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A mix of plant-derived extracellular vesicles significantly improves the outcome of assisted reproductive technologies in over 30s women: the results of an open clinical study

Submission date
29/10/2025

Recruitment status
No longer recruiting

Registration date
18/11/2025

Overall study status
Completed

Last Edited
21/11/2025

Condition category
Urological and Genital Diseases

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

Plain English summary of protocol
Background and study aims
Infertility is increasingly common among women over the age of 30 years, mainly due to a natural decline in the number and quality of oocytes (eggs). Assisted reproductive technologies (ART), such as in-vitro fertilization (IVF), offer a solution, but their success rate decreases with age. One of the main biological factors associated with this decline is oxidative stress, caused by an imbalance between free radicals and antioxidants in the body. This study aims to evaluate whether a food supplement containing a mix of plant-derived extracellular vesicles (PDEVs) — naturally occurring nanoparticles extracted from fruits and vegetables — can improve ovarian function and IVF outcomes in women aged 31–38 years. The supplement used, Exocomplex® Fertilità, is rich in natural antioxidants and bioactive molecules that may help restore redox balance and support oocyte quality.

Who can participate?
Women aged 31–38 years who will undergo ART (IVF or ICSI) for infertility of any cause will be eligible to participate. All participants will be in good general health, with normal or slightly high body weight, and will provide written informed consent to participate and to share clinical data for research purposes.

What does the study involve?
Participants are randomly assigned to two groups. Group A (Exocomplex® group) will take one capsule of Exocomplex® Fertilità daily for 3 months before starting ART. The control group will undergo the standard ART protocol without supplementation. All participants will follow a controlled ovarian stimulation (COS) protocol to help the ovaries produce more oocytes. The primary outcome will be the number of retrieved oocytes. The secondary outcomes will include:
1. Number of oocytes which were mature and ready for fertilisation
2. Number of inseminated oocytes, determined by counting oocytes subjected to fertilization

3, Fertilization rate
4. Embryo development rate, determined as the number of embryos which developed well
5. Clinical pregnancy rate of the women after embryo transfer

What are the possible benefits and risks of participating?
The possible benefits include an improvement in ART success rates, such as a higher number of retrieved and fertilized oocytes, better embryo quality, and increased clinical pregnancy rate. The supplement contains naturally derived antioxidant components with no known side effects; therefore, participation is expected to carry minimal risk. Patients will be monitored for vital signs and adverse events to assess tolerability and safety.

Where is the study run from?
The study will be conducted at Centro Megaride, Clinica Villa Angela, a private fertility clinic located in Naples, Italy.

When is the study starting and how long is it expected to run for?
January 2025 to December 2025

Who is funding the study?
ExoLab Italia S.r.l.

Who is the main contact?
Dr Ida Ferrara, idaferrara@libero.it

Contact information

Type(s)
Principal investigator

Contact name
Dr Ida Ferrara

Contact details
Vicoletto Belledonne, 9
Napoli
Italy
80121
+39 (0)3473542174
idaferrara@libero.it

Type(s)
Scientific

Contact name
Dr Stefano Fais

Contact details
Tecnopolo d’Abruzzo
L'Aquila
Italy
67100

+39 (0)3408063642
stefano.fais@exolabitalia.com

Type(s)
Public

Contact name
Dr Mariantonia Logozzi

Contact details
Viale Regina Elena 299
Roma
Italy
00161
+39 (0)3285762894
mariantonia.logozzi@exolabitalia.com

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
A mix of plant-derived extracellular vesicles helps to avoid repeated assisted reproductive technologies through an antioxidant effect

Acronym
EXOFERT

Study objectives
Assisted reproductive technologies (ART) are between the most used approach to give to couples that have problems of infertility . A gap between overall aging and reproductive aging is highly recognized and understanding of fertility decline in middle aged females is essential to elucidate the mechanism of reproductive aging. One of the most recognized factors in influencing aging is an increase of free radicals at both systemic and organs levels. On the basis of an in vivo preclinical study, this study will test the hypothesis that using natural anti-oxidants contained in plant-derived extracellular vesicles we can improve the effectiveness of ART in women with problems of infertility, thus saving them from repeated hormonal treatments.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 26/07/2025, AIMF (Italian Association of Functional Medicine) Ethics Committee (Via Manzoni 35, Lesmo, 20855, Italy; +39 (0)3473542174; Aimfhealth.segreteria@gmail.com), ref: AIMF-IRB-2025-EXO

Study design
Monocentric controlled parallel-group randomized open-label two-arm age-stratified study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Infertility

Interventions
All included patients are treated with Exocomplex® Fertilità, a food supplement based on plant-derived extracellular vesicles (PDEVs) extracted from a mix of organically grown fruits and vegetables (tomato, blonde and red orange, lemon, mango, pink grapefruit, and bergamot). Each gastro-protected capsule contains approximately 7 billion plant exosomes, together with natural antioxidants such as SOD-1, catalase, glutathione, ascorbic acid, and phenolic compounds. The supplement was administered at the dose of one capsule daily for 3 months prior to in vitro fertilization (IVF) treatment. Upon recruitment, the patients are randomly assigned to placebo or treated (Exocomplex® Fertilità) groups according to a pre-defined randomization procedure stratified by age to ensure a balanced age distribution between groups. Participants will be randomised by the drawing of envelopes containing randomisation numbers. The random number list will be generated by an investigator with no clinical involvement in the trial. Women receiving Exocomplex® Fertilità (Group A, n = 32) were compared with an age-matched control group (standard ART protocol only, Group B, n = 32) that did not receive any supplement. The intervention aimed to evaluate whether pretreatment with Exocomplex® Fertilità could improve the number and quality of retrieved, secondary, inseminated and fertilized oocytes, as well as fertilization rate, embryo development, and clinical pregnancy rate in women aged 31–38 years undergoing ART (Assisted Reproductive Technologies).

Controlled ovarian stimulation was conducted using recombinant follicle-stimulating hormone (r-FSH, Gonal-F®; Serono, Geneva, Switzerland) combined with pituitary suppression by a gonadotropin-releasing hormone (GnRH) antagonist (cetrorelix acetate, Cetrotide®; Merck KGaA, Serono, Germany). Follicular growth was monitored by transvaginal ultrasound starting on day 4 of gonadotropin administration, and serum estradiol levels were measured to confirm adequate follicular development before triggering.

The total number of oocytes retrieved during transvaginal ultrasound-guided ovum pick-up was recorded for each participant as the primary efficacy outcome, comparing women pretreated for three months with Exocomplex® Fertilità (one capsule daily, orally) to those undergoing standard ART without supplementation.

Intervention Type
Supplement

Primary outcome(s)
Number of retrieved oocytes, measured during the oocyte pick-up (OPU) procedure performed approximately 35 hours after ovulation triggering with leuprolide acetate (Lupron®), following controlled ovarian stimulation (COS) within a standard in vitro fertilization (IVF) protocol.

Key secondary outcome(s))
1. Number of secondary oocytes (metaphase I), measured by microscopic evaluation at the time of oocyte denudation following oocyte retrieval (OPU).
2. Number of inseminated oocytes, determined by counting the total oocytes subjected to fertilization by conventional IVF or intracytoplasmic sperm injection (ICSI) immediately after retrieval and denudation.
3. Number of fertilized oocytes, measured by microscopic evaluation of pronuclei formation (2PN stage) approximately 16–18 hours after insemination, under the same inverted microscope system.
4. Fertilization rate, calculated as the percentage of fertilized oocytes (2PN) over the total number of inseminated oocytes, measured 16–18 hours after insemination.
5. Embryo development rate, evaluated as the proportion of embryos reaching the blastocyst stage (day 5) under standard embryo culture conditions. Embryo morphology was assessed using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon, Tokyo, Japan) equipped with a Hoffmann modulation contrast system at 400× magnification, according to standard morphological criteria to select the best embryos for transfer.
6. Clinical pregnancy rate, defined as the presence of a gestational sac visualized by transvaginal ultrasound 4–6 weeks after embryo transfer.

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Women aged 31 to 38 years
2. Diagnosed with infertility (any cause) and scheduled for IVF-ET/ART treatment
3. Undergoing controlled ovarian stimulation (COS) protocol
4. BMI within normal to overweight range (as in study, matched groups)
5. No major systemic illnesses that could compromise ovarian function or ART outcomes
6. Provided written informed consent to participate in the study and share clinical outcomes

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
31 years

Upper age limit

38 years

Sex
Female

Total final enrolment
64

Key exclusion criteria
1. Presence of severe systemic diseases (e.g., uncontrolled diabetes, cardiovascular disease, autoimmune disorders) that could compromise ART outcomes.
2. History of ovarian surgery or conditions leading to premature ovarian insufficiency.
3. Known chromosomal abnormalities or genetic disorders affecting fertility.
4. Use of experimental fertility treatments or participation in another interventional clinical trial within the past 3 months.
5. Active infections of the reproductive tract.
6. Current or recent (within 6 months) chemotherapy, radiotherapy, or other gonadotoxic treatments.
7. Known allergy or intolerance to components of the Exocomplex® supplement.
8. Substance abuse (alcohol, drugs, or other agents) that may interfere with ovarian function or ART outcomes.
9. Inability or unwillingness to comply with the study protocol or provide informed consent.

Date of first enrolment
01/08/2025

Date of final enrolment
18/08/2025

Locations

Countries of recruitment
Italy

Study participating centre
Clinica Villa Angela - Centro Megaride
Via Alessandro Manzoni 141
Naples
Italy
80147

Sponsor information

Organisation
Exolab Italia S.r.l.

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Stefano Fais (stefano.fais@exolabitalia.com).

Individual participant-level data (de-identified) that underlie the results reported in this study will be made available upon reasonable request to the investigators. Data will be anonymised to protect participant privacy, and no information that could identify an individual will be shared. The data will be accessible after publication of the main study results and will be available for up to 5 years thereafter. Supporting documents (such as the study protocol and statistical analysis plan) may also be shared upon request. Access will be granted for research purposes only, subject to approval of a data sharing agreement.

IPD sharing plan summary
Available on request

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