wisconsin fertility
INSTITUTE

Egg Freezing

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Welcome to the Wisconsin Fertility Institute, and thank you for your interest in our Egg Freezing program. This packet is designed to act as a resource for you as you begin the journey through the complex world of assisted reproduction. We have attempted to provide as many answers to your questions as we could anticipate. However, this is not a stand-alone document meant to answer all your questions and concerns; rather, this packet is meant to provide an overview and to supplement information obtained from your doctor, the nursing team, and other members of the Wisconsin Fertility Institute.

Here at WFI, we are firm believers in the partnership between medical team and couple to achieve a goal that is decided upon in a collaborative manner. We do not practice paternalistic directives; nor do we pretend to necessarily know what is always in your best interest. Instead, we will do our best to explain what we prefer to do and why we do it. If you feel confused or pressured, please speak up and let us know as this is not our intent. We strive to create an atmosphere of trust and cooperation, and we can only do that if you are an active member of the team voicing your concerns if you feel your needs are not being met.

We realize that creating a family is a serious endeavor, and that your decision to pursue egg freezing is a commitment to sacrificing considerable time and expense. We also understand how anxiety-provoking the process can be. To this end, we have attempted to minimize the stress by providing a safe, comfortable environment. We also have a number of ancillary services available via local professionals, designed to aid in your ability to cope with the pressure of assisted reproduction. Please ask us about these services.

Once again, thank you for your interest in and support of the Wisconsin Fertility Institute. We sincerely hope to help you build the family of your dreams, and we are honored to have the privilege of working with you.

Elizabeth A. Pritts, M.D.
Founder

Gretchen E. Collins, M.D.

A BRIEF HISTORY OF *IN-VITRO* FERTILIZATION

Robert Edwards, a Ph.D. physiologist, and Patrick Steptoe, a gynecologist, pioneered IVF in Great Britain during the 1970's. Edwards had spent the 1960's working with bits of human ovaries removed at surgery and had achieved the first fertilization of a human egg outside the body in 1967. During these same years, Steptoe was helping to develop the new surgical technique of laparoscopy. By 1971 the two men had met and begun to collaborate. Initially they retrieved eggs from the ovaries of volunteers by laparoscopy and focused on improving the timing of egg retrieval and *in-vitro* culture conditions. By the mid-1970's they felt ready to attempt pregnancy. Their initial pregnancy was, unfortunately, a tubal pregnancy (ectopic) in 1976. Then came true success and the first IVF baby, Louise Brown, was born in July 1978.

Steptoe and Edwards' original group of patients had undergone "natural IVF", meaning they were not given fertility drugs. Instead they were monitored closely and when ovulation appeared imminent, even if it was 3:00 AM, a laparoscopy was done and an attempt made to aspirate the single mature egg. As might be suspected, they didn't always obtain the egg. Two Australian groups were only two years behind in achieving IVF pregnancies but they chose a different route. They stimulated their patients with fertility drugs in hopes of recovering more than one egg. As their initial success rates, about 5% per attempt, were higher than that of Steptoe and Edwards, all subsequent new IVF programs also used "stimulated IVF". Eventually Steptoe and Edwards adopted this approach as well.

The 1980's saw continued improvement in embryology culturing techniques, refinements in fertility drug protocols, and the ability to retrieve eggs with a vaginal ultrasound probe instead of laparoscopy. As a result, IVF success rates began to climb slowly but steadily, reaching 20-25% per attempt for women under the age of 40 by the end of the decade.

The 1990's have seen additional improvements in the process, such as better treatment protocols for women 40 years of age and older and the development of ICSI (Intracytoplasmic Sperm Injection), a revolutionary treatment for severe male factor problems. With ICSI, a single sperm can be injected into an egg and thereby achieve fertilization. For women 35 years of age and older, a technique called Assisted Hatching and the ability to grow embryos longer (3 to 5 days before transfer) have helped improve the odds. Also, the process of egg donation (IVF using eggs donated by a younger woman) was perfected, producing high pregnancy rates in previously hopeless situations.

EGG FREEZING

Human **oocyte cryopreservation (egg freezing)** is a process in which a woman's eggs (oocytes) are extracted, frozen and stored. Later, when she is ready to become pregnant, the eggs can be thawed, fertilized, and transferred to the uterus as embryos.

History

Cryopreservation itself has always played a central role in assisted reproductive technology. With the first cryopreservation of sperm in 1953 and of embryos thirty years later, these techniques have become routine. Dr Christopher Chen of Singapore reported the world's first pregnancy in 1986 using previously frozen oocytes. This report stood alone for several years followed by studies reporting success rates using frozen eggs to be much lower than those of traditional in vertro fertilization (IVF) techniques using fresh oocytes. Providing the lead to a new direction in cryobiology, Dr. Lilia Kulesiva was the first scientist to achieve vitrification of human oocytes that resulted in a live birth in 1999. Then recently, two articles publishes in the journal, *Fertility and Sterility,* reported pregnancy rates using frozen oocytes that were comparable to those of cryopreserved embryos and even fresh embryos. These newer reports affirm that oocyte cryopreservation technology is advancing.

Indications

Oocyte cryopreservation is aimed at three particular groups of women: those diagnosed with cancer who have not yet begun chemotherapy or radiation therapy; those undergoing treatment with assisted reproductive technologies who do not consider embryo freezing an option; and those who would like to preserve their future ability to have children, either because they do not yet have a partner, or for other personal or medical reasons.

Over 50,000 reproductive-age women are diagnosed with cancer each year in the United Stated. Chemotherapy and radiation therapy are often toxic for oocytes, leaving few, if any, viable eggs. Egg freezing offers women with cancer the chance to preserve their eggs so that they can have children in the future.

Oocyte cryopreservation is an option for individuals undergoing IVF who object, either for religious or ethical reasons, to the practice of freezing embryos. Having the options to fertilize only as many eggs as will be utilized I the IVF process, and then freeze any remaining unfertilized eggs can be a solution. In this way, there are no excess embryos created, and there need be no disposition of unused frozen embryos, a practice which can complex choices for certain individuals.

Social egg freezing is a term used to describe the use of egg-freezing as an attempt to delay child-bearing in a non-medical context. There has been a proliferation in the marketing of this kind of egg freezing since October 2012 when the American Society for Reproductive Medicine lifted the experimental label from the technology.

Additionally, woman with a family history of early menopause have an interest in fertility preservation. With egg freezing, they will have a frozen store of eggs, in the likelihood that their eggs are depleted at an early age.

Method

The egg retrieval process for oocyte cryopreservation is the same as that for in vitro fertilization. This includes one to several weeks of hormone injections that stimulate ovaries to ripen multiple eggs. When the eggs are mature, the final maturation is performed by using a GnRH agonist or human chorionic gonadotropin (hCG). The eggs are subsequently removed from the body by transvaginal oocyte retrieval, a procedure performed under conscious sedation. The eggs are immediately frozen.

Eggs are the largest cells in the body, and as such are extremely vulnerable to damage when freezing. Past methodology results in poor survival and pregnancy rates. However, today eggs are frozen using a flash-freezing process known as vitrification, a huge improvement over older methods of oocyte freezing. Vitrification is associated with higher survival rates and better development compared to older methods.

Success Rates

In a 2013 analysis of more than 2,200 cycles using frozen eggs, scientists found the probability of having a live birth after three cycles was 31.5 percent for women who froze their eggs at age 25, 25.9 percent at age 30, 19.3 percent at age 35, and 14.8 percent at age 40.

Two recent studies showed that the rate of birth defects and chromosomal defects when using cryopreserved oocytes in consistent with that of natural conception.

In 2014, a scientist review compared vitrification (the newest technology) versus slow freezing (the oldest one). Key results of that review showed that the clinical pregnancy rate was almost 4 times higher in the oocyte vitrification group than in the slow freezing group.

WHAT ARE THE RISKS ASSOCIATED WITH IVF INCLUDING EGG FREEZING?

The track record of safety for IVF over the years has been very good. Nonetheless, there are risks that you should be aware of:

Multiple Pregnancies: The risk of multiples is directly linked to the number of embryos transferred. Multiple pregnancies carries with it the problems of greater discomfort, higher risks of miscarriage, pregnancy-induced hypertension, fetal growth and development problems, and cesarean section delivery compared to singleton pregnancies. The biggest threat, however, is prematurity. Premature infants can have a host of problems ranging from minor disabilities to major mental or physical impairment to even death. Two methods to minimize high-order multiple gestations (triplets or more) is to transfer no more than two embryos or to selectively reduce the number of embryos after multiple pregnancy occurs.

Ectopic Pregnancy*:* The world's first IVF pregnancy in 1976 ended up in the woman's fallopian tube instead of her uterus. Even though the embryos are placed in the uterus, they are incapable of embedding in the endometrium immediately and may drift into a fallopian tube. In women with normal fallopian tubes, 1-2% of all IVF pregnancies are ectopic. For those with damaged tubes, the risk can be as high as 4-5%. This is still considerably below the risk for ectopic pregnancies in women with abnormal tubes who conceive naturally. We can usually diagnose most ectopic pregnancies very early in pregnancy, before any risk of rupture of the fallopian tube, which allows a choice between two forms of treatment: laparoscopic surgery to remove the ectopic pregnancy or an injection of a drug called methotrexate to dissolve it.

Ovarian Hyperstimulation: The fertility drugs used in IVF usually cause the ovaries to enlarge somewhat. Some women's ovaries are so sensitive to these medications that they enlarge 4 or 5 times normal size and cause discomfort and leakage of fluid from the blood vessels into the abdomen, a problem called Ovarian Hyperstimulation Syndrome (OHSS). Severe OHSS occurs in less than 1% of patients but usually requires hospitalization and careful treatment to avoid your getting very sick. The hospital stay can sometimes be several weeks, particularly if you are pregnant.

We minimize the risk of severe OHSS by carefully monitoring your progress during drug treatment, and adjusting the drug doses as necessary.

Infection: There is a 0.1 percent (1 per 1,000) risk reported in the medical literature that a pelvic infection would occur after egg retrieval. These infections have been mild in some cases and severe, even to the point of requiring major surgery, in others. We always attempt to minimize this risk by using sterile technique and treating you with antibiotics.

***Cancer*:** A study in 1994 showed a possible increase in the risk of ovarian cancer in women who took the fertility pill clomiphene citrate (Clomid) for a long period of time (12 or more months). Clomid is rarely used in IVF, and no studies to date have indicated any increased risk for other IVF medications, but perhaps studies in the future will. However, given the difficulty of demonstrating an increased risk of ovarian cancer despite nearly 30 years of IVF, it is likely that even if the risk is increased it is a slight increase! Counterbalancing this theoretical risk is the known benefit of pregnancy, which substantially lowers the risks of cancer of the breast, ovary and uterus.

PRE-CYCLE TESTING FOR IVF

Tests	Description	Female Partner	Male Partner	Egg Donor	Egg Donor's Partner	Surrogate	Surrogate's Partner
AMH	Blood test done to check the ability of the ovaries to respond to fertility medication and to determine the ovarian reserve	X		X			
HIV	Test for infection	X	X	X	X	X	X
HTLV-1 & II	A virus that can cause leukemia and neurologic disease					X	X
VDRL/RPR	Test for syphilis	X	X	X	X	X	X
Hep B S Ag	Test for Hepatitis B	X	X	X	X	X	X
Hep C Ab	Test for Hepatitis C	X	X	X	X	X	X
CMV-IgM	Test for Cytomegalovirus that can cause fetal damage if a woman is pregnant with active infection					X	

THE TREATMENT CYCLE FOR EGG FREEZING: A COMPLETE GUIDE

Evaluation and Preparation Phase

You will begin the road to egg freezing by consulting with one of the doctors at the Wisconsin Fertility Institute. At that visit, the doctor will review all treatment options available to you, as well as their likelihood of success and approximate cost. The doctor may also suggest additional tests to further refine the likelihood of success with each option. If you should then opt for egg freezing you will meet with a member of the nursing staff who will review which tests are required prior to beginning the egg freezing treatment. Once these tests are completed and we have the results, you will again meet with your doctor and a nurse, review the test results and, if all are normal, proceed to treatment. If one or more tests is abnormal this will be discussed with you and treatment plans reconsidered.

Cycle of Treatment

There are a number of different approaches to drug administration for egg freezing treatment cycle, and each has been found to be the best approach in some patients. However, no approach works in everyone, and occasionally a poor response to medication may necessitate a discontinuation of treatment, with resumption later using a different drug combination. In this center, three approaches are used primarily, although small variations may sometimes occur for individual patients:

(1) ***Antagonist:*** This is the most common regimen that is currently used. With the beginning of the menstrual period, a baseline visit is conducted. This visit consists of three steps: (a) an ultrasound to show that nothing has begun to grow on the ovaries, (b) a blood estrogen level to confirm that nothing was missed on ultrasound, and (c) a check to make sure consent has been obtained. If the ovaries are quiet, the estrogen level is low, and consent forms are signed, we are ready to begin stimulation of the ovaries. Follistim or Gonal F is begun on this day and continued for 9-14 days. It is given subcutaneously (SQ), (small needle just under the skin). Periodic ultrasound examinations and blood estrogen levels are performed. When the largest ovarian follicle (egg surrounded by fluid) measures 14 mm, daily injections of Cetrotide or Ganirelix are administered SQ each morning until a large number of eggs are fully grown and mature. The drugs are then discontinued and either Ovidrel/Lupron or a combination of both (trigger shots) is administered to allow the retrieval of the eggs. These SQ drugs are given 35 hours before harvesting your eggs, and is responsible for their final maturation and readiness to be mixed with sperm.

(2) ***Agonist suppression***: With this approach, women begin a drug called Lupron after a couple of weeks on oral contraceptives. The drug is administered daily by SQ injection. When a subsequent period begins, the woman comes to the clinic for a baseline visit. The Lupron is continued Follistim or Gonal F is added each day for 9-14 days total. Once the eggs are mature you will take the trigger shots 35 hours before egg harvesting.

(3) ***Microdose flair:*** In patients with a previous poor response to stimulation, who are age 40 or over, or who have a day 3 FSH value over 10, or an AMH less than 1.5, another approach to stimulating the ovaries is Microdose Flair. The idea behind this treatment protocol is to use the body's own FSH in combination with Follistim or Gonal F to stimulate the ovaries to grow eggs. The day after your period begins you have a baseline visit, and if all is acceptable you administer a low dose of Lupron subcutaneously twice daily. After the first 2 days of Lupron, Follistim or Gonal F are added at a dose of 450 units daily. This is continued, with periodic ultrasound examinations and blood estrogen tests, until a reasonable number of eggs have grown and matured (usually 9-14 days). The previous drugs are then discontinued and 2 Ovidrel (trigger shots) are administered to allow the eggs to be retrieved.

Egg Retrieval

Thirty five hours after the administration of Ovidrel, Lupron or a combination of both, you will undergo a procedure called egg retrieval. You will be instructed not to eat or drink anything after midnight the night before the egg retrieval, and also the morning of the retrival, due to the anesthesia given. You will need a ride home that day. On the day of the retrieval, a fresh semen sample will be obtained for use in the fertilization process. In certain situations, a sample can be obtained earlier and cryopreserved or frozen. The specimen would then be then thawed for use on the day of retrieval.

The egg retrieval procedure is done at our office under light anesthesia (intravenous sedation). A needle guided by ultrasound is passed through the top of the vagina and into the follicles in the ovary. It takes about 30 minutes to retrieve the eggs, and then 60-90 minutes to rest in our recovery room.

The fluid we remove from the follicles is given immediately to our embryologists who use their microscopes to find the otherwise invisible eggs. The eggs will be frozen shortly after retrieval.

The day of retrieval you will begin an antibiotic called doxycycline (2 times daily) which will help decrease risk of infection. You will continue this drug for 5 days after the retrieval.