Study information ProFET

Treatment with Progesterone after IVF with Frozen Embryo Transfer in a natural cycle with ovulation

The ProFET trial has its name from Progesterone, and FET, short for Frozen Embryo Transfer.

Information to participants in the trial
We hereby ask for your participation in the ProFET study. In this document we provide information about the project and what participation may entail.

What kind of research project is this? Why are we asking you to participate?
In IVF treatment (In Vitro Fertilisation) it has become increasingly common to transfer a frozen/thawed embryo. Frozen embryo transfer accounts for 46 % of all IVF treatments in Sweden (www.qivf.se, Annual report 2020). The increased use of frozen embryo transfer is due to improved results after the introduction of new freezing procedures and embryo culture methods.

The corpus luteum, occurring in the ovary after ovulation, produces progesterone to support an early pregnancy. In IVF-cycles, where no ovulation has occurred, extra progesterone is needed and provided as medication after embryo transfer. In the same way, treatment with progesterone is given to all patients undergoing IVF stimulation with transfer of a fresh embryo, as the own hormone production during these treatments is suppressed.

Today, it is not known whether progesterone treatment after a frozen embryo transfer in a natural ovulatory cycle, improves the chance of live birth. Nevertheless, this treatment is sometimes given, despite its lack of known benefits to the patient.

The ProFET trial aims to find out if the addition of progesterone after a frozen embryo transfer in a natural cycle increases the chances of live birth. Each participant will be randomly assigned to one out of three groups. Group A will undergo frozen embryo transfer without the addition of progesterone. This group corresponds to normal clinical routine. Group B will be treated with progesterone, taken as a vaginal tablet, three times daily under three weeks. Group C will be treated with progesterone, taken as a vaginal tablet, three times daily during seven weeks. Some women will be asked for an additional blood sample, to measure their blood progesterone levels, before frozen embryo transfer.

Stadelmann C, *et al. BMJ Open* 2022; 12:e062400. doi: 10.1136/bmjopen-2022-062400

You are asked to participate because you are currently undergoing IVF treatment with a planned frozen embryo transfer in a natural cycle. You are between 18 to 43 years of age, have a BMI (body mass index) between 18.5 – 35 kilogram/m^2, a regular menstrual cycle, and understand Swedish, English or Arabic.

The research principal for the project is the Reproductive Medicine unit at the Sahlgrenska University Hospital, Region Västra Götaland.

Research design

The section below describes the participation in the trial.

1. You will be in contact with a doctor or nurse, in order to plan your frozen embryo transfer. If you meet the criteria for participation and wish to participate, you are asked to sign a consent form at the clinic or a digital consent form via 1177. You will also receive a questionnaire where you will keep notes on any symptoms after embryo transfer. You will receive this form even if you belong to the group that does not take any medicine.

2. Once you have a positive ovulation test, we ask you to contact your clinic according to ordinary routines and schedule an appointment for a frozen embryo transfer. One of the study doctors or nurses will randomly assign you to one of the three groups. The participants in Group A undergo a frozen embryo transfer without any additional treatment. Group B is prescribed vaginal tablets containing progesterone three times daily for three weeks. Group C is prescribed vaginal tablets containing progesterone three times daily for seven weeks. It is not possible, as a participant in the clinical trial, to ask to be placed in a particular group. The group allocation is computerised. If you are allocated to one of the groups treated with progesterone, you commence your treatment three times daily, starting three days after the positive ovulation test. You can pick up the medicine at any pharmacy, e-prescriptions are sent by the responsible doctor.

   When possible, we will draw a blood sample three days after the positive ovulation test, but before starting the progesterone treatment. A blood sample is taken even if you belong to the group that does not receive progesterone. The blood sample is drawn from a vein in the arm. Approximately 5 ml, roughly the amount of a teaspoon is needed. The test is called S-Progesterone and measures the level of progesterone (corpus luteum hormone) in the blood.

3. Frozen embryo transfer.

4. A urinary pregnancy test is taken at home according to routine instructions given after a frozen embryo transfer. Contact via phone with the doctor/nurse responsible for the trial, regarding outcomes/results:

   Not pregnant: Your participation in the trial ends. Questionnaire is handed in. If you belong to one of the groups treated with progesterone (Groups B or C), your treatment with the drug ends.

   Pregnant: If you belong to Groups B or C (treated with progesterone) you continue with your treatment for three or seven weeks, respectively, based on what group you were assigned to. If you belong to the group that will take progesterone tablets for seven weeks, a new e-prescription will be sent for prolonged treatment.
   A transvaginal ultrasound is scheduled for gestational week eight or nine to confirm pregnancy. Questionnaire is handed in. Routine ultrasounds during pregnancy will be offered, as standard for all pregnant women. After gestational week 22 you will receive a phone call by the study nurse, who will ask about how your pregnancy proceeds.

Participants in the trial are required to fill out a questionnaire regarding unexpected symptoms, which can be attributed to the administered drug, or to other causes. Participation may require self-administration of a vaginal tablet three times per day for a period of three or seven weeks.

Expenses for progesterone tablets, will be reimbursed financially by the ProFET trial at the Reproductive Medicine unit at the Sahlgrenska University Hospital.

We will also collect data from national registries (Pregnancy Register, Swedish Neonatal Quality Register, Statistics Sweden) and from medical records on antenatal care and delivery, as well as your child's records, regarding your child's condition.

Possible outcomes and risks

The treatment does not involve any risk unless you have a hypersensitivity to the drug or have any of the diseases contraindicating the use of the study drug. Patient with any of these conditions will be allowed to participate in the trial.

Participation in the trial does not entail discomfort or pain. Some patients experience the vaginal suppository as smudgy. There are no known long-term side effects related to treatment with vaginal progesterone suppositories, that could lead to injury or risk.

Should you experience discomfort or have any questions, you are welcome to contact the study nurse during office hours. In case of acute gynaecological problems outside office hours, you should contact a gynaecological emergency department. If you become ill in some way, are hospitalised or on sick leave, you must report this to the study nurse or the doctor

responsible for the trial, as all illness during an ongoing trial must be reported in accordance with current rules.

Information about your stored data

The project will collect data and keep relevant records about you. The IVF treatment will be recorded in the clinic's regular medical record system and is protected by confidentiality. If a blood sample is drawn, the test result will be entered in your medical chart and in a specific research database. Collected research data will be stored without name or social security number, but instead under a study code number, protected in a designated research data base. All personal data is confidential, and no unauthorized person will be able to access it.

When the collected data is analysed, no individual can be identified. The same also applies when the trial and its result are reviewed by an independent safety committee, and when results from the trial is published in scientific journals.

Data will be archived for fifteen years, in accordance with research regulations. Data analysis is solely for research purposes, and the legal basis is public interest/research in accordance with EU:s data protection regulation for the treatment.

The collected data is the responsibility of the board of the Sahlgrenska University Hospital. In accordance with EU:s data protection regulation you are entitled – without cost – to view your own trial records. You are also entitled to have any potentially false data corrected. You are also entitled to request your records being erased or limited in access. If you want to review your records, please contact the Principal Investigator, dr Åsa Magnusson, Reproduktionsmedicin, Sahlgrenska Universitetssjukhuset, e-mail: asa.magnusson@vgregion.se Telephone: 031-342 10 00. Data protection officer is reachable at: Sahlgrenska Universitetssjukhuset, Dataskyddsombudet, 413 45 Göteborg. Telephone 031-343 27 15. sahlgrenska.universitetssjukhuset.dso@vgregion.se. Any complaint with how your personal data is handled, may be submitted to the Integrity Protection Authority which is supervisory authority.

How do I get information about the results from the trial?

The research will be published in international scientific journals. The research team encourages all participating IVF clinics to present the results on their respective websites.

Insurance and compensation

IVF treatment is covered by the Swedish patient injury insurance. Participation in the trial does not involve any additional costs, and therefore no compensation is offered for participation.

Participation is voluntary

Your participation is entirely voluntary, and you may at any time withdraw your consent without giving an explanation. A withdrawal will not impact on your future care or treatment.

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Should you wish to stop your participation, please contact the responsible parties for the trial. (See information below.)

Responsible for the trial

The main investigators are:

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- Dr. Caroline Stadelmann, e-mail caroline.stadelmann@vgregion.se telephone 031-343 67 59

both at Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg.

The following sections are edited for each clinic. Locally responsible for the trial are at:

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Consent to participate in the study

I have received oral and written information about the trial and have had the opportunity to ask questions. I may keep the written information.

I agree to participate in the study "ProFET". At the same time, I agree that information about me is processed in the manner described in the research study information and that data from described records and registers may be obtained.

Study participant

Social security number: ……..

Place and date	Signature
	Name clarification

Doctor who receives consent:

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Place and date	Signature
	Name clarification

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