Assessment and Prevention of Pain During Ovarian Stimulation in Patients With Endometriosis

NCT04002141

Consent Form

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

Study Title: ASSESSMENT AND PREVENTION OF PAIN DURING OVARIAN STIMULATION IN PATIENTS WITH ENDOMETRIOSIS

Consent form for group: History of Endometriosis

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This is a clinical research study. Your study doctor(s), Marcelle Cedars, M.D., Kaitlyn Wald M.D., and colleagues from the UCSF Division of Reproductive Endocrinology and Infertility will explain the study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have endometriosis and are planning to undergo controlled ovarian hyperstimulation. Ovarian hyperstimulation is a menstrual cycle in which several ovarian follicles develop simultaneously, resulting in multiple mature eggs. This is a standard procedure in assisted reproduction and is used in conjunction with in vitro fertilization and other assisted reproductive techniques.

Why is this study being done?

The purpose of this study is to evaluate the impact of ovarian hyperstimulation on endometriosis-related symptoms and the impact of letrozole use during ovarian hyperstimulation with respect to endometriosis-related symptoms, embryo/egg quality and pregnancy rates. Letrozole is a Food and Drug Administration (FDA) approved medication for the treatment of estrogen receptor positive breast cancer. Although used to treat breast cancer, letrozole is not a chemotherapy agent, and has also been shown to: (1) improve pain symptoms in patients with endometriosis and (2) keep estrogen levels low in breast cancer patients undergoing ovarian hyperstimulation, without negatively impacting their cycle outcomes. In this study, you will get either letrozole or a placebo pill. The use of letrozole in this study is considered experimental because it is not FDA approved to treat endometriosis-related symptoms in women undergoing ovarian hyperstimulation.

Who pays for this study?

This study is funded by a Society for Reproductive Investigation and Bayer Discovery/Innovation Grant and the UCSF Center for Reproductive Health. The Society for Reproductive Investigation, Bayer and UCSF Center for Reproductive Health have no financial interests in this study.

How many people will take part in this study?

About 60 women will take part in this study. Of those women, 40 women will have a history of endometriosis and 20 will have no prior history of endometriosis.

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

If you agree to take part in this study, you will undergo a standard ovarian stimulation protocol chosen by your doctor. You will have a baseline transvaginal ultrasound performed to determine your antral follicle count (number of eggs), and if you have an ovarian cyst that may delay your ovarian stimulation protocol. A baseline ultrasound is performed on the first or second day of your cycle. The term "ovarian stimulation" refers to the injectable hormone medications that your doctor will prescribe to help you release more than one egg. At the end of all ovarian stimulation protocols for egg or embryo freezing, in research studies and in routine clinical care, eggs are retrieved with a needle using transvaginal ultrasound guidance. The treating physician will be able to explain more of this to you at your appointment.

You will also be asked to complete electronic surveys at the time of your baseline ultrasound appointment, the day you administer your trigger shot, 3 weeks following your egg retrieval, 6 weeks following your egg retrieval, and 12 weeks following your egg retrieval. We will also ask to collect follicle fluid for hormonal evaluation on the day of your egg retrieval. This fluid is typically discarded following egg retrieval.

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 assigned. You and your provider will also be unaware to which group you have been assigned ("blind").

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

If you are in Group 1: Letrozole group – You will begin your ovarian stimulation treatment on the day of your baseline scan as per standard of care. The day you start your gonadotropin (ovarian stimulation) injections, you will also start taking letrozole 5 milligrams orally daily until the day of your trigger injection. Letrozole will then be restarted the night of your retrieval and continued for 2 weeks post retrieval.

If you are in Group 2: Placebo Group – A placebo is an inactive substance. You will begin your ovarian stimulation treatment on the day of your baseline scan as per standard of care. The day you start your gonadotropin (ovarian stimulation) injections, you will also start taking the

placebo pill until the day of your trigger injection. Placebo will then be restarted the night of retrieval and continued for 2 weeks post retrieval.

All IVF medication administration instruction will be provided to you by your nurse as is standard for IVF care. The study medication will be provided to you by the study team.

Before you begin the main part of the study...

You will need to have completed all pre-ovarian hyperstimulation requirements as determined by your primary provider and team.

During the main part of the study...

	*Standard Care	Letrozole Group	Placebo Group
Ovarian stimulation protocol	Standard gonadotropin stimulation	Same as standard care	Same as standard care
Randomization to letrozole or placebo. You will have a 50/50 chance of either medication.	Letrozole is not routinely used in endometriosis patients. It is s commonly used in the United States for cancer patients undergoing ovarian stimulation.	Letrozole commonly used in United States to prevent estrogen-receptor positive tumor growth during egg freezing. Also used for treatment of pain related to endometriosis outside of ovarian stimulation.	Placebo is an inactive substance.
Monitoring by ultrasound	Average 5 times	Same as standard care	Same as standard care
Series of blood draws	Average 5 times. Each draw = about 1/3 tablespoons Total: about 2 tablespoons	Average 5 times. Each draw = about 1/3 tablespoons Total: about 2 tablespoons You and providers blinded to estradiol levels.	Average 5 times. Each draw = about 1/3 tablespoons Total: about 2 tablespoons You and providers blinded to estradiol levels.
Endometriosis symptom surveys	None	Total of 5 electronic surveys. To be completed at baseline ultrasound, day of trigger shot, 3, 6 and 12 weeks following egg retrieval.	Total of 5 electronic surveys. To be completed at baseline ultrasound, day of trigger shot, 3, 6 and 12 weeks following egg retrieval.
Ovulation trigger	Hormonal trigger shot	Same as standard care	Same as standard care

shot			
Egg retrieval procedure	Standard retrieval	Standard retrieval with collection of follicular fluid for hormone testing	Standard retrieval with collection of follicular fluid for hormone testing
Eggs and embryos are monitored individually	Standard protocol	Same as standard care	Same as standard care
The rest of ovarian stimulation treatment	Standard protocol	Same as standard care	Same as standard care

*"Standard Care" is what you would get if you were not in the study

Management of your ovarian stimulation will be done by your primary doctor based on their knowledge, expertise, and established standard of care guidelines. You will continue to come to the clinic for transvaginal ultrasound visits to track your follicle development. You will also have routine blood draws, to measure blood hormone levels, until you are ready for an ovulation trigger injection before your egg retrieval procedure.

Due to the suppressive effect of letrozole on serum estrogen levels, both you and your providers will be blinded to your serum estradiol levels during your controlled ovarian hyperstimulation cycle. Hormone blood draws will still be obtained with each scheduled ultrasound, as routinely done during ovarian stimulation. At UCSF, providers routinely monitor estradiol levels to guide cycle management, however many IVF clinics rely solely on ultrasound findings and do not routinely use estradiol levels. Further, when letrozole is used, estradiol levels can no longer be used for clinical management. Given letrozole is routinely used in patients with estrogen sensitive cancers undergoing ovarian stimulation without any negative impact on their cycle outcomes, we do not anticipate any negative impact from the blinding of your serum estrogen levels. The cost of estrogen blood draws will be removed from your IVF package cost.

When your follicles are an adequate size (as advised by your doctor), you will be instructed to take your trigger shot. The trigger shot is an injectable hormone medicine that helps to prepare your eggs for egg retrieval, as is standard for all IVF procedures.

On the day of your egg retrieval procedure, the treating physician will use standard of care transvaginal aspiration to drain all of the visible follicles in order to retrieve your eggs. The follicular fluid from the first follicle aspirated on each side will be collected for evaluation of hormone levels.

Throughout the process you will be asked to complete electronic surveys about symptoms that you may be experiencing related to your diagnosis of endometriosis. These will be completed at the time of your baseline ultrasound, the day of your trigger shot, 3 weeks following egg retrieval, 6 weeks following egg retrieval, and 12 weeks following egg retrieval.

The remainder of your ovarian stimulation cycle will continue as it was previously determined by you and your doctor.

After you have completed your ovarian stimulation cycle…

Regardless of whether you have completed your ovarian stimulation treatment with letrozole or placebo, you will be scheduled for a post-IVF visit with your treating physician to discuss the outcome. This visit is a standard of care procedure for all IVF patients. Your nurse will be able to schedule this for you.

You will also be contacted at 3, 6 and 12 weeks following your egg retrieval for the completion of the aforementioned surveys.

Study location

All study procedures will take place at the UCSF Center for Reproductive Health clinic at 499 Illinois Street, San Francisco, California.

How long will I be in the study?

The total duration will be approximately 14 weeks. You will be asked to take letrozole or placebo throughout your ovarian stimulation and for 2 weeks following retrieval. You will be asked to complete surveys up to 12 weeks following retrieval. The study will involve long-term follow-up, including periodic review of your medical records to evaluate future treatments you received to treat your endometriosis and to evaluate the use and outcomes of the eggs/embryos you preserved during your ovarian stimulation cycle.

Can I stop being in the study?

Yes, you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He/she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so that any risks from the discontinuation of letrazole or placebo medications can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/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?

Letrozole use is standard during ovarian stimulation in patients with cancer sensitive to estrogen. This treatment has been well-tolerated and studies have shown no negative impact on ovarian stimulation outcomes in this patient population.

You may, however, have side effects while in the study. Everyone taking part in the study will be

watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or more serious. Serious side effects from letrozole are unlikely. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking letrozole. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you experience while taking part in the study.

Risks and side effects related to the study drug letrozole include:

Likely

- Flushing
- Mood changes
- Hot flashes
- Bloating

Less likely

- Headache
- Fatigue
- Insomnia

Rare but serious

- Headache with vision changes
- Blood clot

Overall, each of the study medications is unlikely to significantly raise the risk of the above side effects, since you will likely only take the medication for a total of 4 weeks. For more information about risks and side effects, ask your study doctor.

Other risks in this study

1. Randomization risks: 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.
2. Placebo risks: If you are in the group that receives placebo, your condition will go without the treatment of letrozole.
3. Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.
4. Follicular fluid aspiration: Typically, during a standard egg retrieval performed during an IVF cycle, fluid and cells are collected from the ovarian follicles using an ultrasound-guided, transvaginal approach. After the egg has been isolated, the excess fluid and cells are usually discarded. However, the follicular fluid from the first follicle aspirated in each ovary will be collected to perform hormone assays. This may involve one

additional needle puncture per ovary and a possible slight increase in risk for bleeding. Your egg retrieval procedure will otherwise not change by being in this study.

5. 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?

Taking part in this study may or may not make your health better. If you are in the letrozole group and letrozole proves to treat your condition better than the placebo group, you may benefit from participating in the study, but this cannot be guaranteed.

Information gained will help improve the IVF process for future patients, particularly for patients with endometriosis.

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

If you decide not to participate in the study, you will continue to proceed with starting your ovarian stimulation protocol and receive the standard dose of medications.

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

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you 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 and some of your research 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. Study tests that are performed by research labs and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. 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.

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of the University of California
- Governmental agencies (such as the Food and Drug Administration (FDA)) are also involved in keeping research safe for people

Are there any costs to me for taking part in this study?

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

Will I be paid for taking part in this study?

In return for your time, effort, and travel expenses, you will be paid $60 in compensation. You will receive $30 after the completion of survey two and an additional $30 after the completion of survey five.

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

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 and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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 Marcelle Cedars, M.D, 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 Institutional Review Board at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights 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 participate or to withdraw at any point in this study 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