Oocyte Cryopreservation

Process, Risk, and Consent

While embryos and sperm have been frozen and thawed with good results for many years, eggs have proved much more difficult to manage. Newer egg freezing methods have been more successful, at least in younger women, the main population in which the techniques have been studied. Egg freezing takes place by one of two methods: a slow freeze protocol, or a different "flash freeze" method known as vitrification. USF IVF uses the newer vitrification technology exclusively.

This consent reviews the Oocyte freezing process process from start to finish, including the risks that this treatment might pose to you and your offspring. While best efforts have been made to disclose all known risks, there may be risks of oocyte freezing that are not yet clarified or even suspected at the time of this writing.

Oocyte cryopreservation typically includes the following steps or procedures:

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Removal of cumulus cells, the surrounding support cells from the eggs
- Freezing of mature oocytes with vitrification

Is pregnancy achieved as successfully with frozen eggs as with fresh eggs?

As mentioned, most studies have looked at success rates using either donor eggs or women who produced larger numbers of eggs. The best studies randomly assign patients into two groups (fresh eggs versus frozen eggs) and compare the outcomes. There are four strong studies of this design currently published. In these studies, fertilization rates, implantation rates, and pregnancy rates using frozen eggs appear similar to rates using fresh eggs in these studies. One caution is that there are still only small numbers of studies available, and these results may not be the same at all centers or in older women.

Other information on egg freezing comes from Italy, where the law limits the number of eggs that may be fertilized in a cycle. Italian patients with extra eggs available have been offered egg freezing for many years now, and at many different centers. These types of studies show higher fertilization rates, implantation rates, and pregnancy rates when using fresh eggs instead of frozen eggs. The rates were also higher with the use of frozen embryos rather than frozen eggs.

Other non-randomized studies in the US show fertilization, implantation, and pregnancy rates that are similar with frozen eggs and fresh eggs when the woman providing the eggs was under 35 years old.

What are the reasons a woman would elect to freeze her eggs?

- Chemotherapy for cancer or other medical conditions can be toxic to the ovaries. Women undergoing treatment may not have a male partner, or they may have ethical concerns about

freezing embryos. Pregnancy and success rates from this group of women are limited, but egg freezing is recommended in this group after appropriate discussion of the procedure and its risks and limitations.

- Some genetic disorders like the BRCA mutations carry a high risk for ovarian cancer, and removal of the ovaries may be suggested in this group. Other genetic conditions can lead to premature menopause. Egg freezing could be considered in these groups, although data on success, safety of pregnancy, and risks of genetic problems in children born in these groups are not known.
- In some cases, there may not be enough sperm to fertilize the eggs on the day of egg retrieval in couples undergoing IVF. In this case, surplus eggs can be frozen and used in the future when more sperm are available.
- Some patients undergoing IVF do not want to freeze embryos for ethical or other reasons. In these cases, even though pregnancy rates using frozen eggs may be lower than pregnancy rates using frozen embryos, any eggs not inseminated may be frozen for future use.
- Some women may choose to freeze eggs in order to delay childbearing. Unfortunately, the success rates with egg freezing appear to decline significantly for older women (38 years or older). There are no data available that look at success rates for women choosing to freeze eggs in order to delay childbearing. Therefore, it is impossible to determine the success rates and cost-effectiveness of freezing eggs in this population of women. Freezing eggs is not a guarantee of the ability to conceive a biologically-related child in the future. Women wishing to freeze eggs for this purpose should carefully consider the success rates available at their clinics, and the available alternatives.

Oocyte Freezing Procedures

Medications to Grow Multiple Eggs

- **The likelihood of achieving pregnancy from frozen eggs largely depends on growing multiple eggs at once.**
- **Injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose.**
- **Additional medications are used to prevent premature ovulation.**
- **An overly vigorous ovarian response can occur, or conversely an inadequate response.**

Medications may include the following (not a complete list):

- ***Gonadotropins, or injectable "fertility drugs"*** (Follistim®, Gonal-F®, Bravelle®, Menopur®): These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Low-dose hCG (human chorionic gonadotropin) can be used in lieu of LH. These medications are given by subcutaneous injection. Proper dosage of these drugs and the timing of egg recovery require monitoring of the ovarian response, usually by way of blood tests and ultrasound examinations during the ovarian stimulation.

  As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to these drugs. The intent of giving these medications is to mature multiple follicles, and many women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Although less likely in absence of embryo transfer, some women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section that follows]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

  Even with pre-treatment attempts to assess response, and even more so with abnormal pre-treatment evaluations of ovarian reserve, the stimulation may result in very few follicles developing. The end result may be few or no eggs obtained at egg retrieval or even cancellation of the treatment cycle prior to egg retrieval.

  Concerns have been raised that the risk of ovarian cancer may increase with the use of fertility drugs, but recent studies have not confirmed this. A major risk factor for ovarian cancer is infertility per se, and early reports may have falsely attributed the risk resulting from infertility to the use of medications to overcome it (see 2.b.2 for further discussion).

- ***GnRH-agonists (leuprolide acetate) (Lupron®):*** This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for 1-3 months. The primary role of this medication is to prevent a premature LH surge, which could result in the release of eggs before they are ready to be retrieved. Since GnRH-agonists initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (U.S. Food and Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way for more than 20 years. Potential side effects usually experienced with long-term use include, but are not limited to: hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. No long term or serious side effects are known. Since GnRH-a are oftentimes administered after

ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception (condoms) the month you will be starting the GnRH-a. GnRH-a has not been associated with any fetal malformations, however you should discontinue use of the GnRH-a immediately if pregnancy is confirmed.

- ***GnRH-antagonists (ganirelix acetate or cetrorelix acetate)*** (Ganirelix®, Cetrotide®): These are another class of medications used to prevent premature ovulation. They tend to be used for short periods of time in the late stages of ovarian stimulation. The potential side effects include, but are not limited to: abdominal pain, headaches, skin reaction at the injection site, and nausea.

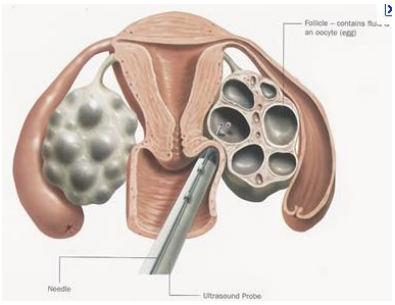
- ***Human chorionic gonadotropin (hCG)*** (Profasi®, Novarel®, Pregnyl®, Ovidrel®): hCG is a natural hormone used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to: breast tenderness, bloating, and pelvic discomfort.

- ***Oral contraceptive pills:*** Some treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to suppress hormone production or to schedule a cycle. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or, very rarely, stroke.

- ***Other medications:*** Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with egg retrieval. Antibiotic use may be associated with vaginal yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, and allergic reactions. Other medications such as steroids, heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.

Transvaginal Oocyte (Egg) Retrieval

- **Eggs are removed from the ovary with a needle under ultrasound guidance.**
- **Anesthesia is provided to make this comfortable.**
- **Complications are rare.**



Oocyte retrieval is the removal of eggs from the ovary. A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A long needle, which can be seen on ultrasound, can be guided into each follicle and the contents aspirated. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa (egg-supporting) cells. Rarely, the ovaries are not accessible by the transvaginal route and laparoscopy or trans-abdominal retrieval is necessary. These procedures and risks will be discussed with you by your doctor if applicable. Anesthesia is generally used to reduce, if not eliminate, discomfort. Risks of egg retrieval include:

Infection: Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian

tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.1%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are sometimes used before the egg retrieval procedure to reduce the risk of pelvic or abdominal infection in patients at higher risk of this complication. Despite the use of antibiotics, there is no way to eliminate this risk completely.

Bleeding: The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels. In addition, there are other blood vessels nearby. Small amounts of blood loss are common during egg retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding may require surgical repair and possibly loss of the ovary. The need for blood transfusion is rare. (Although very rare, review of the world experience with IVF indicates that unrecognized bleeding has lead to death.)

Trauma: Despite the use of ultrasound guidance, it is possible to damage other intra-abdominal organs during the egg retrieval. Previous reports in the medical literature have noted damage to the bowel, appendix, bladder, ureters, and ovary. Damage to internal organs may result in the need for additional treatment such as surgery for repair or removal of the damaged organ. However, the risk of such trauma is very low.

Anesthesia: The use of anesthesia during the egg retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting and in rare cases, death.

***Failure*:** It is possible that the aspiration will fail to obtain any eggs or the eggs may be abnormal or of poor quality and otherwise fail to produce a viable pregnancy. It is possible that none of the eggs obtained will be mature. Immature eggs are not capable of producing a pregnancy, and therefore will not be frozen.

Oocyte Culture and Freezing

After eggs are retrieved, they are transferred to the embryology laboratory where they are kept in conditions that support their needs. The eggs are placed in small dishes or tubes containing "culture medium," which is special fluid developed to support the eggs. The dishes containing the eggs are then placed into incubators, which control the temperature and atmospheric gasses the eggs experience. Mature eggs will be frozen several hours after egg retrieval.

In spite of reasonable precautions, any of the following may occur in the lab that would prevent the establishment of a future pregnancy from frozen eggs:

- Not all frozen eggs will survive warming, or fertilize and develop normally after warming
- Laboratory equipment may fail, and/or extended power losses can occur which could lead to the destruction of eggs.
- Other unforeseen circumstances may prevent any step of the procedure to be performed or prevent the establishment of a pregnancy.
- Hurricanes, floods, or other “acts of God” (including bombings or other terrorist acts) could destroy the laboratory or its contents, including eggs, being stored there.

Quality control in the lab is extremely important. Sometimes immature eggs, that would normally be discarded can be used for quality control. This material may be used for quality control purposes before being discarded in accordance with normal laboratory procedures and applicable laws. None of this material will be utilized to establish a pregnancy or a cell line.

Additional Elements

Intracytoplasmic Sperm Injection (ICSI)

ICSI is required to fertilize all previously frozen eggs. ICSI bypasses the shell around the egg (zona pellucida) and the egg membrane (oolemma) to deliver the sperm directly into the egg. ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle.

ICSI is associated with a slightly higher risk of birth defects. Whether this association is due to the ICSI procedure itself or to inherent sperm defects, if present, has not been determined. The impact of ICSI on the intellectual and motor development of children has also been controversial, but recent studies have not detected any differences in the development of children born after ICSI, conventional IVF, or natural conception.

Certain genetic abnormalities have been shown to increase in IVF offspring. The prevalence of sex chromosome (X and Y) abnormalities in children conceived via ICSI is higher than observed in the general IVF population, but the difference between the two groups is small (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). Translocations (a re-arrangement of chromosomes that can cause miscarriage) may be more common in ICSI offspring (0.36%) than in the general population (0.07%).

Miscellaneous

- **It is the responsibility of each individual with frozen eggs to remain in contact with the clinic on an annual basis.**

Because of the possibility of your death or incapacitation, it is important to decide on the disposition of any cryopreserved oocyte(s) that remain in the laboratory. Since this is a rapidly evolving field, both medically and legally, the clinic cannot guarantee what the available or acceptable avenues for disposition will be at any future date.

Oocytes are understood to be your property, with rights of survivorship. No use can be made of these oocytes without your consent.

In the event of death or incapacitation, the oocytes shall become the sole and exclusive property of the clinic. In this event, I elect to: (please select and initial your choice)

	patient
1) Thaw and discard the oocyte(s)	_____
2) Donate the oocyte(s) for research	_____
3) Donate the oocyte(s) to another recipient	_____

You are free to submit a statement at a later time indicating different choices.

Cryopreserved Oocyte Storage

Maintaining oocytes(s) in a frozen state is labor intensive and expensive. There are fees associated with freezing and maintaining cryopreserved oocytes(s). Patients who have frozen oocytes(s) must remain in contact with the clinic on an annual basis in order to inform the clinic of their wishes as

well as to pay fees associated with the storage of their oocyte(s). In situations where there is no contact with the clinic for a period of **THREE** years or fees associated with embryo storage have not been paid for a period of **THREE** years and the clinic is unable to contact the patient after reasonable efforts have been made, the oocytes(s) will be considered to be abandoned and may be destroyed by the clinic in accordance with normal laboratory procedures and applicable law.

I understand that before I (the patient) reach **55** years of age (DATE __/__/__), the cryopreserved oocytes(s) must be:

1) thawed, inseminated, and transferred
2) donated to another recipient
3) donated to research
4) discarded or
5) transferred to another storage facility

If no disposition has occurred by the above date, I hereby waive any and all interest in said cryopreserved oocytes(s) and the cryopreserved oocyte(s) shall become the sole and exclusive property of the clinic. In this event I elect to: (please initial your choice)

	Patient
1) Thaw and discard the oocytes(s)	_____
2) Donate the oocytes(s) for research	_____
2) Donate the oocytes(s) to another recipient	_____

You are free to submit a statement at a later time indicating different choices, provided you both agree in writing.

Donated Oocyte fate

In certain situations, donating oocytes(s) to another recipient may not be possible or may be restricted by law. While efforts will be made to abide by your wishes, no guarantees can be given that oocytes(s) will be donated to another recipient. In this instance, if after **THREE** years no recipient can be found, or your oocyte(s) are not eligible, your oocytes(s) will be discarded by the lab in accordance with laboratory procedures and applicable laws.

Risks to the Woman

Ovarian Hyperstimulation Syndrome

The intent of giving gonadotropins is to mature multiple follicles, but some women have an excessive response to the medications and are at risk for ovarian hyperstimulation syndrome (OHSS). This is the most serious side effect of ovarian stimulation. Its symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure, or death. The severe cases affect only a very small percentage of women who undergo in vitro fertilization—0.2 percent or less of all treatment cycles—and the very severe are an even smaller percentage. Only about 1.4 in 100,000 cycles has lead to kidney failure, for example. OHSS occurs at

two stages: early, 1 to 5 days after egg retrieval (as a result of the hCG trigger); and late, 10 to 15 days after retrieval.

Cancer

Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. A final answer may require decades of follow-up to resolve. Note that an increased chance for "borderline" ovarian tumors has been observed with IVF, even when compared to the subfertile population (see reference section for citation). More research is required to examine what the long-term impact fertility drugs may have on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical significance, but it is at least possible that use of fertility drugs may indeed cause some increased risk of uterine cancer.

Risks to Offspring

Overall Risks

Since the first birth of an IVF baby in 1978, more than 5 million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. A major problem in interpreting the data arises from the fact that comparing a group of patients needing assisted reproduction to unassisted group is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

Birth Defects

The risk of birth defects in the normal population is 2-3%, and is slightly higher among patients undergoing assisted reproduction. Most of this risk is due to delayed conception and the underlying infertility issues, if present. Some of the disorders/abnormalities that have been suggested to be associated with assisted reproduction includes Imprinting Disorders. These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed.

Childhood cancers. Most studies have not reported an increased risk with the exception of retinoblastoma: In one study in the Netherlands, five cases were reported after IVF treatment which is 5 to 7 times more than expected. Further studies have not supported this finding.

Infant development. In general, studies of long-term developmental outcomes have been reassuring so far; most children are doing well. However, these studies are difficult to do and suffer from limitations.

Ethical and Religious Considerations in Assisted Reproduction Technology Treatment

Assisted reproduction treatment can raise concerns and questions of an ethical or religious nature for some patients. Patients who so desire are encouraged to consult with trusted members of their religious or ethic community for guidance on assisted reproduction treatment.

Psychosocial Effects of Infertility Treatment

The use of assisted reproduction can be a devastating and life-altering event that impacts on many aspects of a patient's life. Assisted reproduction treatment can affect a patient medically, financially, socially, emotionally and psychologically. Feelings of anxiety, depression, isolation, and helplessness are not uncommon among patients undergoing assisted reproduction.

Patients may consider working with mental health professionals who are specially trained in the area of assisted reproduction, as well as their health care team, to minimize the emotional impact of fertility treatments. National support groups are also available, such as RESOLVE, (www.resolve.org, Tel. 1-888-623-0744) or The American Fertility Association (AFA), (www.theafa.org, Tel: 1-888-917-3777).

Reporting Outcomes

The 1992 Fertility Clinic Success Rate and Certification Act requires the Centers for Disease Control and Prevention (CDC) to collect cycle-specific data as well as pregnancy outcome on all assisted reproductive technology cycles performed in the United States each year and requires them to report success rates using these data. Consequently, data from my/our IVF procedure will be provided to the CDC, and to the Society of Assisted Reproductive Technologies (SART) of the American Society for Reproductive Medicine (ASRM) (if my/our clinic is a member of this organization). The CDC may request additional information from the treatment center or contact me/us directly for additional follow-up. Additionally, my/our information may be used and disclosed in accordance with HIPAA guidelines in order to perform research, data aggregation and/or quality control. All information used for research will be de-identified prior to publication. De-identification is a process intended to prevent the data associated with my/our treatment being used to identify me/us as individuals.

Additional Information

General IVF overviews available on the internet

www.reproductivefacts.org

www.sart.org/

www.cdc.gov/art/

www.resolve.org/site/PageServer

Intracytoplasmic sperm injection

Genetic considerations related to intracytoplasmic sperm injection (ICSI). The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S103-S105.

Ovarian Hyperstimulation

Ovarian hyperstimulation syndrome. The Practice Committees of the American Society for Reproductive Medicine. Fertil Steril 2006; 86 (suppl 4): S178-S183.

Risks of pregnancy

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Risk of borderline and invasive tumours after ovarian stimulation for *in vitro fertilization* in a large Dutch cohort. FE van Leeuwen, H Klip, et al. Human Reproduction, 2011;26(12):3456-65.

Risks to offspring

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Multiple pregnancy associated with infertility therapy. The Practice Committees of the American Society for Reproductive Medicine Fertil Steril 2006; 86 (suppl 4): S106-S110.

Imprinting diseases and IVF: A Danish National IVF cohort study. Lidegaard O, Pinborg A and Anderson AN. Human Reproduction 2005; 20(4):950-954.

Bergh C, Wennerholm U-B. Obstetric outcome and long-term follow up of children conceived through assisted reproduction. Best Practice & Research Clinical Obstetrics and Gynaecology (2012), doi:10.1016/j.bpobgyn.2012.05.001.

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive Technologies and the risk of birth defects. N Engl J Med 2012;366:1803-13. Doi:10.1056/NEJMoa1008095).

Reproductive technologies and the risk of birth defects. MJ Davies, VM Moore, et al. New England Journal of Medicine 2012; 366(19):1803-13.

I acknowledge that I have read and understood the information provided above regarding the oocyte cryopreservation process and its risks, and agree to go forward with this treatment as my signatures below testify.

_____ Patient name printed

Patient Signature Date

_____ _____ _____ Assisted Reproduction Treatment
(Including injections, egg retrieval etc.)

_____ _____ _____ Cryopreservation of matured oocytes

USF IVF Staff_____ _____

Consent is valid for 1 year from date of signature