# The influence of the menstrual cycle on diagnostic results of cardiovascular diseases - The Cycle Study II

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To investigate whether the menstrual cycle influences diagnostics in patients with cardiovascular disease

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Cardiac disorders, signs and symptoms NEC |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON48937

**Source**
ToetsingOnline

**Brief title**
The Cycle Study II

### Condition

- Cardiac disorders, signs and symptoms NEC
- Cardiac and vascular disorders congenital

**Synonym**
Cardiovascular disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vasculaire geneeskunde
**Source(s) of monetary or material Support:** Hartstichting

## Intervention

**Keyword:** Cardiac symptoms, Diagnostics, Hyperlipidemia, Menstruation

## Outcome measures

### Primary outcome

In the patients presenting with palpitations, the incidence of cardiac arrhythmias is the main study parameter.

In the patients presenting with chest pain, the time to ST depression during symptom limited exercise testing is the main study parameter.

In the FH patients, lipid levels (TC, LDL-C, HDL-C, TG, apoB and Lp(a)) are the main study parameter.

### Secondary outcome

In the patients presenting with palpitations, the incidence of symptomatic vs. silence arrhythmias is the secondary endpoint.

In the patients presenting with chest pain that do not show ST depressions during symptom limited exercise testing, the subjective experience of chest pain is the secondary endpoint.

# Study description

### Background summary

The menstrual cycle plays a significant role in women*s health and disease. Exacerbation of various different medical conditions such as migraine,

epilepsy, asthma and rheumatoid arthritis at specific menstrual cycle phases is a well-recognized phenomenon (1).
However the knowledge about menstrual cycle-related cardiovascular disease is scarce. This is remarkable because other forms of cyclicity such as diurnal and seasonal patterns have been linked to the occurrence of many cardiac symptoms such as several arrhythmias including paroxysmal tachycardia and atrial fibrillation (2, 3). Although case series and case reports have implicated a relationship between cardiac symptoms and the menstrual period (4-6) no systematic research has been performed on this topic and the association between specific phases of the menstrual cycle and cardiac complains is not routinely examined by health care professionals.
Moreover, previous research has shown that plasma lipids and lipoproteins in healthy regularly menstruating women are lower in the luteal phase compared to the follicular phase(7). These changing lipid levels could cause under or overtreatment of women on lipid lowering therapy when lipid levels are only measured in one menstrual phase. However, until now these cyclic lipid fluctuations have not yet been determined in women with hyperlipidemia.

**Study objective**

To investigate whether the menstrual cycle influences diagnostics in patients with cardiovascular disease

**Study design**

We will perform three pilot studies.
Pilot study 1: 32 women with diagnosed arrhythmia(s) with a regular menstrual cycle.
Pilot study 2: 221 women who are performing an exercise test for medical reasons.
Pilot study 3: 71 women with familial hypercholesterolemia and 71 healthy controls.
The goal is to investigate whether the menstrual cycle influences diagnostic results in cardiac symptoms and lipids.

1.Participants are eligible if they have diagnosed arrhythmia(s) ) and have a regular menstrual cycle (21-35 days).
2.Participants are eligible if they are performing an exercise test for medical reasons in the Erasmus MC and have a regular menstrual cycle (21-35 days)
3.Participants are eligible if they are diagnosed with either heterozygous or homozygous FH based on DNA tests or according to the Dutch Lipid Network Criteria.

Menstrual phase will be determined by asking the participants to report their

first day of vaginal bleeding of their last menstruation to the investigators and will be confirmed by female hormone blood levels 4 times in the menstrual cycle. For study 2, blood samples will be collected one-time only at the same day of the exercise test.
For study 1, blood samples will be collected with at-home finger prick self-tests and for study 3 with venapunctions. The participants are asked to perform the finger prick self-test/venapunction four times in one menstrual cycle:
- the follicular phase (day 3-5)
- during ovulation* (around day 14)
- the luteal phase: mid-luteal (8 days after ovulation) and late-luteal (2 days before expected menstruation)
* determined by the participant to which we provide self-administrable tools to estimate ovulation

Interventions:
Pilot study 1: participants will be connected to the AEM for ±4 weeks (1 menstrual cycle). They will keep an electronic diary to report their symptoms of palpitations. Blood will be collected four times with finger prick self-tests to determine the endogenous female hormone levels. A short digital survey on intake of specific food/drinks/drugs survey will be send on the same days as their finger prick self-tests and they will be asked to weigh themselves that morning.
Pilot study 2: One-time only blood collection (4 EDTA tubes of 7 mL) to determine endogenous female hormone levels and lipids.
Pilot study 3: Blood lipid levels will be determined with venapunction in the participants in 4 different phases of the menstrual cycle. On the same day as the finger prick self-tests, the participants will receive 24 hour recall dietary survey Compl-eat and are asked to report their weight in the morning of that day.

The AEM connection, replacement and removal will take place at the Vascular medicine outpatient clinic of the Erasmus MC. Blood samples from pilot study 2 will be collected at the central place for blood collection of the Erasmus MC. Finger prick self-tests for pilot study 1 and 3 will be carried out at home.

Inclusion will start after METC approval of the study protocol. The total duration of the study is expected to be 1 year.

**Intervention**

1. Patients with palpitations (appendix 1a)
Step 1: Arrhythmia diagnostics and symptoms
AEM
The AEM will be connected to the participating woman at the Vascular Medicine outpatient clinic in the Erasmus MC. After two weeks, the AEM will be disconnected and a new one will be connected. This will be repeated during

until two menstrual cycles of the women have passed.

Diary
All subjective experiences of palpitations will be recorded with an electronic diary during the time of AEM connection.

Step 2: Blood sampling
Blood samples required
4 EDTA tubes (7 mL, plasma)
- 2 to confirm menstrual phase (LH, FSH, estrogen and progesterone)
- 2 for lipid profile (TC, LDL-C, HDL-C, TG, apoB and Lp(a))

Assessing the menstrual phase:
Blood samples of will be collected three times per menstrual cycle to measure levels of LH, FSH, estrogen and progesterone.

Timing:
- First blood sample: 3 to 5 days after start of the menstruation (menstruation or early follicular phase).

- Second blood sample: directly during (same day or day after) the LH-peak (determined by the patient by a self-administrable tool to estimate ovulation).

- Third blood sample: 21 to 28 days after the first day of menstruation (luteal phase).

When the patient uses the contraceptive pill:
- First blood sample: at the first day of a new pack with instructions to take the first pill after blood is drawn.

- Second blood sample: around day 10 of the pack.

- Third blood sample: around day 21 of the pack

2. Patients with chest pain
Step 1: Cardiac ischemia diagnostics and symptoms
Symptom limited exercise testing
The symptom limited exercise testing will be performed at the same days as the blood sample collections (same as in palpitations population).

Step 2: Blood sampling
Same as in palpitations population.

3. Patients with FH

Blood sampling
Same as in palpitations population.

4. Controls
Step 1: Cardiac ischemia/arrhythmia diagnostics and symptoms
Same as in palpitations/chest pain population

Step 2: Blood sampling
Same as in palpitations population.

**Study burden and risks**

We expect a minimim burden and a negligible risk for the participators.

# Contacts

**Public**
Selecteer

's Gravendijkwal 230
Rotterdam 3000CA
NL
**Scientific**
Selecteer

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- 18 years or older
- Regular menstrual cycle
- Cardiac complaints or diagnosed Familial Hypercholesterolemia
- Treated by a cardiologist/GP for their complaints

## Exclusion criteria

- <18 years of age
- Postmenopausal
- Use of contraception that affects the menstrual cycle (except for the oral contraceptive pill with monthly stopping)
- Underwent ovariectomy
- Pregnant
- Otherwise does not have a regular menstrual cycle
- Unable to give informed consent

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 01-10-2019 |
| Enrollment: | 324 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 03-04-2019 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 02-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# 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 | NL66384.078.18 |