Comparing Intra-vaginal Culture of Embryos to In-vitro Culture of Embryos with Minimal Stimulation

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: COMPARING INTRA-VAGINAL CULTURE OF EMBRYOS USING INVOCELL DEVICE TO IN-VITRO CULTURE OF EMBRYOS

This is a medical research study. Your study doctors, Marcelle Cedars, M.D. and Asima Ahmad, M.D., M.P.H., and colleagues from the UCSF Division of Reproductive Endocrinology and Infertility will explain this study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating, and discuss your decision with your family or friends if you wish. If you have any questions, you may ask the researchers.

You are being asked to take part in this study because you are seeking infertility treatment.

Why is this study being done?

The purpose of this study is to determine if allowing your embryos to initially grow inside your body, using intra-vaginal culture (IVC) with the FDA-approved INVOcell device, during minimal stimulation protocols can result in similar pregnancy outcomes than allowing your embryos to initially grow inside the laboratory, using in-vitro fertilization (IVF) and culture. Minimal stimulation protocols are medication protocols that require a smaller amount of medication than full stimulation protocols. In other words, you will be using less medication to stimulate your ovaries to grow eggs.

In this study, you will either have IVC or IVF. You will not be asked to do both.

How many people will take part in this study?

About 50 female patients will take part in this study.

What will happen if I take part in this research study?

If you agree to take part in this study, your embryos will initially either be grown inside your body using the FDA-approved INVOcell device (IVC) or in the embryology laboratory (IVF). When you come to the clinic for your appointment, your treating physician will describe both options to you. You will also be given a handout on the INVOcell device for reference.

If you agree to participate, you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in.

You will have an equal change of being placed in either group:

1. **If you are in Group 1:** Intra-vaginal culture (IVC) Group – After your eggs are retrieved, your eggs and sperm will be placed into the INVOcell device. This device will be placed inside your vagina by the treating physician and will remain there for three days to allow the embryos to grow within your body. During this time, you will have minimal restrictions on activities, which will be explained to you. On the third day, you will return to clinic to have the device removed by the treating physician. You will have your embryos transferred into your uterus on the same day.
2. **If you are in Group 2:** In-vitro fertilization and culture (IVF) Group – After your eggs are retrieved, your eggs and sperm will be placed in a culture dish in the embryology lab. This will remain within the lab for three days. On the third day, you will return to clinic to have your embryos transferred into your uterus.

During your initial visit, your doctor will assess you to see if you qualify for the study. If you meet the requirements for the study, you will meet with a physician or research study member who will explain the study to you in detail. They will also have a sample of the INVOcell device and retention device for you to see in person and provide you with an informational handout about the INVOcell device.

Your participation in the study and randomization to a study group will not affect your standard of care that you receive from the UCSF Center for Reproductive Health (CRH). A summary of the standard of care, and care as part of each of the study groups is outlined below:

	Standard of care	**IVC Group**	**IVF Group**
First infertility evaluation and consultation visit	Medical history, physical examination, vital sign assessment (blood pressure, heart rate, height, weight), pelvic ultrasound assessment, laboratory evaluation	Same as standard care	Same as standard care
Ovarian stimulation cycle	Office visits requiring pelvic ultrasound, +/- blood draw	Same as standard care	Same as standard care
Egg retrieval	In-office procedure requiring anesthesia for removal of eggs from ovaries	Same as standard care	Same as standard care
Fertilization of and growth of embryos	In embryology laboratory	In INVOcell device	Same as standard care
Placement of embryos into uterus	Performed after a determined number of days (3, 5, etc) of growth or frozen	Performed three days after egg retrieval. Same as stanadard of care.	Performed three days after egg retrieval. Same as stanadard of care.

Study location: All these procedures will be done at the UCSF Center for Reproductive Health.

How long will I be in the study?

The active portion of the study, during which you will undergoing fertility treatment, will last from the day of your initial visit to the clinic until your embryo(s) is placed you're your uterus. The data collection portion of the study continues further depending on your pregnancy status:

a) if you do not become pregnant, the study ends with the results of your pregnancy test
b) if you do become pregnant, the study ends after the birth of your child(ren)

Can I stop being in the study?

Yes. You can decide to stop at any time. Just tell the study researcher or staff person right away if you wish to stop being in the study.

Also, the study researcher may stop you from taking part in this study at any time if he or she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

Randomization risk: You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Side effects risk: You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. As with anyone undergoing fertility treatments, side effects may be mild or serious.

Fertility treatment risks (either Group 1 or Group 2 participants):

- You will be receiving fertility medications to stimulate your ovaries to grow multiple eggs. Some of the more common side effects from this treatment include: bloating, cramping, nausea, headache, visual changes, hot flashes, and mood changes.
- You also have a small risk of more serious side effects or complications including ovarian hyperstimulation syndrome (OHSS), dehydration, lightheaded/dizziness, and abdominal discomfort.
- From the egg retrieval process, there are risk associated with anesthesia and procedural risks such as bleeding, infection and injury that your treatment physician will describe to you in more detail during the consenting process.
- Your ovaries will be stimulated using the minimal stimulation protocol. This is a lower cost stimulation and sometimes can produce a smaller quantity of eggs than full stimulation. Due to the smaller number of eggs, there may be a reduced pregnancy rate.

INVOcell device risks (Group 1 participants):

- There is a small risk that the placement and retention of the INVOcell device may be slightly uncomfortable for the patient, though studies have shown there has been no significant report of discomfort.
- There is also a chance that the device may be expulsed from the vagina. This has never occurred with the device, and if it were to occur, you will have been trained on how to replace the device into the vagina.
- There is a small risk of failure of embryo development that may occur regardless of which study group you are in. This risk may be slightly increased with the INVOcell device.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

There will be no direct medical benefit to you. However, you will be taking part in a study that will:

1) allow your embryos to grow inside you versus in a laboratory
2) help health professionals identify cost-efficient ways for patients to be able to undergo fertility treatments who might not otherwise be able to afford it
3) help health professionals identify cost-efficient ways for providers to be able to provide fertility services in resource-limited and rural settings
4) receive a discounted price for the treatment

What other choices do I have if I do not take part in this study?

Your other choices may include not getting treatment, getting standard treatment for your condition without being in a study, or taking part in another study. If you decide not to take part in this study, there will be no penalty to you. You will not lose any of your regular benefits, and you can still get your care from the UCSF Center for Reproductive Health the way you usually do.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will information about me be kept private?

Participation in research involves some loss of privacy. We will do our best to make sure that the personal information gathered for this study is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form, whether you used the INVOcell device and results will be added to your UCSF medical record.

Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation.

Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Additionally, the makers of INVOcell, INVO Bioscience will not have direct access to your personal identifying information. They may, however, have access to the results of the treatment, to help with improvements in the device for the future.

Organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include:

- The University of California
- The Food and Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- Society for Assisted Reproductive Technology (SART)

What are the costs of taking part in this study?

There will be no difference in cost based on what treatment group you are in.

The cost of the associated fertility treatments, however, will be charged to your insurance carrier. If your insurance company does not cover these costs, then you will be responsible for these costs. You will be paying for the cost of the minimal stimulation protocol treatment and associated treatments at a reduced price.

The regular cost of the minimal stimulation protocol is: $5885 + anesthesia cost + medications (not included). The reduced price for participation in the study is: $4000 + anesthesia cost + medications (not included).

Will I be paid for taking part in this study?

You will not be paid for taking part in this study. However, you will receive a discounted price for the treatment.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Cedars, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at (415) 353-7475.

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs

of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from our institution the way you usually do.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns or complaints you have about this study. Contact your study doctor, Dr. Marcelle Cedars, at 415-353-7475.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

CONSENT

You have been given copies of this consent form, the Experimental Subject's Bill of Rights and an informational handout about INVOcell to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to be in this study, or to withdraw from it at any point without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent