Female subfertility: a first sign of metabolic and cardiovascular anomalies?

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

Summary

ID

NL-OMON43743

Source
ToetsingOnline

Brief title
Female subfertility: a metabolic and vascular profile

Condition

- Other condition
- Sexual function and fertility disorders

Synonym
infertility, subfertility

Health condition

metabool syndroom, veneuze reservacapaciteit, endotheelfunctie

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: female, metabolic, subfertility, vascular

Outcome measures

Primary outcome

Study 1: Prevalence of metabolic syndrome in subfertile women compared to fertile controls.

Study 2:The cardiovascular profile, in women with an unexplained subfertility or an *expected* decreased ovarian reserve, consisting of:

1. The uterine artery pulsatility index as measure for uterine perfusion
2. The plasma volume as measure for venous reserve capacity
3. The intima media thickness (IMT) of the carotid arteries as proxy for chronic strain
4. The endothelial function of the vascular system (FMD)

Study 3: The cardiovascular profile, in women with a poor ovarian response, consisting of:

1. The uterine artery pulsatility index as measure for uterine perfusion
2. The plasma volume as measure for venous reserve capacity
3. The intima media thickness (IMT) of the carotid arteries as proxy for chronic strain

4. The endothelial function of the vascular system (FMD)

Secondary outcome

not applicable.

Study description

Background summary

Overall, 10 * 15% of couples seek specialist help once in their lives when a spontaneous pregnancy does not occur. These couples are defined subfertile when there is at least one year of unprotected intercourse without conceiving. Subfertility can have different causes. A basic fertility work-up focuses on the reproductive system of the couple. After this basic fertility work up the subfertility remains unexplained in 16-24% of the couples. We hypothesize that cardio-metabolic and hemodynamic abnormalities reducing cardiovascular reserves relate to circulatory redistribution at the expense of uterine perfusion and with it women*s fertility. This could especially be important in the subgroups with an unexplained subfertility and a decreased ovarian reserve. For all possible assessed abnormalities, proven effective treatments are available such as primarily life style corrective actions. Furthermore these interventions could lead to better results in fertility treatment, better obstetric outcome and reduced life long health risks.

Study objective

The overall objective of this study is to examine specific cardio-metabolic and cardiovascular parameters in women of subfertile couples. This study protocol is divided in 3 studies to evaluate several cardio-metabolic/cardiovascular parameters in different subgroups of female subfertility compared to fertile women.

- Study 1 *The metabolic syndrome and female subfertility*: To evaluate the prevalence of metabolic syndrome in all women who are assessed for subfertility. We will also study this prevalence in diverse subgroups as identified by their cause for the subfertility as compared to fertile women.

- Study 2 *The cardiovascular profile in female subfertility*: To study if women with female subfertility classified as unexplained or *expected* decreased ovarian reserve have a less favourable cardiovascular profile than fertile women. For this study we want to evaluate the uterine artery pulsatility index (PI) as measure of uterine perfusion, the plasma volume as measure of venous reserve capacity, the intima media thickness of the carotid

arteries as proxy of chronic strain and the endothelial function, measured by flow mediated dilatation (FMD) of the brachial artery.

- Study 3 *The cardiovascular profile of women with a poor ovarian response*:
To study if women of an IVF population with a *proven* decreased ovarian reserve have a less favourable cardiovascular profile than healthy women.
With these different studies, we hope to identify possible cardio-metabolic/cardiovascular causes for female subfer tility. This can lead to new treatment options for female subfertility, enhancing reproductive and obstetric outcome, and a risk assessment for later in life.

Study design

Cross-sectional studies

Study burden and risks

Study 1: The study of the metabolic syndrome can be synchronized with the basic fertility work- up. Most measurements can be performed on days they have regular examinations for their basic fertility work up. The extra blood samples can be taken on menstrual cycle day 3 when the patient already needs to give a regular blood sample for hormonal status. These blood samples need to be taken in a fasting state of the patient. Patients have to collect a morning urine sample for measurement of albuminuria on cycle day 10, the day they come for a regular ultrasound. The measurement of blood pressure for half an hour can be combined with the bloodsampling on cycle day 3, because the blood pressure must be measured in the follicular phase (before menstrual cycle day 7). Other measurements necessary for the metabolic syndrome (BMI, waist and hip measurement, questionnaire) are part of the regular basic fertility work-up.
All the extra measurements for metabolic syndrome are easily combined with the regular clinical work up and do not induce extra risks for the patient.

Study 2: For the second study the measurements of the uterine artery pulsatility index, the plasma volume, the intima media thickness (IMT) and the endothelial function (FMD) need to be performed before patients start hormonal treatment. For the measurement of the uterine artery pulsatility index patients need an extra hospital visit between menstrual cycle day 3 and 7 for a transvaginal ultrasound. This ultrasound gives no extra risk for the patient.
This visit can be combined with the measurements of the IMT and the endothelial function and is scheduled for 2 hours. The intima media thickness and endothelial function will be measured by an experienced researcher (E. Mulder or V. Lopes van Balen). The IMT measurement is performed within 10 minutes and not invasive. For the measurement of the flow mediated dilatation a blood pressure cuff will be put on the fore arm and the pressure will be increased until 200 mm Hg for 5 minutes. These 5 minutes can be slightly uncomfortable for the patient. After this first measurement the patient receives sublingual

nitrate, which causes vasodilatation. Then the IMT measurement will be repeated to differentiate between endothelial dependent and independent vasodilatation. The patient can experience harmless side effects due to the vasodilatation like headache, short moment of weakness or short drop of the blood pressure. Overall, women endure this examination well. The measurement of the plasma volume takes place on the Nuclear Department. For this measurement 5 microcurie radioactive iodine-125 albumin will be injected. The radiation of iodine-125 is very small (< 0,1 microsievert), even less than the received radiation from a flight. Radiation is a natural phenonomen which is all around us, in our food, the ground and in the air. The small dosage used for the measurement of the plasma volume gives no extra risk for diseases or adverse effects for the patient and is a routine performed measurement in the Nuclear Department. The injection of the radioactive albumin can give a cold feeling at the place of the injection, because it has to be saved in a refrigerator. After the injection in one arm three venous samples need to be taken from the other arm (from one inserted venous canula). Incidentally, this venapuncture can lead to a hematoma. Apart from sporadic extravasation or inability to collect blood, the last 20 years of invasive plasma volume measurement in our clinic has not led to any serious adverse events.

For the patients in study 3, who had an IVF treatment in the period of 2010 * 2013, this study implies they have to come back for one or two hospital visits. The same examinations as described in study 2 will be performed.

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

Study 1*The metabolic syndrome and female subfertility* :
Study group:
- primary subfertility, defined as having no previous pregnancy, or secondary subfertility, defined as a fertility problem after an ongoing pregnancy
- age 18 * 41 years
Control group:
- women with an uneventful pregnancy in history
- at least 6 months post partum
- age 18 * 41 years;Study 2 *The cardiovascular profile in female subfertility*:
Study groups:
- primary subfertility, defined as having no previous pregnancy, or secondary subfertility, defined as a fertility problem after an ongoing pregnancy
- age 18 * 41 years
- participation in study 1
- no abnormalities in the basic fertility work up (*unexplained subfertility*); studygroup 1, or *expected* decreased ovarian reserve (Follicle Stimulating Hormone (FSH) > 8 u/l); studygroup 2
Control group:
- women with an uneventful pregnancy in history
- at least 6 months post partum
- age 18 * 41 years;Study 3 *The cardiovascular profile in women with a poor ovarian response* :
Study group:
- primary or secondary subfertility
- age 18 * 40 years
- IVF / ICSI treatment in the period from 2010 - 2013
- proven decreased ovarian response (* 3 oocytes at an ovum-pick up)
- maximal stimulation dosage of 250 IU FSH per day
Control group:
- primary or secondary subfertility
- age 18 * 40 years
- IVF / ICSI treatment in the period from 2010 - 2013

- severe male factor (TMC < 3 million spermatozoa)
- retrieved * 4 oocytes at an ovum-pick up
- normal stimulation dosage of 150 IU FSH per day

Exclusion criteria

Study 1 *The metabolic syndrome and female subfertility*
There are no exclusion criteria for the study of the metabolic syndrome in the subfertile women.
For the control group exclusion criteria are:
- current pregnancy
- hormonal medication
- breastfeeding;Study 2 *The cardiovascular profile in female subfertility*
For the studies of the measurement of the uterine artery PI, plasma volume, intima media thickness and endothelial function exclusion criteria in all women are:
- hypertension, defined as a blood pressure exceeding 140 mm Hg systolic or 90 mm Hg diastolic, or the use of antihypertensive medication
- diabetes mellitus, defined as a fasting glucose level above 6,1 mmol/L or the use of antidiabetic medication
Additional exclusion criteria for the control group:
- hormonal medication
- current pregnancy
- breastfeeding;Study 3 *The cardiovascular profile in women with a poor ovarian response*
For the study group as well as the control group exclusion criteria are:
- extirpation of an ovary
- cystectomie
Both exclusion criteria can be a reason for a decreased ovarian response.

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):	16-04-2014
Enrollment:	516
Type:	Actual

Ethics review

Approved WMO Date:	16-10-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-07-2016
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	NL42486.068.12