The contribution of paternal chromatin to chromosome segregation errors in human pre-implantation embryos.

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We aim to: 1) Characterize differences between paternal and maternal chromatin organization and pericentric heterochromatin formation after fertilization and during pre-implantation embryo development. 2) Analyze if this asymmetry affects formation...

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

Summary

ID

NL-OMON35343

Source
ToetsingOnline

Brief title
Impact of paternal chromatin on embryo aneuploidy.

Condition

- Sexual function and fertility disorders

Synonym
Embryo quality, sperm quality

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,•Portugal National PhD grant aan M. Avo Santos: Fundacao para a Ciencia e Tecnologia (FCT) Project no

SFRH/BD/39063/2007

Intervention

Keyword: aneuploidy, pericentric heterochromatin, pre-implantation embryos

Outcome measures

Primary outcome

In the first part of the study, human tripronuclear zygotes and surplus embryos will be arrested at prometaphase by colcemid treatment, to visualize chromosomes and study protein markers by immunofluorescence. In addition mRNA expression of relevant genes will be assessed. The second part uses an established assay that generates a high frequency of chromosome attachment errors by treatment with monastrol, followed by monastrol withdrawal and monitoring of the correction of these attachment errors.

For part I, the primary study parameter is presence and localization of a set of marker proteins, informative for heterochromatin formation and associated proteins on the pericentric region from paternal versus maternal chromosomes in embryos at different stages of development. For part II, the primary outcome measure is the frequency of alignment failure of paternal versus maternal chromosomes.

Secondary outcome

N.A.

Study description

Background summary

Screening of human embryos for chromosomal aneuploidies before transfer in in vitro fertilization by us and others has revealed the majority of embryos to be chromosomally abnormal. The bulk of these errors arise during the first mitotic divisions of early pre-implantation development, resulting in chromosomally mosaic embryos. Research into the origin of embryo aneuploidy has so far focused on meiotic segregation errors and on identifying causative factors in the oocyte. This study aims to address the paternal contribution to embryo aneuploidy.
Upon fertilization, the paternal genome, contributed by the sperm, is unpacked by removing the protamines; small basic proteins that allowed compaction of the genome in the small sperm head. The protamines are immediately replaced by maternally provided histones, the basic building blocks of chromatin in all somatic cells. However, part of the paternal genome was already packaged by histones when it entered the oocyte, and these histones are not replaced. Histones may be modified by methylation, acetylation, and other modifcations. Such *marks* provide epigenetic information that may influence the regulation and behavior of chromosomes. In the context of cell divisions, the histones and histone modifications on pericentric heterochromatin are important. Pericentric heterochromatin is the region on the chromosome that flanks the centromere. Correct establishment of the epigenetic signature of this region is well known to be crucial for chromosome segregation in somatic cells. We now have evidence indicating that sperm-inherited epigenetic marks are required for pericentric heterochromatin formation in the zygote. Interestingly, variable nucleosome content is a frequent characteristic of human sperm, particularly of subfertile men. We hypothesize that paternal and maternal chromosomes differ in the composition of pericentric heterochromatin which in turn impacts on segregation behavior of paternal and maternal chromosomes during pre-implantation embryo development.

Study objective

We aim to:
1) Characterize differences between paternal and maternal chromatin organization and pericentric heterochromatin formation after fertilization and during pre-implantation embryo development.
2) Analyze if this asymmetry affects formation of the kinetochore; a specialized protein structure that is required for microtubule attachment during metaphase and cell cycle checkpoint function.
3) To functionally investigate the capacity of paternal and maternal chromosomes to align properly on the metaphase plate in tripronuclear zygotes.

Study design

The first part of the study is descriptive, involving fixed material: human tripronuclear zygotes and surplus embryos. The second part uses an established assay to assess chromosome alignment and error correction in tripronuclear

zygotes.

Study burden and risks

The study will not interfere with the standard IVF and embryo transfer procedures and will only use surplus embryos. 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 to increase our understanding of factors contributing to the high rates of embryo aneuploidy in IVF. If our results show that paternally derived chromosomes are more frequently involved in alignment failure, and if this can be related to the pericentric heterochromatin signature, the next step would be to relate this to the variable nucleosome content in sperm and sperm quality parameters. Finally this may lead to the development of improved sperm cell selection protocols, which may aid in lowering the frequency of embryo aneuploidy in embryos from 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

Written informed consent

Exclusion criteria

No surplus embryos available
Surplus embryos with excessive degeneration or fragmentation (>50%)

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2012
Enrollment:	621
Type:	Actual

Ethics review

Approved WMO

Date:	13-03-2012
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	NL38053.000.11