Oocyte Warming and Insemination

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. There are two sources of frozen eggs. Some women may have chosen to have had their eggs frozen for the purpose of fertility preservation at some time prior to warming. Other women may have obtained frozen eggs donated by an egg donor.

This consent reviews the Oocyte warming 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, subsequent warming, and the IVF process, that are not yet clarified or even suspected at the time of this writing.

Oocyte warming and subsequent embryo transfer typically includes the following steps or procedures:

- Medications to prepare the uterus to receive embryos
- Oocyte warming
- Insemination of eggs that have survived warming with sperm, using intracytoplasmic sperm injection (ICSI)
- Culture of any resulting fertilized eggs (embryos)
- Placement (transfer) of one or more embryos into the uterus
- Support of the uterine lining with hormones to permit and sustain pregnancy

In certain cases, these additional procedures can be employed:

- Assisted hatching of embryos to potentially increase the chance of embryo attachment (implantation)
- Cryopreservation (freezing) of embryos

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.

Procedures

Medications for Endometrial Preparation and Pregnancy Support

- **Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support.**
- **Estrogen and progesterone are routinely given for this purpose.**

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

- ***Oral contraceptive pills:*** Some treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before estrogen and progesterone endometrial preparation and support 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.

- ***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 an egg from developing and ovulating prematurely. 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. 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

- ***Estrogen and Progesterone:*** Estrogen and Progesterone are hormones normally produced by the ovaries. They are required to prepare the endometrium (uterine lining) to receive embryos and allow embryos to implant. Estrogen can be taken by oral, trans-dermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the application site if given by the trans-dermal route and the risk of blood clots or stroke. Progesterone is usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories). Estrogen and Progesterone will be continued for some weeks after a pregnancy has been confirmed. Progesterone has not been associated with an increase in fetal abnormalities. Side effects of progesterone include depression, sleepiness, allergic reaction, and if given by intra-muscular injection, includes the additional risk of infection or pain at the injection site.

- ***Other medications:*** Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with embryo transfer. Antibiotic use may be associated

with vaginal yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, and allergic reactions. Anti-anxiety medications or muscle relaxants may be recommended prior to the embryo transfer. The most common side effect is drowsiness. Other medications such as steroids, heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.

Whenever injectable medications are used, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to any of these drugs.

Oocyte Warming

All frozen oocytes are warmed following standardized laboratory procedures developed for each particular oocyte cryopreservation techniques. These techniques are updated regularly based on emerging information, technology or outcomes. For the commercial eggs banks, the USF-IVF embryology and medical team maintain close contact with the different banks for protocol optimization.

In vitro fertilization, intracytoplasmic sperm injection (ICSI) and embryo culture

- **Sperm and eggs are placed together in specialized conditions (culture media, controlled temperature, humidity and light) to achieve fertilization.**
- **Culture medium is designed to permit normal fertilization and early embryo development, but the content of the medium is not standardized.**
- **Embryo development in the lab helps distinguish embryos with more potential from those with less or none.**

Once the eggs are warmed, individual sperm are injected into each surviving egg in a technique called Intracytoplasmic Sperm Injection (ICSI) (see below). The eggs are then returned to the incubator, where they remain to develop. Periodically over the next few days, the dishes are inspected so the development of the embryos can be assessed.

The following day after eggs have been warmed and injected with a single sperm (ICSI), they are examined for signs that the process of fertilization is underway. At this stage, normal development is evident by the still single cell having 2 nuclei; this stage is called a zygote or a 2PN embryo. Subsequently, the resulting embryo(s) from the ICSI procedure is (are) monitored daily until the day of transfer (Day 5, which is typically the stage of blastocyst formation) and cryopreservation of surplus good quality blastocyst(s).

It is important to note that since many eggs and embryos are abnormal, it is expected that not all eggs will fertilize and not all embryos will divide at a normal rate. The chance that a developing embryo will produce a pregnancy is related to many factors including whether its development in the lab is normal, but this correlation is not perfect. This means that not all embryos developing at the normal rate are in fact also genetically normal, and not all poorly developing embryos are genetically abnormal. Nonetheless, their visual appearance is the most common and useful guide in the selection of the best embryo(s) for transfer.

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

- Fertilization of the egg(s) may fail to occur.
- An egg may be fertilized abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos may not be transferred.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Bacterial contamination or a laboratory accident may result in loss or damage to some or all of the eggs or embryos.
- Laboratory equipment may fail, and/or extended power losses can occur which could lead to the destruction of eggs, sperm and embryos.
- 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 any sperm, eggs, or embryos being stored there.

- ***Some of the commercially available egg banks have some guarantee program incorporated in their consent. Patient should be knowledgeable of any of the egg banks guarantee programs.***

Intracytoplasmic Sperm Injection (ICSI)

- **ICSI is necessary for fertilization of frozen eggs**
- **An increased risk of genetic defects in offspring is reported.**

Intracytoplasmic sperm injection (ICSI) is performed after previously frozen eggs are warmed. ICSI is necessary because of changes to the structure and function of the egg after freezing. 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.

In addition to being used to fertilize previously frozen eggs, ICSI is used to help couples with male factor infertility achieve pregnancy. ICSI allows couples with male factor infertility to achieve fertilization and live birth rates similar to those achieved with in vitro fertilization (IVF) using conventional methods of fertilization in men with normal sperm counts. ICSI can be performed even in men with no sperm in the ejaculate if sperm can be successfully collected from the epididymis or the testis.

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 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%). Although these differences might result from the ICSI procedure itself, men with abnormal semen analyses are more likely themselves to have chromosome abnormalities and may produce sperm with abnormal chromosomes. These abnormalities could be passed to their offspring.

Some men with extremely low or absent sperm counts have small deletions on their Y chromosome. When viable sperm can be obtained to fertilize eggs with ICSI, sperm containing a Y chromosomal microdeletion may result in male offspring who also carry the microdeletion and may be infertile. A Y chromosome microdeletion can often, but not always, be detected by a blood test.

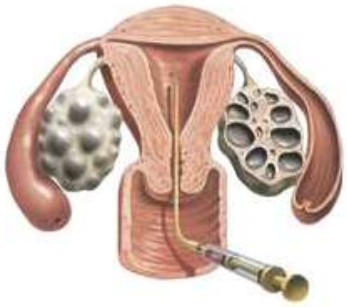
Men who are infertile because of congenital bilateral absence of the vas deferens (CBAVD) are affected with a mild form of cystic fibrosis (CF). When sperm aspiration and ICSI results in conception, the CF gene will be passed on to the offspring. Men with CBAVD and their partners should be tested for CF gene mutations prior to treatment. However, some CF mutations may not be detected by current testing, so that some parents who test negative for CF mutations could still have affected children.

Disposition of unfertilized eggs, sperm, or abnormal embryos

Quality control in the lab is extremely important. Sometimes unfertilized eggs, sperm or abnormal embryos (abnormally fertilized eggs or embryos whose lack of development indicates they are not of sufficient quality to be transferred) 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.

Embryo transfer

- **After a few days of development, the best appearing embryos are selected for transfer.**
- **The number chosen influences the pregnancy rate and the multiple pregnancy rate.**
- **The age of the eggs at freezing, and the appearance of the developing embryo have the greatest influences on pregnancy outcome.**
- **Embryos are placed in the uterine cavity with a thin tube.**
- **Excess embryos of sufficient quality that are not transferred can be frozen.**



After a few days of development, one or more embryos are selected for transfer to the uterine cavity (Day 5, which is typically the stage of blastocyst formation). Embryos are placed in the uterine cavity with a thin tube (catheter). Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. Although the

possibility of a complication from the embryo transfer is very rare, risks include infection and loss of, or damage to, the embryos.

The number of embryos transferred influences the pregnancy rate and the multiple pregnancy rate. The age of the woman or egg donor at the time her eggs were frozen, and the appearance of the developing embryo, have the greatest influence on pregnancy outcome and the chance for multiple pregnancy. While it is possible, it is unusual to develop more fetuses than the number of embryos transferred. It is critical to discuss with your doctor the number to be transferred before the transfer is done.

In an effort to help curtail the problem of multiple pregnancies (see multiple pregnancies), national guidelines published in 2013 recommend limits on the number of embryos to transfer (see Tables below). These limits should not be viewed as a recommendation on the number of embryos to transfer. These limits differ depending on the developmental stage of the embryos and the quality of the embryos and take into account the patient's personal history. Embryos identified as euploid (46 chromosomes) by preimplantation genetic screening (PGS) should be transferred singly.

Recommended limits on the number of embryos to transfer

Age at Egg Freeze	Age < 35	Age 35-37	Age 38-40	Age >40
Embryos				
--favorable	1 or 2	2	3	5
--not favorable	2	3	4	5
Blastocysts				
--favorable	1	2	3	3
--not favorable	2	2	3	3

In some cases, there will be additional embryos remaining in the lab after the transfer is completed. Depending on their developmental normalcy, it may be possible to freeze them for later use. (See section 2.c. for an in-depth discussion of embryo cryopreservation).

Additional Elements

Assisted Hatching

- **Assisted hatching involves making a hole in the outer shell (zona pellucida) that surrounds the embryo.**
- **Hatching may make it easier for embryos to escape from the shell that surrounds them.**

The cells that make up the early embryo are enclosed within a flexible membrane (shell) called the zona pellucida. During normal development, a portion of this membrane dissolves, allowing the embryonic cells to escape or "hatch" out of the shell. Only upon hatching can the embryonic cells implant within the wall of the uterus to form a pregnancy.

Assisted hatching is the laboratory technique in which an embryologist makes an artificial opening in the shell of the embryo. The hatching is usually performed on the day of transfer, prior to loading the embryo into the transfer catheter. The opening can be made by mechanical means (slicing with a needle or burning the shell with a laser) or chemical means by dissolving a small hole in the shell with a dilute acid solution.

Some programs have incorporated artificial or “assisted hatching" into their treatment protocols because they believe it improves implantation rates, and ultimately, live birth rates although definitive evidence of this is lacking.

Risks that may be associated with assisted hatching include damage to the embryo resulting in loss of embryonic cells, or destruction or death of the embryo. Artificial manipulation of the zygote may increase the rates of monozygotic (identical) twinning which are significantly more complicated pregnancies. There may be other risks not yet known.

Embryo Cryopreservation

- **Freezing of embryos can provide additional chances for pregnancy.**
- **Frozen embryos do not always survive the process of freezing and thawing.**
- **Ethical and legal dilemmas can arise when couples separate or divorce, especially for embryos; disposition agreements are essential.**
- **It is the responsibility of each couple with frozen embryos to remain in contact with the clinic on an annual basis.**

Freezing (or “cryopreservation”) of embryos is a common procedure. Since multiple frozen eggs (oocytes) are often inseminated, on occasion there are more embryos available than are considered appropriate for transfer to the uterus. Such embryos can be frozen for future use. Furthermore, the availability of cryopreservation permits patients to transfer fewer embryos during the cycle, reducing the risk of high-order multiple gestations (triplets or greater).

Risks of cryopreservation: There are several techniques for embryo cryopreservation, and research is ongoing. Traditional methods include “slow,” graduated freezing in a computerized setting, and “rapid” freezing methods, called “vitrification.” USF IVF uses vitrification exclusively. Current techniques deliver a high percentage of viable embryos thawed after cryopreservation, but there can be no certainty that embryos will thaw normally, nor be viable enough to divide and eventually implant in the uterus. Cryopreservation techniques could theoretically be injurious to the embryo. Extensive animal data (through several generations), and limited human data, do not indicate any likelihood that children born of embryos that have been cryopreserved and thawed will experience greater risk of abnormalities than those born of fresh embryos. However, until very large numbers of children have been born following freezing and thawing of embryos, it is not possible to be certain that the rate of abnormalities is no different from the normal rate.

Because of the possibility of you and/or your partner’s separation, death or incapacitation, it is important to decide on the disposition of any cryopreserved embryo(s), which 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. At the present time, alternatives at USF IVF are:

1) Discarding the cryopreserved embryo(s)
2) Donating the cryopreserved embryos to another couple in order to attempt pregnancy (You may be asked to undergo additional infectious disease testing and screening recommended by the FDA if you select this option.)

Embryos are understood to be your property, with rights of survivorship. No use can be made of these embryos without the consent of both partners (if applicable).

a) In the event of divorce or dissolution of the marriage or partnership, the ownership and/or other rights to the embryo(s) will be as directed by court decree and/or settlement agreement.

b) In the event of the death or incapacitation of one partner, the embryo(s) will become the sole and exclusive property of the surviving partner.

c) In the event of death or incapacitation of both partners or of a last surviving partner, the embryo(s) shall become the sole and exclusive property of the clinic. In this event, I/we elect to: (please select and initial your choice)

	patient	partner
1) Thaw and discard the embryo(s)	_____	_____
2) Donate the embryos to another couple	_____	_____

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

Cryopreserved Embryo Storage

Maintaining embryo(s) in a frozen state is labor intensive and expensive. There are fees associated with freezing and maintaining cryopreserved embryo(s). Patients/couples who have frozen embryo(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 embryo(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 embryo(s) will be considered to be abandoned and may be destroyed by the clinic in accordance with normal laboratory procedures and applicable law.

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

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

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

	patient	partner
1) Discard the cryopreserved embryo(s)	_____	_____
2) Donate the cryopreserved embryos to another couple	_____	_____

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

Donated embryo fate

In certain situations, donating embryo(s) to another couple 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 embryo(s) will be donated to another couple. In this instance, if after **THREE** years no recipient can be found, or your embryos are not eligible, your embryo(s) will be discarded by the lab in accordance with laboratory procedures and applicable laws.

Risks to the Woman

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 of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions (see Table below from the Executive Summary of a National Institute of Child Health and Human Development Workshop held in September 2005, as reported in the journal *Obstetrics & Gynecology*, vol. 109, no. 4, pages 967-77, 2007). Some of these risks stem from the higher average age of women pregnant by IVF and the fact that the underlying cause of infertility may be the cause of the increased risk of pregnancy complications. This was demonstrated in an Australian study that reviewed adverse obstetric and perinatal outcomes in sub-fertile women conceiving without ART (see Table below). There may be additional risks related to the IVF procedure per se, but it is difficult to assign the relative contributions.

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies in a control population)	Relative Risk of Non-IVF Infertile Patients (vs. control population)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)	1.29 (1.02-1.61)
Placenta previa	2.4%	2.9 (1.5--5.4)	
Placental abruption	2.2%	2.4 (1.1--5.2)	
Gestational diabetes	6.8%	2.0 (1.4--3.0)	1.25 (0.96-1.63)
Cesarean delivery *	26.7%	2.1 (1.7--2.6)	1.56 (1.37-1.77)

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, non-infertile 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. However, the third column indicates the increased risk of adverse outcome in infertile women conceiving without ART suggesting that being infertile increases the risk of adverse outcomes unrelated to ART/IVF. The numbers in parentheses (called the "Confidence Interval") indicate the range in which the actual Relative Risk lies.

* Please note that most experts believe the rate of Cesarean delivery to be well above the 26.7% rate quoted here.

Multiple gestations, which account for 30% of IVF pregnancies, increase the risk of pregnancy complications. The most important maternal complications associated with multiple gestations are preterm labor and delivery, pre-eclampsia, and gestational diabetes. Placenta previa (placenta extends over the cervical opening), vasa previa (one or more of the blood vessels extends over the cervical opening), and placental abruption (premature separation of the placenta) are also more common in multiple gestations. Postpartum hemorrhage may complicate 12% of multifetal deliveries. Having triplets or more increases the risk of more significant complications including post-partum hemorrhage and transfusion. Other complications of multiple gestations include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms.

Although embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies have occurred either alone or concurrently with a normal intra-uterine pregnancy. These abnormal pregnancies oftentimes require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy.

Risks to Offspring

- **IVF babies seem to be at a slight increased risk for birth defects.**
- **The risk for a multiple pregnancy is significantly higher for patients undergoing IVF, even when only one embryo is transferred.**
- **Multiple pregnancies are the greatest risk for babies following IVF.**
- **Some risk may also stem from the underlying infertile state, or from the IVF techniques, or both.**

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 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.

Birth Defects

The risk of birth defects in the normal population is 2-3%, and is slightly higher among infertile patients. Most of this risk is due to delayed conception and the underlying infertility issues. In a recent large study performed in Australia (see reference), the risk of birth defects was not increased among women who had routine IVF treatment, but was higher among those who employed ICSI as part of the treatment. No higher risk was seen in frozen embryo transfer and donor egg cycles.

Imprinting Disorders. These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies of children with the imprinting disorder called Beckwith-Weidemann Syndrome, more were born after IVF 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. 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. 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

	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)	Relative Risk for infertile women without ART
Preterm birth	11.5%	2.0 (1.7--2.2)	1.32 (1.05-1.67)
Low birth weight (< 2500 g)	9.5%	1.8 (1.4--2.2)	1.44 (1.11-1.85)
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)	0.99
NICU (intensive care) 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)	2.19 (1.10-4.36)
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.

Risks of a Multiple Pregnancy

Currently, more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies, and may occur more frequently after blastocyst transfer.

Prematurity accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Triplet (and greater) pregnancies deliver before 32 weeks (7 months) in almost half of cases. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. Multifetal pregnancy reduction (where one or more fetuses are terminated) reduces, but does not eliminate, the risk of these complications.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus.

Multiple fetuses that share the same placenta, as in most identical twins, have additional risks. Twin-twin transfusion syndrome, in which excess or insufficient amniotic fluid results from an imbalance of circulation between the fetuses, may occur in up to 20% of twins sharing a placenta. Twins sharing the same placenta have a higher frequency of birth defects compared to twins with two placentas. After the first trimester, death of one fetus in a twin pregnancy is more common with a shared placenta and may cause harm to the remaining fetus.

Long-term consequences of multiple gestations include the major complications of prematurity (cerebral palsy, retinopathy of prematurity, and chronic lung disease), as well as those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons. It is not clear to what extent these risks are affected by IVF per se.

The Option of Multifetal Pregnancy Reduction: The greater the number of fetuses within the uterus, the greater is the risk for adverse perinatal and maternal outcomes. Patients with more than twins are faced with the options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, or undergoing a procedure called multifetal pregnancy reduction. By reducing the number of fetuses, multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates important ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggest that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%, although this risk increases when the number of fetuses prior to the procedure is greater than three.

Ethical and Religious Considerations in Infertility Treatment

Infertility treatment can raise concerns and questions of an ethical or religious nature for some patients. The technique of in vitro fertilization (IVF) involves the creation of human embryos outside the body, and can involve the production of excess embryos and/or “high-order” multiple pregnancy (triplets or more). Patients and their spouses or partners who so desire are encouraged to consult with trusted members of their religious or ethic community for guidance on their infertility treatment.

Psychosocial Effects of Infertility Treatment

A diagnosis of infertility can be a devastating and life-altering event that impacts on 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 anxiety, 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.

Rearing of twins and high-order multiples may generate physical, emotional, and financial stresses; and the incidence of maternal depression and anxiety is increased in women raising multiples.

Patients may consider working with mental health professionals who are specially trained in the area of infertility care, as well as with their health care team, to minimize the emotional impact of infertility 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

Number of Embryos to Transfer

Criteria for number of embryos to transfer: a committee opinion. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2013; 99(1):44-6.

Culturing Embryos to the Blastocyst Stage

Blastocyst culture and transfer in clinical-assisted reproduction. 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): S89-S92.

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.

Embryo hatching

The role of assisted hatching in in vitro fertilization: a review of the literature. A Committee opinion. 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): S124-S126.

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.

We (I) acknowledge that we have read and understood the information provided above regarding the oocyte warming and insemination process and its risks, and agree to go forward with this treatment as our signatures below testify.

_____ Patient name printed **_____ Partner name printed**

Patient Signature Partner Signature (if applicable) Date

_____ _____ _____ **In Vitro Fertilization**
(Including egg warming, embryo culture and transfer)

_____ _____ _____ **Intracytoplasmic Sperm Injection (ICSI)**

_____ _____ _____ **Assisted Hatching**

_____ _____ _____ **Embryo Cryopreservation**

USF IVF Staff_____ _____

Consent is valid for 1 year from date of signature

Oocyte Warming and Insemination
Treatment Plan

Patient name: _____ Date: _____

Spouse / partner name: _____

Provider of Frozen Oocyte.

We (I) plan to use oocyte from:

- ❑ **Banked Donor Oocyte:**
- ❑ **Me /autologous:**
- ❑ **Other (specify arrangement): _____**

Initials: _____ / _____

Provider of Sperm.

We (I) plan to use sperm from:

- ❑ **Spouse / partner**
- ❑ **Donor (specify name or number): _____**
- ❑ **Other (specify arrangement): _____**

Initials: _____ / _____

Carrier of embryos.

We (I) plan to transfer the embryos into:

- ❑ **Me, the intended parent**
- ❑ **A Gestational Carrier**

----if known, her name: _____

Initials: _____ / _____

Method of Insemination.

We (I) acknowledge that we (I) have discussed the need for ICSI with our (my) physician and understand, agree and consent that:

- ❑ **ICSI *will be*** used.

Initials: _____ / _____

Plan for Embryos NOT Transferred.

Regarding the disposition of embryos not transferred, we (I) elect the following option:

- ❑ **Freeze Excess Embryos for my/our own use**
- ❑ **Freeze Excess Embryos to donate to another person/couple**
- ❑ **Discard Excess Embryos.** This disposal will follow ASRM Ethical Guidelines. These extra embryos will no longer be available for attempting a pregnancy.

Initials: _____ / _____

Plan for Preimplantation Genetic Testing / Screening.

We (I) choose:

- ❑ **No genetic testing / screening of embryos**
- ❑ **Genetic testing of all blastocysts no matter how few are available**

Initials: _____ / _____

Patient signature: _____

Partner / spouse signature: _____

USF IVF Staff signature: _____

Date: _____