GnRH analogues for ovarian stimulation and embryo quality: monitoring embryo development using a time lapse incubator.

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To investigate if the use of different stimulation protocols / GnRH-analogues affects embryo developmental kinetics after IVF treatment. We hypothesize that GnRH analogues differentially affect embryo development through differences in follicular…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual function and fertility disorders
Study type	Observational invasive

Summary

ID

NL-OMON47282

Source
ToetsingOnline

Brief title
GnRH Analogues and Monitoring Embryo Development (GAMED)

Condition

- Sexual function and fertility disorders

Synonym
fertility disorder, Subfertility

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Embryo quality, EmbryoScope, GnRH Agonist, GnRH antagonist

Outcome measures

Primary outcome

The aim of the study is to analyze the effect of the GnRH analogue used on embryo developmental kinetics. The main study parameter is the time needed from completion of the first cleavage division until reaching the 4-cell stage, determined by retrospective analysis of time lapse recordings.

Secondary outcome

Secondary study parameters on embryo developmental kinetics will be the time interval between:

- Disappearance of the pronuclei and first cleavage of the embryo, as well as reaching the 2-cell, 4-cell and 8-cell stage;
- Completion of first cleavage and reaching the 3-cell and 8-cell stage;
- The 3-cell and 4-cell stage.

We will also analyze embryo morphology on Day 3 and determine the proportion of good quality embryos, as defined by embryos with 8 cells, <20% fragmentation, equally sized blastomeres and no irregularities observed in the cytoplasm. For the embryo that is selected for transfer, the implantation potential will be recorded.

Study description

Background summary

Selection of the best embryo for transfer is the key to achieve high implantation rates and is still largely based on morphological assessments at fixed time points. Newly emerging techniques, enabling safe time-lapse photography of embryo development, demonstrate that morphological changes occur rapidly around the time of cell division, with an initial increase in fragmentation, followed by re-uptake. Therefore, if observed at the wrong moment, good quality embryos can be erroneously classified as poor quality. During a previous randomized trial, comparing the effect of ovarian stimulation protocols with GnRH agonist or GnRH antagonist co-treatment on embryo aneuploidy rates, we made observations indicating that GnRH antagonist embryos may be developmentally delayed in reaching the 8-cell stage on Day 3. If confirmed, optimal timing of embryo morphology assessment may be different from what is routine practice in labs optimized for GnRH agonist stimulation protocols. Morphological selection of GnRH antagonist embryos may thus occur at a suboptimal moment and lead to selection of the *wrong* embryo. Optimizing timing of embryo morphology assessment for GnRH antagonist embryos may thus result in improved embryo implantation rates.

Study objective

To investigate if the use of different stimulation protocols / GnRH-analogues affects embryo developmental kinetics after IVF treatment. We hypothesize that GnRH analogues differentially affect embryo development through differences in follicular growth during stimulation. To chart these changes, we aim to perform time-lapse photography using the EmbryoScope* on embryos from IVF patients, randomized for either GnRH-agonist or antagonist co-treatment. To analyze underlying molecular pathways, mRNA and protein expression of a panel of relevant genes will be assayed in cumulus cells from individual oocytes in relation to the analogue used. Furthermore we will perform RNA-sequencing. To explain variations in gene expression, we will also assay epigenetic programming in these cumulus cells.

Study design

Prospectively randomized multicenter interventional trial in 82 women undergoing IVF treatment.
Randomization to one of two routinely applied ovarian stimulation protocols:
(1) GnRH agonist long stimulation protocol with daily administration of recombinant FSH.
(2) GnRH antagonist stimulation protocol starting with administration of rFSH on cycle day 5, with GnRH antagonist treatment start on stimulation day 1.

Study burden and risks

This study will not interfere with the standard IVF and embryo transfer procedures, except that embryos will be cultured in the EmbryoScope*. Available data from international studies and our own validation show that this is a safe incubator for human embryos and may even improve culture conditions. Cumulus cells are normally discarded. The study will not negatively affect pregnancy rates, nor will it affect the women*s or children*s health. Insight gained from this study will help increase our understanding of factors influencing embryo development and may improve embryo selection and IVF outcomes for future IVF patients.

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

Female age <= 37 years

BMI < 32 kg/m2
Regular cycle (25-35 days)
Partner with normal semen parameters (Volume: >= 1.5 ml, concentration: >15*10^6/ml, progressively motile sperm > 32%, so with a VCM >= 7.2)
Standard indication for IVF
Undergoing first or second IVF cycle

Exclusion criteria

Indication for ICSI
Endometriosis
Expected poor response
One previous IVF treatment not resulting in embryo transfer
Medical contra indication for pregnancy or IVF treatment

Study design

Design

Study type: Observational invasive

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-08-2012
Enrollment:	82
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cetrorelix acetate
Generic name:	cetrotide
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	triptorelin-acetate
Generic name:	Decapeptyl
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-04-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-03-2020
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
EudraCT	EUCTR2011-005919-91-NL
CCMO	NL37697.000.12