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Clinical trial for the treatment of infertility due to poor oocyte quality

Submission date
03/09/2019

Recruitment status
No longer recruiting

Registration date
19/09/2019

Overall study status
Completed

Last Edited
19/09/2019

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
There is a significant number of IVF patients who continue to suffer from infertility. Such patients go through numerous cycles of traditional IVF and after failing in the end are offered egg donor programs to be able to have a family or healthy child. Furthermore, according to reports from the Centers for Disease Control and Prevention (CDC), by 2016 women aged 30 or older exhibited a higher birth rate than women aged 25–29. Maternal age is a critical factor in women's fertility - as many as half of oocytes (eggs) from IVF patients over the age of 38 years contain errors in chromosome numbers. The emerging trend of delaying having children combined with the fertility problems associated with advanced maternal age calls for clinical trials of new IVF techniques to include investigating age-related infertility. The aims of this study are: 1) to assess whether undergoing meiosis (cell division) in a young healthy cytoplasm can reduce the rate of aneuploidy (abnormal number of chromosomes) for "old" oocytes and 2) to assess whether removal of defective oocyte cytoplasm followed by complete replacement with healthy, young donor cytoplasm alleviates preimplantation embryonic developmental arrest and increases the rate of healthy embryos. As a preliminary step, patient oocytes are reconstructed via nuclear transfer. Reconstructed oocytes contain the nucleus (carrying all of the chromosomes, which provide the genetic instructions for the body) from the patient and the ooplasm (non-nuclear cellular material) from the donor egg. The reconstructed oocyte is fertilized at the MII stage with the partner or donor's sperm to create an embryo, which is then screened for chromosomal abnormalities before transferring to the mother.

Who can participate?
Infertile women with a regular menstrual cycle who have had at least three previous failed IVF attempts

What does the study involve?
In order not to lyse (break) the oocyte during removal of the nucleus, Cytochalasin membrane relaxants are used. Germinal vesicles (GV) transfer into fresh, enucleated donor GV oocyte (under 32 years old) is the first step for the age-related infertility participants (over 41 years of age), followed by in vitro maturation (IVM). Nuclear transfer at the immature GV stage allows the patient nucleus to undergo meiosis (to mature) in a young healthy cytoplasm. When the reconstituted GV matures in vitro to the MII stage, the second nuclear transfer step is conducted

(spindle nuclear transfer) into an in-vivo (grown in the mother) MII donor oocyte. This is because numerous model studies have shown that the manipulated oocytes grown in vitro (not in the mother) do not produce live offspring successfully. In addition, if the matured MII oocyte displays a viable polar body, it may also undergo Polar Body 1 Genome transfer (PBGT). The PBGT technique involves the transfer of the first polar body (PB) of the unfertilized MII oocyte to another enucleated donor oocyte and may create an additional embryo which increases opportunities for every patient affected by infertility. The procedure is similar to the Spindle Nuclear Transfer, with the notable difference that the polar body is transferred instead of the oocyte's spindle. If the MII oocyte from the patient does not display a visible spindle, it is fertilized at the MII phase, and pronuclear transfer is performed next-day at the zygote stage, when the egg is fertilized. After fusion of the donor ooplast with the patient nucleus, one of the partner/donor's sperm is injected into each reconstituted eggs. All other IVF processes are applied in a routine manner. For patients under 41 years of age with non-age-related infertility, the treatment starts with Spindle Nuclear Transfer, or if no spindle is visible, with fertilization and next-day pronuclear transfer. Resulting pregnancies from euploid balstocysts are followed up until delivery and newborns are followed regularly by pediatricians until the age of 18.

What are the possible benefits and risks of participating?
Treatment with novel IVF techniques may be able to overcome infertility which was not successfully treated with traditional IVF methods and could be a reasonable alternative to egg donation. This may give the opportunity of participants to have children who are genetically related to them. Currently there are 10 babies born from nuclear transfer, to the researchers' knowledge, the oldest of whom is a 3-year-old girl. As per her last medical screenings at Nadiya Clinic, she is in full health. Although long-term follow up is undoubtedly necessary, regulatory bodies such as the HFEA in the UK has concluded that there is no reason to believe that the cytoplasmic replacement technique is an unsafe procedure.
Although nucleus to ooplasm fusion procedures with Cell Fusion Reagents have been applied to eggs and embryos of several animal models and in a limited number of human live births, their application and long-term consequences in the human are unknown. The long-term consequences of Cytochalasin during human oocyte micromanipulations are largely unknown. The long-term consequences of mitochondrial heteroplasmy in the human blastocyst are largely unknown. The long-term epigenetic effects from cytoplasmic replacement is largely unknown. Patients in the trial are informed that there is no guarantee for a pregnancy. Due to the recent move from basic research into clinical trials, patients are informed of the uncertainty whether individuals resulting from nuclear transfer may develop unknown symptoms or disease because of the novel procedures. At the time of enrollment, patients considering to participate in the trial are informed of the latest status of clinical trial progress.

Where is the study run from?
Darwin Life-Nadiya LLC (Ukraine)

When is the study starting and how long is it expected to run for?
October 2017 to January 2022

Who is funding the study?
Darwin Life-Nadiya LLC (Ukraine)

Who is the main contact?
1. Dr John Zhang
info@darwinlife.com
2. Dr Valery Zukin
info@ivf.com.ua

Contact information

Type(s)
Scientific

Contact name
Dr John Zhang

Contact details
Darwin Life INC
4 Columbus Cir
New York City
United States of America
10019
+1 (0)212 315 4359
info@darwinlife.com

Type(s)
Scientific

Contact name
Dr Valery Zukin

Contact details
Clinic of reproductive medicine NADIYA
Kyiv
Ukraine
03037
+38 (0) 44 537 7 98
info@ivf.com.ua

Type(s)
Scientific

Contact name
Dr Stoyana Alexandrova

Contact details
Darwin Life INC
4 Columbus Cir
New York City
United States of America
10019
+1 (0)212 315 4359
info@darwinlife.com

Type(s)
Scientific

Contact name
Mr Pavlo Mazur

Contact details
Clinic of reproductive medicine NADIYA
Kyiv
Ukraine
03037
+38 (0)44 537 7 598
info@ivf.com.ua

Type(s)
Scientific

Contact name
Dr Dmytro Mykytenko

Contact details
Clinic of reproductive medicine NADIYA
Kyiv
Ukraine
03037
+38 (0)44 537 7 598
info@ivf.com.ua

Type(s)
Scientific

Contact name
Dr Hui Liu

Contact details
Darwin Life INC
4 Columbus Cir
New York City
United States of America
10019
+1 (0)212 315 4359
info@darwinlife.com

Type(s)
Scientific

Contact name
Mrs Lada Dyachenko

Contact details
Clinic of reproductive medicine NADIYA
Kyiv
Ukraine
03037

+38 (0)44 537 7 598
info@ivf.com.ua

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
N-001 and N-002

Study information

Scientific Title
Clinical trial for the treatment of infertility via replacement of poor quality ooplasm

Acronym
NToocytes

Study objectives
1. Can replacement of “old” cytoplasm in the germinal vesicle oocyte with healthy, young donor cytoplasm allow the process of meiosis to occur correctly and reduce, at least in a proportion of the cases, the rate of aneuploid blastocysts?
2. Can replacement of defective oocyte cytoplasm with healthy, young donor cytoplasm alleviate cleave stage developmental arrest and increase the rate of healthy embryos?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/12/2018, Commission of Bioethics of National Academy of Sciences of Ukraine (54, Volodymyrska Str., room 232, Kiev-30, 01601, Ukraine; Tel: +380 (0)44 239 6623; Email: biomed@nas.gov.ua), ref: 882/983

Study design
Interventional non-randomized prospective study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Infertility which cannot be successfully treated via traditional IVF: infertility due to oocyte maturation arrest, embryo cleavage arrest before blastulation, mitochondrial mutation (ie 8993T > G), tubulin mutation (ie TUBB8), or absence of euploid embryos.

Interventions
Patients who have failed 3 or more traditional IVF cycles begin with standard, non-investigational IVF stimulation, followed by retrieval and cryopreservation of germinal vesicle (GV) oocytes or mature (MII) oocytes. The collected oocytes and their partner sperm then undergo international export to the designated Darwin Life-Nadiya clinical facility in Ukraine, if they are not already there, where the clinical investigation takes place. The collected oocytes then undergo nuclear transfer procedures. Depending on the patient infertility phenotype, oocytes are processed via one of the following techniques: germinal vesicle nuclear transfer (GVT), spindle nuclear transfer (SNT), sequential nuclear transfer (GVT-SNT), polar body 1 genome transfer (PBGT), or pronuclear transfer (PNT). In order to maximize the number of embryos created and increase the efficiency of clinical outcome, PBGT may be conducted for any consented oocytes with intact 1st polar bodies. For any GVT procedures, a donor with fresh GV oocytes is provided on the day of nuclear transfer procedures, whereas for the other nuclear transfer methods frozen oocytes are primarily utilized. After all types of nuclear transfer procedures at MII stage, standard ICSI, and PGD/PGS are conducted. Resulting embryo(s) are biopsied and frozen using vitrification. The biopsies are used for preimplantation comprehensive chromosomal screening for aneuploidy, and in case of mtDNA patients for determination of mtDNA carryover levels. Euploid embryos undergo frozen embryo transfer to the patients, and any resulting children are followed up long-term as per patient agreement. For every patient oocyte, whenever possible reverse-nuclear transfer is conducted (donor nucleus transferred in patient oocyte) for control purposes. If there are surplus unmodified donor oocytes for any patient they are fertilized with their partner/donor sperm and provided to the patient for their own use in a future IVF cycle.

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Blastocyst rate measured using a noninvasive timelapse imaging system on Day 5 – Day 7 post insemination
2. Euploidy rate measured via array-based comparative genomic hybridization (aCGH) or next generation sequencing (NGS) analysis of trophectoderm biopsy from embryos on Day 5 – Day 7 post insemination
3. Clinical pregnancy rate as measured by rising beta hCG levels starting at 7 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. In specific, a pediatrician will examine the child 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))
1. Germinal vesicle maturation rates measured using morphological observations at 24, 30 and /or 48 hours post commencement of in vitro maturation (IVM). At each time point during IVM the germinal vesicle oocytes will be scored for maturation via (i) brightfield microscope observations for the extrusion of the first polar body and (ii) polarized light microscope observations for the formation of the metaphase II birefringent spindle
2. Fertilization rates measured using a noninvasive timelapse imaging system at 17 ±1 hours post

ICSI
3. Miscarriage rates calculated from the total number of patients scored as pregnant based on the primary outcome measure point #3

Completion date
01/01/2022

Eligibility

Key inclusion criteria
Group 1: 41 years old or older, having failed three or more IVF cycles, and still has a regular menstrual cycle. Group 2: 40 years old or younger AND with regular menstrual period AND having failed three or more IVF cycles, OR carrier of Mitochondrial DNA Disease OR a history of failure to form blastocysts.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
Female

Key exclusion criteria
1. No regular menstrual cycle
2. Poor ovarian reserve

Date of first enrolment
07/01/2018

Date of final enrolment
01/01/2023

Locations

Countries of recruitment
Ukraine

Study participating centre
Darwin Life-Nadiya LLC
Maksyma Kryvonosa St, 19a
Kyiv
Ukraine
03037

Sponsor information

Organisation
Darwin Life, INC

Organisation
Clinic of reproductive medicine NADIYA LLC

Funder(s)

Funder type
Research organisation

Funder Name
Darwin Life

Funder Name
Nadiya LLC

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file		23/08/2019	19/09/2019	No	No
Protocol file		23/08/2019	19/09/2019	No	No