomised controlled trial

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Primary objectives:To determine the difference in effect of prophylactic daily LMWH injections with standard high risk antenatal care compared to standard high risk antenatal care only for the prevention of preeclampsia and IUGR and to assess the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Maternal complications of pregnancy
Study type	Interventional

Summary

ID

NL-OMON41162

Source
ToetsingOnline

Brief title
The EPPI Trial

Condition

- Maternal complications of pregnancy

Synonym
Intrauterine growth restriction, Low birthweight for gestational age, pre-eclampsia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Enoxaparin, Intrauterine Growth Restriction, Low Molecular Weight Heparin, Preeclampsia, Pregnancy induced hypertension, Small for Gestational Age, Toxemia of pregnancy

Outcome measures

Primary outcome

Primary Outcome

Preeclampsia and/or SGA <5th centile

(The term IUGR is used to describe a fetus failing to reach its full growth

potential. However, this is a difficult term to define and measure and

therefore our surrogate marker for this will be the more objective measure of

small for gestational age (SGA) by customised birthweight centiles)

Secondary outcome

Secondary Outcomes

1. Preeclampsia and/or SGA <10th centile

2. Preeclampsia and/or SGA <10th centile delivered <35+6 weeks

3. Preeclampsia and/or SGA <10th centile delivered <33+6 weeks

4. Preeclampsia delivered at any gestation

5. SGA <10th centile delivered at any gestation

6. SGA <5th centile delivered at any gestation

7. SGA <3rd centile delivered at any gestation

8. Preeclampsia and SGA <10th centile delivered at any gestation

9. Severe Preeclampsia

10. Placental abruption

11. Unexplained intrauterine fetal death

12. Gestational age at delivery

13. Mean birthweight

14. Mean birthweight centile

15. Neonatal Intensive Care Unit (NICU) admission

16. LSCS rate

17. Antepartum haemorrhage (APH)

18. Postpartum haemorrhage (PPH)

19. Abnormal uterine artery Doppler at 20 or 24 weeks

20. Abnormal umbilical artery Doppler at 20 or 24 weeks

Study description

Background summary

Preeclampsia and intrauterine growth restriction (IUGR) are two of the most common causes of maternal and perinatal morbidity and mortality. Preeclampsia complicates approximately 5% of pregnancies and is the second most common cause of direct maternal death in the Developed World. IUGR is more difficult to define and measure but 10% of all infants will be born small for gestational (SGA) by customised growth centiles. Women who have had previous preeclampsia and/or IUGR are at significant risk of recurrence.

Of all preventative therapies which have been assed only aspirin therapy has shown to lead to a modest reduction in preeclampsia and small for gestational age (SGA) infants. Calcium also has shown to reduce preeclampsia rates in women at high risk of preeclampsia.
Heparin acts as an anticoagulant but also has additional actions on placental function and development that further make it a potential candidate for the prevention of preeclampisa and IUGR. Unfractionated heparin (UFH) combined with aspirin therapy has shown to prevent recurrent miscarriage in women with

Antiphospholipid syndrome (SGA). This has led to interest in the use of heparin for the prevention of more types of placental mediated problems such as preeclampsia and IUGR. However evidence suggesting significant benefits associated with heparin treatment of these pregnancy complications is scarce. Randomised controlled trials specifically aimed at women at risk of preeclampsia and IUGR are required before advocating the introduction of heparin, which is expensive and administered by injection, into clinical practice. LMWH has several advantages over unfractionated heparin, including a reduced risk of bleeding, more stable and predictable pharmacokinetics, reduced risk of thrombocytopenia and a much lower risk of osteoporosis. The safety and effectiveness of LMWH use in pregnancy has been reviewed and accepted.

Study objective

Primary objectives:
To determine the difference in effect of prophylactic daily LMWH injections with standard high risk antenatal care compared to standard high risk antenatal care only for the prevention of preeclampsia and IUGR and to assess the size of the effect in this population.

Secondary objectives:
To determine the effect of LMWH on
• uterine artery Doppler waveforms
• maternal serum markers and placental and angiogenic growth factors
• maternal serum treated trophoblast explants
• trophoblast deportation
and compare differences in those developing disease to those with normal pregnancies.

Study design

A single centre open-label randomised controlled trial of LMWH therapy (enoxaparin with as alternatives dalteparin or nadroparin) and highrisk pregnancy surveillance vs highrisk pregnancy surveillance alone.

Intervention

Enoxaparin (Clexane) 40 mg daily s.c. (alternatives: dalteparin (Fragmin) 5000IU once daily or nadroparin (Fraxiparin) 2850 IU once daily) will commence at 6 weeks gestation or time of recruitment (whichever is later) up to a gestation of 15+6 weeks. Commencement of treatment as close to 6 weeks as possible. Injections will continue to 35+6 weeks.

Study burden and risks

If women are randomised to take the LMWH injections (enoxaparin, dalteparin or

nadroparin) they will be taught how to give themselfs daily injections starting from the time they enter the study and the injections will continue until 36 weeks of pregnancy.
At the low, prophylactic, dose of LMWH, side-effects are very uncommon but include bruising or skin reactions at the injection site. Rare side effects include heparin induced thrombocytopenia, the chance of this occurring is less than 0.1%. Osteoporosis does not occur at this dose.

Special extra blood tests at the time of joining the study, at 20 weeks and again at 30 weeks will be performed. These tests will be perfomed at the same time women have routine pregnancy blood tests.
A study investigator will perform an extra ultrasound in addition to the 20 week ultrasound at 24 weeks to measure the growth of the baby and assess blood flow to the placenta. For some women this will be part of their routine antenatal care. All other care during the pregnancy will be similar to that given to women not taking part in the study who have comparable high-risk pregnancies.

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

1. Previous preeclampsia delivered < 36 weeks (ie. up to 35+6 weeks - spontaneous or iatrogenic) in last ongoing pregnancy reaching >12 weeks.
2. Previous SGA <10th C delivered < 36 weeks (ie. up to 35+6 weeks - spontaneous or iatrogenic) in last ongoing pregnancy reaching >12 weeks.
3. Previous SGA <3rd C delivered at any gestation in last ongoing pregnancy reaching >12 weeks.

Exclusion criteria

1. Any contraindication to LMWH
2. Requirement for LMWH eg. previous thrombosis, APS (referring clinician decision)
3. Previous successful pregnancy with LMWH treatment
4. Multiple pregnancy
5. Known pre-existing type 1/2 diabetes or renal disease (with serum creatinine >150)
6. Thrombocytopenia (platelet count <80) prior to randomisation
7. Known major fetal anomaly/chromosomal abnormality
8. Known cause of prior FGR other than reduced uteroplacental blood flow eg. maternal infections associated with FGR, use of cigarettes, alcohol, illicit drugs or other toxic exposures such as medication associated with FGR (referring clinician decision).

Study design

Design

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

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2014
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clexane
Generic name:	Enoxaparin
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

Ethics review

Approved WMO

Date:	06-08-2014
Application type:	First submission
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
Other	ACTRN12609000699268
EudraCT	EUCTR2014-001308-22-NL
CCMO	NL48800.018.14