# Effects of IVF culture conditions on the embryonic genome, methylome and transcriptome: a study to evaluate the safety and quality of different culture systems

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To study the effects of in vitro culture conditions, such as different culture media or oxygen tension, on omic layers (i.e. genome, epigenome and transcriptome) of preimplantation human embryos and to relate this to chromosoom instability (CIN).

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48079

**Source**
ToetsingOnline

**Brief title**
IVF culture conditions and embryonic multi-omics

### Condition

- Other condition

**Synonym**
subfertility

**Health condition**

subfertiliteit

## Sponsors and support

**Primary sponsor:** Medisch Universitair Ziekenhuis Maastricht
**Source(s) of monetary or material Support:** fertility foundation

## Intervention

**Keyword:** chromosome instability, culture conditions, epigenome, IVF

## Outcome measures

### Primary outcome

a) To evaluate the effect of 4 (previously) widely used IVF culture media (Sydney IVF Medium, G3, G5 and HTF) on the genome, epigenome (mainly methylome and chromatin accessibility) and transcriptome of human pre-implantation embryos. These culture media have been associated with differences in early life outcomes.

b) To evaluate the effect of preimplantation human embryo culture at different oxygen concentrations (5% and 20% oxygen), on the genome, epigenome (mainly methylome and chromatin accessibility) and transcriptome of pre-implantation human embryos. Both concentrations have been widely used in human ART.

### Secondary outcome

c) To establish whether there are links between the epigenome (mainly methylome and chromatin accessibility), genome and transcriptome that could explain high levels of CIN seen in human IVF embryos.

d) To develop in silico methods for lineage tracing that can be used to determine the fate of chromosomally abnormal cells during embryo development.

# Study description

### Background summary

The success rates of human assisted reproductive technologies (ART), such as in vitro fertilisation (IVF), are relatively low. This is probably caused by a combination of treatment and patient related factors, although the exact aetiology and underlying mechanisms are still unknown. A growing body of evidence shows that the IVF culture conditions, such as culture media or oxygen tension, influence outcomes, including embryo development, pregnancy rates and even short- and long-term health outcomes of the offspring. On the other hand, a high rate of aneuploidy is seen in IVF embryos, which is also associated with treatment failure. As it has been shown in cancerous cells, that global hypomethylation is associated with chromosome instability (CIN), and that in the post-zygotic stage of an embryo global demethylation takes place, that is vulnerable for environmental cues, we hypothesize that IVF culture conditions can alter the epigenome (in particular methylome) and transcriptome landscape of preimplantation IVF embryos and, in turn, affect aneuploidy and treatment success rates.

### Study objective

To study the effects of in vitro culture conditions, such as different culture media or oxygen tension, on omic layers (i.e. genome, epigenome and transcriptome) of preimplantation human embryos and to relate this to chromosoom instability (CIN).

### Study design

Observational, retrospective study using donated surplus cryopreserved human embryos from ART treatments carried out in the past (between 2003-2006 and 2010-2013). Before cryopreservation on day 3, embryos were cultured in G3-1 or G5-1 (Vitrolife), K-SICM (Cook), or HTF (Lonza) under either physiological (5%) or atmospheric (20%) oxygen tension. After thawing, single cells will be isolated either immediately, i.e. at cleavage-stage (day-3), or after extended culture until the blastocyst-stage (day-5/6) in a time-lapse incubator. Single cells will be analysed using single-cell multi-omic assays, e.g. single-cell nucleosome, methylation and transcription sequencing (ScNMTseq), which simultaneously profiles the chromatin accessibility, methylome and transcriptome of a single cell. Parental genome data, obtained from DNA isolated from saliva, will be used to distinguish between parental alleles in the embryo. The latter is of great importance to investigate when and how maternal molecular components, e.g. maternal RNA, are superseded by embryonically derived components.

### Intervention

The embryo's will be cultured in the medium and oxygen level they were cultured in before freezing. This can be one of the following media: HTF, G3, G5, Sydney IVF Medium, and one of the following oxygne concentrations: 5% or 20%.

### Study burden and risks

There is no risk or burden for participating couples, except for the donation of their embryos and ceding a saliva sample.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Inclusion criteria

- MUMC: embryos from couples who took part in the MEDIUMtrial-0 or the MEDIUMtrial-1
- UMCG: embryos from couples who underwent an IVF treatment between January

2012 and December 2013.

### Exclusion criteria

- embryo's that do not survive the thawing procedure

## Study design

### Design

**Study type:** Interventional

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Basic science |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 16-03-2020 |
| Enrollment: | 219 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 16-01-2020 |
| Application type: | First submission |
| 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 | NL71199.000.19 |