Center for Advanced Reproductive Services
Informed Consent Form

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Title of Research Study: A double-blinded prospective randomized clinical trial comparing euploidy rates among embryos created from sibling oocytes exposed to sperm after ultrashort abstinence compared with standard abstinence

IRB Number: 25-238-1

Sponsor: The Center for Advanced Reproductive Services (CARS)

Funding Source: None

Name of Research Participant: _____

Name of Research Participant Partner: _____

Overview of the research

You are being asked to provide consent to participate in a research study. Participation is voluntary. You can say yes or no. If you say yes now you can still change your mind later. Some key points to consider are summarized in this overview, but you should consider all of the information in this document carefully before making your decision.

This research is being done to determine if shortening the duration of abstinence prior to providing a semen sample will be effective in improving the rates of embryos with normal chromosomes (structures that carry genetic information) during in vitro fertilization (IVF) treatment. To do this, this research will involve collecting semen after a period of ultrashort abstinence, an experimental protocol which is defined in this research as one hour of abstinence (collecting a second ejaculate one hour after first ejaculation).

Participation will involve providing one extra semen sample on the day of egg retrieval. As part of the study, a part of both sperm samples will be used to do IVF. You will not be asked to take

any investigational drugs, to provide blood samples, or come for extra office visits beyond what is required for IVF.

The most severe risks of participating in this study, although uncommon, are anxiety about participating in the study or about undergoing IVF, and a breach of your confidential data. Risks are described in more detail later in this form.

There may also be benefits from participation. If a shorter duration of abstinence is effective at improving rates of normal chromosomes among embryos, you may experience an improvement in the number or quality of your embryos; but this is not guaranteed. This research may also result in information that leads to improved treatment options that may help others in the future.

A more detailed description of this research follows.

What is the purpose of this research study?

The in vitro fertilization (IVF) process involves removing eggs from the ovaries and inseminating (mixing) or injecting the eggs with sperm in the lab. Typically, sperm samples are produced on the day of egg retrieval to be used for IVF.

The current recommendation for abstinence prior to providing a sperm sample on the day of egg retrieval is 2-7 days. New research has shown that there may be improved outcomes with a shorter period of abstinence.

Sperm DNA fragmentation analysis is a method to determine the integrity of sperm DNA. Increased sperm DNA fragmentation may lead to worsened IVF outcomes including reduced fertilization rates, embryo quality, and pregnancy rates. It has been proposed that sperm DNA fragmentation may be improved with a shorter duration of abstinence by decreasing the amount of time that sperm is exposed to stress and biochemical changes that can occur in the sperm transit system.

In addition to improving sperm DNA fragmentation, shorter abstinence has also been associated with improved sperm parameters, such as motility and shape, embryo quality, implantation rates, pregnancy rates, and live birth rates. One small study found that shorter abstinence may also lead to a higher rate of chromosomally normal embryos.

Though these prior studies are promising, there is a lack of good-quality studies looking at the rates of embryos with normal chromosomes created after a short duration of abstinence compared to the standard, longer duration of abstinence.

The purpose of this research study is to determine whether using a sperm sample collected after one hour of abstinence increases the rates of embryos with normal chromosomes. At the time of egg retrieval, participants will have their eggs randomized (like the flip of a coin) into two groups. Half of the eggs will be exposed to sperm produced after 2 – 5 days of abstinence. The

other half of the eggs will be exposed to sperm produced after 1 hour of abstinence. The goal is to determine the rate of embryos with normal chromosomes in each group. Other goals include looking at differences in semen parameters, fertilization, embryo quality, how many embryos are tested and how many patients get pregnant after embryo transfer.

Why am I invited to participate?

You are invited to take part in this study because you are a female aged 18-42 years who is about to undergo an IVF cycle with standard insemination or intracytoplasmic sperm injection (ICSI). You have also elected to undergo testing of the embryos for chromosome analysis.

Is participation voluntary?

Participation in this study is voluntary. Before making a decision about whether to participate in this research study, please read this consent form carefully and discuss any questions you have with the researcher. You may also want to talk with family members, your primary care physician or a friend before making a decision.

You can choose to not participate in this study. If you decide to participate in the study, you are free to withdraw from it at any time. If you decide not to participate or withdraw from the study, your decision will not affect any present or future medical care you receive at the Center for Advanced Reproductive Services and/or the University of Connecticut Health Center. There will be no penalty or loss of benefits to which you are otherwise entitled.

How many other people do you think will participate?

Up to 187 patients will enroll in this study. This study is only being conducted at the Center for Advanced Reproductive Services (CARS). There are no additional study sites.

What are the costs to me for participating in this study?

There will be no additional costs to you for participating in this study. Preparation of the sperm from the second sample will be free of charge. You may have to take time away from work to come to the appointments for your treatment. This is the same for all IVF patients. Insurance coverage for IVF varies from one insurance carrier to another.

You will not receive financial compensation for taking part in this research.

What procedures will be done as part of the study? Are they safe?

On the day of egg retrieval:

Participation will involve providing two sperm samples on the day of egg retrieval: one after 2-5 days of abstinence and a second after one hour of abstinence. This means that participation

requires providing a second sperm sample one hour after providing the first sample. Both sperm samples will be used to do IVF.

During your IVF cycle:

If you agree to participate in the study and at least 6 mature eggs (if your plan is for intracytoplasmic sperm injection (ICSI)) or at least 8 eggs (if your plan is for standard insemination) are retrieved at the time of your egg retrieval, your eggs will be divided into two groups at the time of egg retrieval. If you meet the criteria to be included, one group of eggs will be exposed to sperm produced after 2-5 days of abstinence and the other group of eggs will be exposed to sperm produced after 1 hour of abstinence. The eggs will be exposed to sperm with either standard insemination or intracytoplasmic sperm injection (ICSI) according to the plan you have made with your physician. On the day of egg retrieval if a lower number of eggs are retrieved or the fresh sperm samples are insufficient for use, the sperm will be processed according to your physician's preference.

Neither you, the study doctor, nor the embryologist will know which group each individual egg or resulting embryo were randomized to. The andrologist (a member of the lab team who helps to prepare and evaluate sperm for fertility treatments) is the only research team member who will know which group each individual egg or resulting embryo were randomized to and will separate the sperm samples into two groups as determined by the study group allocation on the day of your egg retrieval (day 0). The embryologist will separate your eggs into two groups. The embryologists will then expose your eggs to sperm.

All embryos will be followed in standard fashion by the embryology team. This includes a check on the day after injection with sperm (day 1), day 2, day 3, and day 5. If there are no high-quality embryos that have reached the blastocyst stage (an embryo that is able to be biopsied to remove cells for chromosome testing) on day 5, then they will be checked again on days 6 and 7. On days 5, 6, and 7, if any embryos can be biopsied, then they will be biopsied at that time for chromosome testing and then frozen. All procedures and equipment for embryo culture including culture media, culture dishes, and incubators (all components involved in creating the environment in which the embryo grows in the lab) are the same as those used for patients not participating in this study.

The results of the chromosome testing will take a couple of weeks to return. If there is an embryo with normal chromosomes, regardless of which study group it came from, that embryo will be chosen for transfer in a subsequent cycle. If there are multiple embryos with normal chromosomes, the highest quality embryo based on morphology (how the embryo looks) will be chosen, regardless of which group the embryo came from. This method of choosing the best embryo for transfer is the same for all IVF patients regardless of your participation in the study. If there are no embryos with normal chromosomes, then your participation in the study will end.

After your IVF cycle:

Your doctor will determine the best way to prepare your uterine lining for embryo transfer if you develop one or more embryos with normal chromosomes. The selected embryo will be transferred on the day specified by your transfer protocol. Information from your medical record (including embryo transfer protocol information, laboratory data such as pregnancy hormone levels, and ultrasound results) will be collected to follow your pregnancy outcome.

What will happen to the samples I give during the study?

The partners of all patients enrolled in the study will be providing two semen samples to complete their IVF treatment. Normally, after IVF is completed, the remainder of both samples are discarded. However, as part of the study, these samples can be frozen and stored for subsequent analysis of the sperm as a part of the study. These frozen samples cannot be used for IVF in the future.

You and your partner may decide to opt in or opt out of freezing these semen samples by placing your partner's initials at the end of this consent form on the appropriate line. A minimum post-processing semen volume of 100 µl is required to freeze this leftover sample.

These samples will be coded (labeled) per protocol by assigning a 2-letter study abbreviation followed by a 3-digit number that is unique to you. All samples will be frozen and stored at the Center for Advanced Reproductive Services. A master key that links names and codes will be maintained in a separate and secure location. Once the initial study is completed, tests including sperm DNA fragmentation, methylation, and metabolomic analyses will be performed. These tests look for breaks in the sperm DNA, genes within the sperm DNA that are turned on or off, and the molecules involved in sperm metabolism. This research will not include whole genome sequencing. Once the analyses are complete the samples will be discarded. The results of the analyses will be recorded in your research record apart from your medical record. You will not be notified of the results of these tests. All samples will be destroyed at the end of the study.

What happens to the sample if I withdraw from the study?

If you choose to withdraw from the study after the semen sample has been obtained, we will destroy all records in our research files connecting your identity with your sample. The portion of the samples that have not been used for IVF will be destroyed per protocol. Data collected before your withdrawal from the study will remain in the research database.

What drugs will I be asked to take? Are they safe?

If you choose to participate in this study, you will be asked to take IVF stimulation medications that are standard for all patients doing IVF through our center. No additional research or experimental medications will be given to you.

What other types of risk are involved if I choose to participate?

The additional risks to you or your embryos are minimal if participating in this study. This study does not involve any additional interventions to standard procedure during ovarian stimulation so there are no additional physical risks to participants. The risk to the embryos for eggs exposed to sperm after a shortened period of abstinence is also minimal.

One risk to you includes a possible breach of confidentiality. While we will protect the confidentiality of the information you provide, confidentiality cannot be guaranteed. There is a chance that people outside of the research team may learn of your study participation. If you discuss this with your employer, co-workers, family or friends your study participation may also become known to others. Despite the measures taken and outlined below in this form, there still is a slight chance that someone may be able to link the summary information to you. This may expose you and your family to unwanted publicity. It is also possible this study may present risks to you, or to the embryo or fetus, that at this time are not known.

What are the benefits of participating in this study?

Since this study is for research only, you are not expected to receive any medical benefit. However, there may be a benefit of improved embryo development and improved number of embryos with normal chromosomes. The data collected in this study may lead to more effective methods of selecting, evaluating, and selecting the most viable sperm to create euploid embryos in the future.

Will I be compensated for participating in this study?

You will not be compensated for participation in this study. The sponsor does not intend for you to share in any profits if a commercially valuable product is developed from this research.

What alternative procedures or treatments are available to me?

An alternative would be to undergo an IVF cycle without participating in the study. If you decide not to participate in this study, or you are excluded on the day of your egg retrieval based on the number of eggs retrieved or sperm parameters, the sperm will be processed in the standard way at CARS.

How will my personal information be protected?

The information collected for this research study will be accessible to authorized persons. Authorized persons include study team members, representatives of CARS and UConn Health; and, as may be applicable, representatives of the Sponsor and/or representatives of Federal agencies when required by law, such as representatives from the Food and Drug Administration for research involving a drug, device or biologic and/or the Department of Health and Human Services when the research is federally funded or supported. You should know that the sponsor, the Department of Health and Human Services, the Food and Drug Administration, the Health

Center's Institutional Review Board, and the Human Subjects Protection Office may inspect records. They may inspect records to ensure that the study is being done correctly.

All information related to your participation in this study will be kept in a research record, apart from your medical record. Only researchers officially appointed to work on this project, the sponsor and agencies or departments with responsibility for research compliance will have access to your information while it is stored in an identifiable format.

The study staff (principal investigator, research coordinator, co-investigators etc.) will keep all study records (including any codes to your data) locked in a secure location. Research records will be labeled with a code, and all contents of the research record will be labeled with only that code. The code will be derived from a 2-letter study abbreviation followed by a sequential 3-digit number that reflects how many people have enrolled in the study. A master key that links names and other identifying information to the code will be maintained in a separate and secure location. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Data that will be shared with others will be coded as described above to help protect your identity. Any lab results will be stored in both your medical record which is available to insurers and a coded copy will be stored in your research record.

After removal of identifying information, the de-identified information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

At the conclusion of this study the researchers intend to publish articles on their findings. Information will be presented in summary format and you will not be identified in any publications or presentations.

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.

What if I decide to stop participating in the study?

You are free to refuse to participate in the study or to stop taking part in this study at any time. If you refuse to participate or decide to withdraw from the study you can continue to proceed with fertility treatment according to your personal physician's treatment plan. It will in no way jeopardize your current or any future fertility treatment, and your relationship with your doctors, the Center for Advanced Reproductive Services, and/or UConn Health will not be affected.

If you decide to withdraw from the study, the data that has been collected up until the time you withdraw will be retained in the study database.

If you decide to withdraw we ask that you let us know by calling Dr. Lawrence Engmann at 860-321-7082 or by writing to Dr. Lawrence Engmann at The Center for Advanced Reproductive Services, 2 Batterson Park Road, Farmington, CT 06032.

Can someone else make me stop participating in this study?

The researcher or the Food and Drug Administration may prevent you from continuing in this study. This may happen if:

- The Principal Investigator feels it is necessary for your health, your safety, or the safety of the embryos that result from IVF. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- The Principal Investigator feels that you may not achieve the required number of eggs to participate in the study. During your IVF cycle, if it appears as though your response to stimulation was suboptimal and you will not have at least 6 mature eggs retrieved, you may be withdrawn from the study by the principal investigator.
- You do not meet the criteria to be included in the study after you have already decided to participate.
- You were hospitalized for some reason unrelated to the study in which you could not be monitored by the study team.
- You have not followed study instructions.
- The principal investigator or the FDA has decided to stop the study.

If you are prevented from participating in this study it would not jeopardize any of your present or future medical care. You will be informed by the study team if you are withdrawn from the study.

What if I experience an adverse (bad) event related to my participation?

Participation in this study does require one additional semen sample on the day of egg retrieval but does not involve any additional other testing, visits, or use of any investigational drugs or devices. Adverse (bad) events are rare, but if you have an adverse event you should tell the principal investigator as soon as possible. You may contact Dr. Lawrence Engmann by calling 860-321-7082.

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you or your embryos might develop a reaction or injury from being in this study. If such problems occur during the course of the study, you should contact your study doctor immediately. CARS, UConn Health, or the principal investigator has not set aside funds to pay you for any such reactions or injuries, or for the related medical care.

If you were to have an adverse event during the study period you should report this to study personnel and you will be treated appropriately.

Financial compensation for such things as lost wages, disability or discomfort due to the injury is not routinely available and is not offered by CARS or UConn Health. However, by signing this form you do not give up any of your legal rights.

UConn Health does not provide insurance coverage to compensate for injuries incurred during this research. However, compensation may still be available. A claim may be filed against the State of Connecticut seeking compensation. For a description of this process contact a representative of the UConn Health Institutional Review Board at 860-679-4849 or 860-679-8729.

UConn Health and CARS do not offer free care. However, treatment for a research related injury can be obtained at UConn Health or CARS for the usual fee.

What if you learn about something that may make me change my mind?

We will tell you about any new information that may affect your willingness to participate. If we think you need to know quickly the researcher or study coordinator may call you or send you a letter. If we do not think you need to know quickly, we will tell you at your next visit. If you still want to participate we will ask you to sign a new consent form.

Will the results be shared with me at the end of the study?

You will not be provided with the overall results of the study or your individual results as it pertains to the study (i.e. which embryos came from each group of sperm). If you are interested in learning about your individual embryo-related results, please ask your doctor and these results will be made available to you once your participation in the study has ended.

What if I have questions?

The Principal Investigator is willing to answer any questions you have about the research. You are encouraged to ask questions before deciding whether to take part. You are also encouraged to ask questions during your study participation. If you have questions, complaints or concerns about the research, you should call the Principal Investigator Dr. Lawrence Engmann at 860-321-7082 or write to Dr. Lawrence Engmann at The Center for Advanced Reproductive Services, 2 Batterson Park Road, Farmington, CT 06032.

If you have questions about your rights as a research participant you may contact a coordinator at the Institution Review Board at 860-679-8729, or 860-679-4849. You may also call a coordinator at the Institutional Review Board if you want to talk to someone who is not a member of the research team in order to pass along any suggestions, complaints, concerns or compliments about your involvement in the research, or to ask general questions or obtain information about participation in clinical research studies.

Please do not call the IRB number for medical related issues or to schedule or cancel an appointment.

Consent To Participation:

By signing this form you and your partner acknowledge that you have read, or have had read to you, this informed consent document, have talked with research personnel about this study, have been given the opportunity to ask questions and have them satisfactorily answered, and voluntarily consent to participate in this project as described in this form.

By signing this form the individual obtaining consent is confirming that the above information has been explained to the participant and partner and that a copy of this document, signed and dated by both the person(s) giving consent and the person obtaining consent, along with a copy of the Research Participant Feedback Form, will be provided to the participant.

Role	Printed Name	Signature	Date	Time
Participant				
Partner				
Research Staff				

Partner to select one option regarding freezing and storing the semen sample for future analysis:

_____ *I AGREE to the freezing and storing of the excess semen samples for future analysis.*

_____ *I DECLINE the freezing and storing of the excess semen samples for future analysis.*