Heart Failure and Related Risk Factors after Preeclampsia

Published: 12-08-2014
Last updated: 20-04-2024

Part I- To determine the impact of PE on incidence of macro-and micro-vascular dysfunction reflected by surrogate measures for coronary artery disease (CAD) and HFpEF, and potential deterioration over time.- To perform a genome wide association...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON54718

Source
ToetsingOnline

Brief title
Heart Failure after Preeclampsia

Condition

- Heart failures
- Pregnancy, labour, delivery and postpartum conditions
- Vascular hypertensive disorders

Synonym
Heart failure and Preeclampsia;

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: Cardiovascular Diseases, Cardiovascular risk factors, Heart failure, Preeclampsia

Outcome measures

Primary outcome

Main study parameters/endpoints

Primary endpoints

- The prevalence of HFpEF after PE

- Novel biomarker detection in former PE patients associated with HF in general

and HFpEF in particular.

o Identifying biomarkers that share common pathways for HFpEF and

PE or predict the risk of developing HFpEF after PE.

o Discovery of diagnostic proteins and miRNAs from extracellular

vesicles and circulating cells as well as miRNA from blood samples

for HFpEF in women.

o Discover responses of plasma to cell functions that are key to

vascular endothelial dysfunction using an integrated high content analyses

platform and associate the responses with the presence of HFpEF.

o Elucidate causal relationship of the potential biomarkers with

HFpEF in vitro by linking biomarker analysis to the HFpEF fenotype.

Secondary outcome

Part I

• Lifestyle (questionnaire)

• Cognitive ability (questionnaire)

• Depression score (questionnaire)

• Metabolic syndrome (MetS)

• Arterial endothelial function (Flow mediated dilation (FMD))

• Intima Media Thickness (IMT)

• Glycocalyx thickness (by means of the Glycocheck)

• Venous function (plethysmograph)

• Electrocardiogram (ECG) Ergometry

• Plasma volume measurement

• Hemodynamic status by means of Ultrasonic Cardiac Output Monitor (USCOM)

Part II

• Cardiac MRI

• Cerebral MRI

• Transcranial Doppler measurements

• Neurocognitive assessment

Study description

Background summary

Part I
In western countries, more women than men die of cardiovascular disease (CVD)), making CVD in women an important public health issue. Misdiagnosis of CVD in women is frequently observed, posing the clinician for diagnostic and therapeutic dilemmas that can easily result in inadequate treatment and worse prognosis. Despite these challenges, CVD in women has been underexposed in scientific research.
Women have gender-specific risk factors like a history of preeclampsia (PE) that contribute to their risk for CVD.5 PE complicates 5-10% of first pregnancies, recurs in ~25%, and is associated with a 2-4 fold increased risk for CVD. Moreover, the pre-symptomatic heart failure (HF) stage B occurs in 40% of women with a history of PE. HF stage B is thought to precede the development

of the, mortality related, clinical HF stages C and D (structural heart disease in combination with symptomatic disease). Early detection and tailored intervention of women in with stage B HF decreases progression to the clinical stages and might therefore improve clinical outcome and cardiovascular related mortality.
Phenotypic presentation of HF is currently split up between systolic HF or also called HF with reduced ejection fraction (HFrEF) and diastolic HF or HF with preserved ejection fraction (HFpEF). Women more often have HFpEF in contrast to men. Different pathophysiology and disease progression in women compared to men seems to be an important underlying factor. The current clinical HF diagnostic tools (e.g. natriuretic hormones and high sensitivity troponins) fail to identify early changes that prelude adverse cardiac remodelling and HF, and do not discriminate between HFrEF and HFpEF. Moreover, there are sex-related differences in biomarker levels for detection of CVD. As a result, clinicians are forced to wait for the failing heart to become clinically evident before they can intervene. Therefore, there is an urgent need to assess novel biomarkers that could help select high risk women further needing further follow up and intervention. Biomarkers may not only improve early diagnosis but may also unravel disease pathways of HFpEF. Especially when combined with measurements of subclinical, surrogate risk markers.
Part II
Moreover, a quarter of women with a history of PE report symptoms like impaired concentration and memory capabilities. Several neuropsychological test studies showed measurable deterioration in cognitive function in the field of (working) memory, attention and executive control after PE, with cognitive impairments measurable up till 7 years after the problematic pregnancy suggestive for cerebral small vessel disease (cSVD). cSVD refers to a group of pathological processes that affect the small vessels of brain, including small arteries, arterioles, venules and capillaries. cSVD is associated with derangement of the blood-brain barrier (BBB) and may lead to ischemic lesions in the brain, showing as cerebral white matter lesions at MRI,known for their strong relation to cognitive impairment, micro bleedings and cerebrovascular diseases (CBVD). Contrary, many women experience PE as a traumatic experience, which is further enhanced by premature birth or death of the child. The symptoms and cognitive impairments after PE are very similar to those of posttraumatic stress disorder (PTSD). Several brain imaging studies showed that PTSD symptoms are associated with altered functional brain activity and reduced volume of amygdala/hippocampal regions. By integrated assessment, the interrelated or separate involvement of dysfunctional neuronal and vascular components can be unraveled.

Study objective

Part I
- To determine the impact of PE on incidence of macro-and micro-vascular dysfunction reflected by surrogate measures for coronary artery disease (CAD) and HFpEF, and potential deterioration over time.

- To perform a genome wide association study (GWAS) and associate novel biomarker expression levels with endothelial function, cardiac diastolic function and IMT measurement.
- To identify risk factors and surrogate measures for CVD in a) former PE patients without HFpEF, b) former PE patients with HFpEF and c) healthy parous controls, and changes over time.

Part II
- To evaluate the role of cardiac fibrosis and cardiac small vessel disease in women with HF.
- To evaluate the role of cerebral small vessel disease on cognitive functioning in women with HF.
- To perform a genome wide association study (GWAS) and associate novel and conventional biomarker expression levels with cardiac and cerebral function determined by Magnetic Resonance Imaging (MRI).

Study design

This study consists of 2 parts. Part one is a cross-sectional case-control study where classical as well as more innovative risk factors for CVD will be explored. Part two is a case control study to evaluate the relation between reduced cognitive function in relation to PE and/or reduced cardiac function. All participants within part 1 will be invited for follow-up measurements after a minimum of 2 years.

Study burden and risks

The examinations all occur during one morning in the MUMC+. The visit lasts approximately 5 hours. The only invasive procedure is a venapunction where 135 ml blood will be extracted, and access for infusion of Voluven is ensured. The only unfavourable side effect can be a small hematoma (rare). The IMT and endothelial function will be measured by experienced researchers. The IMT measurement is performed within 10 minutes and is not invasive. For the measurement of the FMD a blood pressure cuff will be placed around the forearm and the pressure will be increased until 200 mmHg and kept at this pressure for 5 minutes. These 5 minutes are slightly uncomfortable for the patient, but experience has shown that patients endure this examination well. After these endothelium dependent tests, sublingual Nitroglycerin (NTG) will be administered to test the endothelium independent response. NTG will be the only medication provided. NTG has a very short bioactive period (T1/2 = 1-4 min).There is a chance of minor and temporary development of adverse effects, such as mild headache (36% of patients), facial flushing, head throbbing, fainting, hypotension and or tachycardia. Clinically, participants will be advised based on their risk profile following standard *cardiovasculair risicomanagement*.(10) Transthoracic echocardiography will be performed by qualified technicians at the cardiovascular department at the MUMC. Experience

shows that this investigation is not experienced as uncomfortable. All measurements will be performed or supervised by an experienced researcher. These investigations are already approved previously in other METC applications (CMO-nr: 2008/226; 2009/004; 10-2-066). The other measurements (questionnaires, blood pressure (BP), weight measurement, urine collection, IMT- and glycocalyx measurement and venous compliance) do not cause any discomfort for the patient beside the time that it takes. On the other hand, potential health improvement and early detection of CV risk profiles and initiation of already existing effective prevention strategies that improve lifestyle are important benefits. Part II Participants who are selected for participating in part II need to visit the hospital again to undergo the additional measurements (cardiac and cerebral MRI, TCD, and neurocognitive tests). Participants will have to lay down two hours for the cardiac MRI and 1.5 hours for the cerebral MRI. If that is too long for the participant, the MRI*s will be divided in more sessions (i.e. two times one hour with a break in between). Patients with contra-indications for MRI, such as pacemakers, metal implants, vessel clips, or metal splinters in the eye will be excluded from the study part II. The administration of the contrast agents is relatively safe. The side effects of the MRI contrast agent (Gadobutrol) are rare and are amongst others nausea (0.25%), vomiting (0.05%), urticaria (0.04%), feeling of warmth, tachycardia, wheals (for each 0.03%), dizziness, itching, vasodilatation, itchy throat (for each 0.02%) and cough, dyspnoea, flushing, hives, generalized itching, oral dryness, facial redness, sensation of heat, skin disorder and aggravated nausea (for each, 0.01%). Out of 14 299 patients, two serious ADRs occurred (0.01%), which were considered by the treating physician to be probable associated with the administration of Gadobutrol; one patient had a severe anaphylactic reaction and the other presented with itching and swelling in the throat. In most cases side effects occur immediately after the start of contrast infusion, and therefore patients will remain in the hospital under supervision for at least 30 minutes after infusion is finished. Adenosine will be used for a cardiac perfusion scan in the resting state and during stress induction. The half-life of adenosine is <10 seconds and all side effects are therefore most likely to be eliminated soon after stopping the infusion. The most prevalent side effects are amongst others: >10% changes in cardiac rhythm or heart frequency, dyspnoea, in <10% headache, dizziness, nausea, flushing, angina pectoris, and anxiety. In <1% palpitations, severe bradycardia, syncope, convulsions, hyperventilation, vomiting, transpiration, and general aching. The neurocognitive tests are not invasive and last for approximately 1 hour. The TCD is also non-invasive and lasts approximately also for 15 minutes.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

P Debeyelaan 25
Maastricht 6202 AZ
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

P Debeyelaan 25
Maastricht 6202 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Cases:
• Women aged >= 18 years
• * till 30 years after the complicated pregnancy
• Experienced PE in any pregnancy. PE defined as hypertension (systolic BP >= 140 mmHg and/or diastolic BP >= 90 mmHg) developed after 20 weeks of pregnancy with the development of proteinuria (>= 300 mg/ 24 hours).
• Women who had their last delivery at least 6 months ago., Controls:
• Women aged >= 18 years
• * till 30 years after the pregnancy that matches the sequence number of pregnancy of the
specifically matched case.
• Experienced pregnancies that were not complicated by pregnancy induced hypertension, preeclampsia, HELLP-syndrome, intrauterine growth restriction and/or abruption placentae.
• Women who had their last pregnancy at least 6 months ago.

Exclusion criteria

Cases: • Women with auto-immune diseases prior to the complicated pregnancy. • Chronic hypertension prior to the complicated pregnancy. • Renal disease prior to the complicated pregnancy. • Pregnant women • Women who do not want to be informed about the results of the tests, or women who do not want their general practitioner and specialist(s) to be informed about the test results., Control group: • Women with auto-immune diseases • Chronic hypertension prior to the matched pregnancy. • Pregnant women • Women who do not want to be informed about the results of the tests, or women who do not want their general practitioner and specialist(s) to be informed about the test results. • Women with IUGR in the matching pregnancy (p<10) • Preterm delivery (gestational age <37 weeks) • Abruptio placentae in obstetric history

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-12-2014
Enrollment:	2580
Type:	Actual

Ethics review

Approved WMO

Date:	12-08-2014

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-06-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL47252.068.14