# BRCA mutations and Ovarian ageing in women applying for in vitro fertilization and preimplantation genetiC diAgnosis

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Ethische beoordeling Status	Positief advies Werving gestopt
Type aandoening	
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

## Samenvatting

#### ID

NL-OMON21616

Bron NTR

Verkorte titel BROCA-2

#### Aandoening

BRCA1/2, ovarian reserve (AFC, AMH, ovarian response), ongoing pregnancy BRCA1/2, ovariele reserve (AFC, AMH, ovariele response), doorgaande zwangerschap

## Ondersteuning

**Primaire sponsor:** Participating sites: UMC Utrecht, Maastricht UMC+, Academic Hospital Brussels, UMC Groningen, Academic Medical Center Amsterdam **Overige ondersteuning:** Self funding

## **Onderzoeksproduct en/of interventie**

## Uitkomstmaten

#### Primaire uitkomstmaten

Serum AMH level

## **Toelichting onderzoek**

#### Achtergrond van het onderzoek

Rationale:

The study proposal aims to confirm the observation of a reduced quantity of the follicle pool in BRCA (Breast Cancer) mutation-positive women. If confirmed, advanced ovarian ageing in BRCA mutated women will have a major impact on their general health and fertility prospects. Furthermore, identification of genes that contribute to the endowment and wastage of follicles in the ovaries and thus timing of menopause will add to the understanding of the physiological mechanism of the ovarian ageing process.

In the current study we will be able to study the effect of BRCA mutations on the ovarian ageing process, by comparing serum anti-Müllerian hormone (AMH) levels between cohorts of BRCA mutation-positive women and normal controls, applying for in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD).

The main hypothesis is that normo-ovulatory women with a deleterious BRCA mutation have lower levels of AMH compared to normal controls, with at least a difference of 0.90 ng/ml, suggesting an effect size of approximately five years in menopausal age.

Objective:

To demonstrate the presence of a reduced age specific ovarian reserve status in BRCA mutation carriers by:

1.using serum AMH as ovarian reserve test

2.using the antral follicle count (AFC) as ovarian reserve test

3.using ovarian response to ovarian hyperstimulation for IVF as proxy variable of ovarian reserve status

Study design: The study is designed as an observational prospective cohort study in exposed and non-exposed women during their first IVF with ICSI and PGD treatment cycle

Study population: Couples, with normo-ovulatory women between 18 and 41 years old, applying for their first IVF with ICSI and PGD treatment cycle in view of their status as carrier of a female BRCA mutation will be asked to participate. Normo-ovulatory women between 18 and 41 years old, who visit the department of Reproductive Medicine for their first IVF, with ICSI and PGD treatment cycle unsuspected for reduced ovarian reserve, are asked to participate as control group.

Main study endpoints: The main study endpoint will be advanced ovarian ageing measured by serum AMH levels.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The nature and extent of the burden and risks associated with participation can be stated as negligible. Participating is not associated with (medical) benefits.

#### Doel van het onderzoek

The main hypothesis is that normo-ovulatory women with a deleterious BRCA mutation have lower levels of AMH compared to normal controls, with at least a difference of 0.90 ng/ml, suggesting an effect size of approximately five years in menopausal age.

#### Onderzoeksopzet

The aim is to investigate a total of 34 BRCA mutation positive women and 91 controls in a period of approximately 4 years. Data analysis and publishing results will take  $\frac{1}{2}$  year, resulting in a total study duration of approximately 5 years.

#### **Onderzoeksproduct en/of interventie**

blood sample

## Contactpersonen

## **Publiek**

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## Wetenschappelijk

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## **Deelname eisen**

# Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Case group (BRCA mutation carriers)

- Female age > 18 years and < 40 years
- Regular menstrual cycles (i.e. mean cycle length of 21-35 days)
- First IVF with ICSI and PGD treatment cycle due to a female pathogenic BRCA mutation
- Written informed consent

Controle group (non suspected for BRCA mutation):

- Female age > 18 years and < 40 years
- Regular menstrual cycles (i.e. mean cycle length of 21-35 days)

- First IVF with ICSI and PGD treatment cycle due to an indication unsuspected for reduced ovarian reserve status

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## Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Case group (BRCA mutation carriers)

- Ovarian surgery
- Chemo therapy
- Radiation therapy to the pelvis, lower abdomen or total body radiation

 Known female endocrine or autoimmune abnormalities (i.e. Cushing syndrome, type I Diabetes Mellitus, hypothyroidism, hyperprolactinemia, adrenal insufficiency, hypoparathyriodism, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus)

- Body Mass Index > 35 kg/m2
- Polycystic Ovarian Syndrome (Rotterdam criteria)
- Early follicular FSH > 15 IU/L
- Known Human immunodeficiency virus (HIV) infection

- Known female genetic abnormalities suspected for subfertility (structural or numerical abnormalities of the X-chromosome (i.e. Turner; s syndrome, fragile X syndrome), or abnormalities of human autosomal functionally relevant genes, other than a BRCA mutation, suspected for subfertility

Controle group (non suspected for BRCA mutation):

- Ovarian surgery
- Chemo therapy
- Radiation therapy to the pelvis, lower abdomen or total body radiation

 Known female endocrine or autoimmune abnormalities (i.e. Cushing syndrome, type I Diabetes Mellitus, hypothyroidism, hyperprolactinemia, adrenal insufficiency, hypoparathyriodism, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus)

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## Onderzoeksopzet

## Opzet

Туре:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

## Deelname

Nederland	
Status:	Werving gestopt
(Verwachte) startdatum:	01-08-2014
Aantal proefpersonen:	125
Туре:	Werkelijke startdatum

## Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

## **Ethische beoordeling**

Positief advies Datum: Soort:

25-07-2014

Eerste indiening

## Registraties

## Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

Register	ID
NTR-new	NL4347
NTR-old	NTR4703
Ander register	UMC Utrecht : 14-175

## Resultaten

## Samenvatting resultaten N/A