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Prediction and prevention of preeclampsia, intrauterine growth restriction, prenatal stress and fetal programming of child's psychological development

Submission date
28/02/2007

Recruitment status
No longer recruiting

Registration date
06/09/2007

Overall study status
Completed

Last Edited
05/07/2018

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

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
2010

Study information

Scientific Title
Prediction and prevention of preeclampsia, intrauterine growth restriction, prenatal stress and fetal programming of child's psychological development

Acronym
PREDO (to PREDict preeclampsia with DOppler)

Study objectives
Study domain:
1. Prediction of preeclampsia and IUGR
2. Genetic markers predisposing to preeclampsia and affecting fetal growth
3. Maternal prenatal stress, including stress experiences arising from various life domains, anxiety and depression, and stress-predisposing psychological characteristics during pregnancy that may be relevant for understanding the development of preeclampsia.
4. The connection of heart diseases to maternal pre-eklampsia

Hypotheses:
1. To study the role of Doppler ultrasound measurement performed at 12th to 14th week of gestation in predicting preeclampsia and Intrauterine Growth Restriction (IUGR) in women whose medical history implies an increased risk for these conditions
2. To study the role of aspirin (AcetylSalicylic Acid; ASA) in preventing preeclampsia and IUGR in women at high risk for these conditions on the basis of early Doppler velocimetry abnormalities.
3. To study the role of biochemical markers (alone or in combination with Doppler velocimetry waveform assessment) in predicting preeclampsia or IUGR.
4. To study the effect of preeclampsia on fetal growth and metabolism.
5. To assess the additive and interactive effects of family history of cardiovascular and related disorders on the risk of preeclampsia.
6. To provide a basis for a follow-up study of later cardiovascular morbidity and risk factors in the mothers and children.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Committee of Helsinki University Hospital, 09/02/2006, ref: 44/2006 Dnro 18/E9/06 and 19/E9/06

Study design
Prospective double-blind randomised placebo-controlled longitudinal trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

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

Interventions
The subjects are enrolled among women who visit antenatal clinics at Hyvinkää Hospital, Helsinki, Tampere and Kuopio University Hospitals, Tampere City Hospital, Päijät-Häme, Joensuu and Iisalmi Hospitals. In Hyvinkää, Joensuu and Päijät-Häme the patients are enrolled when they come to the first ultrasound screening at 12 to 14 weeks of gestation.

Those women who belong to risk group on the basis of their medical history are screened by transvaginal ultrasound at 12th to 14th weeks of gestation. Subjects who have bilateral early diastolic notch in the uterine arteries will be randomized into the ASA or placebo group. Women who meet one of the inclusion criteria but who do not have bilateral notch in the uterine artery measurements will be included in the control group. Women with normal pregnancies, without the aforementioned risk factors and with normal ultrasound results will form a follow-up group.

The randomization will be stratified with each study centre being assigned an approximately equal number of subjects receiving ASA or placebo. The assignment will be conducted at the Pharmacy of the Tampere University Central Hospital.

The dose of ASA is 100 mg once a day (1-2 mg/kg/day) orally. The treatment is started at 12th to 14th gestational week and will continue until 34 completed weeks of gestation. Patients will be given oral and written information of the medication. The side effects of the medication will be followed by a notification form which the patients are asked to return if any side effects appear as well as instructions how to contact the obstetricians in charge. The effect and safety of ASA is described in more detail in the investigators brochure. The National Agency of Medicines will be given an announcement about this study.

Ultrasound examination will be performed to all subjects at 12th to 14th weeks of gestation. Patients in the ASA and placebo groups will be re-examined between 18th to 20th and 26th to 28th weeks of gestation. Blood and urine samples are taken from all subjects as follows.

The women will fill in a detailed questionnaire about their medical and family history. Information from the Health Care Registers is collected for epidemiologic study.

The patient will be asked for consent to contact the family later for eventual follow-up studies on the effects of pregnancy conditions on later outcome. The data about patients health status, pregnancy and labour is recorded. Patients will be given a questionnaire about their health status.

Intervention Type

Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Acetylsalicylic acid

Primary outcome measure
1. Gestational weeks of 12th to 14th:
1.1. Womens weight and blood pressure
1.2. Ultrasound examination (Doppler velocimetry)
1.3. Blood for biochemical and genetic analysis (30 ml)
1.4. Urine (10 ml)
1.5. Randomisation for the ASA and placebo groups

2. Gestational weeks of 18th to 20th and 26th to 28th :
2.1. Weight and blood pressure measurements are repeated
2.2. Ultrasound examinations (Doppler velocimetry)
2.3. Fasting blood (30 ml) and urine (10 ml) samples
2.4. A 2-hour oral glucose tolerance test (only at 26th to 28th weeks of gestation)

3. At delivery:
3.1. Information collected from the clinical records of the mother and the newborn
3.2. Blood (30 ml) and urine (10ml) samples
3.3. Cord blood sample

4. Biochemical measurements: samples are obtained at 12th to 14th, 18th to 20th and 26th to 28th weeks of gestation and within 12-24 hours after delivery. The biochemical measurements include:
4.1. Indices of antioxidant status: serum uric acid (enzymatic assay using uricase)
4.2. Indices of placental insufficiency:
4.2.1. Serum activin A
4.2.2. Inhibin A and B (two site enzyme immunoassay)
4.2.3. Serum leptin (Radioimmunoassay [RIA] or Enzyme-Linked Immunosorbent Assay [ELISA])
4.2.4. Serum Flt1 (ELISA)
4.3. Indices of endothelial function:
4.3.1. Serum asymmetric dimethylarginine (ADMA)
4.3.2. Serum fibronectin (ELISA)
4.3.3.Serum e-selectin (ELISA)
4.3.4. Serum c-reactive protein (immunotubidimetry or immunonefelometry)
4.4. Lipids:
4.4.1. Serum triglyserides (enzymatic)
4.4.2. Serum free fatty acids (enzymatic)
4.5. Glucose metabolism:
4.5.1. Serum insulin (RIA)
4.5.2. Serum glucose (enzymatic)
4.5.3. 2-hour glucose tolerance test
4.5.4. Serum Sex Hormone-Binding Globulin (SHBG) (Time-Resolved Fluorescence Immunoassay [TR-FIA])
4.6. Biochemical measurements from the cord blood

5. The biochemical compounds to be measured in the study population include:
5.1. Insulin- insulin-like growth factor system:
5.1.1. Serum insulin (RIA)
5.1.2. IGF- I (RIA)
5.1.3. IGF- II (RIA or ELISA)
5.1.4. IGF-binding proteins 1 and 2 (ELISA)
4.1.5. adiponectin (ELISA)
5.2. Hypothalamic-pituitary-adrenal axis:
5.2.1. Corticotrophin-releasing hormone
5.2.2. Cortisol (RIA or LC-MS/MS)
5.2.3. Cortisol-binding globulin (RIA)
5.3. Regulation of fetal cortisole exposure: 11β- hydroxysteroid dehydrogenase 2 (determined from placental sample) (LC-MS/MS)
6. The incidence of pre-eclampsia in ASA and placebo groups

Secondary outcome measures
1. To test whether infants born to mothers with preeclampsia are characterized by greater behavioral difficulty in emotional, social and cognitive domains of development than infants born to mothers without preeclampsia. The aim is also to test whether infant developmental outcomes are predicted by maternal prenatal stress, depression and anxiety measured and the mothers stress-predisposing / buffering traits and characteristics, together or independently of preeclampsia and potential postnatal environmental factors.

2. Healthcare register study
We collect data from the following sources:
2.1. National Population Register: to identify the parents and siblings (including half-siblings)
2.2. Medication reimbursement: hypertension, coronary heart disease, cardiac insufficiency, diabetes, asthma, death register (time and cause of death)
2.3. Hospital diagnosis register: diagnosis related to cardiovascular disease and obstetrics
2.4. Birth register: birth measurements, gestational age and possible pre- and postnatal complications of siblings and half-siblings of newborn infant
2.5. Hospital records of the women and their mothers: pregnancy follow-up and newborn
2.6. Permission to collect and link the data applied by the Ministry of Social and Health Affairs

Overall study start date
01/01/2007

Completion date
31/12/2010

Eligibility

Key inclusion criteria
Inclusion criteria (one of the following):
1. Preeclampsia in a previous pregnancy
2. IUGR in a previous pregnancy
3. Essential hypertension
4. Gestational diabetes in a previous pregnancy
5. Diabetes mellitus type 1
6. Previous pregnancy with fetal demise (> 22 gestational weeks or over 500 g)
7. Body Mass Index (BMI) greater than 30 kg/m^2 prior to pregnancy

8. Age younger than 20 or older than 40 years at the day of admission
9. Systemic Lupus Erythematosus (SLE)
10. Sjögren's syndrome

Definitions for inclusion criteria:
1. Preeclampsia is defined as de novo hypertension and proteinuria. Proteinuria is defined as presence of 0.3 g/day or more of protein in a 24-hour urine specimen
2. IUGR is defined as birth weight below -2 standard deviations below mean for sex and gestational age according to Finnish standards
3. Essential hypertension is defined as systolic blood pressure 140 mmHg or more and diastolic blood pressure 90 mmHg or more before 20th gestational week or medication for blood pressure
4. Gestational diabetes is defined by one or more abnormal values in two-hour oral glucose tolerance test

Subjects invited to participate in the study will be given written and oral information about the study. Each participant will sign an informed consent.

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
1000

Key exclusion criteria
1. Asthma (diagnosed by a physician)
2. Allergy to ASA
3. Tobacco smoking (during pregnancy)
4. Previous peptic ulcer
5. Previous placental ablation
6. Inflammatory bowel diseases (Crohn´s disease, colitis ulcerosa)
7. Rheumatoid arthritis
8. Hemophilia or trombophilia (previous venous or pulmonary thrombosis and/or coagulation abnormality)
9. Gestational weeks less than 12th more than 14th
10. Multiple pregnancy

Date of first enrolment
01/01/2007

Date of final enrolment
31/12/2010

Locations

Countries of recruitment
Finland

Study participating centre
Kuopio University Hospital
Kuopio
Finland
70210

Sponsor information

Organisation
Academy of Finland (Finland)

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BOX 99
FI-00501
Helsinki
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Sponsor type
Government

Website
http://www.aka.fi

ROR
https://ror.org/05k73zm37

Funder(s)

Funder type
Government

Funder Name
Academy of Finland (Finland)

Alternative Name(s)
Suomen Akatemia, Finlands Akademi, Academy of Finland, AKA

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Finland

Funder Name
Helsinki and Kuopio University Hospitals (Finland)

Funder Name
The Academy of Finland, Helsinki and Kuopio University Foundations (Finland)

Funder Name
Sohlberg Foundation (Finland)

Funder Name
Suomen Lääketieteen Säätiö

Alternative Name(s)
Finnish Medical Foundation

Funding Body Type
Private sector organisation

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

Location
Finland

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	03/07/2018		Yes	No