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Whole cytoplasmic replacement at zygote stage (day 1 embryo) for the treatment of infertility

Submission date
14/04/2021

Recruitment status
No longer recruiting

Registration date
01/05/2021

Overall study status
Stopped

Last Edited
13/04/2023

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Assisted reproductive technology (ART) is used to treat infertility. There are still many gaps in the knowledge base of ART. One of the persistent obstacles is recurrent implantation failure (RIF), commonly of unknown origin, where the embryo fails to implant onto the side of the uterus wall. Fortunately, recent advances in ART as well as in the knowledge of human biology have clarified at least some of the causes of this condition. Some genes may cause the oocyte (human egg) to be unable to develop into a competent embryo. A number of other conditions may also have an impact on RIF. The only reasonable alternative for patients with RIF is oocyte donation (usually from non-related young healthy women). For some, the loss of having a genetic connection with the child is unacceptable. This complex psychology involves social, ethical and religious considerations. Whole cytoplasm replacement using donor oocytes could potentially offer a solution.
In the UK, only patients at risk of transmitting mitochondrial disease (inherited from the mother only, extremely rare diseases that have a disastrous impact on health and lifespan) are potential candidates for this type of treatment, whereas infertile couples who have undergone multiple failed cycles following ART are barred from such options. Recent data suggests that the attempt to treat mitochondrial diseases with pronuclear transplantation could possibly have consequences because mitochondria are inherited randomly and the distribution process among cells and tissues of a fetus is not well understood. It could potentially lead to mitochondrial disease occurring at a later age. RIF is a more promising indication for applying a pronuclear transplantation technique, because it is not necessarily associated with mitochondrial mutations. The aim of this study is to enhance embryo development following pronuclear transplantation (PNT), replacing the patient's zygote (fertilized egg) cytoplasm with the cytoplasm from a fertile donor zygote.

Who can participate?
Infertile women and men with repeated implantation failure after ART and poor embryo development in previous cycles.

What does the study involve?
Patients will sign a written consent form where they are informed of the uncertainty of whether individuals resulting from nuclear transfer may develop unknown symptoms or disease because

of the novel procedures. Alternatives to the experimental protocol must be offered. A consultation with an attending IVF physician going over each of the steps and detailing alternatives and limitations is part of the protocol. The protocol has been approved by an institutional review board.
Patients and oocyte donors undergo standard follicular stimulation cycles, with the option of cryopreservation of oocytes by vitrification (ultra-fast freezing). The patient and donor oocytes are injected with the patient's partner’s sperm and are grown until blastocyst stage (Day 5 to 7 embryos) in an incubator, and several cells are taken for genetic testing. Only a single tested thawed embryo is transferred to the patient's uterus. The resulting pregnancy rate is measured and the health of the baby is assessed at birth and long-term follow-up on a yearly basis for the first 7 years, and then on a bi-yearly basis until age 18.

What are the possible benefits and risks of participating?
Whole cytoplasm replacement via PNT may be able to overcome infertility which was not successfully treated with traditional ART techniques and could be a reasonable alternative to egg donation. This may give the opportunity to have genetically related children. It is known that the zygotes develop normally to blastocyst stage (the stage at which genetic testing and cryopreservation are routinely performed), but the long-term consequences of PNT are unknown.

Where is the study run from?
Nadiya Clinic (Ukraine)

When is the study starting and how long is it expected to run for?
February 2014 to September 2022

Who is funding the study?
Nadiya Clinic (Ukraine)

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Pronuclear transplantation (PNT) in patients with repeated failure following assisted reproduction

Study objectives
The whole cytoplasm replacement via pronuclear transplantation may potentially provide more suitable embryos for embryo transfer and result in more ongoing pregnancies in selected cohort of patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 10/03/2015, Ukrainian association of reproductive medicine (58005, Chernivtsi, Trepko str., 1-A, Ukraine; +38(044) 465-10-46, +38 (095) 853 81 35; uarm.kiev@gmail.com), ref: not applicable
2. Approved 28/12/2018, Commission of Bioethics of the National Academy of Sciences of Ukraine (54, Volodymyrska Str., room 232, Kiev-30, 01601, Ukraine; Tel: +380 (0)44 239 6623; biomed@nas.gov.ua), ref: 882/983

Study design
Interventional pilot non-randomized study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Recurrent implantation failure associated with poor embryo development that cannot be overcome by standard IVF

Interventions
Patient and donor are usually stimulated simultaneously via standard stimulation protocols in order to achieve simultaneous oocyte retrieval and fertilization. In some instances, follicular stimulation may not be synchronized and either patient or donor oocytes may be cryopreserved.

In ~12 hours after fertilization of both patient and donor oocytes with patient's partner's sperm pronuclear transplantation is applied. During the procedure both pronuclei from the patient's zygote and from the donor zygote are exchanged between their zygotic cytoplasts. The resulting reconstituted zygotes, as well as reversely reconstituted zygotes (RPNT), are then left in a time-lapse incubator until the blastocyst stage (Day 5 to Day 7 of culture). All suitable blastocysts will undergo the trophectoderm biopsy procedure to perform array-based comparative genomic hybridization (aCGH) or next-generation sequencing (NGS) analysis and then will be vitrified. Only a single euploid blastocyst will be used for embryo transfer per each embryo transfer cycle.

In a case of pregnancy amniocentesis is performed in order to confirm euploidy status. The pregnant woman will be monitored during the pregnancy. After the delivery, the child's blood should be taken to confirm paternity and to measure mitochondrial heteroplasmy level. All children are then followed up periodically with parental approval.

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Blastocyst rate measured using a non-invasive time-lapse imaging system on Day 5 – Day 7 post insemination
2. Euploidy rate measured via aCGH or NGS analysis of trophectoderm biopsy from embryos on Day 5 – Day 7 post insemination
3. Clinical pregnancy rate measured by rising beta hCG levels starting at 10 days post embryo transfer, presence of gestational sac at 6-7 weeks post embryo transfer, and presence of fetal

heartbeat at 6-7 weeks post embryo transfer
4. Health of baby at birth and long-term follow-up, assessed by pediatrician examination on a yearly basis for the first 7 years, and then on a bi-yearly basis until age 18. This includes periodic completion of a quality of life questionnaire related to the offspring produced in the clinical trial

Key secondary outcome(s))
Miscarriage rates calculated from the patients who delivered babies to the total number of patients scored as clinically pregnant based on the primary outcome measure 3, calculated each month, quarter and annually

Completion date
01/09/2022

Reason abandoned (if study stopped)
War in Ukraine

Eligibility

Key inclusion criteria
1. No less than two failed previous IVF attempts with preimplantation embryonic lethality (embryo arrest)
2. Low blastulation rates
3. Low number or absence of euploid embryos

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
29

Key exclusion criteria
1. Fertile patients
2. Fertile homosexual female couples
3. Male factor infertility

Date of first enrolment
23/09/2015

Date of final enrolment
20/03/2019

Locations

Countries of recruitment
Ukraine

Study participating centre
Nadiya Clinic
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Sponsor information

Organisation
Nadiya Clinic

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Nadiya Clinic

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes