



# IN VITRO FERTILIZATION CONSENT BOOKLET

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## **I. In Vitro Fertilization**

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In Vitro Fertilization (IVF) has become an established treatment for many forms of infertility. The main goal of IVF is to allow a patient the opportunity to become pregnant using her own eggs or donor eggs and sperm from her partner or from a donor. This is an elective procedure designed to result in the patient's pregnancy when other treatments have failed or are not appropriate.

This consent reviews the IVF process employed by the Fertility and Reproductive Health team at Lucile Salter Packard Children's Hospital at Stanford (Stanford) from start to finish, including the risks that this treatment might pose to you and your offspring. Stanford is an academic medical center affiliated with the Stanford University School of Medicine. As part of the medical education and training programs, postgraduate fellows, residents, medical students, and other approved healthcare practitioners may observe care, and if appropriately trained, participate in aspects of the process. These practitioners will be under the supervision of a Fertility and Reproductive Health team attending physician.

The medical risks of IVF vary with respect to each specific step of the procedure. Your physician will discuss with you the following primary risks of IVF as they relate to you and your care plan specifically:

An IVF cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Insemination of eggs with sperm
- Culture of any resulting fertilized eggs (embryos)
- Placement ("transfer") of one or more embryo(s) into the uterus
- Support of the uterine lining with hormones to permit and sustain pregnancy

In certain cases, these additional procedures can be employed:

- Intracytoplasmic sperm injection (ICSI) to increase the chance for fertilization
- Assisted hatching of embryos to potentially increase the chance of embryo attachment ("implantation")
- Preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) to test for genetic abnormalities
- Cryopreservation (freezing) of eggs or embryos

## II. IVF Procedures

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### Medications for IVF Treatment

- The success of IVF 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”:** These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Low-dose hCG (human chorionic gonadotropin) can be used in lieu of LH. These medications are given by subcutaneous 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 that follows]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

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

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

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

contraception (condoms or oral contraceptives) the month you will be starting the GnRH-a. GnRH-a has not been associated with any fetal malformations, however you should discontinue use of the GnRH-a immediately if pregnancy is confirmed.

- **GnRH-antagonists:** 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):** hCG is a natural hormone used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to: breast tenderness, bloating, and pelvic discomfort.
- **Progesterone, and in some cases, estradiol:** Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg retrieval in some women, the ovaries will not produce adequate amounts of these hormones for long enough to fully support a pregnancy. Accordingly, supplemental progesterone, and in some cases estradiol, are given to ensure adequate hormonal support of the uterine lining. Progesterone is usually given by injection or by the vaginal route after egg retrieval. Progesterone is often 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. Estradiol, if given, can be 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.
- **Oral contraceptive pills:** Some treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to suppress hormone production or to schedule a cycle. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or, very rarely, stroke.
- **Other medications:** Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with egg retrieval or 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.

## Transvaginal Oocyte (Egg) Retrieval

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

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

**Infection:** Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.1%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are sometimes used before the egg retrieval procedure to reduce the risk of pelvic or abdominal infection in patients at higher risk of this complication. Despite the use of antibiotics, there is no way to eliminate this risk completely.

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

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

**Failure:** It is possible that the aspiration will fail to obtain any eggs or the eggs may be abnormal or of poor quality and otherwise fail to produce a viable pregnancy.

## **In vitro fertilization 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.

After eggs are retrieved, they are transferred to the Stanford embryology laboratory where they are kept in conditions that support their needs and growth. The eggs are placed in small dishes or tubes containing "culture medium," which is special fluid developed to support development of the eggs and embryos made to resemble that found in the fallopian tube or uterus. The dishes containing the eggs are then placed into incubators, which control the temperature and atmospheric gasses the eggs and embryos experience.

A few hours after eggs are retrieved, sperm are placed in the culture medium with the eggs, or individual sperm are injected into each mature 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 inseminated or 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. Two days after insemination or ICSI, normal embryos have divided into about 4 cells. Three days after

insemination or ICSI, normally developing embryos contain about 8 cells. Five to six days after insemination or ICSI, normally developing embryos have developed to the blastocyst stage, which is typified by an embryo that now has 80 or more cells, an inner fluid-filled cavity, a small cluster of cells called the inner cell mass, and an outer group of cells called the trophectoderm.

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.

Stanford takes great care of all eggs, embryos and sperm in the lab. In spite of reasonable precautions, there are many reasons why pregnancy may not happen:

- The eggs may fail to fertilize.
- An egg may be fertilized abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos will not be transferred if testing is performed which detects the abnormality.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Rarely, the eggs or embryos may be harmed by contact with bacteria in the lab.
- In spite of having backup systems in place, lab equipment may fail or power may be lost. Both can lead to the destruction of eggs, sperm, and embryos.
- A lab accident or human error can happen and can lead to sperm, egg or embryo loss.
- Other unplanned events may prevent any step of the process from being performed or prevent pregnancy from occurring.
- Earthquakes, 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.

During the first 3 days of embryo culture after fertilization, Stanford may use an embryo imaging system within our incubators that captures key events during early development. Information from these automated cell division measurements are used to enhance the ability to select the most viable embryo from the cohort and provide some information about the embryo’s potential. Long-term effects on the embryos of this imaging are unknown but the amount of additional light exposure to the embryos is minimal and equivalent to approximately the same or less amount of light that an embryo is exposed to during traditional evaluations outside of the incubator.

## **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.**
- **A woman’s age 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 called a catheter.**
- **Surplus 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. 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 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 if one of the embryos splits into identical twins. It is critical to discuss with your doctor the number to be transferred before the transfer is done.

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 below for an in-depth discussion of embryo cryopreservation).

## Hormonal support of the uterine lining

- **Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support.**
- **Progesterone, given by the intramuscular or vaginal route, is routinely given for this purpose.**

Successful attachment of embryos to the uterine lining (endometrium) depends on adequate hormonal support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. However, in IVF cycles, this support is not always adequate. Therefore, progesterone is routinely given, and in some cases, estradiol is also prescribed. Progesterone is given by the intramuscular or vaginal route. Estradiol is given by the oral, vaginal, trans-dermal or intramuscular route. The duration of this support is from 2 to 10 weeks.

## III. Additional Elements

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### Intracytoplasmic Sperm Injection (ICSI)

- **ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal.**
- **An increased risk of genetic defects in offspring is reported.**
- **ICSI will not improve oocyte defects.**

The use of ICSI provides an effective treatment for male factor infertility. The negative effects of abnormal semen characteristics and sperm quality on fertilization can be overcome with ICSI if viable sperm are available because the technique bypasses the shell around the egg (zona pellucida) and the egg membrane (oolemma) to deliver the sperm directly into the egg. ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle. ICSI 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.

## 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 is made by mechanical means, thinning the shell with a laser.

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 but these risks are very low. 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.

## Pre-Implantation Genetic Testing (PGD or PGS)

If you decide to undergo PGD or PGS, the eggs will be fertilized by either standard IVF procedures or by sperm microinjection procedure, using intracytoplasmic sperm injection (ICSI). PGD involves the removal of several cells from a day 5 or 6 embryo (called a trophectoderm biopsy). Under rare circumstances, 1-2 cells from a day 3 embryo (called a blastomere biopsy) or 2 cells from an egg (called a polar body biopsy) may be offered as an alternative to day 5 biopsy. This testing occurs prior to embryo transfer.

The specific tests done for your embryos will depend on your history and test results. Preimplantation genetic testing is sometimes referred to as Preimplantation Genetic Screening (PGS) when the screening is done to count the number of chromosomes in the embryo rather than to test for a specific genetic disorder caused by one gene which is called Preimplantation Genetic Diagnosis (PGD). The genetic material from these cells is analyzed to determine whether the egg or embryo carries an abnormal number of whole chromosomes or large segments of chromosomes that may lead to a decreased chance for pregnancy or an increased chance for early miscarriage of a pregnancy. If relevant to your particular situation, the cells may be tested to see if any embryo has a specific genetic condition which may cause abnormalities in the resulting child. Your physicians at Stanford will be provided with the results of these tests to help inform your decision about which embryos to transfer.

The advantage of PGD and PGS are that they are performed earlier than standard prenatal diagnosis and, therefore, can potentially reduce the likelihood of having an affected child and/or the need for a termination of a pregnancy due to a genetic condition which may affect the health of the fetus.

#### **Risks:**

There is no risk of bodily injury to the recipient as a result of participation in the PGD or PGS procedure beyond the risks associated with the standard IVF procedures. There may be a risk to your eggs or embryos from the embryo biopsy procedures beyond the risks of standard IVF. The process of removing the cells may cause unexpected damage to the embryo. Unexpected damage may include destruction of the embryo, such that it would not be suitable for implantation. With a skilled embryologist, the risk of damaging the embryo is expected to be very low. Embryo biopsy has been performed for over 20 years with thousands of babies born. Studies indicate that the risk of congenital defects is similar to the general population rate which is about 3%. However, it is not definitively known whether or not there are any long-term risks of embryo biopsy.

No genetic testing is error proof. It is possible that the test will indicate that an embryo is abnormal when in fact the embryo is viable. Therefore, there is a risk of unintentionally withholding a normal embryo from transfer. In addition, errors may be due to technical or biological limitations of testing, including chromosomal mosaicism. The term "chromosomal mosaicism" refers to the presence of normal and abnormal chromosomes within the same sample. If reported, a mosaic result may indicate higher rates of adverse outcomes when compared to embryos with normal chromosomes. These outcomes may include implantation failure, pregnancy complications, or health complications in the resulting fetus. Genetic counseling regarding the implications of transferring a mosaic embryo is recommended. Mosaicism cannot be ruled out regardless of the result. The diagnostic procedures used in PGD and PGS are not designed to identify all possible genetic abnormalities and a tested egg or embryo could result in the birth of a child with genetic abnormalities. PGD and PGS do not provide information regarding multifactorial or adult onset conditions. It is possible the resulting pregnancy may have abnormalities of non-genetic etiology. At most, the chance of such an abnormality would be the same as if the embryo were transferred without the diagnostic procedure. We estimate the risk of misdiagnosis in PGD and PGS is less than 10%. Therefore, we recommend that you undergo standard prenatal testing of your developing baby as recommended by your obstetrician. Prenatal options may include ultrasound, chorionic villus sampling (CVS), amniocentesis, or blood tests to detect abnormalities in the pregnancy. There is a risk that PGD and PGS could have adverse consequences that are currently unknown.

## **Cryopreservation**

- Freezing of eggs and embryos can provide additional chances for pregnancy in the future.
- Frozen eggs and 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 eggs and / or embryos to remain in contact with LPCH on an annual basis.

## Embryo Cryopreservation

Freezing (or “cryopreservation”) of eggs or embryos is a common procedure. Since multiple eggs (oocytes) are often produced during ovarian stimulation, there may be more embryos available than are considered appropriate for transfer to the uterus. Such embryos can be frozen for future use. Alternatively, some eggs can be frozen before being exposed to sperm. Both strategies save the expense and inconvenience of stimulation to obtain additional eggs in the future.

Furthermore, the availability of cryopreservation permits patients to transfer fewer embryos during a fresh cycle, reducing the risk of high-order multiple gestations (triplets or greater). Other possible reasons for cryopreservation of embryos include freezing all embryos in the initial cycle to prevent severe ovarian hyperstimulation syndrome (OHSS), if there is a greater chance of pregnancy expected in a frozen cycle, if genetic testing is being performed with no results available for a fresh transfer, if a couple were concerned that their future fertility potential might be reduced due to necessary medical treatment (e.g., cancer therapy or surgery), or for personal reasons.

### *Indications:*

- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures or for personal reasons
- To increase the chance of having one or more pregnancies from a single cycle of ovarian stimulation
- To minimize the medical risk and cost to the patient by decreasing the number of stimulated cycles and egg retrievals
- To temporarily delay pregnancy and decrease the risks of hyperstimulation (OHSS- see below) by freezing all embryos, when this risk is high
- To await results of genetic testing
- To increase pregnancy rate if there are concerns about uterine lining in a fresh cycle

**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.” Current techniques deliver a high percentage of viable eggs and embryos thawed after cryopreservation, but there can be no certainty that eggs and 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.

## Egg Cryopreservation

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.

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

Other information on egg freezing comes from Italy, where the law limits the number of eggs that may be fertilized in a cycle. Italian patients with extra eggs available have been offered egg freezing for many years now, and at many different centers. These types of studies show higher fertilization rates, implantation rates, and pregnancy rates when using fresh eggs instead of frozen eggs. The rates were also higher with the use of frozen embryos rather than frozen eggs. Other non-randomized studies in the US show fertilization, implantation, and pregnancy rates that are similar with frozen eggs and fresh eggs when the woman providing the eggs was under 35 years old.

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

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

***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 Down Syndrome. 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.

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. Success rates can be expected to vary among clinics. 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.

## **Frozen Embryo Transfer**

If there is a desire to attempt pregnancy with frozen embryos, one or more of the frozen embryos will be thawed. Only those embryos which are considered to be potentially viable in the reasonable medical judgement of the Stanford physicians and embryologists will be transferred. Transfer of the embryos requires a normal uterine lining and very close synchronization to the normal process of ovulation. Therefore, a cycle to transfer frozen embryos may use some of the same medications used in ovulation induction for a fresh cycle as well as blood tests and ultrasound monitoring. The protocol selected is based on individual patient characteristics and parameters. The embryo transfer procedure is similar to the process described above for a fresh embryo transfer.

There is a small possibility that an embryo will not survive the thaw. If an embryo does not survive the thawing process and there are additional suitable embryos available, an additional embryo can be thawed and transferred. It is recommended that all patients pregnant after ICSI/AH/PGD undergo routine prenatal care and testing.

## **Frozen Oocyte Transfer**

A cycle to transfer frozen oocytes (eggs) may use some of the same medications used in ovulation induction for a fresh cycle as well as ultrasound monitoring. The protocol selected is based on individual patient characteristics and parameters. Fertilization, embryo culture and the embryo transfer procedure are similar to what is outlined above for a fresh cycle.

There is a possibility that not all oocytes will survive the freezing and thawing process. Therefore, multiple eggs may be thawed. In addition, not all oocytes will fertilize and reach the blastocyst stage. If more embryos are created than are desired for embryo transfer, good quality embryos can be frozen at the blastocyst stage. It is recommended that all patients pregnant after ICSI/AH/PGD undergo routine prenatal care and testing.

## **Disposition of Excess Embryos or Oocytes**

Stanford desires to provide you with relevant and appropriate information so that you may make an informed and voluntary choice regarding the disposition of any embryos remaining following your treatment. Because of the possibility of you and/or your partner's separation, divorce, death or incapacitation after embryos have been produced, it is important to decide on the disposition of any embryos (fresh or cryopreserved) that remain in the laboratory in these situations. 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.

Your physician will discuss with you the following options and you will be required to complete Stanford's *Disposition of Embryos* consent form prior to commencing treatment:

1. Storing (cryopreservation) any unused embryo(s)
2. Discarding any unused embryo(s)
3. Donating any unused embryo(s) for approved research studies
4. Donating any unused embryos to another individual in order to attempt pregnancy.
5. Use by one partner with the contemporaneous permission of the other for that use

## **Disposition of Clinically Unsuitable or Non-Selected Materials**

In most cycles, some eggs retrieved during the in vitro fertilization process are immature, fail to fertilize, or are abnormally fertilized and incapable of further development. Some embryos are determined to be nonviable because they stop developing in vitro. These eggs and embryos that are unsuitable for transfer, which would normally be discarded, could be of use to our clinical team in undertaking quality control or trying to improve IVF techniques or to researchers interested in the study of human reproduction or development or human embryonic stem cell research. The determination that an egg or embryo is unsuitable for clinical use will be made by staff embryologists who are not performing the research. In addition, in cycles in which PGD is performed, PGD embryos that you and your physician agree will not be used for your care (due to abnormality or other documented reason) may be donated to research or quality improvement techniques or discarded, in accordance with your choice.

In certain situations, donating materials to research may not be possible; in this instance, your materials will be discarded in accordance with current institutional and departmental policies.

Deciding that you do not want to donate to research or technique improvement will have no effect on your future care at Stanford. Even if you do decide now that you would like to donate, you may change your mind by notifying Stanford at any time up until the time of your discharge from our clinic after the oocyte retrieval procedure.

*All patients are required to complete the Disposition of Eggs or Disposition of Embryos consent form, as applicable, prior to oocyte retrieval. That form outlines the choices you have with regard to the disposition of oocytes and embryos in a variety of situations that may arise. You are free to submit a statement at a later time indicating different choices, provided you both agree in writing. It is also incumbent upon you to remain in touch with Stanford regarding your contact information, and to pay for storage charges as they come due.*

## **IV. Risks to the Woman**

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### ***Ovarian Hyperstimulation Syndrome***

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

smaller percentage. Only about 1.4 in 100,000 cycles has lead to kidney failure, for example. OHSS occurs at two stages: early, 1 to 5 days after egg retrieval (as a result of the hCG trigger); and late, 10 to 15 days after retrieval (as a result of the hCG if pregnancy occurs). The risk of severe complications is about 4 to 12 times higher if pregnancy occurs which is why sometimes no embryo transfer is performed to reduce the possibility of this occurring.

## 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 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. 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 substantially 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.

## V. 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, 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. There are ongoing studies.

**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.

### ***Risks of a Multiple Pregnancy***

Many IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), generally as a result of more than one embryo being transferred. Some multiple pregnancies are due to identical twinning which 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 and may not be acceptable to all couples.

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 if more than one embryo is transferred. 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 medical risk of MFPR. However, current data suggest that such medical complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 2-3%, although this risk increases when the number of fetuses prior to the procedure is greater than three.

## **VI. Ethical and Religious Considerations in Infertility Treatment**

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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 ethics community for guidance on their infertility treatment.

## **VII. Psychosocial Effects of Infertility Treatment**

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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. You may call the Stanford Fertility and Reproductive Health clinic at 650-498-7911 or a national support group, such as RESOLVE, ([www.resolve.org](http://www.resolve.org), Tel. 1-888-623-0744) or The American Fertility Association (AFA), ([www.theafa.org](http://www.theafa.org), Tel: 1-888-917-3777).

## **VIII. Alternatives to IVF**

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There are alternatives to IVF treatment including gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) or tubal embryo transfer (TET) where eggs and sperm, fertilized eggs or developing embryos, respectively, are placed into the fallopian tube(s). Using donor sperm, donor eggs, adoption, or not pursuing treatment are also options. Gametes (sperm and/or eggs), instead of embryos may be frozen for future attempts at pregnancy in an effort to avoid potential future legal or ethical issues relating to disposition of any cryopreserved embryos.

## **IX. Reporting Obligations and Privacy**

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Stanford will use all reasonable efforts to protect the privacy of your medical information, in accordance with legal requirements and the Lucile Packard Children’s Hospital at Stanford Notice of Privacy Practices (which you have received). Stanford sends data to the Society for Assisted Reproductive Technology, an affiliate of the American Society for Reproductive Medicine, who in turn sends the data to the Federal Center for Disease Control and Prevention (“CDC”) national registry. The

1992 Fertility Clinic Success Rate and Certification Act requires that the CDC collect data on all assisted reproductive technology cycles performed in the United States annually and report success rates using these data. This information is identifiable, and it is possible that at some time in the future, information regarding the fertility treatment of a particular Recipient would be part of an audit. Such audit may include, but not be limited to, examination of medical and laboratory records and comparison of the data in the medical records with the data in the CDC's reporting database. Because sensitive information will be collected by the CDC, the CDC has obtained an "assurance of confidentiality" for this project under the provision of the Public Health Service Act, Section 308(d). Additionally, your 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 your treatment being used to identify you as an individual.