A study of the effects of a novel ovarian stimulation regimen on embryo aneuploidy rates in IVF, and the impact of aneuploidy on implantation, as assessed in an in vitro model.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON33651

Source
ToetsingOnline

Brief title
Aneuploidy in IVF embryos and impact on implantation

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Abortions and stillbirth
- Sexual function and fertility disorders

Synonym
embryo aneuploidy

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,NWO-AGIKO stipendium (G. Teklenburg)

Intervention

Keyword: aneuploidy, in vitro implantation, IVF, preimplantation genetic screening

Outcome measures

Primary outcome

Proportion of chromosomally abnormal and mosaic day 3 embryos per patient based on PGS analysis.

Secondary outcome

- Number of oocytes retrieved, fertilization rates and proportion of morphologically high quality embryos on day 3.
- Serum estradiol, LH, progesterone, androgen and hCG levels on cycle day 3 and day of hCG.
- Developmental and in vitro implantation potential: invaded, attached or not-attached.
- Total number of embryonic cells and proportion of aneuploid cells on day 10 after extended culture.

Study description

Background summary

By limiting the number of embryos transferred to the uterus to only a single embryo, the risk of multiple gestation can be reduced. In order to improve the

effectiveness of single embryo transfer, the ability to select the embryo with the highest potential to develop into a healthy child is of vital importance. While embryos rated as high quality by standardized morphological assessment are associated with higher implantation and pregnancy rates, it is still not possible to predict with certainty which embryo will implant and has the highest potential to develop into a healthy child. An increasing body of evidence indicates that the incidence of chromosomal abnormalities in embryos is extremely high and good embryo morphology does not necessarily exclude an abnormal chromosomal constitution. Since aneuploidies are considered the main cause of embryonic wastage and loss, this phenomenon may be primarily responsible for the relatively poor pregnancy rates reported after IVF.
The introduction of fluorescent in-situ hybridization (FISH) techniques for preimplantation genetic diagnosis has enabled screening of embryos for chromosomal aneuploidies before transfer. Preimplantation genetic screening (PGS) is now applied clinically in numerous IVF laboratories throughout the world. However, a recent meta-analysis has shown that PGS is yet to have a significant impact on IVF outcomes. This may partly be explained by the fact that most aneuploidies observed at this stage originate during the first mitotic divisions of early preimplantation development, resulting in chromosomally mosaic embryos. If a chromosomally mosaic embryo is biopsied, this cell may not be representative for the remaining embryo.
Our group recently completed the first prospectively designed, randomized trial, comparing embryo aneuploidy rates following two ovarian hyperstimulation regimens in a group of 111 IVF patients. Milder stimulation was associated with a reduction in the number of oocytes retrieved and embryos generated. However, the proportion of chromosomally normal embryos was significantly increased. These results showed for the first time a direct correlation between the ovarian stimulation protocol and the incidence of chromosome abnormalities in the embryo. The observation that mild stimulation in some patients still resulted in a high oocyte yield and concurring higher proportions of abnormal embryos , underscores the need of further development of minimal stimulation approaches.

Study objective

In this study we aim to compare the effect of two different ovarian stimulation protocols on embryo quality in a group of women of 39 years or younger, in a prospectively randomized controlled trial. PGS will be performed to assess chromosomal competence of the resulting embryos, as we have previously shown this to reflect embryo quality. Embryos diagnosed as chromosomally normal will be transferred or cryopreserved. Embryos diagnosed as aneuploid or mosaic will be investigated for their implantation and developmental potential, by transferring them to an in vitro implantation model. After an extended culture period, implantation behaviour will be assessed and the entire embryo is reanalysed to detect the proportion of chromosomally abnormal cells. The implantation behaviour will be correlated to the type of abnormality and the

chromosome(s) involved.

Study design

Prospectively randomized, clinical study in 110 women undergoing IVF treatment

Study burden and risks

There is an ongoing debate as to whether biopsy of embryos may decrease the implantation potential of the embryo. To date, this has not been directly investigated. It is likely that any decreased developmental potential is counteracted by the effect of not transferring aneuploid embryos. The biopsy of two cells may have more impact on development, but has also been shown to increase the accuracy of the diagnosis.
As the in vitro implantation procedure will use only embryos diagnosed as abnormal or mosaic after PGS analysis which would otherwise be discarded, there is no additional risk involved. This model will, however, yield unique data on the significance of chromosomal mosaicism for the implantation potential of the embryo.

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 * 39 years
BMI <32 kg/m2
Regular cycle (25-35 days)
Standard indication for IVF
No major uterine abnormalities

Exclusion criteria

Indication for IVF male factor with a total motile sperm count < 10x106
ICSI or andrological indication
Known abnormal (male or female) karyotype
Oocyte donation
One previous IVF treatment not resulting in embryo transfer
Poor response (< 4 oocytes obtained at oocyte pick-up) in the first or second cycle
Female age 39 in case of a previous poor response (< 4 oocytes obtained at oocyte pick-up) at the age of 38
History of recurrent abortion

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-10-2008
Enrollment:	110
Type:	Actual

Ethics review

Approved WMO Date:	17-12-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2010
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	NL18499.000.07