Molecular studies on reduced ovarian reserve and embryo competence in BRCA1/2 mutation carriers

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Investigate the association between BRCA1/2-mutations, DNA damage, apoptosis and oocyte/embryo quality in immature germinal vesicle (GV) bearing oocytes, immature metaphase 1 (MI) and unfertilized mature metaphase 2 (MII) oocytes and affected early-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive tract and breast disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON44516

Source
ToetsingOnline

Brief title
BRCA1/2, ovarian reserve and embryo competence (ORCA)

Condition

- Reproductive tract and breast disorders congenital
- Breast neoplasms malignant and unspecified (incl nipple)
- Breast disorders

Synonym
hereditary breast cancer; subfertility

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: particuliere stichting

Intervention

Keyword: BRCA gene, Breast cancer, Embryo competence, Ovarian reserve

Outcome measures

Primary outcome

Morphology, the presence of apoptosis, DNA damage and chromosomal aberrations in the (im)mature oocytes and embryos of BRCA1/2-mutation carriers compared to oocytes and embryos of controls.

Secondary outcome

NA

Study description

Background summary

Previously, it has been shown that females carrying a BRCA1-mutation produce less mature oocytes upon ovarian stimulation compared to non-carriers. Mice carrying a Brca1-mutation also have less primordial follicles and their oocytes and surrounding ovarian tissue show more DNA damage. In addition, Brca1-mutant embryos also have increased amounts of numerical and structural chromosomal aberrations after γ-irradiation compared to wild-type and heterozygous litter mates. These suggest that female BRCA1-mutation carriers undergoing in vitro fertilization (IVF) with or without pre-implantation genetic diagnosis (PGD), to avoid transmission of their BRCA1-mutation to offspring, would have a decreased chance on a successful IVF/PGD procedure. These results also suggest that the quality of the embryos of female BRCA1-mutation carriers could be diminished. At the moment, the mechanism behind these clinical observations is not clear. We hypothesize that a decrease in ovarian reserve is the result of an increase in DNA damage in oocytes, leading to an increased induction of apoptosis and chromosomal instability. This is plausible since BRCA1, as well as BRCA2, plays an important role in the repair of DNA damage.

Study objective

Investigate the association between BRCA1/2-mutations, DNA damage, apoptosis

and oocyte/embryo quality in immature germinal vesicle (GV) bearing oocytes, immature metaphase 1 (MI) and unfertilized mature metaphase 2 (MII) oocytes and affected early-developmental stage embryos from BRCA1/2-mutation carriers compared to controls.

Study design

Prospective cohort study.
Human (im)mature oocytes and embryos of females undergoing IVF/PGD treatment will be collected. Only residual material will be used, i.e. GV, MI oocytes, unfertilized MII oocytes and embryos with the BRCA1/2-mutation or with another genetic disorder, diagnosed by PGD. To determine oocyte and embryo quality, their morphology will be scored during IVF procedure. By using immunocytochemical staining of the acquired material, DNA damage and apoptosis will be investigated. SNP arrays will be used to screen for structural and numerical chromosomal variations genome-wide and determine parental origin.

Study burden and risks

Participation in the study will not involve any risk or additional burden for the patient. No additional visits, physical examinations or other tests, blood samples or other biological material other than those already required for IVF/PGD is needed. Participation has no effect on IVF treatment of the patient nor will it have an added value for the patient at this stage of the study.

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

-IVF/PGD treatment for a BRCA1/2-mutation, both male and female mutation carriers (Control group A and Test group, respectively)
-IVF/PGD treatment because the male partner has an autosomal dominant hereditary disorder (such as but not restricted to Huntingtons disease or Marfan syndrome) or both male/female partners carry a autosomal recessive hereditary disorder (such as but not restricted to cystic fibrosis or spinal muscular atrophy)(Control group B)

Exclusion criteria

- Known hereditary disease other than due to BRCA1/2-mutations in the female
- Known genetic abnormalities in female leading to diminished ovarian reserve: carriers of fragile X syndrome or abnormalities of the X-chromosome
- Hereditary disease in male known to affect embryo development
- Known history of a malignancy in the female
- Endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or renal)
- History of cancer treatment in the female or male
- Non-Dutch couples, not able to understand the patient information to give informed consent properly

Study design

Design

Study type:	Observational non 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):	25-02-2015
Enrollment:	104
Type:	Actual

Ethics review

Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	NL50432.000.14