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Evaluation of the safety of ovarian support cell in vitro maturation (OSC-IVM) application during in vitro fertilization procedures for infertility treatment

Submission date
28/10/2023

Recruitment status
No longer recruiting

Registration date
31/10/2023

Overall study status
Completed

Last Edited
18/06/2025

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
An oocyte is a female reproductive cell, commonly referred to as an egg cell. Oocyte maturation rates play a crucial role in the success of in vitro fertilization (IVF). Currently, the standard practice is to discard all immature oocytes when they are retrieved. However, in cases of minimal stimulation, most of the retrieved oocytes are immature, so they need to undergo in vitro maturation (IVM) to become usable. IVM offers the potential to reduce the use of certain hormones during traditional IVF, which can improve patient care, safety, and make IVF more affordable.

In this study, we're examining the outcomes of a product called Fertilo, which is used to enhance the quality of embryos and pregnancies during IVF. Fertilo is a system made from human induced pluripotent stem cells (hiPSC), which are used to create ovarian supporting cells (OSC) that function similarly to the natural granulosa cells in the body. These cells are thoroughly tested during production and serve as support for developing oocytes in Fertilo, a process known as ovarian support cell in vitro maturation (OSC-IVM). It's important to note that Fertilo is entirely an in vitro product, meaning it doesn't directly interact with the patient inside their body.

The aim of this study is to assess the safety of using Fertilo for oocyte treatment and its impact on embryological and gestational outcomes. Throughout the study, we will closely monitor various measures of success at each stage of the treatment, with a specific focus on the well-being of the patients and any potential adverse events.

Who can participate?
Females, 18-37 years seeking IVF with no clinical diagnosis of major hormonal abnormalities, major uterine or ovarian abnormalities, or greater than 2 failed previous IVF attempts, as well as their healthy male partner or a suitable sperm donor.

What does the study involve?
This study will take place at two medical centers in Lima, Peru and Mexico City, Mexico, for the first phase and a single center in Lima, Peru for the second phase and involve around 40 female participants who are suitable candidates for in vitro fertilization (IVF).

Once the participants provide written consent during the initial Screening Visit, they will undergo specific assessments as part of the study. The results of these assessments and screening tests will be carefully reviewed to determine whether the participants meet the criteria for study inclusion or exclusion. This assessment will be done before beginning the controlled ovarian stimulation (COS) process.

During the study, the participants will receive a minimal amount of gonadotropin stimulation, typically involving 5 days of 100 mg clomid plus 1-3 injections of recombinant follicle stimulating hormone (rFSH), and a mild human chorionic gonadotropin (hCG) trigger. Oocytes (egg cells) will be collected from follicles that are less than 12mm in size using standard techniques for oocyte retrieval.

All cumulus oocyte complexes (COCs), which are a combination of egg cells and surrounding cells, will be placed in a special environment known as the "Fertilo condition" for 30 hours. For a limited cohort in the second phase of the study, the same condition will be utilized except for the absence of Fertilo cells to serve as a comparator control. After this, the patient-derived cumulus cells will be removed from the complexes until all oocytes are without these cells. The maturity of the oocytes will be determined through visual examination.

Following this, in vitro fertilization (IVF) will be carried out according to the standard medical practice. This involves intracytoplasmic sperm injection (ICSI) for mature oocytes and in vitro culture of embryos until they reach the blastocyst stage, which can take up to seven days. Genetic testing for chromosomal abnormalities (aneuploidy) will also be performed. The highest-quality, chromosomally normal embryo will be stored and later thawed for frozen embryo transfer (FET), in which a single embryo is transferred to the uterus after standard uterine preparation. If the first embryo transfer does not result in a live birth, additional embryos may be thawed and used for further attempts.

Throughout the study, the participants will be monitored to evaluate the success of implantation, clinical and ongoing pregnancies, as well as the occurrence of live births. The health of both the female participants and any offspring will be closely monitored for any adverse events.

What are the possible benefits and risks of participating?
Patients undergoing fertility treatment will benefit from the study by receiving the treatment at no cost. They will also benefit as the oocyte maturation treatment under study requires a significantly smaller dose of hormones compared to standard IVF and thus has a safer side effect profile up to oocyte retrieval. There is no additional direct benefit to the study participants.

The risks associated with this study are similar to those of IVF treatments. However, for the minimal stimulation protocol, the use of reduced hormonal stimulation is expected to decrease the side effects of the stimulation cycles.

The risks associated with the hormonal stimulation are, Ovarian Hyperstimulation Syndrome and Ovarian Torsion.

These risks, though rare, are expected to be lower in the minimal stimulation protocol utilized versus conventional treatment, as the dosage of hormones administered to participants is reduced.

The risks associated with pregnancy and delivery are common to IVF and natural reproduction. These risks include:
1. Pregnancy complications such as intrauterine fetal demise, preterm labor, preeclampsia, hypertension, HELLP, bleeding or abruption, and general complications during labor
2. General risks to the fetus include gestational diabetes, low birth weight, NICU admission, or general congenital abnormality.

Where is the study run from?
The study is run from two centers: one in Lima, Peru, the laboratorio de Reproducción Asistida y Genética CONCEBIR and one in Mexico City, Mexico, the Fertilidad Integral fertility center for the observational single arm phase of the study. For the randomized control trial phase of the study, it will be performed in a single center, in Lima, Peru, the laboratorio de Reproducción Asistida y Genética CONCEBIR

When is the study starting and how long is it expected to run for?
June 2023 to December 2025.

Who is funding the study?
Gameto Inc. (USA)

Who is the main contact?
Luis Guzman, luis.guzman@pranor.com

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Study information

Scientific Title

Observational longitudinal cohort study and randomized controlled trial of live birth rate for ovarian support cell in vitro maturation (OSC-IVM) application during in vitro fertilization procedures for infertility treatment

Acronym
OSC-IVM-CL-2/3

Study objectives
Current study hypothesis:

The objective of this observational study and randomized controlled trial is to evaluate the safety of the ovarian support cell in vitro maturation (OSC-IVM) product application, known as Fertilo, during in vitro fertilization (IVF) treatment of infertility through evaluation of embryological, pregnancy and live birth outcomes.

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Previous study hypothesis:

The objective of this observational study is to evaluate the safety of the ovarian support cell in vitro maturation (OSC-IVM) product application, known as Fertilo, during in vitro fertilization (IVF) treatment of infertility through evaluation of embryological, pregnancy and live birth outcomes.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/09/2023, Comité Institucional de Ética en Investigación Facultad de Medicina Humana USMP (Alameda del Corregidor N° 1531 Urb. Los Sirius III Etapa – La Molina, Lima, 15023, Peru; +51 365-2300 anexo 160; etica_fmh@usmp.pe), ref: Fertilo P1

Primary study design
Interventional

Study design
Multi-center observational and single-center randomized controlled trial

Study type(s)
Screening, Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Treatment of infertility via in vitro fertilization (IVF) treatment

Interventions
Current interventions as of 28/02/2025:
The cohort selected for observation will undergo ovarian support cell in vitro maturation (OSC-IVM) application, using the product Fertilo, on immature oocytes obtained from minimal gonadotropin stimulation during in vitro fertilization (IVF) treatment for infertility. Embryos resulting from oocytes matured in vitro using the OSC-IVM application are used for single

embryo transfer for reproductive purposes. Observations are made of embryological outcomes, patient health during stimulation and retrieval, as well as patient and progeny health during gestation and live birth. A limited cohort comparator will be generated using a control IVM condition, which contains the same treatment parameters as the intervention except for lacking the use of the Fertilo active ingredient.

Previous interventions:
The cohort selected for observation will undergo ovarian support cell in vitro maturation (OSC-IVM) application, using the product Fertilo, on immature oocytes obtained from minimal gonadotropin stimulation during in vitro fertilization (IVF) treatment for infertility. Embryos resulting from oocytes matured in vitro using the OSC-IVM application are used for single embryo transfer for reproductive purposes. Observations are made of embryological outcomes, patient health during stimulation and retrieval, as well as patient and progeny health during gestation and live birth.

Intervention Type
Mixed

Primary outcome(s)
Cumulative Live Birth Rate, measured as the birth of at least one newborn after 24 weeks' gestation that exhibits any sign of life (twin will be a single count).

Key secondary outcome(s)
IVM and Embryo Outcomes
1. Number of COCs retrieved:
Defined as the number of COCs containing an oocyte at the time of retrieval.
2. MII formation:
A Metaphase II (MII) oocyte is defined as an oocyte with a first polar body (PB1).
3. Fertilization:
Fertilization is assessed 16 to 18 hours after ICSI by assessment of pronuclei formation. The presence of 2 pronuclei and two polar bodies is considered normally fertilized. Embryos with 1 pronuclei or more than 2 pronuclei will be kept for evaluation, as timing and fragmentation /vacuoles can affect pronuclei visualization without deleterious effect on embryo formation. Embryos with zero pronuclei are considered failed to fertilize.
4. Embryo cleavage:
Cleavage is assessed on day 3 post-ICSI. Embryos with the presence of 2 or more cells are considered to be cleaved. Fertilized embryos displaying a single cell will be considered not cleaved.
5. Blastocyst formation:
Blastocyst formation is assessed at day 5, 6 and 7 post-ICSI. Embryos that have successfully passed the morula stage, as indicated by cavitation, will be designated as blastocysts.
6. Euploid blastocyst formation rate:
Euploid embryos are determined by PGT-A analysis of trophectoderm biopsies showing no evidence of chromosomal or segmental aneuploidy. The PGT-A laboratory will use next generation sequencing (NGS) with thresholds set to distinguish two categories: euploid vs. aneuploid blastocysts. Low level mosaicism will not be counted as aneuploid.
7. Blastocyst quality scores:
Quality scores are recorded at the time of assessment for biopsy and vitrification either on Day 5, 6 or 7 post-ICSI. Qualitatively assessed as a score for each individual embryo according to the Gardner Scale. Blastocyst quality scores are assessed individually for each biopsied/vitrified blastocyst.

8. Vitrified blastocyst number:
Vitrified blastocyst number is determined when blastocysts are vitrified as the number of blastocysts vitrified per patient.

Pregnancy Outcomes (following Frozen Embryo Transfer of Euploid Blastocysts)
1. Cumulative Biochemical pregnancy:
The level of hCG in the patient's blood (serum) is determined 9 to 10 days after embryo transfer. A value >5mIU/ml is considered a positive pregnancy test.
2. Cumulative Clinical pregnancy:
Pregnancy with gestational sac visible with ultrasound at 7 weeks' gestation, reported as a patient with a clinical pregnancy.
3. Early miscarriage:
Defined as loss of a clinical pregnancy before the 12th week of gestation.
4. Ectopic pregnancy:
Ectopic pregnancy is defined as the implantation of an embryo outside of the uterus.
5. Cumulative Ongoing pregnancy:
An ongoing pregnancy is defined as a fetal sac visualized with ultrasound with detectable fetal heart rate at 10 weeks' gestation, it may include all clinical pregnancies with a beating fetal heart that result in either a live birth or a miscarriage.
6. Late miscarriage:
Defined as loss of a clinical pregnancy between the 12th and 24th week of gestation.
7. Preterm delivery:
Measured as birth of a baby, with secondary analysis by time of delivery with three groups: <28 weeks, 28-34 weeks, and 34-37 weeks.
8. Gestational age at delivery:
Gestational age at delivery is defined as the date of the delivery minus the date of the embryo transfer.
9. Birth mass:
Measured in grams at time of birth, with a secondary analysis split between singletons and twins.
10. Twins/Multiples:
Twins and triplets are assumed to have arisen from a single embryo transfer, as only one embryo is transferred at a time in this study. Twins and triplets arising after transfer of a single blastocyst regardless of whether they are monochorionic or multi chorionic are considered monozygotic (identical) twins or triplets.
11. Stillbirth:
Stillbirth is defined as a loss of baby life after 24 weeks of pregnancy before or during birth.

Patient health and adverse events outcomes (during stimulation and after embryo transfer)
1. Ovarian hyperstimulation syndrome (OHSS):
Evidence of OHSS will be assessed during and after stimulation and categorized as mild, moderate or severe. Grade I (mild) - characterized by ovarian enlargement (ovary size 5 to 7 cm), may be accompanied by abdominal discomfort of varying degrees. Grade II (moderate) - characterized by distinct ovarian cysts (ovary size 8 to 10 cm), accompanied by abdominal pain and tension, nausea, vomiting, and diarrhea. Grade III (severe) - characterized by enlarged cystic ovaries (ovary size >10 cm), accompanied by ascites and occasionally hydrothorax. In rare cases, Grade III OHSS may be further complicated by the occurrence of thromboembolic events.
2. General health side effects of stimulation:
General health effects of stimulation will be measured through a patient questionnaire during and after retrieval, specifically the day of oocyte pickup (OPU), 8 to 10 hours after OPU, and two weeks after OPU. Patients will be asked their pain level on a scale of 1-10 and instances of pain medication usage, abdominal swelling and tenderness, nausea or vomiting, breast swelling and tenderness.

3. Complications of Pregnancy:
Complications during pregnancy will be assessed by phone questionnaires self reported by the patient. These complications include but are not limited to preeclampsia, hypertension, bleeding, abruption, HELLP, and infections.
4. Congenital abnormalities:
Congenital abnormalities will be assessed by phone questionnaires self reported by the patient. These abnormalities include but are not limited to congenital diabetes, congenital genetic disease, and NICU admission.

Completion date
30/12/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 18/06/2025:

1. Written informed consent
2. Premenopausal, age 18-37 years at the time of providing informed consent, who is an appropriate candidate for IVF
3. Hormone levels within 6 months of consent: anti-mullerian hormone (AMH) level ≥ 2 ng/ml, follicle stimulating hormone (FSH) level on cycle day 2 or 3 < 10 mIU/ml, estradiol (E2) on cycle day 2 or 3 <70pg/ml
4. Body Mass Index (BMI) of 21-30 kg/m²
5. Antral Follicle Count ≥ 20
6. No evidence of hormonal disorders as determined by measurements of thyroid stimulating hormone (TSH), prolactin (PRL), sex hormone binding globulin (SHBG).
7. Normal uterine cavity as assessed by hysteroscopy, hysterosalpingography or sonohysterography within 2 months of screening
8. Negative and up to date cervical cancer screening. All those positive for high-risk human papillomavirus must be negative on subsequent cytology.
9. Presence of both ovaries with no major obstructions (ovarian fibroids, ovarian cysts, endometriosis)
10. Plan to use one of the resultant embryos within 2 months of egg retrieval
11. Willing and able to take contraceptives
12. Male partner/sperm donor: age of 21-45 years
13. Male partner/sperm donor:t: provide ejaculated sperm with a normal semen analysis with: Volume(≥1,4 ml), Sperm Count (concentration) (≥16 M/ml), Motility (≥30%), Morphology (≥4% Strict Morphology), Vitality (≥54%)
14. Consent to a study that involves low doses or no doses of gonadotropins followed by retrieval of immature oocytes
15. Willing to have embryos subjected to PGT-A testing

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Previous inclusion criteria as of 28/02/2025:

1. Written informed consent
2. Premenopausal, age 20-37 years at the time of providing informed consent, who is an appropriate candidate for IVF
3. Hormone levels within 6 months of consent: anti-mullerian hormone (AMH) level ≥ 2 ng/ml,

follicle stimulating hormone (FSH) level on cycle day 2 or 3 < 10 mIU/ml, estradiol (E2) on cycle day 2 or 3 <70pg/ml
4. Body Mass Index (BMI) of 21-30 kg/m²
5. Antral Follicle Count ≥ 20
6. No evidence of hormonal disorders as determined by measurements of thyroid stimulating hormone (TSH), prolactin (PRL), sex hormone binding globulin (SHBG).
7. Normal uterine cavity as assessed by hysteroscopy, hysterosalpingography or sonohysterography within 2 months of screening
8. Negative and up to date cervical cancer screening. All those positive for high-risk human papillomavirus must be negative on subsequent cytology.
9. Presence of both ovaries with no major obstructions (ovarian fibroids, ovarian cysts, endometriosis)
10. Plan to use one of the resultant embryos within 2 months of egg retrieval
11. Willing and able to take contraceptives
12. Male partner/sperm donor: age of 21-45 years
13. Male partner/sperm donor:t: provide ejaculated sperm with a normal semen analysis with: Volume(≥1,4 ml), Sperm Count (concentration) (≥16 M/ml), Motility (≥30%), Morphology (≥4% Strict Morphology), Vitality (≥54%)
14. Consent to a study that involves low doses or no doses of gonadotropins followed by retrieval of immature oocytes
15. Willing to have embryos subjected to PGT-A testing

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Previous inclusion criteria:

1. Written informed consent
2. Premenopausal, age 25-35 years at the time of providing informed consent, who is an appropriate candidate for IVF
3. Hormone levels within 6 months of consent: anti-mullerian hormone (AMH) level ≥ 2 ng/ml, follicle stimulating hormone (FSH) level on cycle day 2 or 3 < 10 mIU/ml, estradiol (E2) on cycle day 2 or 3 <70pg/ml
4. Body Mass Index (BMI) of 21-30 kg/m²
5. Antral Follicle Count ≥ 20
6. No evidence of hormonal disorders as determined by measurements of thyroid stimulating hormone (TSH), prolactin (PRL), sex hormone binding globulin (SHBG) and total testosterone.
7. Normal uterine cavity as assessed by hysteroscopy, hysterosalpingography or sonohysterography within 2 months of screening
8. Negative and up to date cervical cancer screening. All those positive for high-risk human papillomavirus must be negative on subsequent cytology.
9. Presence of both ovaries with no major obstructions (ovarian fibroids, ovarian cysts, endometriosis)
10. Plan to use one of the resultant embryos within 2 months of egg retrieval
11. Willing and able to take contraceptives
12. Male partner/sperm donor: age of 21-45 years
13. Male partner/sperm donor:t: provide ejaculated sperm with a normal semen analysis with: Volume(≥1,4 ml), Sperm Count (concentration) (≥16 M/ml), Motility (≥30%), Morphology (≥4% Strict Morphology), Vitality (≥54%)
14. Consent to a study that involves low doses or no doses of gonadotropins followed by retrieval of immature oocytes
15. Willing to have embryos subjected to PGT-A testing

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
37 Years

Sex
Female

Total final enrolment
40

Key exclusion criteria
Current exclusion criteria as of 28/02/2025:

1. Recurrent pregnancy loss (defined as ≥ 2 clinical pregnancies without live birth)
2. AMH < 2 ng/ml
3. Presence of other etiologies (congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome)
4. Contraindications to being pregnant or to any of the IVF hormonal medications to be used in this study
5. Presence of uterine anomaly: mullerian defect (septum, didelphic uterus, bicornuate uterus, unicornuate uterus, arcuate uterus); presence of fibroid(s) affecting the endometrium (myoma, leiomyoma); history of thin endometrium (will not become thicker than 6.9 mm with treatment using exogenous gonadotropins and/or exogenous estrogen); asherman syndrome (intrauterine adhesions)
6. Currently taking: lithium, opioids, and/or thyroid medications (other than for treatment of subclinical hypothyroidism) or other known teratogenic medications
7. Participation in another investigational drug/device trial within previous 30 days of enrollment, or 5 half-lives of the investigational drug, whichever is longer; or planning to participate in an investigational drug/device trial within 30 days of study completion.
8. Greater than 2 previous failed IVF attempts
9. Known history of oocyte maturation defect or cleavage arrest defect
10. Tobacco or nicotine use in the past 12 months
11. History of substance abuse, including alcohol abuse
12. Abnormal, undiagnosed vaginal bleeding at the time of screening
13. Abnormal serum iron, HbA1c, prolactin, Hb levels
14. Any medical or surgical condition that in the Investigator's judgment renders a subject unsuitable for study participation
15. Inability to comply with study procedures
16. Condition that requires PGT-M or PGT-SR
17. Male partner/sperm donor: Known or positive test for high DNA fragmentation in sperm

18. Male partner/sperm donor: requirement for retrograde ejaculation procedures or surgical sperm retrievals

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Previous exclusion criteria:

1. Recurrent pregnancy loss (defined as ≥ 2 clinical pregnancies without live birth)
2. AMH > 6 ng/ml or < 2 ng/ml
3. Clinically diagnosed PCOS as defined by the presence of at least two of the following: Oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome)
4. Contraindications to being pregnant or to any of the IVF hormonal medications to be used in this study
5. Presence of uterine anomaly: mullerian defect (septum, didelphic uterus, bicornuate uterus, unicornuate uterus, arcuate uterus); presence of fibroid(s) affecting the endometrium (myoma, leiomyoma); history of thin endometrium (will not become thicker than 6.9 mm with treatment using exogenous gonadotropins and/or exogenous estrogen); asherman syndrome (intrauterine adhesions)
6. Currently taking: lithium, opioids, and/or thyroid medications (other than for treatment of subclinical hypothyroidism) or other known teratogenic medications
7. Participation in another investigational drug/device trial within previous 30 days of enrollment, or 5 half-lives of the investigational drug, whichever is longer; or planning to participate in an investigational drug/device trial within 30 days of study completion.
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9. Known history of oocyte maturation defect or cleavage arrest defect
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Date of first enrolment
15/11/2023

Date of final enrolment
02/04/2024

Locations

Countries of recruitment
Mexico

Peru

Study participating centre
Laboratorio de Reproducción Asistida y Genética CONCEBIR
Calle Los Olivos 364 San Isidro.
Lima
Peru
15073

Study participating centre
Clinica Fertilidad Integral
Av. Ejército Nacional Mexicano 769-Piso 16, Granada, Miguel Hidalgo
Mexico City
Mexico
11520

Sponsor information

Organisation
Gameto Inc.

Funder(s)

Funder type
Industry

Funder Name
Gameto Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analyzed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Participant information sheet	version 7	08/10/2023	31/10/2023	No	Yes
Protocol file		02/07/2024	18/06/2025	No	No
Statistical Analysis Plan			18/06/2025	No	No