South Jersey Fertility Center (SJFC)
Informed Consent for Assisted Reproduction:
In Vitro Fertilization and Embryo Freezing

Please sign your name(s) below to indicate which components of IVF treatment you agree to undertake in your upcoming treatment cycle. By signing below you also indicate that you have read and understand this consent packet. If you do not understand the information provided, please speak with your treating physician. No cross outs are allowed of items in the consent without explicit approval from the IVF director.

1) In Vitro Fertilization (including egg retrieval and embryo transfer):

Patient                        Partner (if applicable)                 Date
_________________________________    ______________________________   __/__/_____

2) Embryo Freezing (Cryopreservation):

You must sign below as to whether you want to pursue embryo freezing (cryopreservation) which is described on page 10-11. Sign either line A or line B:

A. I/We request cryopreservation of suitable excess embryos. If signing (A) for Embryo Cryopreservation, then you must also place your initials below to indicate your decision regarding disposition of any frozen embryos for the future.

Patient                        Partner (if applicable)                 Date
_________________________________    ______________________________   __/__/_____

Please select and initial one of the following choices. This option is to be utilized if SJFC loses contact with either of you. You will continue to be billed for storage until a disposal form is signed by both of you. This is NOT your final disposition of embryos.

Date __/__/______   Patient   Partner

1) Thaw and discard the embryo(s)   _____   _____
2) Donate the embryo(s) for research  _____   _____
3) Donate the embryos to another couple  _____   _____

If the option of “donation to another couple” is chosen above, then patient and partner must complete our “Donor Profile” questionnaire (provided to you by our staff on request) prior to embryo freezing.

B. I/We do NOT want excess embryos to be cryopreserved. They are to be disposed of in accordance with the policies of SJFC.

Patient                        Partner (if applicable)                 Date
_________________________________    ______________________________   __/__/_____

3) Intracytoplasmic Sperm Injection (ICSI):

ICSI is commonly recommended when sperm parameters are abnormal. In such cases it dramatically increases the chance for egg fertilization by injecting a single sperm directly into the egg. ICSI differs from "standard" IVF, which simply places a droplet of approximately 100,000 sperm on to the same droplet as the egg in the petri dish. When the semen analysis is consistently normal, there is no evidence that ICSI gives an advantage, so medical insurance will rarely cover ICSI in such cases.

On some occasions the semen specimen provided on the day of egg retrieval is below the normal parameters (in spite of a normal analysis in the past). In such cases the fertilization rate would likely benefit from the ICSI procedure. Another example of an "urgent" need to consider ICSI is if none of the eggs demonstrate fertilization the day after the egg-sperm incubation. This example is called "rescue ICSI."

By signing below I/we agree to have ICSI done if it appears that it would benefit the chances for fertilization. We understand that we would be notified by SJFC prior to the performance of ICSI if it had not already been discussed with us as the planned procedure. (In most cases of IVF, the ICSI procedure is not needed unless it has already been recommended to you during the pre-IVF consultation.)

There is another situation where we believe ICSI may be beneficial and yet not be covered by medical insurance. This situation is where the infertile couple has not had a pregnancy together within the past 5 years despite having tried at least 3 IUI treatments. In these cases we recommend that the infertile couple have ICSI performed on at least half of her eggs to overcome any possible inherent problem with sperm-egg recognition. It is not a requirement to do ICSI in this situation, but the couple should seriously consider it.

By signing below I/we agree to have ICSI done if it appears that it would benefit the chances for fertilization.

4) Preimplantation Genetic Screening (PGS/PGD)

Select and sign one of the 2 options below. We agree to SJFC performing an embryo biopsy for PGS or PGD. We have read the information on page 9. Please choose one of the following options and both initial on corresponding line.

<table>
<thead>
<tr>
<th>Patient (Initials)</th>
<th>Partner (if applicable)</th>
<th>Date</th>
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<tbody>
<tr>
<td>1) No genetic testing/screening of embryos</td>
<td></td>
<td></td>
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<tr>
<td>2) Genetic testing of some or all blastocysts (in consultation with Embryology lab staff)</td>
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By signing below I/we agree to SJFC performing an embryo biopsy for PGS or PGD.

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5) **Quality Control Measures**

Quality control in the lab is extremely important. Sometimes immature or 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. You are being asked to allow the clinic to use this material for quality control purposes before being discarded in accordance with normal laboratory procedures and applicable laws. Your signature in either line below does not permit the use of your sperm, eggs, or embryos to be used in a research fashion for producing a cell line on any pregnancy other than for your intended use. Please indicate your choice below:

_____ I/We hereby **CONSENT** to allow the clinic to utilize my/our immature or unfertilized eggs, left-over sperm or abnormal embryos for routine quality control and training purposes before they are discarded.

<table>
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<tbody>
<tr>
<td>__________________________</td>
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_____ I/We hereby **DO NOT CONSENT** to allow the clinic to utilize my/our immature or unfertilized eggs, left-over sperm or abnormal embryos for routine quality control and training purposes.

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OVERVIEW

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 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 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 IVF which are not yet clarified or even suspected at the time of this writing.

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 increase the chance of embryo attachment ("implantation")
- Embryo Cryopreservation (freezing)

A. Technique of IVF

Core elements and their risk

Medications for Ovarian Stimulation

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. Pelvic bloating is common as the ovaries enlarge with egg maturation. Additional medications are used to prevent premature ovulation. An overly vigorous ovarian response can occur, or conversely an inadequate response.

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

- Gonadotropins, or injectable “fertility drugs” (Follistim®, Gonal-F®, Menopur®): These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Luveris®, recombinant LH, can also be given as a separate injection in addition to FSH or alternatively, low-dose hCG can be used. 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 a moderate or severe form of Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section which

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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.

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

- **GnRH-agonists (Leuprolide acetate)** (Lupron®): This medication is taken by injection. The primary role of this medication is to prevent a premature LH surge, which could result in the release of eggs before they are ready to be retrieved. Since GnRH-agonists initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way since 1990. 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 often times 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 the birth control pill the month you will be starting the GnRH-a. GnRH-a have not been associated with any fetal malformations however you should discontinue use of the GnRH-a as soon as pregnancy is confirmed.

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

- **Human chorionic gonadotropin (hCG)** (Profasi®, Novarel®, Pregnyl®, Ovidrel®): hCG is a natural hormone used in IVF to induce the eggs to become mature and able to fertilize. 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 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 estradiol, are given to ensure adequate hormonal support of the uterine lining. Progesterone is usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prometrium®) 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 application site. Estradiol, if given, can be by oral, trans-dermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the site if given by the trans-dermal patch route and the risk of blood clots or stroke.

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

- **Other medications**: 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 causing a 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 corticosteroids (Medrol), heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.
Cycle cancellation: A cycle may be cancelled prior to the egg retrieval for any of the following reasons:

1. If after five days, there is no response to gonadotropin (FSH/hMG) stimulation.
2. If the serum Estradiol level is low and if there are less than 3 mature size follicles formed on the day hCG (Ovidrel) is to be given, or if there is a dramatic drop in the Estradiol level.
3. If the risk of ovarian hyperstimulation is unacceptably high due to excessively high estradiol or excessively large number of follicles are present.
4. Medical illness during the course of treatment.
5. If there is an LH surge or evidence that ovulation has already occurred or may occur too early.

If the patient is cancelled prior to the egg retrieval, she will be required to pay only the fee for services rendered including office visits, ultrasound examinations, blood assay, and the cost of hormonal injections provided by the office.

Transvaginal Oocyte Retrieval

Eggs are removed from the ovary with a needle under ultrasound guidance
Anesthesia is provided to make this comfortable
Injury and infection are rare

Oocyte retrieval is the removal of eggs from the ovary. A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A 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 transabdominal retrieval is necessary. These procedures and risks will be discussed with you by your doctor if applicable. Anesthesia by intravenous sedation is used to eliminate discomfort. Risks of egg retrieval include:

Infection: Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. 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 will frequently require either surgical repair or an interventional radiology procedure. The need for blood transfusion is rare. (Although very rare, review of the world experience with IVF indicates that unrecognized bleeding has led to death.)

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

Anesthesia: The use of anesthesia during the egg retrieval can produce unintended complications such as 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) in hopes of 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 embryology laboratory where they are kept in conditions that support their needs and growth. 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 following day after eggs have been either 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 single cell having 2 nuclei; this stage is called a zygote. 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 6-8 cells. By four days of culture, the embryos are usually at the morula stage which resembles a “bunch of grapes” with too many cells to accurately count. Five days after insemination or ICSI, normally developing embryos have reached the blastocyst stage, which is typified by an embryo that has 80 or more cells, an inner fluid-filled cavity, and a small cluster of cells called the inner cell mass.

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 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.
- One or more eggs may be fertilized abnormally resulting in an entire set of extra chromosomes.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Very rarely 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.

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. Excess embryos of sufficient quality that are not transferred can be frozen before the 7th day of development for future pregnancy attempts if the patient so chooses.

After a few days of development, one or more embryos are selected for transfer to the uterine cavity. Our recommendation is to transfer a single blastocyst embryo. The embryo is placed in the uterine cavity with a thin tube. 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. No anesthesia is needed.

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. Identical twinning occurs in about 1% of embryo transfers. It is critical to discuss 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 differ depending on the developmental stage of the embryos and the quality of the embryos and take into account the patient’s personal history to determine “favorable” or “unfavorable.”

### Recommended limits on number of 3-4 day old embryos to transfer

<table>
<thead>
<tr>
<th>Embryos</th>
<th>age &lt;35</th>
<th>age 35-37</th>
<th>age 38-40</th>
<th>age 41+</th>
</tr>
</thead>
<tbody>
<tr>
<td>favorable</td>
<td>1 or 2</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>unfavorable</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

### Recommended limits on number of 5-6 day old embryos to transfer

<table>
<thead>
<tr>
<th>Blastocysts</th>
<th>age &lt;35</th>
<th>age 35-37</th>
<th>age 38-40</th>
<th>age 41+</th>
</tr>
</thead>
<tbody>
<tr>
<td>favorable</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>unfavorable</td>
<td>2</td>
<td>2</td>
<td>3</td>
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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 on “embryo cryopreservation”).

**Hormonal support of uterine lining**

Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support. Progesterone, given by the vaginal or intramuscular route, is routinely given to provide a portion of this hormonal support. Estradiol oral tablets provide the rest of the hormonal support.

Successful attachment of embryos to the uterine lining 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 and estradiol are routinely given. The duration of this support is 10 weeks gestation.

**Additional Elements and their risk**

*Intracytoplasmic Sperm Injection (ICSI)*
ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal. ICSI will not improve oocyte defects. In cases with poorly or non-motile sperm and sperm obtained directly by aspiration from the scrotum, ICSI is essential to achieve fertilization. ICSI is needed if preimplantation diagnosis (PGD) is planned.

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 pipette. ICSI allows couples with male factor infertility to achieve fertilization and live birth rates close 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.

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

The prevalence of sex chromosome abnormalities in children conceived via ICSI is higher than observed in the general IVF population not needing ICSI, but the absolute difference between the two groups is small (0.6% in ICSI offspring vs. 0.2% in the general IVF population). The reason for the increased prevalence of chromosomal anomalies observed in ICSI offspring is not clear. Whereas it may result from the ICSI procedure itself, it might also reflect a direct paternal effect. Men with sperm problems (low count, poor motility, and/or abnormal shape) are more likely themselves to have genetic abnormalities (which can be the cause of the poor sperm production) and often produce sperm with abnormal chromosomes; the sex chromosomes (X and Y) in the sperm of men with abnormal semen parameters appear especially prone to abnormalities. If sperm with abnormal chromosomes produce pregnancies, these pregnancies will likely carry these same defects. The prevalence of translocations (a re-arrangement of chromosomes that increases the risk of abnormal chromosomes in egg or sperm and can cause miscarriage) in ICSI offspring (0.36%) also appears higher than in the general population (0.07%).

Some men have no sperm in their ejaculate because their testes do not produce adequate quantities (non-obstructive azoospermia). This can be due to a number of reasons such as prior radiation, chemotherapy or undescended testicles. In some men, small deletions on their Y chromosomes lead to extremely low or absent sperm counts. Testicular biopsy and successful retrieval of viable sperm can be used to fertilize eggs with ICSI. However, any sperm containing a Y chromosomal microdeletion will be transmitted to the offspring. Thus the risk that male offspring might later manifest disorders including infertility is very real. However, men without a detectable deletion by blood testing can generate offspring having a Y chromosome microdeletion, because the chromosomes in the sperm may not be the same as those seen when tested by a blood test.

Some men are infertile because the tubes connecting the testes to the penis did not form correctly. This condition, called congenital bilateral absence of the vas deferens (CBAVD), can be bypassed by aspirating sperm directly from the testicles or epididymis, and using them in IVF with ICSI to achieve fertilization. However, men with CBAVD are affected with a mild form of cystic fibrosis (CF), and this gene will be passed on to their offspring. All men with CBAVD, as well as their partners, should be tested for CF gene mutations prior to treatment, so that the risk of their offspring having CF can be estimated and appropriate testing performed. It is important to understand that there may be CF gene mutations that are not detectable by current testing and parents who test negative for CF mutations can still have children affected with CF.

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 which 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 with use of a laser. The hatching is usually performed on the day of transfer, prior to loading the embryo into the transfer catheter.

Our program has incorporated artificial or “assisted hatching” into our treatment protocol because we 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.

**Biopsy of Embryo for Genetic Testing – Preimplantation Genetic Screening (PGS) or Preimplantation Genetic Diagnosis (PGD)**

Preimplantation Genetic Screening (PGS) and Preimplantation Genetic Diagnosis (PGD) are specialized techniques to screen embryos for either chromosomal disorders (PGS) or specific genetic disorders (PGD).

The embryo biopsy can be performed 5-6 days after the egg retrieval when the embryo(s) have developed to the blastocyst stage. The biopsy of the embryo(s) is performed by making a small opening in the outer membrane of the embryo(s). Approximately 5 cells will be removed which should not damage or alter the embryo(s). The sample(s) are then shipped by courier to the genetics lab for testing. The embryos(s) will be cryopreserved and remain in our laboratory until we have obtained the results. The results usually available in 10 days.

Once we have received the results, the patient will be contacted and the information will be reviewed.

- **Normal embryos** – These embryos will be kept frozen and ready for a subsequent frozen embryo transfer (FET) cycle to establish a pregnancy.
- **Abnormal embryos** – These may be discarded at the patient’s discretion
- **Inconclusive** – The embryos may have to be thawed and if they are viable, rebiopsied and refrozen. The sample will be sent to the outside laboratory for more confirmation.

**Risks involved with the biopsy:**

Many studies have shown that the embryo biopsy does not affect the normal development of the child(ren). Some of the possible risks in performing the biopsy are:

- Unable to perform the biopsy because the eggs did not fertilize or develop properly
- Technical problem prevents the biopsy from being performed.
- Biopsied sample(s) are lost during transport to outside laboratory

An embryo can be damaged during the biopsy which could make it unusable.
- Cryopreserved embryos might not survive the thawing process, and if they do survive, their quality might be too poor to allow the biopsy to be done.
- Previously cryopreserved embryos may not survive the thaw
- Testing of embryos(s) has an accuracy of 99%

**Embryo disposition**
Frozen embryos do not always survive the process of freezing and thawing. Freezing of EGGS before fertilization is currently much less successful than freezing of EMBRYOS (fertilized eggs). Ethical and legal dilemmas can arise when couples separate or divorce; embryo disposition agreements are essential. It is the responsibility of each couple with frozen embryos to remain in contact with the clinic on a biannual basis (every 6 months).

Freezing (or “cryopreservation”) of embryos is a common procedure. Since multiple eggs (oocytes) are often fertilized during ovarian stimulation, on occasion there are more embryos available than are considered appropriate for transfer to the uterus. These embryos, if viable, can be frozen for future use. This saves 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), or if a couple were concerned that their future fertility potential might be reduced due to necessary medical treatment (e.g., cancer therapy or surgery). Overall pregnancy rates using FROZEN embryos are two-thirds as good as with FRESH embryos. This, at least in part, results from the routine selection of the best-looking embryos for fresh transfer, reserving the 'second-best' for freezing. There is some evidence that pregnancy rates are similar when there is no such selection.

**Indications:**
- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures
- 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 the risks of OHSS occurs by freezing all embryos, when this risk is high.

**Risks of embryo 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." Embryos are stored in liquid nitrogen tanks at minus 196 degrees Celsius (-321 F). Our technique yields an average embryo survival rate of 88% upon thawing. We only cryopreserve embryos of acceptable quality. Usually a minimum of two good quality embryos is required to consider cryopreservation. 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. Embryos can be re-frozen after being thawed, if necessary.

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 embryo(s), fresh or cryopreserved that remain in the laboratory. Since this is a rapidly evolving field, both medically and legally, the clinic cannot guarantee what the available or acceptable avenues for disposition will be at any future date. At the present time, the alternatives are:

1. Discarding the cryopreserved embryo(s)
2. Donating the cryopreserved embryo(s) for approved research studies.
3. 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 SJFC.

**Cryopreserved embryo storage**
Maintaining embryos in a frozen state is labor intensive and expensive. There are fees associated with freezing and maintaining cryopreserved embryos. The fee to freeze and to store embryos for the first 6 months is to be paid prior to the cryopreservation procedure. Patients/couples who have frozen embryo(s) must reply to our mail contact from SJFC on a biannual basis (every 6 months) in order to inform the clinic of their wishes as well as to pay fees associated with the storage of their embryos. This also helps us maintain your correct address for correspondence. In situations where there is no contact with the clinic for a period of 9 months or fees associated with embryo storage have not been paid for a period of 9 months 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.

**Fate of donated embryos**

In certain situations, donating embryo(s) for research or 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 used for research or donated to another couple. In these instances, if after 4 years no recipient or research project 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.

**B. Risks to the Woman**

### 1. Ovarian Hyperstimulation Syndrome

To increase the number of eggs that develop, a series of hormone shots are given which can result in overly enlarged ovaries. The enlarged ovaries can cause pelvic discomfort and, on occasion, severe health risks such as ovarian hyperstimulation syndrome (OHSS). OHSS can manifest as nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, and in the most severe cases, blood clots, kidney failure, or death. The severe cases affect only a small percentage of women who undergo in vitro fertilization—1 percent or less of all treatment cycles—and the very severe are an even smaller percentage. 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 made by the pregnancy, if present). Measures can be taken to improve the symptoms by removing the extra fluid accumulating in the abdomen or lung. The syndrome eventually fully resolves in 2-4 weeks. A woman with OHSS must limit her physical activity and drink plenty of fluids.

### 2. Cancer

Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast and ovarian 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.

### 3. 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. 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**
C. Risks to Offspring

IVF babies may 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

1. Overall risks

Since the first birth of an IVF baby in 1978, more than 3 million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for IVF babies as compared to naturally conceived babies.

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born from IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

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

2. Birth Defects

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

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

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

**Infant Development.** In general, studies of long-term developmental outcomes have been reassuring so far; most children are doing well. However, these studies are difficult to do and suffer from limitations. A more recent study with better methodology reports an increased risk of cerebral palsy (3.7 fold) and developmental delay (4 fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

### Potential Risks in Singleton IVF Pregnancies

<table>
<thead>
<tr>
<th>Risk</th>
<th>Absolute Risk (%) in IVF</th>
<th>Relative Risk (vs. non-IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Preganacies</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>11.5%</td>
<td>2.0 (1.7--2.2)</td>
</tr>
<tr>
<td>Low birth weight (&lt; 2500 g)</td>
<td>9.5%</td>
<td>1.8 (1.4--2.2)</td>
</tr>
<tr>
<td>Very low birth weight (&lt; 1500 g)</td>
<td>2.5%</td>
<td>2.7 (2.3--3.1)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>14.6%</td>
<td>1.6 (1.3--2.0)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>17.8%</td>
<td>1.6 (1.3--2.0)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.2%</td>
<td>2.6 (1.8--3.6)</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>0.6%</td>
<td>2.0 (1.2--3.4)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0.4%</td>
<td>2.8 (1.3--5.8)</td>
</tr>
<tr>
<td>Genetic risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- imprinting disorder</td>
<td>0.03%</td>
<td>17.8 (1.8--432.9)</td>
</tr>
<tr>
<td>- major birth defect</td>
<td>4.3%</td>
<td>1.5% (1.3--1.8)</td>
</tr>
<tr>
<td>- of a sex chromosome</td>
<td>0.6%</td>
<td>3.0</td>
</tr>
<tr>
<td>- of another chromosome</td>
<td>0.4%</td>
<td>5.7</td>
</tr>
</tbody>
</table>

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.

### 3. Risks of a Multiple Pregnancy

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Triplets and above increase the risk to the mother of more significant complications including post-partum hemorrhage and transfusion. Prematurity accounts for most of the excess problems associated with multiple gestations. Moreover, IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers. 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 selectively terminated) reduces, but does not eliminate, the risk of these complications.

Fetal death rates per 1000 for singleton, twin, and triplet pregnancies are 4.3, 15.5, and 21, 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 or mother. No excess perinatal or maternal morbidity has been described resulting from a “vanishing” embryo.

Demise of a single fetus in a twin pregnancy after the first trimester is more common when they share a placenta, ranging in incidence from 0.5% to 6.8%, and may cause harm to the remaining fetus.

Multiple fetuses (including twins) that share the same placenta (which can happen only in cases of “identical twins”) have additional risks. Twin to twin transfusion syndrome in which there is an imbalance of circulation between the fetuses may occur in up to 20% of twins sharing a placenta. Excess or insufficient amniotic fluid may result from twin-to-twin transfusion syndrome. Twins sharing the same placenta have a higher frequency of birth defects compared to pregnancies having two placentas. Twins sharing the same placenta appear to occur more frequently after blastocyst transfer.
Placenta previa and vasa previa are more common complications in multiple gestations. Premature separation of the placenta also is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries. Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity, and chronic lung disease). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. 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. 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 Selective Reduction:** Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. 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 option of continuing the pregnancy with all risks previously described or reducing the number of fetuses in an effort to decrease the risk of maternal and perinatal morbidity and mortality. Multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates profound 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%.

In general, the risk of loss after MFPR increases if the number of fetuses at the beginning of the procedure is more than three. While there is little difference between the loss rates observed when the final number of viable fetuses is two or one, the loss rate is higher in pregnancies reduced to triplets. Pregnancies that are reduced to twins appear to do as well as spontaneously conceived twin gestations, although an increased risk of having a small for gestational age fetus is increased when the starting number is over four. The benefit of MFPR can be documented in triplet and higher-order gestations because reduction prolongs the length of gestation of the surviving fetuses. (This has been demonstrated for triplets; triplets have a 30-35% risk of birth under 32 weeks compared to twins which is 7 to 10%)

**D. 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). A patient can request that a limited number of eggs be inseminated with sperm in order to avoid “excess” embryo production. In such cases the extra eggs can be cryopreserved if the patient so desires (there is a separate consent form for egg cryopreservation). Limiting the number of eggs inseminated can lower the chance for pregnancy in many cases. Patients should inquire to our doctors or IVF nurses if they have such concerns. We encourage patients and their spouses or partners who so desire to consult with trusted members of their religious or ethics community for guidance on their infertility treatment.

**E. 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 anxiousness, depression, isolation, and helplessness are not uncommon among patients undergoing infertility treatment. Strained and stressful relations with spouses, partners and other loved ones are not uncommon as treatment gets underway and progresses.

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

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

- loss of interest in usual activities
- depression that doesn't lift
- strained interpersonal relationships (with partner, family, friends and/or colleagues)
• difficulty thinking of anything other than your infertility
• high levels of anxiety
• diminished ability to accomplish tasks
• difficulty with concentration
• change in your sleep patterns (difficulty falling asleep or staying asleep, early morning awakening, sleeping more than usual for you)
• change in your appetite or weight (increase or decrease)
• increased use of drugs or alcohol
• thoughts about death or suicide
• social isolation
• persistent feelings of pessimism, guilt, or worthlessness
• persistent feelings of bitterness or anger

Our health care team can assist you in locating a qualified mental health professional who is familiar with the emotional experience of infertility. We often recommend the services of Pamela Pressman and Associates (www.pressmanandassociates.com 856-435-1944) or you can contact a national support group such as RESOLVE, (www.resolve.org 888-623-0744) or The American Fertility Association (AFA), (www.theafa.org 888-917-3777).

F. Legal Considerations and Legal Counsel

The law regarding embryo cryopreservation, subsequent thaw and use, and parent-child status of any resulting child(ren) is, or may be, unsettled in the state in which either the patient, spouse, partner, or any donor currently or in the future lives, or the state in which the ART Program is located. We acknowledge that the ART Program has not given us legal advice, that we are not relying on the ART Program to give us any legal advice, and that we have been informed that we may wish to consult a lawyer who is experienced in the areas of reproductive law and embryo cryopreservation and disposition if we have any questions or concerns about the present or future status of our embryos, our individual or joint access to them, our individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.