



Documentation of Informed Consent for Assisted Reproduction: Oocyte Freezing

I, _____ (name of the patient), have had a full discussion with _____ (name of doctor), and have had a chance to ask questions and receive answers about assisted reproduction. I have made a choice about oocyte cryopreservation treatment and wish to document that choice, and I have initialed each page to indicate that I have read and understand the information provided.

NOTE: If you do not understand the information provided, please let your treating physician know and you will then have a further discussion to help you decide. There are a few locations within the consent form where you are being asked to confirm your decision. Please make sure to initial your choice and sign where requested so we all understand how we will proceed.

OVERVIEW

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. Both methods remove the surrounding support cells, the cumulus, from the eggs prior to freezing. Once the cumulus cells are removed, eggs may not fertilize readily. In addition, the zona pellucida “shell” around the egg hardens with freezing. For these two reasons, injection of sperm directly into the egg (ICSI) is currently recommended after eggs have been frozen.

When eggs are vitrified, they may come in direct contact with liquid nitrogen. This could carry a risk of transmitting infection if the liquid nitrogen should be contaminated, although there has never been a case of infection reported by this means.

The techniques for freezing eggs, both with the slow freeze method and with vitrification, have become successful enough that they are no longer considered experimental. Implantation and pregnancy rates may be lower with frozen eggs than with fresh eggs. Most reports have focused on young women who have responded well to the medications used for egg retrieval, so success rates in older women or poor responders

may not be as good. Many good reasons exist for freezing eggs rather than embryos, such as ethical concerns or medical problems that can affect fertility in women without male partners. In women who wish to freeze their eggs solely to delay childbearing, extreme caution should be exercised due to limited data on success and safety.

This consent form reviews the ART process from start to finish, including the known 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 cryopreservation that are not yet clarified or even suspected at the time of this writing.

An oocyte cryopreservation cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs.
- Retrieval of eggs from the ovary or ovaries.
- Cryopreserving the eggs.

Note: At various points in this document, rates are given that reflect what are currently believed to be U.S. national averages for those employing ART treatments. These include items such as pregnancy rates, Cesarean delivery rates, and preterm delivery rates. These rates are not meant to indicate the rates of these outcomes within individual practices offering IVF, and are not to be understood as such. Individual practices may have higher or lower pregnancy and delivery rates than these national averages, and also higher or lower risks for certain complications. It is appropriate to ask each practice about their specific rates.

Also note that while this information is believed to be up to date at the time of publication (2010), newer reports may not yet be incorporated into this document.

Outline of Consent for Oocyte Cryopreservation

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A. Technique of Oocyte Retrieval

1. Core elements and their risk

a. Medications for ART Treatment

- The success of oocyte retrieval 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®, 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. These medications are given by subcutaneous or intramuscular 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. Up to 2.0 % of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section below]. 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, which may require further medical or surgical treatment.

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, and the end result may be few or no eggs obtained at egg retrieval or even cancellation of the treatment cycle prior to egg retrieval.

Some prior research suggests that the risk of ovarian tumors may increase in women who take any fertility drugs over a long period of time. These studies had significant design flaws that limited the strength of the conclusions. More recent studies have not confirmed this risk. A major risk factor for ovarian cancer is infertility alone, suggesting that early reports may have falsely attributed the risk resulting from infertility to the use of medications to overcome it. In these studies, conception (being pregnant) lowered the risk of ovarian tumors to that of otherwise fertile women.

- **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 (Federal Drug Administration) approved medication, use for the purposes of IVF is off-label, and 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 other significant side effects are known. Since GnRH-agonists are often 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-agonist. GnRH-agonists have not been associated with any fetal malformations however you should discontinue use of the GnRH-agonists as soon as pregnancy is confirmed.

- **GnRH-antagonists (Ganirelix Acetate or Cetrotorelix Acetate)** (Antagon®, 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)** (Novarel®, 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 the maximum number of mature eggs. Potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort.
- **Oral contraceptive pills:** Many 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 stroke.
- **Other medications:** Other medications such as steroids, heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.

b. Transvaginal Oocyte Retrieval

- Eggs are removed from the ovary with a needle under ultrasound guidance
- Anesthesia is provided to make this comfortable
- Injury and infection 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, which may mean the oocyte retrieval with our clinic is not possible. 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 0.5%. 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.

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/vaginal spotting are common during/after egg retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding will frequently require surgical repair and possible 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 led 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 low.

Anesthesia: The use of anesthesia during the egg retrieval can produce unintended complications such as a reversible 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.

After eggs are retrieved, they are transferred to the embryology laboratory where the surrounding cells will be removed and mature eggs are cryopreserved. If no mature eggs are identified, then no eggs will be cryopreserved.

2. Additional Elements and their risk

a. Intracytoplasmic Sperm Injection (ICSI)

- **ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal**
- **Overall success rates with ICSI are slightly lower than for conventional insemination**
- **An increased risk of genetic defects in offspring is reported**
- **ICSI will not improve oocyte defects**
- **ICSI will be needed to fertilize any eggs that have been cryopreserved**

ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle.

Reports on the risk of birth defects associated with ICSI (compared to those associated with conventional fertilization in IVF cycles) have yielded conflicting results. The most comprehensive study conducted thus far, based on data from five-year-old children, has suggested that ICSI is associated with an increased risk of certain major congenital anomalies. However, whether the association is due to the ICSI procedure itself, or to inherent sperm defects, could not be determined because the study did not distinguish between male factor conditions and other causes of infertility. Note that even if there is an increased risk of congenital malformations in children conceived with ICSI, the risk is relatively low (4.2% versus ~3% of those conceived naturally). The impact of ICSI on the intellectual and motor development of children conceived via ICSI also has been controversial. An early report suggested that development in such children lagged significantly behind that of children resulting from conventional IVF or those conceived naturally. However, more recent studies from larger groups, using standardized criteria for evaluation, have not detected any differences in the development or the abilities of children born after ICSI, conventional IVF, or natural conception.

The prevalence of sex chromosome abnormalities in children conceived via ICSI is higher than observed in the general IVF population, but the absolute difference between the two groups is small (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). The reason for the increased prevalence of chromosomal anomalies observed in ICSI offspring is not clear. Whereas it may result from the ICSI procedure itself, it might also reflect a direct paternal effect. Men with sperm problems (low count, poor motility, and/or abnormal shape) are more likely themselves to have genetic abnormalities and often produce sperm with

abnormal chromosomes; the sex chromosomes (X and Y) in the sperm of men with abnormal semen parameters appear especially prone to abnormalities. If sperm with abnormal chromosomes produce pregnancies, these pregnancies will likely carry these same defects. The prevalence of translocations (a rearrangement of chromosomes that increases the risk of abnormal chromosomes in egg or sperm and can cause miscarriage) of paternal origin and of de novo balanced translocations in ICSI offspring (0.36%) also appears higher than in the general population (0.07%).

b. Specimen cryopreserved, storage, disposition

This informed consent relates to the medical procedure(s) you are undertaking with regard to assisted reproduction. To the extent Clinic or the University of Michigan stores any of your specimens, that service is outside the context of this consent and all terms and conditions related thereto are contained in the Clinic's Cryopreservation Specimens Storage Agreement (CSSA). The Clinic will not store your specimens unless, and until, you execute a CSSA.

B. Risks to the Woman

1. Ovarian Hyperstimulation Syndrome

To increase the number of eggs that develop, a series of hormone shots are given. The hormones used in this regimen are known to have, or suspected of having a variety of side effects, some minor and some potentially major.

The most serious side effect of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). 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 (as a result of the hCG if pregnancy occurs). The risk of severe complications is about 4 to 12 times higher if pregnancy occurs.

2. 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. More research is required to examine what the long-term impact fertility drugs may be 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.

C. Risks to Offspring

One concern with the use of egg freezing is that the cellular machinery that helps to separate the chromosomes of the eggs could be damaged, leading to chromosomal abnormalities such as Trisomy 21 (Down Syndrome) or other aneuploidies. However, a large study looking at 900 live births after egg freezing, most done via the slow freeze method, showed no increased risk of birth defects compared to the general US population. Another study of 200 live births from eggs that had been vitrified showed no difference in birth defects or birth weight in those children and the children who had been born after IVF cycles using fresh eggs. There is no information about children born after egg freezing in older women, or from follow-up years after birth.

1. Overall risks.

Since the first birth of an IVF baby in 1978, more than 3 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. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for IVF babies as compared to naturally conceived babies.

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. 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.

Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under 5 pounds nine ounces (2500 grams) is 12.5% vs. 7% in naturally conceived singletons.

2. Birth Defects.

The risk of birth defects in the normal population is 2-3 %. In IVF babies the birth defect rate may be 2.6-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects.

Imprinting Disorders. These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies approximately 4% of children with the imprinting disorder called Beckwith-Weidemann Syndrome were born after IVF, which is more than expected. A large Danish study however found no increased risk of imprinting disorders in children conceived with the assistance of IVF. Since the incidence of this syndrome in the general population is 1/15,000, even if there is a 2 to 5-fold increase to 2-5/15,000, this absolute risk is very low.

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.

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. A more recent study with better methodology reports an increased risk of cerebral palsy (3.7 fold) and developmental delay (4-fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

Potential Risks in Singleton IVF Pregnancies

Perinatal Risks	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)
Preterm birth	11.5%	2.0 (1.7--2.2)
Low birth weight (< 2500 g)	9.5%	1.8 (1.4--2.2)
Very low birth weight (< 1500 g)	2.5%	2.7 (2.3--3.1)
Small for gestational age	14.6%	1.6 (1.3--2.0)
NICU admission	17.8%	1.6 (1.3--2.0)
Stillbirth	1.2%	2.6 (1.8--3.6)
Neonatal mortality	0.6%	2.0 (1.2--3.4)
Cerebral palsy	0.4%	2.8 (1.3--5.8)
Genetic risks		
-imprinting disorder	0.03%	17.8 (1.8--432.9)
-major birth defect	4.3%	1.5% (1.3--1.8)
-chromosomal abnormalities (after ICSI):		
-of a sex chromosome	0.6%	3.0
-of another chromosome	0.4%	5.7

In this table, the Absolute risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a relative risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the "Confidence Interval") indicate the range in which the actual Relative Risk lies.

D. Psychosocial Effects of Infertility Treatment

The need or desire to cryopreserve oocytes can be a devastating and life-altering event that impacts many aspects of a patient's life. Infertility and its treatment can affect a patient and her spouse or partner medically, financially, socially, emotionally and psychologically. Feelings of anxiousness, depression, isolation, and helplessness are not uncommon among patients undergoing infertility treatment. Strained and stressful relations with spouses, partners and other loved ones are not uncommon as treatment gets underway and progresses.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany treatment. In addition to working with our health care team to minimize the emotional impacts of treatments, patients may also consider working with mental health professionals who are specially trained in the area of care.

While it is normal to experience emotional ups and downs when pursuing treatment, it is important to recognize when these feelings are of a severe nature. If you experience any of the following symptoms over a prolonged period of time, you may benefit from working with a mental health professional:

- loss of interest in usual activities
- depression that doesn't lift
- strained interpersonal relationships (with partner, family, friends and/or colleagues)

- difficulty thinking of anything other than your treatment
- high levels of anxiety.
- diminished ability to accomplish tasks
- difficulty with concentration
- change in your sleep patterns (difficulty falling asleep or staying asleep, early morning awakening, sleeping more than usual for you)
- change in your appetite or weight (increase or decrease)
- increased use of drugs or alcohol
- thoughts about death or suicide
- social isolation
- persistent feelings of pessimism, guilt, or worthlessness
- persistent feelings of bitterness or anger

Our health care team can assist you in locating a qualified mental health professional who is familiar with the emotional experience of infertility, or you can contact a national support group 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).

E. 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 of 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 the 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 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.

I have discussed all of this information with my treating team and people that I trust such as my parent(s), partner, my religious advisor, etc. and have agreed to the procedures listed above with full knowledge and understanding of these procedures, their risks and possible benefits, my actions and their possible consequences.

Signatures

Patient

Date

Oocyte Cryopreservation

Physician/Witness _____

Initials: Patient _____

References:

General IVF overviews available on the internet

<http://www.sart.org/>

<http://www.cdc.gov/art/>

<http://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 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.