

CCRM MN Quality Dashboard July 2016

Meet or Beat Target / Missed Target

IVF Lab	Target	Month - Actual	YTD - Actual
Fresh Transfer Results			
Pregnancy Rates (Per Fresh Transfer)			
<35 Yrs	> 46%	66.7%	78.6%
35 - 37 Yrs	> 38%	NA	66.7%
38 - 40 Yrs	> 28%	NA	50.0%
> 40 Yrs	> 15%	NA	NA
Donor	> 60%	100.0%	80.0%
Frozen Transfer Results			
Cell Survival	> 90%	100.0%	98.6%
Pregnancy Rates (Non-CCS)			
<35 Yrs	> 46%	50.0%	80.0%
35 - 37 Yrs	> 38%	NA	NA
38 - 40 Yrs	> 28%	NA	NA
> 40 Yrs	> 15%	NA	NA
Donor	> 60%	100.0%	100.0%
Pregnancy Rates (CCS)			
<35 Yrs	> 60%	100.0%	81.8%
35 - 37 Yrs	> 60%	100.0%	91.7%
38 - 40 Yrs	> 50%	100.0%	85.7%
> 40 Yrs	> 40%	100.0%	100.0%
Donor	> 65%	NA	100.0%
Other Key Statistics			
Average # of Embryos Transferred			
Average # of Embryos Transferred - Fresh Transfer	< 2.0	1.4	1.8
Average # of Embryos Transferred - FET no CCS	< 2.0	1.0	1.2
Average # of Embryos Transferred - FET with CCS	< 2.0	1.3	1.1
Blast Conversion Results - Day 5	> 20%	30.8%	27.8%
Blast Conversion Results - Day 6	> 40%	50.3%	46.6%



Acknowledgement, Agreement and Assumption of Risks, Release and Hold Harmless

Definitions

The following defined terms are utilized throughout the following document:

Practice - CCRM Minneapolis is referred to herein as the "Practice."

When the document refers to either the "Practice" it is referring to the defined entity above.

NOTE: THIS WRITTEN CONSENT IS AN IMPORTANT DOCUMENT AND THE COPY PROVIDED TO YOU SHOULD BE RETAINED WITH OTHER VITAL RECORDS FOR FUTURE REFERENCE.

(Print Patient's full name)

DOB

(Print Partner's full name)

DOB

I/We are undergoing egg donation cycle at the Practice and I/we understand that the Practice Egg Donor program describes two types of relationships between the donor and the recipient patients, known donation and anonymous egg donation. I/we understand that an anonymous egg donation cycle means that the egg donor and the recipient couple have never met or had any contact or conversation via phone, internet, mail or otherwise. I/we understand that a known egg donation cycle means there is a relationship, or the two parties have had a conversation regardless of the limited amount of information exchanged between the two parties involved or the nature of that meeting regardless if identifying information was exchanged. The Practice cannot monitor conversations via phone, internet, etc., and the policy is to protect the interest of all parties involved.

This acknowledgement is to inform both the egg donor as well as the recipient couple that it is the policy of the Practice that all known egg donor cycles, both the recipient couple and the egg donor will be required to sign consents that have all parties' names printed on the consent. Both the egg donor and the recipient couple may request a copy of the consent and the consent will become a permanent part of the patients' records. I/we understand that due to the nature of IVF and egg donation, it is imperative that all parties agree to the process and are consenting to the treatment prior to the treatment cycle. I/we understand that if we enter the anonymous program and have had a conversation or meeting with each other, the relationship will change and the treatment cycle will be considered a known relationship requiring the names and signature of all parties written on the known consent. Again, this will be regardless if the conversation was limited.

I/we understand the implications of this and have been offered the opportunity to discuss this with the physician, staff and or mental health counselors at the Practice, should I/we wish to. I/we understand that neither, the Practice, its staff, nor its physicians, will be held liable for any attempts made by the donor to make contact with the recipient nor the recipient making contact with the donor. I/we understand the purpose of this procedure is for the recipient couple to conceive a child. I/we

understand that all ova (eggs) donated will be fertilized and the subsequent embryos, resulting from the fertilization and not transferred during the embryo transfer, belong to the recipient couple. I/we understand that egg donation is a sensitive and emotional treatment and by establishing this policy, the Practice is attempting to protect the interest of all parties involved. By participating in the egg donor IVF cycle, I/we as the recipients are agreeing to rights and responsibilities set forth in the known donor recipient consent or the anonymous egg recipient consents. I as the egg donor understand and agree to the rights and responsibilities of the known egg donor consent or the anonymous egg donation consent. I/we understand this is a voluntary process and understand the risks of this decision described herein and hereby assumes said risks. I/we also release the Practice, its physicians and staff harmless from any and all damages, injuries or losses or hereafter arising out of the use of the donated oocytes.

Patient's Signature

Date

Partner's Signature

Date

Witness/Practice representative

Date

Policy and Guidelines: Number of Embryos to Transfer

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In an effort to reduce the number of higher order pregnancies associated with IVF, the guidelines displayed below have been developed by the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) and were published in November 2009 (Fertil Steril 2009;92:1518-1519).

The physicians of the Practice and embryology laboratory staff of the Lab adhere to these guidelines in recommending the number of embryos to transfer. It is important that you review them prior to your embryo transfer.

Recommended limits on number of 2-3 day old embryos to transfer

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1 or 2	2	3	5
unfavorable	2	3	4	5

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

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1	2	2	3
unfavorable	2	2	3	3

*Favorable - 1st cycle, good embryo quality, excess embryos available for cryopreservation, previous successful IVF cycle. All other situations are considered to be “unfavorable” according to the guidelines.

*Donor Egg Cycles: Age of the egg donor is used to determine the number of embryos to transfer

*Frozen Embryo Transfer – Number of good quality thawed embryos should not exceed the limit on fresh embryos for the age group.

Multiple gestations, including twin pregnancies and especially those involving three or more fetuses, pose a significant medical risk to the patient, the pregnancy and/or resulting offspring. The rise in multiple births is largely due to Assisted Reproductive treatments. I/we have discussed these risks with my physician and medical treatment team at the Practice.

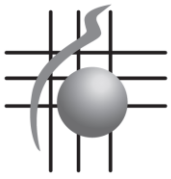
I/we have read and understand these guidelines and understand that it is the policy of the Practice and the Lab to adhere to these guidelines and that any deviation will only be made under extraordinary circumstances and with the approval of the physician performing the embryo transfer.

Patient Name (print) _____ DOB _____

Patient Signature: _____ Date: _____

Partner Name (print) _____ DOB _____

Partner Signature: _____ Date: _____



Consent Form for Egg Donation

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Introduction

I voluntarily give my consent and authorize the physicians at the Practice and their associates, any technical assistants, nurses, nurse coordinators, and any other staff of the Practice to perform an oocyte donation cycle and the necessary assistance and procedures to achieve this. In vitro fertilization (IVF) with donor egg is a treatment that helps patients who are unable to achieve a pregnancy on their own or with their own eggs. The in vitro fertilization technique involves four steps:

1) Developing eggs in the woman’s ovaries; 2) Removing the eggs from her ovaries; 3) Placing the eggs and sperm together in the laboratory to allow fertilization to occur, and 4) Transferring fertilized embryos into the woman’s uterus for the establishment of pregnancy. The main goal of this voluntary procedure using a donor is to allow recipient intended parent(s) to have a child(ren). This is an elective procedure designed to result in a patient’s pregnancy when other treatments have failed or are not appropriate or medically not feasible.

The reproductive potential of some women is compromised because they do not produce eggs, produce defective eggs and/or embryos, or are carriers of a genetic condition. An option for these women is to undergo egg donation. Treatment with egg donation involves a woman who serves as an egg donor and a woman who serves as the recipient. The recipient may be the intended mother or may be assisting a male patient or same-sex couple as the recipient intended parent(s). It is a process where the egg donor has eggs removed from her ovaries. The eggs are then fertilized with sperm in the laboratory. The fertilized eggs (embryos) are then transferred into the uterine cavity of the recipient woman for implantation and the establishment of pregnancy. Following the delivery, the intention is that the recipient will be the rearing parent of the offspring. The existence of the embryo outside of a woman’s body creates the possibility of placement of the embryos into a second woman (gestational carrier), who then carries the pregnancy. The intention following the delivery is to unite the baby or babies with the couple, or individual who will be the rearing parents.

This consent reviews the IVF Donor Egg process from start to finish, including the risks that this treatment might pose to you. This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed.

While best efforts have been made to disclose all known risks, there may be risks of IVF/egg donation, which are not yet clarified or even suspected at the time of this writing.

Purpose of Procedure

The purpose of these procedures is to help couples wishing to achieve a pregnancy and have a child, which is only feasible through egg donation. I understand that while IVF is a relatively new procedure, some aspects of the procedure are considered routine in the delivery of health care. The recipient and partner (if appropriate) sign specific consent for Cryopreservation, Donor Egg, Donor Sperm (if applicable), Preimplantation Genetic Testing/screening (PGS), and Comprehensive Chromosomal Screening (CCS), (if appropriate) separately for each of those procedures.

This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed.

Donor Pre-Treatment Recommendations and Requirements

Donors *should avoid* any activity and behavior or medication that would reduce the quality of the egg or success of the egg donation cycle. Below are requirements for women participating in the egg donation cycle:

1. Submit to any urine tests, cervical cultures, blood tests, or physical examinations.
2. Truthfully disclose aspects of my age, medical, psychological, genetic, sexual and family history.
3. Keep requests for follow-up information in a timely fashion.
4. Keep all scheduled appointments and arrive promptly.
5. Follow all instructions precisely and ask for assistance if I do not understand.
6. Refrain from any attempt to learn the identity of the recipient.
7. If you are a smoker please inform your nursing staff, because this will disqualify you from being a donor. Smoking must be avoided before and during treatment.
8. Recreational drugs are absolutely contraindicated.
9. Ingestion of aspirin or aspirin-like products (e.g. Motrin, Advil, Anaprox, Naprosyn, Aleve, etc.) should be avoided during treatment. Tylenol is a suitable alternative.
10. The use of alcohol should be eliminated during treatment cycle.
11. The use of any and all prescriptions and/or over-the-counter medication or supplements should be discussed with the treatment team.
12. You cannot obtain a tattoo or body piercing while in the donation cycle and you will need to inform the treatment team regarding the date of your last tattoo or piercing.
13. Caffeine should be eliminated during the entire treatment cycle.
14. Avoid ALL herbal and diet supplements.
15. Because the treatment requires stimulation of the ovaries to produce multiple oocytes (eggs), **unprotected intercourse** is discouraged to prevent any unwanted pregnancy during the egg donation cycle, or risk of infectious disease transmission, until birth control can be reestablished. The month following your egg donation, protection should be utilized to avoid an unwanted pregnancy until birth control can

be reestablished.

** The egg donor will undergo steps of ovulation induction and egg retrieval, described in the next section. The recipient will undergo preparation of endometrium, insemination of eggs, embryo transfer, and embryo freezing, which are described below.*

I. Description of Egg Donation Treatment

Egg donation treatment is done in conjunction with IVF, which involves several steps. Success cannot be guaranteed at any or all of these steps. If optimal results are not achieved at any step, it may be recommended that the treatment be stopped and the cycle canceled. The donor will undergo prescreening and testing, followed by ovulation induction and egg retrieval and the recipient will undergo prescreening and testing followed by preparation of the endometrium, utilizing her partner's sperm or anonymous donor sperm for the fertilization of the eggs and have the embryos transferred into her uterus in hopes of achieving a pregnancy. In some cases a gestational carrier may be used to carry the pregnancy for the intended parents. The steps of the treatment are discussed below.

Rescreening, Testing, and Special Considerations in Egg Donation

Infectious Disease Testing

I understand and consent that I must be subjected to federally-mandated infectious disease testing within 30 days of the egg retrieval. I understand and agree that if I test positive for any of the infectious diseases tested for, as mandated by federal law, that my eggs cannot be donated and that the eggs must be disposed of according to the American Society for Reproductive Medicine (ASRM) Ethical Standards. I further understand that if I do not come for the testing required for these infectious diseases within 30 days of the retrieval, the eggs cannot be used and will be discarded and this might cause severe stress for the recipient.

Donor Screening and Testing

I understand and agree that as an egg donor, I have been asked extensive questions about my age, medical, genetic, psychological, sexual and family history. My truthful answers to these questions are critical to the health and safety of the recipient and the child that may be conceived as a result of this egg donation. I agree to answer these questions truthfully. I agree to notify the Practice of any medical condition or disease, particularly genetic diseases, which may arise in my immediate family or in me. I agree to provide medical updates and relevant information to the Practice should the Practice contact me in the future.

Unknown Family History

I understand and agree that if I do not have knowledge about my genetic parents' medical history (for example if I was adopted or conceived with donor gametes) that my eggs may not be suitable for donation to produce a pregnancy. I further acknowledge and consent that medical, psychological, genetic/infectious disease, technical or other considerations may contraindicate or preclude (make impossible) the donation of these eggs to a recipient despite

my request. I agree that the disposition of these eggs will ultimately rely on the best medical judgment of the Practice, and as appropriate, its employees, contractors, and consultants and authorized agents, at the time of the potential donation.

Recipient Matching

Recipients view the donor health history and make their donor selection.

Ovulation Induction

In most cases, the egg donor will take medications to stimulate the development of multiple ovarian follicles (fluid-filled cysts in the ovary that contain eggs).

Egg Retrieval

The egg donor will have the eggs removed from her ovaries.

Preparation of the Endometrium

The uterine cavity of the recipient woman has to be hormonally prepared prior to the embryo transfer to allow implantation to occur.

Fertilization of the Eggs

The eggs and sperm will be placed together in the laboratory and incubated in an effort to achieve possible fertilization and growth of the embryos. The ICSI procedure may be required to achieve fertilization.

Culture

Of any remaining fertilized eggs (embryos).

One or more embryos will be transferred into the uterus of the recipient woman or in some cases a gestational carrier's uterus.

Following the embryo transfer, any remaining embryos of suitable quality may be frozen (cryopreserved) and stored for future embryo transfer(s). The recipient may decide later to donate unused embryos to another infertile couple.

Egg Vitrification: In some cases the recipient may choose to freeze some of the donated eggs and not create embryos for future.

Splitting the Donation: For some donors who produce a larger number of eggs, the Practice may decide to split the fresh or vitrified eggs between more than one recipient.

II. Ovulation Induction

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, or conversely, an inadequate response can occur**

Medications may include the following (not a complete list): Most of the medications that you will be using during your egg donation cycle are administered by injection. You will receive instruction and training prior to attempting self-administration. If you are unable to self-administer the injections, you should have the injections performed by someone who has been trained to perform them appropriately. Questions regarding the injections may be directed to our nursing staff or demonstrated on our partner’s website (www.colocrm.com – click Medication Training on the home page).

Gonadotropins, or injectable “fertility drugs” (Follistim®, Gonal-F®, Bravelle®, Menopur®, Repronex®): These hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the average span of eight to more days. Follicle growth will be monitored beginning on or around day five of the gonadotropin medication start. Most 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 (Menopur®). LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. In some cases your physician may prescribe low-dose hCG (Novarel®, Pregnyl®) in addition to the FSH product. 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 1%-3% of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section which 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.

Ovarian Hyperstimulation Syndrome (OHSS) is a rare complication of ovarian stimulation from gonadotropin medications. Every woman who administers gonadotropins can develop OHSS, but the risk is higher in a woman who is less than 35 years old, has a high blood estradiol level, has a large number of ovarian follicles, or who has a history of hyperstimulation syndrome. It is caused by “fluid leaking” into the abdomen due to hormones released from the ovary. Fluid shifts within the body require close observation and even hospitalization for further observation and treatment (1%-3% of cycles). The high levels of estrogen associated with the use of these medications may alter the way in which the body handles fluids. The symptoms can include increased ovarian size, ovarian cysts, nausea, vomiting, accumulation of fluid in the abdomen or chest cavities, 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. More specifically, the blood vessels may become “leaky” resulting in the accumulation of fluid within the abdominal cavity (ascites) or around the lungs (pleural effusion). This accumulation of fluid may result in abdominal distension and discomfort with associated shortness of breath (due to the diaphragm being pushed upward by the accumulation of fluid in the abdomen). In severe cases, removal of this fluid from the abdomen or from the space around the lungs may be required using a small needle (0.5% of cycles). The “leaky” vessels may also result in the individual becoming dehydrated because the fluid is in the wrong place, i.e. in the abdomen instead of in the blood vessels. Intravenous fluid administration may be required to maintain adequate blood flow to vital organs such as the kidneys. Severe dehydration could result in irreversible organ failure or blood clot formation leading to a pulmonary embolus (blood clots in the lung) or stroke (less than 0.1% of cycles). There are extremely rare reports in the literature of death occurring as a result of complications of OHSS. **OHSS is a risk that is inherent to ovulation induction therapy; prevention cannot be guaranteed.** At times, when monitoring shows that the risk of OHSS is unacceptably high, a cycle may be canceled. Severe OHSS will rarely occur if hCG administration is withheld. Close monitoring of your cycle by the clinic and following its instructions is imperative to reduce these risks. The severe cases affect only a very small percentage of women who undergo in vitro fertilization—0.2% or less of all treatment cycles—and the very severe are an even smaller percentage. Symptoms may resolve without intervention. Only about 1.4 in 100,000 cycles have led to kidney failure, for example.

OHSS occurs at two stages: Early, one to five 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 produced during pregnancy). When the estradiol is significantly elevated or there is a significant risk of ovarian hyperstimulation syndrome, options for care include 1) Canceling the cycle; 2) The physician will decide to coast the cycle (stop gonadotropin medications to allow the estradiol level to decrease). The physician may also prescribe other medications that will be taken after the retrieval to help prevent or lessen the hyperstimulation symptoms. Hyperstimulation may result in ovarian enlargement requiring therapy including hospitalization and possible surgery with removal of an ovary.

Ovarian Torsion (Twisting)

In less than 1% of cases, the enlargement of the ovary from gonadotropins stimulation can cause the ovary to twist on itself, called ovarian torsion. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary. To decrease the risk of torsion, it is recommended that you avoid significant bouncing or physical exertion during stimulation (i.e. high impact aerobics, horseback riding, skiing, Stairmasters, treadmills, etc.).

Cyst Formation

The medications described above may result in large cysts forming on the ovaries. In the majority of cases, ovarian cysts induced by fertility drugs/medications disappear spontaneously without requiring any intervention. In very rare instances (less than 1% of cycles) these cysts could result in significant abdominal discomfort that could result in the need for hospitalization

for observation purposes. One of these cysts could rupture requiring emergency surgery to stop the bleeding and could result in a need for blood transfusions and possible loss of one or both ovaries (this occurs in less than 0.1% of cycles).

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 research studies of women taking fertility drugs. Since all of these cancers are more common in women with infertility, simply comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine the long-term impact fertility drugs may have on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to draw conclusions. There is no clear evidence to suggest the stimulation medications are associated with breast cancer although there are very limited numbers of long-term studies.

Medications

GnRH-agonists (Leuprolide acetate) (Lupron®): This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for one to three 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. After a few days of treatment with a GnRH-agonist, the brain decreases production of both FSH and LH through depletion of the receptors.

Though leuprolide acetate is an FDA (US Food and Drug Administration) approved medication, it has not been approved for use in IVF. However 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, and skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. Since GnRH-agonists are oftentimes administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception (condoms) the month you will be starting the GnRH-agonists. GnRH-agonists have not been associated with any fetal malformations. However, you should discontinue use of the GnRH-agonists as soon as pregnancy is confirmed.

GnRH-Antagonists (Ganirelix Acetate or Cetrorelix Acetate) (Antagon®, Cetrotide®): These are another class of medications used to prevent premature ovulation. These medications work differently than a GnRH-agonist because they block the GnRH receptors in the pituitary gland and avoid premature ovulation preventing release of FSH and LH. 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. Patients who are allergic or have sensitivity to latex must inform the nursing team as the use of Antagon is contraindication. The decision to use a GnRH agonist or antagonist during your egg donation cycle will be decided by your physician based on your personal medical history.

Human Chorionic Gonadotropin (hCG) (Novarel®, Pregnyl®, Ovidrel®): hCG is a natural hormone, similar to LH, used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. It is administered 35 hours prior to egg retrieval by either subcutaneous or intramuscular injection. Potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort.

Oral Contraceptive Pills: Many treatment protocols include oral contraceptive pills to be taken for two to four 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. It is important for donors to understand the birth control utilized in this cycle are not prescribed according to the recommendation of the birth control package insert to prevent pregnancy and donors should use alternative birth control measures during the donation process. The goal of the medication regimen is to produce multiple eggs and the risk of unwanted pregnancy is high. Abstaining from intercourse during this process is highly recommended to avoid unwanted pregnancies.

Steroids: Steroid medications (dexamethasone, prednisone, or methylprednisolone) may be used during your IVF treatment cycle. Steroids are oral medications used to suppress the immune system. The most common side effects with short term usage of steroids include headache, sleep or mood disturbances, weight gain, nausea, and fatigue. Other side effects can occur with long term usage and will be discussed if your treatment requires prolonged use.

Monitoring

During the ovulation induction phase of treatment, monitoring of follicular development is performed with periodic blood hormone tests and vaginal ultrasound exams. The egg growth will be monitored beginning on or about the fifth day of the cycle and will be repeated daily or every other day depending on the physician's recommendation. Monitoring helps the physicians to determine the appropriate dose of medication and the timing of the egg retrieval. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and possibly bruising, bleeding, infection or scar at the needle sites. The need for repeated ultrasound examinations and blood drawing on a frequent basis requires the woman's presence in the vicinity of the Practice's office.

EGG RETRIEVAL/TRANSVAGINAL OOCYTE RETRIEVAL

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

- **Injury and infection are rare**

The egg retrieval is an outpatient procedure. Oocyte retrieval is the removal of eggs from the ovary. In the majority of cases, it is performed under vaginal ultrasound guidance. In this procedure, the woman is placed in the same position as if she was having a pelvic exam. The vagina is cleaned with a sterile solution. The vaginal ultrasound probe is then covered with a sterile sheath and placed in the vagina allowing visualization of the follicles within the ovaries. Under ultrasound visualization, a needle is introduced through the vaginal wall, into the ovary and into an ovarian follicle. Fluid in the follicle is aspirated and examined by the embryologist to see if an egg is present. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa (egg-supporting) cells. This process is repeated with all follicles in both ovaries. The egg retrieval procedure is usually completed within thirty minutes. Rarely the ovaries are not accessible by the transvaginal route and laparoscopy or transabdominal ultrasound guided 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. The patient will be transferred to the recovery room after the procedure and may go home approximately 60-120 minutes after leaving the operating room.

Risks of Egg Retrieval and Donation 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. Antibiotics may be administered 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. A side effect of antibiotics could be an allergic reaction.

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 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 low.

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.

Anesthesia/Surgical Complications

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. Any of these complications could require hospitalization and/or additional unplanned medical and/or surgical therapy. In very rare instances, it may be necessary to remove an ovary or perform a hysterectomy.

Anesthesia

The woman will have a consultation prior to the procedure to review the risks and benefits of the anesthesia. An anesthesiologist or anesthetist will administer the anesthesia. It is mandatory that there is no oral intake after midnight prior to the egg retrieval. Eating or drinking may require a needle to be placed in the patient’s back to administer the anesthesia (epidural-spinal). Complications of anesthesia include nausea, vomiting, drowsiness or an unexpected reaction to anesthetic agents. The ideal anesthetic choice will be discussed by the anesthesiologist or anesthetist prior to the procedure. In most cases anesthesia is administered through an intravenous line placed in your arm and/or by agents inhaled through a mask placed on your face and/or by spinal route. Because anesthesia medications are used, the woman cannot drive and needs to be transported home by another individual and it is recommended to have someone stay with you for the next 24 hours, until the anesthetic has left your body. Making major decisions is ill advised for the rest of day.

Post-Retrieval

Following the egg retrieval vaginal spotting and lower abdominal cramping are normal. If significant bleeding, fever, vomiting, abdominal pain, difficulty breathing or walking, quick and significant weight gain in a short period of time, or any other symptoms develop, the donor should contact the physician on call. During the remainder of the day activities should be limited. Tampons should not be used following the retrieval, as well as restraining from intercourse up to one month following the retrieval. Intercourse could cause a pelvic infection or unwanted pregnancy. Should your birth control choice be the use of the pill, it is important to remember that you are not fully protected the first month starting back on the birth control pill and it is recommended to utilize another form of birth control your first month back on the pill. **Retrieval of the eggs does not guarantee that all of the eggs will be removed; there is still risk of a potential fertilization of an egg that was not retrieved causing an unwanted pregnancy.**

Psychological Issues

As a patient voluntarily requesting to be an egg donor procedure, I understand there are a

number of steps involved in this procedure and that beginning this process does not guarantee that I will complete the egg donor process.

Undergoing treatment with donor egg is stressful. Anxiety and disappointment may occur at any of the phases of treatment. Significant commitment of time and emotional energy is required. The physicians at the Practice encourages patients to meet with the mental health team before undergoing treatment if the procedure induces stressors that impede your normal daily living.

All egg donors are given an opportunity to meet with a counselor prior to their donation cycle. As you consent to egg donation as well as the donor screening process, there may be psychosocial issues that may arise from egg donation, but are not limited to:

- **Although most donors report a positive response to egg donation, you may experience a delayed emotional response to egg donation that may include feelings of loss, attachment or guilt regarding your oocytes or the resulting children.**
- **Although you are consenting to anonymous egg donation, there are also psychological risks associated with the potential of being identified due to changes in law or technology.**
- **Throughout the donor screening, you may be made aware of issues with your own fertility, and there may be the potential for emotional stress due to this information.**
- **The egg donor screening, and IVF cycle can be both physically and emotionally invasive. This may trigger an emotional response, specifically in women with a history of trauma.**

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany egg donation cycle.

Success Rate

There are many complex and sometimes unknown factors that may cause the donor cycle to be cancelled. Known factors, which may prevent the success of an egg donor cycle, include, but are not limited to the following:

1. Despite the fact that all instructions were followed faithfully the ovaries may not respond adequately to the medications, there may not be enough eggs developing and the cycle may need to be cancelled before the egg retrieval.
2. Technical problems including inadequate visualization or the position of the ovaries may prevent retrieval of the eggs.
3. There may be failure to recover an egg because ovulation has occurred prior to the time of the egg retrieval.
4. The eggs may not be recovered.
5. The eggs may not be normal.
6. The egg donor may psychologically reconsider the donation.
7. Equipment failure, infection, technical problems, human errors and/or other unforeseen factors (natural disasters) may result in loss or damage to the eggs, semen sample and/or embryo.

- 8. Pelvic adhesions may prevent access to the ovary with the follicles, thus making the procedure to obtain the egg from the patient’s ovary not possible.
- 9. The age of the patient.
- 10. Infectious disease testing performed within 30 days of the retrieval may be positive.

How will the eggs be used?

I understand, agree, and consent that the selection of the recipient will be determined at the sole discretion of the Practice and the Lab, and as appropriate, its employees, contractors, and consultants; unless I have listed a specific designated recipient couple or individual below:

Please check the appropriate choice and initial:

The Practice may determine the recipient(s) (the person or persons who will receive the eggs) of these eggs.

Donor’s initials: _____

I designate the individual’s listed below as the recipient(s) of these eggs.

Designee _____

Donor’s initials: _____

I understand, agree, and consent that the eggs that I donate may be used fresh or frozen by the recipient (the couple or individual (female or male) who is using the eggs) and that once they have been retrieved, that I will have no further control over these eggs. The recipient may use them in any way she/he/the couple thinks appropriate, and because of confidentiality issues, I will not be notified of how they are used. I understand that the eggs may first be frozen and stored in an Egg Bank before being used by a recipient, and that the recipient may not yet be identified at the time of my donation. Moreover, several different recipients may receive my eggs.

Freezing (Cryopreservation) of Embryos

The donor egg process will yield multiple eggs and embryos will be created in hopes to achieve a pregnancy in the recipient women. All recipient couples will have the option to cryopreserve (freeze) their extra embryos and/or oocytes for future use. As a donor it is important for you to understand that this is an option for all couples going through the egg donor process at the Practice. Couples will receive information on embryo cryopreservation and will be given a choice regarding their decisions regarding the disposition of extra embryos are outlined in the Lab Consent Form: “The Embryo and Pre-Embryo Cryopreservation Program Information, Participation Agreement and Informed Consent,” a description of the available options is listed below:

“The Embryo and Pre-Embryo Cryopreservation Program Information, Participation Agreement and Informed Consent”

All Recipient individuals or couple(s) will have the following choices for future disposition of unused embryo(s). I understand the dispositional choices may include, but not limited, to any of the following:

1. DONATION TO ANOTHER INFERTILE INDIVIDUAL(S) OR COUPLE(S) (MAKE OR FEMALE) FOR PROCREATION.
2. TRANSFERRING THE EMBRYOS TO AN AGENCY OR ENTITY THAT IDENTIFIED AND SELECTS INDIVIDUALS OR COUPLES TO RECEIVE EMBRYOS FOR PROCREATION. OR TRANSFER TO A FACILITY THAT USES THE EMBRYO/EGGS OR TISSUE FOR RESEARCH WHICH COULD INCLUDE STEM CELL RESEARCH.
3. DONATION FOR RESEARCH.
4. DISCARD.

As a donor, once you have completed your donation, all of your retrieved eggs and all resulting embryos, including any embryos which may be frozen, are under the exclusive control of intended parent(s) in accordance with this consent form. Intended parent(s), and not donors, will have the right to make any and all dispositional choices permitted at that time by the Lab or any other entity which may be storing the eggs or embryos. In addition, under some circumstances, frozen eggs or embryos are or may be considered abandoned in which circumstances dispositional decisions may then be made by the Practice or another entity. As a donor, you will not be informed of or have any input into any such choices or decisions.

The recipient may decide to donate the eggs or embryos to research, including stem cell research. Neither I (the egg donor) nor the recipient of my eggs will receive any information about subsequent testing on the embryo or the resulting stem cells. Stem cells and cell lines may be kept for many years. It is possible the donated material may have commercial potential, but the donor will receive no financial or other benefit from any future commercial development. Stem cell research is not intended to provide direct medical benefit to the embryo donor. Embryos donated for research will not be transferred to a woman’s uterus, nor will the embryos survive the human pluripotent stem cell derivation process.

Non-Viable Eggs/Embryos

I understand that some non-viable eggs may be used as a teaching aide for laboratory personnel before being discarded. I understand that non-viable eggs and embryos will be discarded according to ASRM Ethical Guidelines.

Cells and Biological Materials that Would Normally Be Discarded

I understand that some cells (such as granulosa cells which are cells from the ovary that are retrieved along with eggs) and biological materials such as follicular fluid (the fluid that the egg is found in), which are normally discarded, may be used for research studies. These materials

would never be used for any procedures that involve fertilization or creation of an embryo or a cell line without my written consent in advance. When these studies are completed, the materials will be discarded.

Research Use of Viable Eggs

I understand that the viable eggs will not be used for any research without my express written consent in advance. I understand that I would be asked to sign a separate consent to donate my eggs to research instead of donating them for use to produce a pregnancy.

In addition, under some circumstances, frozen eggs or embryos are or may be considered abandoned in which circumstances dispositional decisions may then made by the Practice or another entity. As a donor, you will not be informed of or have any input into any such choices or decisions.

I understand that if I am not comfortable with unrestricted use as described within this consent, I may not be permitted to donate my eggs.

Legal Issues and Documents

The law surrounding egg donation in **Minneapolis** is or may be unsettled. In addition, if you or any other party to the egg donation is from a state other than **Minneapolis**, the laws of that state may have some applicability to your donation/receipt and may also be unsettled. It is the responsibility of donors and intended parents to consult and clarify relevant legal status and other legal issues or concerns they may have regarding their participation in egg donation and the respective legal status, rights or obligations of any interested person, including but not limited to the donor, intended parents, and any resulting child. In addition, if and to the extent a registry is created which may make information available to gamete donors, intended parents, and/or offspring, now or at some time in the future, it is the responsibility of donors and intended parents, and not the Practice, to investigate the availability of such a registry. It is the responsibility of donors and intended parents whether or not they wish to register, request, and/or access any information that may be or become available as a result.

Notwithstanding any other provision in this consent or any other document I may have executed, I agree to be contacted through the Practice in the event the parents of the resulting child contact the Practice and request that I be contacted for a life-threatening medical emergency for the child for which I, as a genetic donor have a unique capacity to be helpful. I understand that the Practice will use reasonable efforts to maintain my anonymity but cannot guarantee that anonymity can be maintained.

I/we acknowledge that the Practice has made no representations, and I/we are not relying on the Practice, regarding the applicable laws, including but not limited to, the parent-child status of any child resulting from egg donation.

The Practice recognizes that egg donors may be recruited by intended parents, the Practice, or an outside donor recruiting program (“Donor Recruiting Program”). There are general legal

issues applicable to all donors and intended parents, which are addressed here. There are also legal issues that are specific to different donors, depending on how and by whom they are recruited to donate, which will be addressed below.

Legal Documents Generally

In the event a donor and/or intended parents execute any legal documents, including, but not limited to, documents with a Donor Recruiting Program or between themselves the Practice is neither a party to, nor is it obligated to learn about or follow any such agreements or terms of such agreements. In the event of any inconsistencies between the Practice consent forms and other documents and any such outside documents on any issues involving the Practice, the Practice's documents will supersede and control all such issues.

Legal Agreements between Donors and Intended Parents Generally

Donor Recruiting Programs have their own guidelines in regards to recipient/donor relationships and legal agreements and therefore it is important to understand that the Practice cannot control the donor/recipient anonymity of these programs. Additionally, because the law regarding egg donation is not completely settled, a private legal agreement negotiated and entered into between a donor and intended parents can offer additional safeguards for all parties entering into such an arrangement. Among other benefits, such a legal agreement can clarify the legal status of the child, donor and intended parents; outline respective medical, legal and psychological risks; clarify any compensation and factors related thereto; and identify whether, when and how any future communications may occur between donor, intended parents, and/or the child. Even between two intended parents, an agreement can serve to confirm and document their joint intentions to parent in the event of a potential future disagreement over parentage. As such, a legal agreement may be very beneficial between both donors and intended parents, as well as between intended parents themselves. For these reasons, as set forth in more detail below, the Practice *requires* a legal agreement be entered into for all donors recruited from a Donor Recruiting Program.

As the Practice has more control over the anonymity of their anonymous donor program, legal contracts are not required. It is understood that it is not feasible to have a legal contract in situations in which the egg donor is going to have her eggs retrieved, then frozen, and later matched with a recipient. In these situations the donor's donated eggs may not be donated for several months and/or years before the eggs are fertilized and used by recipient(s). This is similar to sperm donation in which the sperm can be frozen for an extended period of time before the sample is utilized. It is not the standard to have contracts between sperm donors and the recipient, and it is not feasible to have a legal contract when egg donors are going to have their eggs frozen prior to being matched with a recipient.

For Donors Referred to the Practice by a Donor Recruiting Program

1. A legal agreement is required to be entered into between every donor and every intended parent, which should be facilitated by the Donor Recruiting Program. The agreement should address legal issues such as the legal parent-child relationship, the status of the donor, and

any mutually acceptable future communications. This agreement must be consistent with the Practice policies as stated here regarding limited identity-release and embryo disposition; in the event of any inconsistency the Practice policies and documents will govern.

2. For any legal agreement, a donor must be represented by independent counsel. The attorney representing either the intended parents or the donor must provide the Practice with a legal “clearance letter” before an egg donor cycle can commence, which must confirm that a legal agreement has been entered into, that each party has had separate legal counsel and which confirms, at a minimum, the agreement reached on the issues stated within this section (i.e. the legal parent-child relationship; the status of the donor; and any mutually acceptable future communications). The Practice may offer patients names of experienced reproductive technology lawyers, but does not endorse any lawyers nor is the Practice responsible for any attorney’s legal advice or representation. Patients may select any experienced attorney of their choosing.

3. While the Practice will use reasonable efforts to maintain anonymity for anonymous donor arrangements it cannot guarantee the parties’ anonymity. The Practice cannot be held responsible for meetings, phone conversations, email contacts between the recipient, donor and/or agency outside of the clinics, which are not authorized by the Practice.

4. The Practice has a limited “identity-release” policy: the Practice will release a donor’s name, address, and social security number to the offspring when they have reached the age of 18 years and older, only if and as such documentation, attached hereto as **Exhibit A** is signed and placed on file at or before the time of donation. The Practice will use reasonable efforts to do this through a period of years required by state law, but cannot and does not guarantee that it will be able to provide such information to any party to, or offspring resulting from, an egg donation agreement. **Any additional or different “identity-release” information or future communications between an agency donor and intended parents or an agency donor and the resulting child will be done only through the Donor Recruiting Program.**

5. Information will only be released to the recipient prior to the child turning 18 if and when the child’s physician determines, in writing, that the child has a serious and/or life threatening medical condition for which the donor has the unique capacity to assist. It is understood that the donor retains the right to decline, or refuse to provide any requested assistance and/or information.

For Anonymous Donors Recruited by the Practice:

1. While the Practice will use reasonable efforts to maintain anonymity for anonymous donor and recipient arrangements, it cannot guarantee the parties’ anonymity. I understand that I

will provide to the Practice childhood photographs of myself, which the Practice may post online to assist recipient couples in choosing a donor. I understand that as a result there is an increased possibility that confidentiality may be compromised as a result of such photographs. Donor understands that the Practice cannot be responsible for any republication or unintended use of any photographs donor provides to the Practice for online posting.

2. The Practice offers a limited “identity-release” policy: the Practice will release a donor’s name, address, and social security number to intended parents and/or the offspring only if and as such documentation, attached hereto as **Exhibit A** is signed and placed on file at or before the time of donation. The Practice will use reasonable efforts through a period of years required by state law, but cannot and does not guarantee that it will be able to provide such information to Intended Parents.
3. Donors may provide childhood and/or adult photographs of themselves through the Practice; however, donors and intended parents should be aware of the increased possibility that confidentiality may be compromised as a result of such photographs and, in particular through adult photographs.

Anonymous Versus Known Egg Donation: Egg donors can be either anonymous donors or known to the recipient. If at any point an anonymous donor meets the recipient couple the donation will be considered a known egg donation cycle and additional consents will be obtained to redefine the relationship. These two categories are detailed below:

- A. **Anonymous Donors:** Donors in this category volunteer to participate in the egg donor program at the Practice with the understanding that they will not know the identities of the recipients. Likewise, the recipients will not know the identity of the egg donor. The information the anonymous donors provide to the Practice on the donor profile form, absent her name, date of birth, address, telephone number and photograph will be given to the recipient. This information allows the recipient to see how the donor describes her detailed personal medical and social history and that of her family. The omission of the donor’s name, date of birth, address and telephone number are intentional. Omission of this information will not permit the recipient to know the identity of the donor. The oocytes retrieved from the anonymous donor may be split and allocated to more than one anonymous recipient. Once embryos are created by the recipient(s), the recipient patient(s) subsequently may choose to donate the remaining unused embryos to another couple(s) as designated by the original recipient couple. The Practice complies with national recommendations for egg donor screening as outlined by the American Society for Reproductive Medicine.
- B. **Known Donors:** A specific designated recipient brings Donors in this category to the Practice. The donor knows the identity of the recipient and the recipient knows the identity of the donor. All oocytes retrieved from the known donor are designated for the use of the known recipient. Vitrified (frozen) oocytes may subsequently be

donated to another couple(s) as designated by the original recipient couple.

Acknowledgement of Informed Consent and Authorization

I/We have voluntarily consented to participate in the Practice Donation program by donating my eggs to infertile woman (women), man, or couple in attempt to help the recipient to achieve a pregnancy and/or have a child. I have read this consent form which describes procedures and medications that will be performed.

I am voluntarily participating in the Donor Egg program at the Practice and authorize the Practice, the Practice licensed physicians, and any designated assistants to perform the oocyte retrieval. Participation means that oocytes (eggs) retrieved from my ovaries will be donated to cause pregnancy in a recipient woman. I understand that my egg(s) may be fertilized for the designated recipient. I understand that my egg(s) may be frozen for possible future fertilization. If fertilization takes place, the embryo(s) may be transferred to the uterus of the recipient in the hopes that a pregnancy will occur. It may be necessary for the intended parent to utilize another woman’s uterus to carry the pregnancy, known as a gestational carrier. Oocyte vitrification (freezing eggs) is a new technology which allows patients to freeze eggs for future use rather than creating embryos at the time of egg retrieval. Recipient couples may choose not to fertilize all of the oocytes and to freeze the unused oocytes, which they can decide at a later date to fertilize for their own use, donate to another couple(s), discard, or use for research. As an egg donor, I understand that my eggs may not be immediately fertilized, may be frozen for the future and subsequently fertilized to be transferred into the recipient’s uterus, donated for research, discarded or donated to another couple(s) for subsequent fertilization and transfer of embryos into a different recipient’s uterus.

I further acknowledge and consent that medical, psychological, genetic/infectious disease, technical or other considerations may contraindicate or preclude (make impossible) the donation of these eggs to a recipient despite my request. I agree that the disposition of these eggs will ultimately rely on the best medical judgment of the Practice, and as appropriate, its employees, contractors, and consultants and/or authorized agents, at the time of the potential donation.

When oocytes are retrieved they are accompanied by fluid from the ovary and other ovarian cells. I agree to allow these materials obtained from my body which would ordinarily be discarded, to be studied for research purposes. These studies may lead to advancements in medical knowledge and our understanding of human reproduction. I understand that my anonymity will be protected and that no publication resulting from these scientific studies will contain my name or other information that would allow me to be identified. I understand that information concerning my treatment may be analyzed and could be used in a publication. In accordance with federal law, non-identifying information and information concerning my treatment will be submitted to a national data registry that publishes statistics on ART treatment outcomes.

When the oocyte(s) leave my body, I waive any right and relinquish any claim to the donated

egg(s) as well as any embryos or offspring that might result from their use. I understand that the recipient of my egg(s) may regard the donated egg(s) and any embryo(s) as her own and any offspring from the embryo(s) shall be regarded as the recipient(s) child(ren). I understand that the recipient of the egg(s) has released me from liability for any problem occurring during pregnancy and for any mental or physical disabilities, financial support, care, custody or living expenses, education, health and welfare of the children(en) born as a result of my egg donation.

I understand that the recipient couple may choose not to use some or all of the frozen eggs/embryos resulting from my donation. In that event, I understand and agree that they may make any alternative disposition choices made available to them by the Lab and the Lab is authorized to transfer some or all of the frozen embryos to any recipient individual, agency or entity specified by the recipient, as set forth in detail above. I also understand that stimulation may produce a large number of eggs, which may enable my donated eggs to be shared with and therefore assist multiple recipients.

Such transfer will be subject to any and all additional lab tests, medical information and/or donor eligibility guidelines that may be required and/or recommended by the Practice, or any recipient individual, agency or entity. I understand that any such information transmitted or provided by the Practice will be done in a manner that is intended to protect my anonymity, although mistakes can occur through human error or otherwise. I also understand that the Practice has no control over and is not responsible for the actions of any other persons, agencies or entities with respect to any information transmitted or provided.

The recipient may decide to donate the eggs or embryos to research, including stem cell research. Neither I (the egg donor) nor the recipient of my eggs will receive any information about subsequent testing on the embryo or the resulting stem cells. Stem cells and cell lines may be kept for many years. It is possible the donated material may have commercial potential, but the donor will receive no financial or other benefit from any future commercial development. Stem cell research is not intended to provide direct medical benefit to the embryo donor. Embryos donated for research will not be transferred to a woman's uterus, nor will the embryos survive the human pluripotent stem cell derivation process.

Non-Viable Eggs

I understand that some non-viable eggs may be used as a teaching aide for laboratory personnel before being discarded. We (I) understand that non-viable eggs and embryos will be discarded according to ASRM Ethical Guidelines.

Cells and Biological Materials that Would Normally Be Discarded

I understand that some cells (such as granulosa cells which are cells from the ovary that are retrieved along with eggs) and biological materials such as follicular fluid (the fluid that the egg is found in), which are normally discarded, may be used for research studies. These materials would never be used for any procedures that involve fertilization or creation of an embryo or a cell line without my written consent in advance. When these studies are completed, the materials will be discarded.

Research Use of Viable Eggs

I understand that the viable eggs will not be used for any research without my express written consent in advance. I understand that I would be asked to sign a separate consent to donate my eggs to research instead of donating them for use to produce a pregnancy.

I have completed the genetic family health questionnaire completely and honestly. If I was unsure about a question, I clarified the question with a nurse, physician or genetic counselor. I will alert the Practice should new information arise about my family health history which could be pertinent to the donation of my eggs and potential offspring from my donation.

I understand that during the ovarian stimulation I will be producing multiple follicles which could result in an unintentional pregnancy should I have unprotected intercourse. I understand that it is recommended that **I should abstain from unprotected intercourse to prevent any unwanted pregnancy for a minimum of one month until birth control can be reestablished.** I understand that this requirement begins with the start of medications and continues until the next menstrual cycle following the egg retrieval.

I understand that it is important to share any medical history with the physicians at the Practice that could relate to the donation. I agree to have any previous pertinent medical information sent to the Practice. I understand that if I withhold pertinent medical information that I could be held liable.

I believe that I am a low risk candidate for sexually transmitted diseases (STD's), such as hepatitis, genital herpes, chlamydia, HIV, etc. I agree to be screened for STD's including HIV and understand that I will be informed of positive results. I am fully aware that I cannot contact the diseases by being a donor. ***I agree to inform the Practice if I engage or have engaged in any activities that put me at risk for sexually transmitted disease or STD (i.e. new or multiple partners, sharing needles, tattoo, piercing, blood transfusions and travel abroad having received medical treatment). I will also inform the Practice if I have contracted any new illnesses or been exposed to any infectious diseases, experienced prolonged rashes or fevers.*** I have completed the communicable disease risk assessment/interview with the physician and answered the questions honestly and to the best of my ability. I understand that I can be held liable should I engage in high risk behavior and not inform the Practice staff during this egg donation cycle. I understand that having any body piercing or tattooing is considered to be a risk of a communicable disease exposure. I am hereby confirming that I have not had a tattoo or piercing within one year of this egg donation and will not have a body piercing or a tattoo while I am cycling with the Practice through and including any retrieval procedure. By signing this Consent, I am confirming this information is accurate, current, and complete.

I agree to have the current Practice recommended genetic screening completed as required by the Practice current standard of care for genetic testing for egg donors, these genetic tests are not representative of all genetic diseases, but only a select group of more common recessive disorders. I agree to have the karyotype (chromosome) testing completed as well. I am aware that I may be asked to have additional genetic testing completed based on ethnicity or due to

the recipient having a positive carrier status of a specific genetic disorder. I am aware that I will be offered genetic counseling should these tests detect that I am a carrier of a genetic disorder. If I am found to be a carrier of a genetic disorder, I understand that I may not be allowed to continue with the donation process. I agree to report to the Practice any newly diagnosed or discovered genetic disorders or medical problems that affect any family member or me, which were not identified or discussed during the initial screening process. I understand that should a child be born with a genetic abnormality the recipient may request for me to have further genetic testing only if it benefits the health and welfare of the child. The information may benefit me (the donor), in better understanding the risks for my future children.

I have been given the opportunity to undergo medical and psychological counseling, which has occurred to my satisfaction. I am aware that I can obtain my own legal counseling if I choose and that the intended parents will pay for reasonable legal fees for that purpose in an amount that will be agreed to in advance.

By participating in the program, I accept the responsibilities, conditions and risks involved as set out in this document and as explained to me by the Practice. In addition, I consent to the techniques and procedures required to be an egg donor as they have been described in this document and as they have been explained to me by the treatment team at the Practice.

I acknowledge and agree that my acceptance into treatment and my continued participation is within the sole discretion of the Practice.

I understand that the ability to participate in another cycle of treatment, should this cycle be unsuccessful, will be determined by the physicians at the Practice.

I understand that the information anonymous donors provide to the Practice on the Donor Questionnaire and Consultation form, absent name, date of birth, address and telephone number will be released to the recipient. I understand that my identity will be kept confidential unless law requires disclosure. I also understand that the center posts the profile (absent the identifying information) on a website, in which only recipient patients of the Practice may have access to view, so they can select a donor. I understand that the childhood photos I provide will also be posted on this patient site.

I understand that full costs of the usual procedures; supplies and professional services involved in this program will be paid by the recipient and that none of these routine expenses will be my personal responsibility. I understand that donors are compensated for their time and effort. I understand anonymous donors through the Practice, are compensated **\$5,500** for the first egg donation and **\$6,000** for additional egg donation cycles. I understand that timing is critical and that any variance from the above instructions could jeopardize the success of the procedure. I understand that if I fail to follow directions regarding any part of this process, I may not receive my full compensation (i.e., taking medications at wrong time, not appearing for scheduled appointments, drinking/eating prior to retrieval etc.). I understand that I cannot expect to receive any financial compensation for such items as loss of wages and other direct or

indirect losses.

I also understand that the funds described above represent taxable income and I will receive a 1099 tax form at the end of the year for this income. The egg donor (me) will be responsible for all federal, state or local taxes associated with payments received from the Practice.

For the Practice Recruited Donors

I understand that should I develop a physical injury or medical complication as a result of my participation in the program, all necessary medical facilities are available for treatment. The Practice will provide a supplemental medical insurance plan for the Practice donors. The Practice insurance only covers complications of the egg donation cycle, and it does not cover any other medical conditions. I understand that it is highly recommended that I have my own medical insurance or purchase a temporary insurance plan during the donation cycle. I understand that neither the Practice nor the recipient(s) are financially or legally responsible for any medical complications or physical injury not covered by the supplemental insurance plan purchased for my egg donor cycle. Donors are responsible for all medical care and complications not associated with their egg donor cycle.

I am voluntarily participating in the Egg Donor Program at the Practice. I am consenting to have the information I have provided on the Donor Questionnaire and Consultation form (not including name, date of birth, address and telephone number) be made available to the Practice recipient patients and “potential” recipient patients via posting on the Practice website. I am also consenting to having the childhood photos I have provided to the Practice be made available to the Practice recipient patients and “potential” recipient patients via posting on the Practice website. A “potential” recipient patient is an individual needing the services of an egg donor who has been screened via phone by a Practice nurse, but has not yet made a new patient appointment at the Practice. A Practice recipient patient is a patient of the Practice interested in pursuing infertility treatment utilizing an egg donor.

I acknowledge that there is a risk involved in allowing patients and non-patients to view my personal information and childhood photos. I may also agree to provide adult photographs, and I acknowledge the increased risk that confidentiality may be compromised as a result of such photographs and, in particular through adult photographs. The risks include but are not limited to: my identity may become known, an individual who knows I may be donating may get access to the information, and a “potential” recipient patient may provide false information and be accessing my information for another purpose unknown to the Practice. While the Practice will use reasonable efforts to maintain anonymity for anonymous donor and recipients arrangements it cannot guarantee the parties’ anonymity.

I understand that as a result of posting my information and childhood photos there is an increased possibility that confidentiality may be compromised. I understand that the Practice cannot be responsible for any re-publication or unintended use of the photos and/or information the donor provides to the Practice for online posting. I agree to have the information and photos posted on the Practice website with limited access as stated above.

For Known Practice Donors

I understand that should I develop a physical injury or medical complication as a result of my participation in the program, all necessary medical facilities are available for treatment. I understand that the supplemental insurance plan offered by the Practice to anonymous donors may be purchased by myself or by my known recipient prior to the treatment cycle. I understand that it is highly recommended that I have my own medical insurance or purchase a temporary insurance plan during the donation cycle. I understand that neither the Practice nor the recipient(s) are financially or legally responsible for any medical complications or physical injury not covered by the supplemental insurance plan purchased for my egg donor cycle. Donors are responsible for all medical care and complications not associated with their egg donor cycle.

For Agency Donors

I understand that should I develop a physical injury or medical complication as a result of being an agency donor. I understand that should I develop a physical injury or medical complication as a result of being an agency donor, all necessary medical facilities are available for treatment while in Newport Beach. You will need to work with your Agency to assure that necessary medical facilities are available when you leave the Newport Beach area. Your agency is responsible for providing medical insurance for your egg donor cycle. I understand that it is highly recommended that I do not use an agency that does not provide medical insurance for my egg donation cycle. Agency donors need to work with their agency to determine what insurance is available for treatment unable to be provided at the Practice. I understand that the Practice is not financially or legally responsible for any medical complications or physical injury. Agency donors are responsible for all medical care and complications not associated with their egg donor cycle

For all Donors

I understand that medical information concerning my treatment may be analyzed and could be used in a publication. In accordance with federal law, non-identifying information and information concerning my treatment will be submitted to a national data registry that publishes statistics on treatment outcomes.

I understand that because I am donating my eggs to another patient(s), some of my medical information is relevant to, and therefore may or must be disclosed to, the prospective recipient patient(s) for purposes of furthering the donation. If and to the extent such information would otherwise be legally privileged, I hereby consent to the Practice sharing such information for that purpose. I understand that if my identity is not known to the recipients, the Practice will make reasonable efforts to maintain the confidentiality of my identity but cannot guarantee that my identity will not be disclosed or compromised now or in the future.

By signing this document I acknowledge and confirm that I have read the foregoing information and have been given an opportunity to ask questions and receive answers to my satisfaction. I understand that participation is purely voluntary and that my refusal to participate or withdraw

from the program at any time will not involve any penalty or loss of benefit to which I am otherwise entitled. I/we have been given the opportunity to ask questions which have been answered to my/our satisfaction by the Practice physician and/or nurse coordinator(s). I understand my nurse coordinator can assist me in getting an appointment with one of the physicians. I understand that utilization of donated eggs is being performed at my request and with my full consent.

Signature of Donor DOB _____ Date _____

Spouse/Significant Other DOB _____ Date _____

Witness/Practice Representative Date _____

EXHIBIT C
Refusal of "Identity-Release" Authorization
PLEASE SIGN THIS ONLY IF YOU WISH TO REFUSE TO BE A PART OF PRACTICE LIMITED
IDENTITY-RELEASE POLICY

I, _____ [Donor Name], having been recruited by _____ [Agency Name], a Donor Recruiting Program, understand and acknowledge that, while the Practice has and will use reasonable efforts to maintain anonymity between the participants in anonymous donor arrangements it cannot guarantee the participants' anonymity. The Practice cannot be responsible for other entities and lack of anonymity or any other disclosures by parties outside of the Practice.

OR

I, _____ [Donor Name], ("Donor") having been recruited by the Practice, understand and acknowledge that: While the Practice has and will use reasonable efforts to maintain anonymity between the participants for anonymous donor arrangements, including the Intended Parent(s), Donor, and any resulting child or children (the "Child") it cannot guarantee the participants' anonymity. The Practice cannot be responsible for other entities and lack of anonymity or any other disclosures by parties outside of the Practice.

By signing this Exhibit, I have requested not to participate in the "Identity Release Program."

I understand that regardless of which Exhibit has been signed by the donor in the event the Child has a medical condition or life threatening illness the Practice staff will attempt to contact me on behalf of the Intended Parent(s) and the Child first, to discuss the needs of the Child, at that point I understand that I may refuse further contact.

Donor Signature

DOB

Date

Witness

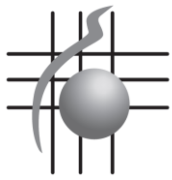
Date

Subscribed and sworn to before me this _____ day of _____, 201____.

Witness my hand and official seal. My commission expires: _____.

Notary Public

(SEAL)



Consent Form for Recipient of Egg Donation

Definitions

The following defined terms are utilized throughout the following document:

Practice – CCRM Minneapolis are referred to herein as the “Practice.”

Lab - Fertility Lab Sciences of Minneapolis, LLC doing business as “CCRM OC” is referred to herein as the “Lab.”

When the document refers to either the “Practice” or the “Lab” it is referring to the defined entities above.

Introduction

I/We voluntarily give my/our consent to and authorize the Practice’s physicians, their associates, any technical assistants, nurses, nurse coordinators, and any other staff of the Practice to perform In Vitro Fertilization (IVF) and embryo transfer utilizing donor egg and the necessary assistance and procedures to achieve this process. In Vitro Fertilization (IVF) has become an established treatment for many forms of infertility. The main goal of IVF with donor egg is to allow a patient the opportunity to become a parent using donor eggs with sperm from her partner or from a sperm donor. In Vitro Fertilization (IVF) with donor egg is a treatment that helps patients who are unable to achieve a pregnancy on their own or with their own eggs. The in vitro fertilization technique involves four steps:

1) developing eggs in the woman’s ovaries; 2) removing the eggs from her ovaries; 3) placing the eggs and sperm together in the laboratory to allow fertilization to occur; and 4) transferring fertilized embryos into the woman’s uterus for the establishment of pregnancy. This is an elective procedure designed to result in the patient’s pregnancy when other treatments have failed or are not medically feasible.

The reproductive potential of some women may be compromised because they do not produce eggs, produce defective eggs and/or embryos, or are carriers of a genetic condition. An option for these women is to undergo egg donation. Treatment with egg donation involves a woman who serves as an egg donor and a woman who serves as the recipient. It is a process where the egg donor has eggs removed from her ovaries. The eggs are then fertilized with sperm in the laboratory. The fertilized eggs (embryos) are then transferred into the uterine cavity of the recipient woman for implantation and the establishment of pregnancy. Following the delivery, the intention is that the recipient will be the rearing parent of the offspring.

The technique involves six steps: 1) medications to develop multiple eggs in the donor’s ovaries; 2) retrieval of the eggs from the ovary or ovaries of the donor; 3) insemination of eggs with sperm which is done by placing the eggs and sperm together in the laboratory to allow fertilization to occur; 4) culture of any resulting fertilized eggs (embryos); 5) placement (“transfer”) of one or more embryo(s) into the recipient woman’s uterus (for the attempted establishment of pregnancy); and 6) support of the uterine lining with hormones to permit and sustain pregnancy.

This consent reviews the IVF donor egg process from start to finish, including the risks that this treatment might pose to you and your offspring. This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed. While best efforts have been made to disclose all known risks, there may be risks of IVF/egg donation which are not yet clarified or even suspected at the time of this writing.

Purpose of Procedures

The purpose of these procedures is for us/me to achieve a pregnancy and have a child through the use of donor egg. I/We understand that while IVF is a relatively new procedure, some aspects of the procedure are considered routine in the delivery of health care. Specific consent for any of the following additional procedures (if applicable), Intracytoplasmic Sperm Injection (ICSI), Assisted Hatching, Cryopreservation, Known or Anonymous Egg Donor, Sperm Donation, and Preimplantation genetic testing/screening (PGS/CCS) and Gestational Carrier arrangements will be obtained separately from me/us for each of those procedures.

This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed.

Pre-treatment Recommendations

I/We understand that women should avoid any activity, behavior or medication that would reduce their chances of conceiving or increase the risk to an unborn child. Below are recommendations for women participating in IVF with egg donor this treatment which I have read and understand:

1. Women should take a prenatal vitamin on a daily basis. These vitamins should contain at least 800 mcg of folic acid, which reduces the chance of neural tube defect (i.e. spina bifida).
2. Smoking must be avoided before, during, and after treatment.
3. Recreational drugs are absolutely contraindicated.
4. Ingestion of aspirin or aspirin-like products (e.g. Ibuprofen, Motrin, Advil, Naprosyn, Aleve, etc.) should be avoided during treatment. Tylenol is a suitable alternative.
5. The use of alcohol should be eliminated during treatment cycle and establishment of a pregnancy, and should be eliminated during pregnancy until and unless otherwise advised by your obstetrician.
6. The use of all prescription and over-the-counter medications should be discussed with the treatment team.
7. Caffeine should be eliminated during the entire treatment cycle.
8. A normal well-balanced diet is encouraged.
9. Avoid **ALL** herbal or diet supplements.

The egg donor will undergo steps of ovulation induction and egg retrieval as described in the next section. The recipient will undergo preparation of endometrium, insemination of eggs, embryo transfer, and embryo freezing which are described below.

I. Description of Egg Donation Treatment

Egg donation treatment is done in conjunction with IVF, which involves several steps. Success cannot be guaranteed at any or all of these steps. If optimal results are not appreciated at any step, it may be recommended that the treatment be stopped and the cycle canceled. The donor will undergo the ovulation induction and egg retrieval and the recipient will undergo preparation of the endometrium, utilizing her partner sperm or anonymous donor sperm for the insemination and fertilization of the eggs and have the embryos transferred into her uterus in hopes of achieving a pregnancy. The steps of the treatment are discussed below.

Ovulation induction: In most cases, the egg donor will take medications to stimulate the development of multiple ovarian follicles (fluid-filled cysts in the ovary that contain eggs).

Egg Retrieval: The egg donor will have the eggs removed from her ovaries by transvaginal ultrasound guided retrieval.

Preparation of the Endometrium: The uterine cavity of the recipient woman has to be hormonally prepared prior to the embryo transfer to allow implantation to occur.

Insemination of the Eggs: The eggs and sperm will be placed together in the laboratory and incubated in an effort to achieve possible fertilization and growth of the embryos.

Culture: Of any remaining fertilized eggs (embryos)

Embryo Transfer: One or more embryos will be transferred into the uterus of the recipient woman.

Embryo Freezing: Following the embryo transfer, any remaining embryos of suitable quality may be frozen (cryopreserved) and stored for future embryo transfer(s). The recipient may decide later to donate unused embryos to another infertile couple.

Egg Vitrification (freezing of the eggs): Donated eggs may be retrieved then vitrified (frozen) for a future donation to a recipient(s).

Splitting the donation: For some donors who produce a larger number of eggs, the Practice may decide to split the fresh or vitrified eggs between more than one recipient.

The menstrual cycle of the two female patients will be carefully coordinated, with the intent that when the egg donor's follicles (eggs) are mature, the lining of the recipient will be ready to receive an embryo. This is achieved with medications that will mimic a woman's normal menstrual cycle. During a woman's menstrual cycle, usually one mature follicle develops within the ovary, which results in the ovulation of a single egg. The growth of the ovarian follicle during the first half of a woman's cycle is influenced by several hormones, including follicle stimulation hormone (FSH) and luteinizing hormone (LH) which are produced in the pituitary gland at the base of the brain. FSH is the main hormone that

stimulates the growth of the follicle, which produces a form of the hormone estrogen called estradiol. When the uterus is exposed to the increasing levels of estradiol the lining begins to thicken. When the follicle is mature, a large amount of LH is released by the pituitary gland. This “LH surge” helps to mature the egg and leads to ovulation 36-40 hours after the initiation. Once ovulation occurs the follicle creates a corpus luteum, which then begins to secrete a hormone called progesterone. Progesterone and estrogen exposure is essential for uterine stability and implantation of an embryo. Egg retrieval occurs when the follicles reach maturity, the patient is given medication (HCG) to create an LH surge and the retrieval is scheduled for 35 hours after that injection occurs. The eggs retrieved will be inseminated or fertilized with the male’s partner’s sperm (or donor sperm) to create embryos. The embryos created will continue to develop in the embryology lab for three to five days at which point one or more the embryos will be transferred into the prepared uterus of the recipient, and others potentially frozen for future transfers.

As a patient voluntarily requesting IVF using donor egg, we understand there are a number of steps involved in this procedure and that beginning this process does not guarantee that either the donor or I/we will complete the process or that I will become pregnant.

II. Ovulation Induction

Donor 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, or conversely, an inadequate response can occur**

Most of the medications that the donor will be using during the egg donation cycle are administered by injection. Both donor and recipient will receive instruction and training prior to any attempt at self-administration. If you are unable to self-administer the injections, you should have the injections performed by someone who has been trained to perform them appropriately. Questions regarding the injections may be directed to our nursing staff or demonstrated on our partner’s website www.colocm.com.

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

The donor will be prescribed -Gonadotropins, or injectable “fertility drugs” (Follistim®, Gonal-F®, Bravelle®, Menopur®, Repronex®): These hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the average span of eight to 14 days or more. Follicle growth will be monitored beginning on or around day five of the gonadotropin medication start. Most injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of the ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH like activity (Menopur®). LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. These medications are given by subcutaneous or intramuscular injection. Proper dosage of these drugs and the timing of egg recovery require monitoring of the ovarian

response, usually by way of blood tests and ultrasound examinations during the ovarian stimulation.

As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to these drugs. The intent of giving these medications is to mature multiple follicles, and many women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 1%-3% of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section which 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.

Ovarian hyperstimulation syndrome is a rare complication of ovarian stimulation from gonadotropin medications. Every woman who is administered gonadotropins can develop ovarian hyperstimulation but the risk is higher in a woman who is less than 35 years old, has a high blood estradiol level, has a large number of ovarian follicles, or who has a history of hyperstimulation syndrome. It is caused by fluid leaking into the abdomen due to hormones released from the ovary. The 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% or less of all treatment cycles—and the very severe are an even smaller percentage. Symptoms may resolve without intervention. Only about 1.4 in 100,000 cycles has led to kidney failure, for example. OHSS occurs at two stages: early, one to five 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 produced during pregnancy). **The physician may prescribe the donor additional medications to be taken after the egg retrieval to help prevent or lesson the hyperstimulation symptom; any additional medications prescribed shall be the financial responsibility of the recipients.**

Ovarian Torsion (Twisting) occurs in less than 1% of cases. The enlargement in the ovary from gonadotropins stimulation can cause the ovary to twist on itself, called ovarian torsion. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary.

Medications

Cancer: Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical

significance, but it is at least possible that use of fertility drugs may indeed cause some increased risk of uterine cancer.

Oral contraceptive pills: The birth control pill allows coordination of the cycles of both women. Many of the treatment protocols include oral contraceptive pills to be taken for two to four weeks before gonadotropin injections and before the initiation of estrogen treatment is started, in order to suppress hormone production and to coordinate the two patients' cycles. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or stroke.

GnRH-agonists (Leuprolide acetate) (Lupron®): This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for one to three months. The primary role of this medication is to prevent a premature LH surge for both the recipient and donor, which could result in the release of eggs before they are ready to be retrieved and to suppress the recipient from ovulating and disrupting the uterine lining. After a few days of treatment with a GnRH-agonist, the brain decreases production of both FSH and LH through depletion of the receptors.

Though leuprolide acetate is an FDA (US Food and Drug Administration) approved medication, it has not been approved for use in IVF. However 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, and skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. Since GnRH-agonists are oftentimes administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception (condoms) the month you will be starting the GnRH-agonists. GnRH-agonists **have not** been associated with any fetal malformations. However, you should discontinue use of the GnRH-agonists as soon as pregnancy is confirmed.

As the recipient female, you will be prescribed estrogen to assist in building the uterine lining. Once the lining has been established and carefully timed with embryo development, progesterone will be added to maintain the uterine lining for an embryo to implant (Progesterone and estradiol are hormones normally produced by the ovaries). As the recipient, you will not have ovarian stimulation and your ovaries will not be producing these hormones naturally, therefore the support will be provided by estrogen and progesterone supplementation to assist in the development and maintaining the uterine lining and will continue until about the 12th week in pregnancy. Accordingly, supplemental progesterone and estradiol are given to ensure adequate hormonal support of the uterine lining and pregnancy. Progesterone is given either by intramuscular injection (progesterone compounded in sesame, olive, cottonseed, or other oil base) or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories) and will be initiated according to the donor's egg retrieval date. Progesterone and/or estradiol are 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, and allergic reaction and if given by intra-muscular injection include the additional risks of infection or pain at the application site.

Estradiol, if given, can be by oral, transdermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, skin irritation, pain and irritation at the injection site (if given by the intramuscular route), and the risk of blood clots or stroke.

Steroids: Steroid medications (dexamethasone, prednisone, or methyl prednisolone) may be used during your recipient treatment cycle. Steroids are oral medications used to suppress the immune system. The most common side effects with short term usage of steroids include headache, sleep or mood disturbances, weight gain, nausea, and fatigue. Other side effects can occur with long term usage and will be discussed if your treatment requires prolonged use.

Aspirin: Aspirin 81 mg (baby aspirin) may be used during your recipient cycle to decrease potentially undiagnosed blood clotting abnormalities and improve pregnancy implantation. If successfully pregnant, we recommend taking aspirin through the 12th week of pregnancy. Side effects are uncommon but may include fever, allergic reaction, heart burn, stomach ulcers and bleeding, and easy bruising.

Other medications: Antibiotics may be given to the donor and you for a short time during the treatment cycle to reduce the risk of infection associated with egg retrieval (donor) or embryo transfer (you). 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 of which is drowsiness. Other medications such as heparin, low molecular weight heparin, or other medications may also be included in the treatment protocol and the risks associated with these will be discussed separately if their use is indicated.

Monitoring

During the endometrium development phase of treatment, monitoring uterine lining development is performed with periodic blood hormone tests and vaginal ultrasound exams. The development of the lining will be monitored beginning on or about the tenth-twelfth day of the cycle and will be repeated depending on the physician's recommendation. Monitoring helps the physicians to determine the appropriate dose of medication and development of the uterine lining as well as the timing of the embryo transfer. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and possibly bruising, bleeding, infection, or scar at the needle sites. The need for repeated ultrasound examinations and blood drawing on a frequent basis requires the woman's presence in the vicinity of the Practice's office (or one of the satellite monitoring sites).

III. Uterine Lining Support

- **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 the purpose of lining development.**
- **Estrogen, given by patch, tablet, or injection is also given for the purpose of lining development.**

Successful attachment of embryos to the uterine lining depends on adequate hormonal development and support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovaries make sufficient amounts of both hormones. The recipient will not have ovarian stimulation and her ovaries will not be producing these hormones naturally, therefore the support will be provided by estrogen and progesterone supplementation to assist in the development of the uterine lining and will continue until about the 12th week in pregnancy. This additional hormone support (estrogen and progesterone) will be administered in the form of patch, pill, injections, or suppositories. The use of these medications (estrogen and progesterone) can cause side effects such as nausea, vomiting, hot flashes, headaches, mood swings, joint pains, and visual symptoms. Some women may have allergic reactions to the drugs. A rare risk of estrogen administration is development of blood clots, which can compromise the blood supply to vital organs and cause serious problems. Additional problems described with estrogen usage include breast cancer, stroke, or heart attack. Any of these conditions may cause death or serious long-term disability. Hormone testing for early pregnancy detection will be done by a blood sample (hCG) approximately seven to ten days following the embryo transfer. Following a positive test result the patient will follow-up with an ultrasound two and a half weeks later to indicate a pregnancy has been achieved. Additional blood draws and ultrasound exams may be necessary.

Embryo Transfer

If embryo(s) are to be transferred, a Practice physician will perform the embryo transfer procedure. Generally, the embryo transfer into the recipient is performed three or five days after the egg retrieval. Transfer of one or more embryos to the uterus is ordinarily painless, or may involve a mild amount of cramping. Transfer of embryos to the uterus involves the passage of a thin tube through the vagina and cervix into the uterine cavity.

The recipient is asked to drink fluid and fill her bladder prior to embryo transfer. An abdominal ultrasound is used to observe the placement of the embryos. The recipient may experience some (typically mild to moderate) cramping during the transfer procedure. Following the transfer the recipient will rest for up to one hour prior to going home. We understand that there is a remote chance of infection as a result of embryo transfer. The most common symptoms associated with infection are pain and fever. If fever, vomiting, abdominal pain or any other symptoms develop following embryo transfer, you should promptly contact a physician at the Practice. Following the transfer procedure, the recipient will be required to remain on bed rest for one hour at the surgery center, and then at home for a total of thirty-six hours bed rest. The Practice physician, along with the Lab embryologist, will assess embryo quality. If remaining embryos are assessed by them as being of good quality the embryos can be cryopreserved for future use; if embryo quality is assessed by them as poor, the remaining embryos will be discarded or used for research, as you consented to in the Lab

Cryopreservation Consent. If there is no evidence of fertilization after seventy-two hours of incubation, the oocytes (incompletely developed eggs) and sperm will be discarded.

Post Transfer Care

I/we understand that in conjunction with the transfer of embryo(s), as the recipient, I will be given natural progesterone by intramuscular injection and/or vaginal suppository along with transdermal, oral estrogen or injectable estrogen to increase the chances for successful implantation. Should pregnancy result, I/we understand that no harmful effects to the recipient or the fetus are presently known to medical science from the use of this natural progesterone. Subsequent to the embryo transfer, I/we understand that blood hormone levels will be evaluated weekly if not more frequently to wean the recipient off of the hormones. I/we understand that it will be necessary to continue taking the estrogen and progesterone until there is clear evidence that the placenta of the developing pregnancy is making sufficient amounts of these hormones to maintain the developing pregnancy. Nine to eleven days after the embryo transfer, a blood pregnancy test will be performed. If this test is found to be positive, a repeat pregnancy test will be performed two days later. If the test results are encouraging, another blood test to evaluate the estrogen and progesterone levels will be performed. Approximately two weeks later a vaginal ultrasound will be performed to determine the status of the pregnancy. Because of the potential complications following the embryo transfer, the recipient should have access to obstetrical medical care up to the time of the pregnancy test and beyond if pregnancy is established. If travel is absolutely necessary, it should be discussed with your Practice physician. If the pregnancy test is negative, all of the hormone support is stopped and a menstrual cycle will follow.

Success Rate

There are many complex and sometimes unknown factors that may prevent the establishment of pregnancy and delivery of a live born infant. Known factors, which may prevent the establishment of pregnancy, include, but are not limited to, the following:

1. The donor’s ovaries may not respond adequately to the medications.
2. Technical problems including inadequate visualization or the position of the ovaries may prevent retrieval of the eggs.
3. There may be failure to recover eggs because ovulation has occurred prior to the time of the egg retrieval.
4. The eggs may not be recovered.
5. The eggs may not be normal.
6. The male partner may be unable to produce a semen sample or the semen sample may be of insufficient quantity or quality.
7. Fertilization of the eggs and sperm to form embryos may not occur.
8. Cell division of the embryos may not occur.
9. The embryos may not develop normally.
10. Embryo transfer into the uterus of the recipient may be technically difficult or impossible.
11. If implantation occurs, the embryo(s) may not grow or develop normally.

12. Equipment failure, infection, technical problems, human errors, and/or other unforeseen factors (natural disasters) may result in loss or damage to the eggs, semen sample and/or embryo.
13. The recipient's uterine lining may not develop normally.
14. Pelvic adhesions may prevent access to the ovary with the follicles, thus making the procedure to obtain any eggs from the donor's ovary impossible.
15. Implantation of the embryo(s) in the uterus after embryo transfer may not occur.
16. The embryo(s) may become infected due to infection in the semen or bacteria from the vagina.
17. The age of the patient.

Freezing (Cryopreservation) of Embryos

Information on embryo cryopreservation and decisions regarding the disposition of extra embryos are outlined in the Lab Consent Form: "The Embryo and Pre-Embryo Cryopreservation Program Information, Participation Agreement and Informed Consent," which I/we will be required to sign prior to fertilization of any embryos.

Risks of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions (See Table "Potential Risks in Singleton IVF Conceived Pregnancies" 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 to these respective risks.

Miscarriage

If pregnancy occurs; there is a risk of miscarriage. The risk of miscarriage in the general population is 15%-20%. The risk of miscarriage increases with the age of the woman who is utilizing her own eggs. The risk of miscarriage in women who conceive with IVF is not believed to be higher than the risk of miscarriage in women who conceive spontaneously with their own eggs. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. Antibiotic therapy may be recommended. In some cases, however, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilation and curettage (D&C). This procedure is usually performed under anesthesia in the operating room and involves placing a suction tube into the uterine cavity to remove the pregnancy tissue. In other circumstances, medications may be given to bring about passage of the tissue. This approach may help avoid a surgical procedure, but that result cannot be guaranteed, and a surgical procedure may be deemed necessary and performed.

Ectopic Pregnancy

Although embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical, and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone

(<5%) or concurrently with a normal intra-uterine pregnancy (heterotopic pregnancy<1%). These abnormal pregnancies often require medical treatments with methotrexate (a chemotherapy drug) or surgery to treat the abnormal pregnancy. Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun, and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding, and injury to any internal organs. Surgery, which includes removing of the ectopic pregnancy and potentially an affected surrounding structure such as the fallopian tube is a standard alternative. As a result of an ectopic pregnancy and removal of the pregnancy, no baby will result. Frequently, in the case of a heterotopic pregnancy, the ectopic pregnancy can be surgically removed without compromising the intrauterine pregnancy, although this cannot be guaranteed.

Bleeding

Bleeding can occur early in pregnancy and is often diagnosed as a sub-chorionic separation (partial separation of the pregnancy from the uterine lining) which is typically treated with bed rest until the separation heals. Bleeding occurring later in the pregnancy can be a sign of a placenta previa, which is a low-lying placenta that covers the cervix or placental abruption, which is a detachment of the placenta from the wall of the uterus. Both of these conditions may result in premature labor and delivery. Uterine bleeding can also occur following a delivery. Management of the bleeding during pregnancy could include bed rest, D&C, transfusion, emergency cesarean section, and/or a possible hysterectomy depending on the circumstances.

Maternal Complications

Women who carry a child are at risk of developing a pregnancy related illness. The most common pregnancy induced diseases are pregnancy-induced hypertension (pre-eclampsia) and pregnancy induced diabetes (gestational diabetes).

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
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)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

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.

All pregnancies may develop the following conditions, but women over age 35 and those with a multiple pregnancy have a higher than normal risk of developing one of these conditions.

Infection

Infections may occur in the bladder, kidneys, the uterine cavity, or at other sites during a pregnancy. Infections could necessitate the use of oral antibiotics. In some cases, hospitalization may be necessary with the administration of intravenous antibiotics. In rare cases, an infection in the uterine cavity following a delivery could result in clot formation in the pelvic vessels that may require heparin treatment.

Gestational Diabetes

Hormonal changes during pregnancy put a woman at risk for developing diabetes. It is estimated that between 1%-12% of women develop diabetes during pregnancy. This risk increases with multiple pregnancy. Management may include daily blood sugar monitoring, adjustment of the diet and possible insulin injections. Diabetes can have a detrimental effect on the fetus. Testing of the fetal well-being may be indicated and may include ultrasound examinations and recording of the fetal heart rate.

Pre-eclampsia

Pre-eclampsia (formerly called toxemia) is a condition that develops during pregnancy and results in high blood pressure, fluid retention and loss of protein in the urine. It occurs in up to 10% of pregnancies. It occurs more frequently in women during their first pregnancy. Other factors that put a woman at risk for the development of toxemia include a history of high blood pressure, kidney problems, diabetes or a multiple pregnancy. Initial treatment includes bed rest. In some cases, hospitalization and/or early delivery may be indicated. In rare cases convulsions may occur as a result of this problem.

Premature labor

The initiation of labor with uterine contractions generally occurs between weeks 37-42 of the pregnancy. The onset of labor may be considered premature if it occurs before the 37th week of pregnancy. Premature labor complicates approximately 10%-12% of pregnancies. Its incidence is increased in multiple pregnancies. Premature labor can result in premature delivery of an infant unable to survive without some assistance. Premature birth is the single greatest cause of death or disability of newborns. Treatment of premature labor could include a hospitalization with extended bed rest and medical therapy.

Route of Delivery

Most deliveries can be accomplished via the vaginal route. However, in approximately 25% of cases there will be the need to perform a cesarean section. In cases of a multiple pregnancy, there is an increased chance of the need for a cesarean section. Delivering the baby through incisions made in the lower abdomen and the uterus is known as a cesarean section. It can be performed under general, epidural or spinal anesthesia. Following a cesarean section, a two to five day hospitalization will be necessary. After discharge recovery may take up to six weeks. Complications from delivery could

include infection, hemorrhage, blood clots in the legs (deep vein thrombosis) or lungs (pulmonary emboli) and other complications that may necessitate additional surgery (i.e., D&C, hysterectomy) or medical treatment.

Postpartum

Generally, it may take up to one to two months following delivery before a woman is able to return to her normal activities. The average weight gain during pregnancy is 25 pounds. Some women do not return to their pre-pregnancy weight. Some of the other physical changes of pregnancy that may not reverse themselves include the development of stretch marks in the abdomen, change in the shape and texture of the breast tissue and vaginal relaxation which can cause protrusion of the colon, bladder or intestines into the vagina that could produce symptoms and require surgery. Following the delivery of the infant you may also experience feelings of depression or anxiety.

General Well Being

Pregnancy affects women in different ways. While some women feel fine during the pregnancy, others have complaints of nausea, fatigue, loss of energy, and may develop various discomforts (i.e., lower abdominal aching, back pain). These symptoms and others may affect a woman's sense of well-being and ability to function at home or at work. Depending on the nature and degree of the symptoms a woman may not be able to function at the work place and therefore may experience lost income. Following a delivery, between 50-70% of women experience the "post-partum blues" characterized by mood swings, depression, fatigue, anxiety, confusion, and difficulty with concentration. Less than 10% of women experience the more severe symptoms of postpartum depression that may necessitate medical intervention.

Time Commitment

Pregnancy lasts an average of 280 days, but may be shorter or last longer depending on the circumstances. During the pregnancy the woman will make frequent visits to her obstetrician to monitor the pregnancy. It may be necessary to remain in the vicinity of your local obstetrician during all or part of the pregnancy. In some cases of premature labor bed rest could be prescribed.

Mortality Rate

The overall mortality rate associated with pregnancy is 0.01% (1 in 10,000). Some of the reasons for death include the following: embolism, hypertensive disease, bleeding, ectopic pregnancy, infection, stroke, and complications from anesthesia.

IV. 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 woman’s underlying infertile state, or from the IVF techniques, or both

Overall Risks

Since the first birth of an IVF baby in 1978, more than three million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for IVF babies as compared to naturally conceived babies. A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make, if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small. Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under five pounds nine ounces (2500 grams) is 12.5% versus 7% in naturally conceived singletons.

Birth Defects

The risk of birth defects in the normal population is 2%-3%. In IVF babies the birth defect rate may be up to 6%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects. Although there are more risks associated with the age of the maternal egg, birth defects and abnormalities can occur with the younger egg as well. ICSI may be performed which carry some additional risks, the ICSI consent will inform you of additional information on risks associated with the ICSI procedure.

Some birth defects are identified at the time of an ultrasound performed around 11-16 weeks of pregnancy. If a congenital anomaly is identified, the option to terminate the pregnancy can be accomplished with medications to induce labor and/or a dilation and evacuation (D&E). This is performed in the operating room under anesthesia. In a multiple pregnancy fetal reduction may be an option.

Potential Risks in Singleton IVF Pregnancies

	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)
Preterm birth	11.5%	2.0 (1.7--2.2)
Low birth weight (< 2500 g)	9.5%	1.8 (1.4--2.2)
Very low birth weight (< 1500 g)	2.5%	2.7 (2.3--3.1)
Small for gestational age	14.6%	1.6 (1.3--2.0)

NICU admission	17.8%	1.6 (1.3--2.0)
Stillbirth	1.2%	2.6 (1.8--3.6)
Neonatal mortality	0.6%	2.0 (1.2--3.4)
Cerebral palsy	0.4%	2.8 (1.3--5.8)
Genetic risks		
-imprinting disorder	0.03%	17.8 (1.8--432.9)
-major birth defect	4.3%	1.5% (1.3--1.8)
-chromosomal abnormalities (after ICSI):		
-of a sex chromosome	0.6%	3.0
-of another chromosome	0.4%	5.7

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

Imprinting Disorders

These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies approximately 4% of children with the imprinting disorder called Beckwith-Weidemann Syndrome were born after IVF, which is more than expected. A large Danish study however found no increased risk of imprinting disorders in children conceived with the assistance of IVF. Since the incidence of this syndrome in the general population is 1/15,000, even if there is a two to five 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 five to seven times more than expected. Currently, due to the extremely low number of cases reported, it cannot be definitively stated whether any or all of the assisted reproductive technologies or associated procedures are or are not associated with these disorders, but it is important to understand that an increased risk may exist. The Practice can make no guarantee of a healthy and genetically normal child(ren).

Infant Development

In general, studies of long-term developmental outcomes have been reassuring so far, as 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 (four fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

Risks of Multiple Pregnancies

When more than one embryo is transferred, the possibility of multiple pregnancies exists. The chance of a multiple pregnancy increases with the number of embryos that are transferred. This is a function of the number and quality of embryos transferred into the uterus as well as the age of the donated egg.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Of note, IVF twins do as well as spontaneously conceived twins. Triplet (and greater) pregnancies deliver before 32 weeks (seven months) in almost half of the cases.

The most important pregnancy complications associated with multiple gestations are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Others include gallbladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Triplets and above increase the mother's risk of more significant complications including post-partum hemorrhage and transfusion.

Prematurity accounts for most of the excess perinatal morbidity and mortality 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 for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus 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 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. Abruption 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) 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. 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 risk of chromosomal abnormalities increases with the age of the woman who provides the egg. A chorionic villi biopsy or a genetic amniocentesis can assess the chromosomal status of the fetus(es).

V. Additional Information

The Option of Selective Reduction

Pregnancies that have more than two 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 options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, 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 and emotional distress are the main risks 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 5 to 10%. Complicated issues can emerge regarding the decision to keep all the embryos or to reduce the pregnancy to twins can produce anxiety, depression and grief for couples.

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 who have a 30%-35% risk of birth under 32 weeks compared to twins which is 7% to 10%.)

Psychosocial Effects of Infertility and Donor Egg 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.

Undergoing treatment with IVF with donor egg can also be stressful. Anxiety, disappointment and second guessing your decision to be the recipient of donor egg may occur at any of the phases of treatment. Significant commitment of time and emotional energy is required. The physicians at the Practice encourage patients to meet with the mental health team before, or while, undergoing treatment if the procedure induces stressors that impede your normal daily living.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany infertility and donor egg treatment.

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

- * Decreased ability to appropriately manage disappointments/stress loss of interest in usual activities;
- * Depression that does not lift;
- * Strained interpersonal relationships (with partner, family, friends and/or colleagues)
- * Difficulty thinking of anything other than the treatment of IVF;
- * 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; and/or
- * Regret or second guessing your decision to use a donor egg.

I/We understand Support groups are available should we need additional support.

Ethical and Religious Considerations in Infertility Treatment and Donor Egg Treatment

Infertility treatment can raise concerns and questions of an ethical or religious nature for some patients. The technique of 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). We encourage the recipient who so desires to consult with trusted members of their religious or ethics community for guidance on their decision to create human embryos, use a donor, and the treatment involved.

Alternatives to IVF and Donor Egg Treatment

There are alternatives to IVF treatment with donor egg 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 embryos, adoption or not pursuing treatment are also options. For some patients, gametes (sperm and/or eggs), instead of embryos may be frozen for future attempts at pregnancy in an effort to avoid potential future legal issues relating to disposition of any cryopreserved embryos. Sperm freezing, but not egg freezing, has been an established procedure for many decades. Egg freezing is considered an experimental procedure at this time; however, the Practice has had several successful pregnancies for patients who have frozen their own eggs.

Screening and Testing for Egg Donors

All anonymous donors will take a written psychological test and meet with a psychologist or licensed mental health professional. All known donors will meet with the psychologist and may be asked to take a written psychological test. Known and anonymous donors will complete a physical exam including a pelvic examination which tests for the sexually transmitted diseases Gonorrhea and Chlamydia. A urine drug screen will be completed. Donors are also screened for sexually transmitted diseases including HIV, Hepatitis B and C, Gonorrhea, Chlamydia, and Syphilis. Screening tests for certain inheritable disorders may also be performed. Donors may, on the basis of their psychological, medical and/or genetic evaluation testing or screening, be deemed ineligible to donate eggs.

Unfortunately, no test or screening process in medicine is perfect or 100% accurate. This includes the unintentional transmission of a genetic characteristic, trait, and/or disease from donor to the embryo. Furthermore, some communicable or other diseases of the donor, depending on the incubation period, may escape detection during the screening process and be transmitted to the recipient. The Practice has never experienced the transmission of disease from donor to recipient. Fortunately, it is estimated that such transmission would be extremely rare. All donors will have genetic screening for karyotype, Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X, and specific ethnicity screening. For known donors these tests are also recommended but not required. Some studies have shown 4% or more additional risk of birth defects with IVF versus spontaneous pregnancy. Information regarding the donor's health history and communicable disease risk questionnaire is provided by the donors, is not independently verified by the Practice, and the accuracy is dependent on the disclosure of the donor.

Information regarding the donor's health history and communicable disease risk questionnaire is provided by the donors and I understand the accuracy is dependent on the disclosure of the donor, is not verified by the Practice, and the Practice cannot be held liable for information the donor may have omitted or inaccurately reported.

VI. Legal Issues and Documents

The law surrounding egg donation in Minnesota is or may be unsettled. In addition, if you or any other party to the egg donation is from a state other than Minnesota, the laws of that state may have some applicability to your donation/receipt and may also be unsettled. It is the responsibility of donors and

intended parents to consult and clarify relevant legal status and other legal issues or concerns they may have regarding their participation in egg donation and the respective legal status, rights or obligations of any interested person, including but not limited to the donor, intended parents, and any resulting child. In addition, if and to the extent a registry is created which may make information available to gamete donors, intended parents, and/or offspring, now or at some time in the future, it is the responsibility of donors and intended parents, and not the Practice, to investigate the availability of such a registry. It is the responsibility of the donor and the intended parents whether or not they wish to register, request, and/or access any information that may be or become available as a result.

Notwithstanding any other provision in her Consent or any other document the donor may have executed, within her consent she has agreed to be contacted through the Practice in the event the parents of a child resulting from her donation contact the Practice and request that she be contacted for a life-threatening medical emergency for the child for which she, as a genetic donor, has a unique capacity to be helpful. The Practice has agreed to use reasonable efforts to maintain all parties' anonymity but cannot guarantee that anonymity can be maintained. Notwithstanding this provision, the Practice cannot and does not guarantee that a donor will be able to be contacted or if contacted will respond as agreed.

I/we acknowledge that the Practice has made no representations, and I/we are not relying on the Practice, regarding the applicable laws, including but not limited to, the parent-child status of any child resulting from egg donation.

The Practice recognizes that egg donors may be recruited by intended parents, the Practice, or an outside donor recruiting program ("Donor Recruiting Program"). There are general legal issues applicable to all donors and intended parents, which are addressed here. There are also legal issues that are specific to different donors, depending on how and by whom they are recruited to donate, which will be addressed below.

Legal Documents Generally

In the event a donor and/or intended parents execute any legal documents, including, but not limited to, documents with a Donor Recruiting Program or between themselves, the Practice is neither a party to, nor is it obligated to learn about or follow any such agreements or terms of such agreements. In the event of any inconsistencies between the Practice consent forms and other documents and any such outside documents on any issues involving the Practice, the Practice's documents will supersede and control all such issues.

Legal Agreements between Donors and Intended Parents Generally

Donor Recruiting Programs have their own guidelines in regards to recipient/donor relationships and legal agreements and therefore it is important to understand that the Practice cannot control the donor/recipient anonymity of these programs. Additionally, because the law regarding egg donation is not completely settled, a private legal agreement negotiated and entered into between a donor and intended parents can offer additional safeguards for all parties entering into such an arrangement. Among other benefits, such a legal agreement can clarify the legal status of the child, donor and

intended parents; outline respective medical, legal and psychological risks; clarify any compensation and factors related thereto; and identify whether, when and how any future communications may occur between donor, intended parents, and/or the child. Even as between two intended parents, an agreement can serve to confirm and document their joint intentions to parent in the event of a potential future disagreement over parentage. As such, a legal agreement may be very beneficial between both donors and intended parents, as well as between intended parents themselves. For these reasons, as set forth in more detail below, the Practice *requires* a legal agreement be entered into for all donors recruited from a Donor Recruiting Program.

As the Practice has more control over the anonymity of their anonymous donor program, legal contracts are not required. It is understood that it is not feasible to have a legal contract in situations in which the egg donor is going to have her eggs retrieved, then frozen, and later matched with a recipient. In these situations the donor's donated eggs may not be donated for several months and/or years before the eggs are fertilized and used by recipient(s). This is similar to sperm donation in which the sperm can be frozen for an extended period of time before the sample is utilized. It is not the standard to have contracts between sperm donors and the recipient, and it is not feasible to have a legal contract when egg donors are going to have their eggs frozen prior to being matched with a recipient.

For Donors Referred to the Practice by a Donor Recruiting Program:

1. A legal agreement is required to be entered into between every donor and every intended parent, which should be facilitated by the Donor Recruiting Program. The agreement should address legal issues such as the legal parent-child relationship, the status of the donor, and any mutually acceptable future communications. This agreement must be consistent with the Practice's policies as stated here regarding limited identity-release and embryo disposition. In the event of any inconsistency, the Practice policies and documents will govern.
2. For any legal agreement, a donor must be represented by independent counsel. The attorney representing either the intended parents or the donor must provide the Practice with a legal "clearance letter" before an egg donor cycle can commence, which must confirm that a legal agreement has been entered into, that each party has had separate legal counsel, and which confirms, at a minimum, the agreement reached on the issues stated within this section (i.e. the legal parent-child relationship; the status of the donor; and any mutually acceptable future communications). The Practice may offer patients names of experienced reproductive technology lawyers, but does not endorse any lawyers nor is the Practice responsible for any attorney's legal advice or representation. Patients may select any experienced attorney of their choosing.
3. While the Practice will use reasonable efforts to maintain anonymity for anonymous donor arrangements it cannot guarantee the parties' anonymity. The Practice cannot be held responsible for meetings, phone conversations, email contacts between the recipient, donor and/or agency outside of the clinics, which are not authorized by the Practice.

4. The Practice has a limited “identity-release” policy. The Practice will release a donor’s name, address, and social security number to the offspring which have reached the age of 18 years and older, only if and as such documentation, blank copies of which are attached hereto as **Exhibit A** (for the Practice recruited donors) and Exhibit B (for Donor Recruiting Program referred donors), is signed and placed on file at or before the time of donation. The Practice will use reasonable efforts to do this through a period of years required by state law, but cannot and does not guarantee that it will be able to provide such information to any party to, or offspring resulting from, an egg donation agreement. **Any additional or different “identity-release” information or future communications between a Donor Recruiting Program donor and intended parents or such a donor and the resulting child will be done only through the Donor Recruiting Program.**
5. Information will only be released to the recipient prior to the child turning 18 if and when the child’s physician determines, in writing, that the child has a serious and/or life threatening medical condition for which the donor has the unique capacity to assist. It is understood that the donor retains the right to decline or refuse to provide any requested assistance and/or information.

For Anonymous Donors Recruited by the Practice:

1. While the Practice will use reasonable efforts to maintain anonymity for anonymous donor and recipient arrangements it cannot guarantee the parties’ anonymity. I/we understand that the donor will provide to the Practice a childhood photograph of herself, which the Practice may post online to assist recipient couples in choosing a donor. I/we understand that as a result there is an increased possibility that confidentiality may be compromised as a result of such photographs. Donors are informed that the Practice cannot be responsible for any republication or unintended use of any photographs donor provides to the Practice for online posting.
2. The Practice offers a limited “identity-release” policy. The Practice will release a donor’s name, address, and social security number to intended parents and/or the offspring only if and as such documentation, blank copies of which are attached hereto as Exhibit A (for the Practice recruited donors) and Exhibit B (for Donor Recruiting Program referred donors), is signed and placed on file at or before the time of donation. The Practice will use reasonable efforts through a period of years required by state law, but cannot and does not guarantee that it will be able to provide such information to intended parents.
3. Donors may provide childhood and/or adult photographs of themselves through the Practice; however, donors and intended parents should be aware of the increased possibility that confidentiality may be compromised as a result of such photographs and, in particular through adult photographs.

VII. Acknowledgement of Informed Consent and Authorization

I/We have voluntarily consented to participate in the Practice’s egg donor program as a recipient of donated eggs, as described within this consent form. Other procedures described involve the use of

sperm (from male partner if applicable), which will interact with donated eggs to cause fertilization. The donor will sign a separate consent form, a copy of which form has been provided to us, and which we have reviewed, understand, and have had an opportunity to ask any questions about if we have such questions.

When the recipient signs this document, she acknowledges that she has read the consent form; had an opportunity to ask questions and receive answers to her satisfaction; and had an opportunity to obtain an independent legal opinion. Furthermore the recipient consents to participate in the egg donor program as a recipient as described in this consent form.

When the male partner of the recipient signs this form, he acknowledges that he has read the consent; had an opportunity to ask questions and receive answers to his satisfaction; and had an opportunity to obtain an independent legal opinion. Furthermore BOTH THE RECIPIENT AND the male partner of the recipient acknowledges that any language in this document that states "she" also means "he;" that "I" also means "we;" that "my" also means "ours;" that the singular tenses in sentence construction also means the plural tense; and that "recipient" also means "recipient and her male partner" except where the interchange of these terms would refer to an act that is not possible biologically.

Without limiting the above acknowledgments as to the entire consent process and form, we also specifically acknowledge the following understandings.

I/We understand that medical information concerning my treatment may be analyzed and could be used in a publication. In accordance with federal law, identifying information and information concerning my treatment will be submitted to a national data registry that publishes statistics on treatment outcomes. I/We understand that no publication resulting from these or other information that would allow me to be identified will be created by the Practice.

I/We have read and understand the sections in this consent form describing preparation of the endometrium and prescription medications and agree to take the medications prescribed to me by the Practice. The medications will help prepare the lining of the uterus for implantation. I understand that the hormones prescribed include formulations of estrogen and progesterone. All medications have potential side effects. Some side effects of estrogen or progesterone may include: blood clots in the legs, arms, heart, lungs, and brain; high blood pressure; gallstones; liver disease; water retention; bloating; breast tenderness; breast discharge; mood changes; depression; cancer of the uterine lining or breast; and birth defects. Frequently injections of medications pose the risk of bruising and tenderness.

I/We have read and understand the section in this consent form describing insemination and/or ICSI of the eggs, as well as read and understood the consent form that the Practice egg donors are required to sign. I understand that eggs might not be recovered from the egg donor; the eggs might not be normal; my male partner (if applicable) or a sperm donor may not be able to produce a sperm sample; fertilization of the eggs may not occur; normal cell division of the embryos may not occur; and the embryos may not develop normally. I/We understand that these occurrences will prevent me from

having an embryo transfer and I will not become pregnant as a result of my participation as a recipient during that treatment cycle.

I/We have read and understand the sections in this consent form describing embryo transfer. I/We request that the Practice assist me in achieving a pregnancy by transferring one or more embryos or gametes (sperm and donated eggs) to my body.

I/We have read and understand the section in this consent form describing complications of embryo transfer. I understand and accept the risks following embryo transfer including discomfort bleeding, infection, multiple pregnancy, miscarriage, ectopic pregnancy, maternal complications, fetal anomalies, and psychological risks. I/We understand that despite the transfer of normal appearing embryos or gametes (sperm and donated eggs) pregnancy might not occur. I/We have been given the opportunity to undergo independent medical and psychological counseling to my satisfaction.

I/We have read and understand the section in this consent form describing embryo freezing. I/We have been given the cryopreservation consent to sign if I/we choose to cryopreserve embryos.

I/We understand that no test or screening process in medicine is perfect or 100% accurate. This includes the unintentional transmission of a genetic characteristic, trait, and disease potential or actual disease from donor to embryo. Furthermore, some diseases of the donor, depending on the incubation period, may escape detection during the screening process and be transmitted to the recipient. I/We accept the risks associated with receiving donated eggs.

I/We accept complete financial responsibility for the care and storage of any embryos frozen for me. I/We understand that anonymous donors expect the right to privacy following egg donation. If I/we am using an anonymous egg donor, I/we clearly and unambiguously agree not to seek the identity of the anonymous egg donor now or in the future.

I/We agree to have any pertinent medical history sent to the Practice for review. We will discuss any pertinent health issues with our Practice physician.

I/We understand that we are required to have communicable disease testing completed. I/We believe that we are a low risk candidate for sexually transmitted diseases (STDs), such as Hepatitis, HIV, Syphilis, Gonorrhea and Chlamydia. We are fully aware that the donor of the egg cannot contract the diseases by giving the eggs for the procedure, but the recipient may be at risk. The recipient may contract a communicable disease through the use of the donor sperm or the donated egg. I/We understand that the risks for STD include but ARE NOT limited to the following: new or multiple partners, sharing needles, tattoo, piercing, blood transfusions, and travel abroad having received medical treatment. I/We each agree that any and all information, including any otherwise privileged information that either of us provides to the Practice, or that is obtained by the Practice, may be shared by the Practice, with either of us or the donor or gestational carrier (if applicable) as it pertains to that individual's health.

I/We understand that that all egg and sperm donors and donor sperm are screened to show that they are free from risk factors for, and clinical physical evidence of, infection due to disease risks. The donor has tested negative for HIV1&2, Hepatitis B, Hepatitis B core Antibody, Hepatitis C, Syphilis and HTLV 1&2 (sperm donors), Gonorrhea and Chlamydia. I/We understand that a thorough communicable disease risk evaluation and interview with the donor has been completed to asses for risks. However, no test or screening process in medicine is perfect or 100% accurate. This includes the unintentional transmission of a genetic characteristic, trait, and disease from donated egg or donor sperm. Furthermore, some communicable diseases of the egg source and sperm source, depending on the incubation period, may escape detection during the screening process and be transmitted to the recipient of the embryo. The Practice has never experienced the transmission of disease from donor to recipient. Fortunately, it is estimated that such transmission would be extremely rare. I/We also understand that the Practice cannot be responsible for donors' answers to risk assessment interview. The Practice educates all donors on communicable disease risk behaviors and instructs the donor to stay away from those behaviors during the donation cycle. The Practice IS NOT AND will not be responsible for unknown risk behavior that the donor has not openly shared with the Practice or us. New FDA recommendations require a second testing of communicable disease testing current within 30 days from the egg retrieval. Should the donor convert to a positive communicable disease the cycle will be canceled and the recipient will be required to choose a new donor.

I/We have read and understand the section in this consent form describing the donor's option for future contact with or by us or the Child, by her electing to either Exhibit A or Exhibit B, and understand the donor may elect to decline identity release (with the exception for life threatening illness necessity) and has elected Exhibit C, copies of which are attached hereto. I/We further understand that we will be advised by the Practice, in writing, which exhibit our selected donor has consented to. A copy of the donors signed Exhibit A or Exhibit B will be placed in our medical file.

By participating in the program, I/we accept all of the responsibilities, conditions and risks involved as set out in this document and as explained to me by the Practice. In addition, I consent to the techniques and procedures required to be a recipient as they have been described in this document and as they have been explained to me by the Practice.

I/we acknowledge and agree that my acceptance into treatment and my continued participation is within the sole discretion of the Practice.

I/We understand this is a voluntary procedure and that adoption, foster parenting or a child free life style may be alternate options for me/us as well as a continuing effort to conceive on our own.

I/We understand that the ability to participate in another cycle of treatment, should this cycle be unsuccessful, will be determined by the physicians at the Practice. I/we understand that I/we can withdraw from the program at any time, but will remain financially responsible and liable for those services rendered and expenses generated by the donor.

Consent to *In Vitro* Fertilization/Embryo Transfer

Definitions

The following defined terms are utilized throughout the following document:

Practice - CCRM Minneapolis is referred to herein as the “Practice.”

Lab - Fertility Lab Sciences of Minneapolis, LLC is referred to herein as the “Lab.”

When the document refers to either the “Practice” or the “Lab” it is referring to the defined entities above.

I voluntarily give my consent and authorize the physicians at the Practice and their associates, any technical assistants, nurses, nurse coordinators, and any other staff employed by the Practice to perform *in vitro* fertilization (IVF) and embryo transfer and the procedures necessary to achieve this. *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.

The technique involves six steps: 1) Medications to develop multiple eggs in the woman’s ovaries; 2) Retrieval of the eggs from the ovary or ovaries; 3) Insemination of eggs with sperm -- placing the eggs and sperm together in the laboratory to allow fertilization to occur; 4) Culture of any resulting fertilized eggs (embryos); 5) Placement (“transfer”) of one or more embryo(s) into the uterus for the establishment of pregnancy); and 6) Support of the uterine lining with hormones to permit and sustain pregnancy. This is an elective procedure designed to result in a patient’s pregnancy when other treatments have failed or are not appropriate or medically not feasible.

This consent reviews the IVF process from start to finish, including the risks that this treatment might pose to you and your offspring. This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed. 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.

Purpose of Procedures

The purpose of these procedures is for us/me to obtain a pregnancy and have a child. I/We understand that while IVF is a relatively new procedure, some aspects of the procedure are considered routine in the delivery of health care. Specific consent for egg retrieval (laparoscopy or ultrasound directed aspiration), intracytoplasmic sperm injection (ICSI), assisted hatching, cryopreservation, donor egg (if applicable), donor sperm (if applicable), and Preimplantation Genetic Testing/Screening (PGS) and Comprehensive Chromosomal Screening (CCS) will be obtained separately for each of those procedures.

Pre-Treatment Recommendations

I/We understand that women should avoid any activity, behavior or medication that would reduce their chances of conceiving or increase the risk to an unborn child. Below are

recommendations for women participating in this treatment, which I have read and understand:

1. Women should take a prenatal vitamin on a daily basis. These vitamins should contain at least 800 mcg of folic acid which reduces the chance of neural tube defect (i.e., spina bifida).
2. Smoking must be avoided before, during, and after treatment (and during pregnancy).
3. Recreational drugs are absolutely contraindicated.
4. Ingestion of aspirin or aspirin-like products (e.g. Motrin, Advil, Anaprox, Naprosyn, Aleve, etc.) should be avoided during treatment. Tylenol is a suitable alternative.
5. The use of alcohol should be eliminated during the treatment cycle.
6. The use of all prescription and over-the-counter medications should be discussed with the treatment team.
7. Caffeine should be eliminated during the entire treatment cycle.
8. A normal well-balanced diet is encouraged.
9. Avoid ALL herbal supplements.

I. DESCRIPTION OF IVF CYCLE

IVF involves several steps. Success cannot be guaranteed at any or all of these steps. If optimal results are not observed at any step, it may be recommended that the treatment be stopped and the cycle canceled. The steps of the treatment are discussed below.

Ovulation induction: In most cases, the female patient will take medications to stimulate the development of multiple ovarian follicles (fluid-filled cysts in the ovary that contain eggs).

Egg Retrieval: The patient will have the eggs removed from her ovaries.

Insemination of the Eggs: The eggs and sperm will be placed together in the laboratory and incubated in an effort to achieve possible fertilization and growth of the embryos.

Culture: Culture of any resulting fertilized eggs (embryos).

Embryo Transfer: One or more embryos will be transferred into the uterus of the patient.

Uterine Lining Support: Support of the uterine lining with hormones to permit and sustain pregnancy.

Embryo Freezing: Following the embryo transfer, any remaining embryos of suitable quality may be frozen (cryopreserved) and stored for future embryo transfer(s). The patient and spouse/significant other may decide later to donate unused embryos to another infertile couple or discard unused embryos.

OVULATION INDUCTION

During a woman's menstrual cycle, usually one mature follicle develops within the ovary which results in the ovulation of a single egg. The growth of the ovarian follicle during the first half of a woman's cycle is influenced by several hormones, including follicle stimulation hormone (FSH) and luteinizing hormone (LH) which are produced in the pituitary gland at the base of the brain. FSH is the main hormone that stimulates the growth of the follicle which produces a form of the hormone estrogen called estradiol. When the follicle is mature, a large amount of LH is

released by the pituitary gland. This “LH surge” helps to mature the egg and leads to ovulation 36-40 hours after the initiation.

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, or conversely, an inadequate response can occur**

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

Most of the medications that you will be using during your IVF cycle are administered by injection. You will receive instruction and training prior to attempting self-administration. If you are unable to self-administer the injections, you should have the injections performed by someone who has been trained to perform them appropriately. Questions regarding the injections may be directed to our nursing staff or demonstrated on our partner website (www.colocrm.com – click medication training on the home page).

Gonadotropins or injectable “fertility drugs” (Follistim®, Gonal-F®, Bravelle®, Menopur®): These hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the average span of 8 to 14 days or more. Follicle growth will be monitored beginning on or around day five of the gonadotropin medication start. Most 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 (Menopur®). LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Low-dose hCG (Novarel®, Pregnyl®, Lupron®) 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 1%-3% of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS below]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

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.

Ovarian Hyperstimulation Syndrome (OHSS) is a rare complication of ovarian stimulation from gonadotropin medications. Every woman who administers gonadotropins can develop OHSS, but the risk is higher in a woman who is less than 35 years old, has a high blood estradiol level, has a large number of ovarian follicles, or who has a history of hyperstimulation syndrome. It is caused by “fluid leaking” into the abdomen due to hormones released from the ovary. Fluid shifts within the body require close observation and even hospitalization for further observation and treatment (1%-3% of cycles). The high levels of estrogen associated with the use of these medications may alter the way in which the body handles fluids. The symptoms can include increased ovarian size, ovarian cysts, nausea, vomiting, accumulation of fluid in the abdomen or chest cavities, 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. More specifically, the blood vessels may become “leaky” resulting in the accumulation of fluid within the abdominal cavity (ascites) or around the lungs (pleural effusion). This accumulation of fluid may result in abdominal distension and discomfort with associated shortness of breath (due to the diaphragm being pushed upward by the accumulation of fluid in the abdomen). In severe cases, removal of this fluid from the abdomen or from the space around the lungs may be required using a small needle (0.5% of cycles). The “leaky” vessels may also result in the individual becoming dehydrated because the fluid is in the wrong place, i.e. in the abdomen instead of in the blood vessels. Intravenous fluid administration may be required to maintain adequate blood flow to vital organs such as the kidneys. Severe dehydration could result in irreversible organ failure or blood clot formation leading to a pulmonary embolus (blood clots in the lung) or stroke (less than 0.1% of cycles). There are extremely rare reports in the literature of death occurring as a result of complications of OHSS. **OHSS is a risk that is inherent to ovulation induction therapy; prevention cannot be guaranteed.** At times, when monitoring shows that the risk of OHSS is unacceptably high, a cycle may be canceled. Severe OHSS will rarely occur if hCG administration is withheld. Close monitoring of your cycle by the clinic and following its instructions is imperative to reduce these risks. The severe cases affect only a very small percentage of women who undergo in vitro fertilization—0.2% or less of all treatment cycles—and the very severe are an even smaller percentage. Symptoms may resolve without intervention. Only about 1.4 in 100,000 cycles have led to kidney failure, for example. OHSS occurs at two stages: early, one to five 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 produced during pregnancy).

When the estradiol is significantly elevated or there is a significant risk of ovarian hyperstimulation syndrome, options for care include 1) canceling the cycle; 2) the physician will decide to coast the cycle (stop gonadotropin medications to allow the estradiol level to decrease). The physician may also prescribe other medications that will be taken after the retrieval to help prevent or lessen the hyperstimulation symptoms. Hyperstimulation may result in ovarian enlargement requiring therapy including hospitalization and possible surgery with removal of an ovary.

Ovarian Torsion (Twisting)

In less than 1% of cases, the enlargement in the ovary from gonadotropins stimulation can cause the ovary to twist on itself, called ovarian torsion. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary. To decrease the risk of torsion, it is recommended that you avoid significant bouncing or physical exertion during stimulation (i.e.; high impact aerobics, horseback riding, skiing, Stairmasters, treadmills, etc.).

Cyst Formation

The medications described above may result in large cysts forming on the ovaries. In the majority of cases, ovarian cysts induced by fertility drugs/medications disappear spontaneously without requiring any intervention. In very rare instances (less than 1% of cycles) these cysts could result in significant abdominal discomfort that could result in the need for hospitalization for observation purposes. One of these cysts could rupture requiring emergency surgery to stop the bleeding and could result in a need for blood transfusions and possible loss of one or both ovaries (this occurs in less than 0.1% of cycles).

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 research studies of women taking fertility drugs. Since all of these cancers are more common in women with infertility, simply comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine the long-term impact fertility drugs may have on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to draw conclusions. There is no clear evidence to suggest the stimulation medications are associated with breast cancer although there are very limited numbers of long-term studies.

Medications

GnRH-agonists (Leuprolide acetate) (Lupron®): This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for one to three months. The primary role of this medication is to prevent 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. After a few days of treatment with a GnRH-agonist, the brain decreases production of both FSH and LH through depletion of the receptors.

Though leuprolide acetate is an FDA (US Food and Drug Administration) approved medication, it has not been approved for use in IVF. However 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. Since GnRH-agonists

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) the month you will be starting the GnRH-agonists. GnRH-agonists **have not** been associated with any fetal malformations. However, you should discontinue use of the GnRH-agonists as soon as pregnancy is confirmed.

GnRH-antagonists (Ganirelix Acetate or Cetrorelix Acetate) (Antagon[®], Cetrotide[®]): These are another class of medications used to prevent premature ovulation. These medications work differently than a GnRH-agonist because they block the GnRH receptors in the pituitary gland and avoid premature ovulation preventing release of FSH and LH. 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.

Patients who are allergic or have a sensitivity to latex must inform the nursing team as the use of Antagon is contraindication. The decision to use a GnRH agonist or antagonist during your IVF cycle will be decided by your physician based on your personal medical history.

Human Chorionic Gonadotropin (hCG) (Novarel[®], Pregnyl[®], Ovidrel[®]): hCG is a natural hormone, similar to LH, used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. It is administered 35 hours prior to egg retrieval by either subcutaneous or intramuscular injection. 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 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 and pregnancy. Progesterone is usually given by intramuscular injection (progesterone compounded in sesame, olive, cottonseed, or other oil base) or by the vaginal route (Endometrin[®], Crinone[®], Prochieve[®], Prometrium[®], or pharmacist-compounded suppositories) after egg retrieval. Progesterone and/or estradiol 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, transdermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the injection site if given by the intramuscular route and the risk of blood clots or stroke.

Oral Contraceptive Pills: Many treatment protocols include oral contraceptive pills to be taken for two to four 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.

Steroids: Steroid medications (dexamethasone, prednisone, or methylprednisolone) may be used during your IVF treatment cycle. Steroids are oral medications used to suppress the immune system. The most common side effects with short term usage of steroids include headache, sleep or mood disturbances, weight gain, nausea, and fatigue. Other side effects can occur with long term usage and will be discussed if your treatment requires prolonged use.

Aspirin: Aspirin 81 mg (baby aspirin) may be used during the IVF cycle to decrease potentially undiagnosed blood clotting abnormalities and improve pregnancy implantation. If successfully pregnant, we recommend taking aspirin through the 12th week of pregnancy. Side effects are uncommon but may include fever, allergic reaction, heart burn, stomach ulcers and bleeding, and easy bruising.

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 heparin, low molecular weight heparin or other medications may also be included in the treatment protocol and the risks associated with these will be discussed separately if their use is indicated.

Monitoring

During the ovulation induction phase of treatment, monitoring of follicular development is performed with periodic blood hormone tests and vaginal ultrasound exams. The egg growth will be monitored beginning on or about the fifth day of the cycle and will be repeated daily or every other day depending on the physician's recommendation. Monitoring helps the physicians to determine the appropriate dose of medication and the timing of the egg retrieval. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and possibly bruising, bleeding, infection or scar at the needle sites. The need for repeated ultrasound examinations and blood drawing on a frequent basis requires the woman's presence in the vicinity of the Practice's office (or one of the satellite monitoring sites).

EGG RETRIEVAL/TRANSVAGINAL OOCYTE RETRIEVAL

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

The egg retrieval is an outpatient procedure. Oocyte retrieval is the removal of eggs from the ovary. In the majority of cases, it is performed under vaginal ultrasound guidance. In this procedure, the woman is placed in the same position as if she was having a pelvic exam. The vagina is cleaned with a sterile solution. The vaginal ultrasound probe is then covered with a sterile sheath and placed in the vagina allowing visualization of the follicles within the ovaries.

Under ultrasound visualization, a needle is introduced through the vaginal wall, into the ovary and into an ovarian follicle. Fluid in the follicle is aspirated and examined by the embryologist to see if an egg is present. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa (egg-supporting) cells. This process is repeated with all follicles in both ovaries. The egg retrieval procedure is usually completed within thirty minutes. 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 is generally used to reduce, if not eliminate, discomfort. The patient will be transferred to the recovery room after the procedure and may go home approximately 60-120 minutes after leaving the operating room.

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. Antibiotics may be administered 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. A side effect of antibiotics could be an allergic reaction.

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 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 low.

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.

Anesthesia

The woman will have a consultation prior to the procedure to review the risks and benefits of the anesthesia. An anesthesiologist or anesthesiologist will administer the anesthesia. It is mandatory that there is no oral intake after midnight prior to the egg retrieval. Eating or drinking may require a needle to be placed in the patient's back to administer the anesthesia (epidural- spinal). Complications of anesthesia include nausea, vomiting, drowsiness or an unexpected reaction to anesthetic agents. The ideal anesthetic choice will be discussed by the anesthesiologist or anesthesiologist prior to the procedure. In most cases anesthesia is administered through an intravenous line placed in your arm and/or by agents inhaled through a mask placed on your face and/or by spinal route. Because anesthesia medications are used, the woman cannot drive and needs to be transported home by another individual. Making major decisions is ill advised for the rest of day.

Post-Retrieval

Following the egg retrieval vaginal spotting and lower abdominal cramping are normal. If significant bleeding, fever, vomiting, abdominal pain, difficulty breathing or walking, quick and significant weight gain in a short period of time or any other symptoms develop the woman should contact the physician on call. During the remainder of the day activities should be limited. Tampons should not be used following the retrieval, as well as restraining from intercourse for up to two weeks following the retrieval.

Information on the insemination of the eggs, evaluation of the embryos, and selection of embryos for transfer can be found on the consent Lab consent form "Consent to In Vitro Fertilization/Embryo Transfer – Routine Procedures Performed in the IVF Laboratory."

Embryo Transfer

If embryo(s) are to be transferred, the physician will perform the embryo transfer procedure. Transfer of one or more embryos to the uterus is ordinarily painless. Transfer of embryos to the uterus involves the passage of a thin tube through the vagina and cervix into the uterine cavity.

The patient is asked to drink fluid and fill her bladder prior to embryo transfer. Typically an abdominal ultrasound is used to observe the placement of the embryos. The patient may experience a mild amount of cramping during the transfer procedure. Following the transfer the patient will rest up to one hour prior to going home. We understand that there is a remote chance of infection as a result of embryo transfer. The most common symptoms associated with infection are pain and fever. If fever, vomiting, abdominal pain or any other symptoms develop following embryo transfer, you should contact a physician at the Practice. Following the transfer procedure, the patient will be required to remain on bed rest for up to one hour at the clinic and then at home for a total of thirty-six hours bed rest. If remaining embryos are of good quality they may be cryopreserved for future use; if embryo quality is poor, the remaining embryos will be discarded or used for research. If there is no evidence of fertilization after seventy-two hours of incubation, the oocytes (incompletely developed eggs) and sperm will be disposed of.

UTERINE LINING SUPPORT

- **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 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 estrogen are routinely given. The duration of this support is from two to ten weeks. This additional hormone support (estrogen and progesterone) will be administered in the form of patch, pill, injections or suppositories. The use of these medications (estrogen and progesterone) can cause side effects such as nausea, vomiting, hot flashes, headaches, mood swings, joint pains and visual symptoms. Some women may have allergic reactions to the drugs. A rare risk of estrogen administration is development of blood clots, which can compromise the blood supply to vital organs, causing serious problems. Additional problems described with estrogen usage include breast cancer, stroke or heart attack. Any of these conditions may cause death or serious long-term disability. Hormone testing for early pregnancy detection will be done by a blood sample (hCG) two weeks from the egg retrieval. Following a positive result the patient will follow-up with an ultrasound two and a half weeks later to indicate a pregnancy has been achieved. Additional blood draws and ultrasound exams may be necessary.

As a patient voluntarily requesting the IVF procedure, we understand there are a number of steps involved in this procedure and that beginning this process does not guarantee that we will complete the process or become pregnant.

Success Rate

There are many complex and sometimes unknown factors that may prevent the establishment of pregnancy and delivery of a live born infant. Known factors, which may prevent the establishment of pregnancy, include, but are not limited to the following:

1. The ovaries may not respond adequately to the medications.
2. Technical problems including inadequate visualization or the position of the ovaries may prevent retrieval of the eggs.
3. There may be failure to recover an egg because ovulation has occurred prior to the time of the egg retrieval.
4. The eggs may not be recovered.
5. The eggs may not be normal.
6. The male partner may be unable to produce a semen sample or the semen sample may be of insufficient quantity or quality.
7. Fertilization of the eggs and sperm to form embryos may not occur.
8. Cell division of the embryo may not occur.
9. The embryos may not develop normally.
10. Embryo transfer into the uterus of the patient may be technically difficult or impossible.

11. If implantation occurs, the embryo(s) may not grow or develop normally.
12. Equipment failure, infection, technical problems, human errors and/or other unforeseen factors (natural disasters) may result in loss or damage to the eggs, semen sample and/or embryo.
13. The patient's uterine lining may not develop normally.
14. Pelvic adhesions may prevent access to the ovary with the follicles, thus making the procedure to obtain the egg from the patient's ovary not possible.
15. Implantation of the embryo(s) in the uterus after embryo transfer may not occur.
16. The embryo(s) may become infected due to infection in the semen or bacteria from the vagina.
17. The age of the patient.

FREEZING (CRYOPRESERVATION) OF EMBRYOS

Information on embryo cryopreservation and decisions regarding the disposition of extra embryos are outlined in the Lab Consent Form: "The Embryo Cryopreservation Program Information, Participation Agreement and Informed Consent."

II. RISKS OF PREGNANCY

Pregnancies that occur with IVF are associated with increased risks of certain conditions (See Table "Potential Risks in Singleton IVF Conceived Pregnancies" 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.

Miscarriage

If pregnancy occurs; there is a risk of miscarriage. The risk of miscarriage in the general population is 15%-20%. The risk of miscarriage increases with the age of the woman who is utilizing her eggs. The risk of miscarriage in women who conceive with IVF is not felt to be higher than the risk of miscarriage in women who conceive spontaneously with their own eggs. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. Antibiotic therapy may be recommended. In some cases, however, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilation and curettage (D&C). This procedure is usually performed under anesthesia in the operating room and involves placing a suction tube into the uterine cavity to remove the pregnancy tissue. In other circumstances, medications may be given to bring about passage of the tissue. This approach may help avoid a surgical procedure, but this cannot be guaranteed.

Ectopic Pregnancy

While embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone (<5%) or concurrently with a normal intrauterine pregnancy (heterotopic pregnancy,

<1%). These abnormal pregnancies oftentimes require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy. Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding and injury to any internal organs. Surgery, which includes removing of the ectopic pregnancy and potentially an affected surrounding structure such as the fallopian tube is a standard alternative. No baby will result from these treatments. Frequently, in the case of a heterotopic pregnancy, the ectopic pregnancy can be surgically removed without compromising the intrauterine pregnancy, although this cannot be guaranteed.

Bleeding

Bleeding can occur early in pregnancy and is often diagnosed as a sub-chorionic separation (partial separation of the pregnancy from the uterine lining) which is typically treated with bed rest until the separation heals. Bleeding occurring later in the pregnancy can be a sign of a placenta previa, which is a low-lying placenta that covers the cervix or placental abruption, which is a detachment of the placenta from the wall of the uterus. Both of these conditions may result in premature labor and delivery. Uterine bleeding can also occur following a delivery. Management of the bleeding during pregnancy could include bed rest, D&C, transfusion, emergency cesarean section and/or a possible hysterectomy depending on the circumstances.

Maternal Complications

Women who carry a child are at risk of developing a pregnancy related illness. The most common pregnancy induced diseases are pregnancy-induced hypertension (pre-eclampsia) and pregnancy induced diabetes (gestational diabetes).

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
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)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

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.

All pregnancies may develop the following conditions, but women over age 35 and those with a multiple pregnancy have a higher than normal risk of developing one of these conditions.

Infection

Infections may occur in the bladder, kidneys and the uterine cavity or at other sites during a pregnancy. Infections could necessitate the use of oral antibiotics. In some cases, hospitalization may be necessary with the administration of intravenous antibiotics. In rare

cases, an infection in the uterine cavity following a delivery could result in clot formation in the pelvic vessels that may require heparin treatment.

Gestational Diabetes

Hormonal changes during pregnancy put a woman at risk for developing diabetes. It is estimated that between 1%-12% of women develop diabetes during pregnancy. This risk increases with multiple pregnancy. Management may include daily blood sugar monitoring, adjustment of the diet and possible insulin injections. Diabetes can have a detrimental effect on the fetus. Testing of the fetal wellbeing may be indicated and may include ultrasound examinations and recording of the fetal heart rate.

Pre-eclampsia

Pre-eclampsia (formerly called toxemia) is a condition that develops during pregnancy and results in high blood pressure, fluid retention and loss of protein in the urine. It occurs in up to 10% of pregnancies. It occurs more frequently in women during their first pregnancy. Other factors that put a woman at risk for the development of toxemia include a history of high blood pressure, kidney problems, diabetes or a multiple pregnancy. Initial treatment includes bed rest. In some cases, hospitalization and/or early delivery may be indicated. In rare cases convulsions may occur as a result of this problem.

Premature Labor

The initiation of labor with uterine contractions generally occurs between weeks 37-42 of the pregnancy. The onset of labor may be considered premature if it occurs before the 37th week of pregnancy. Premature labor complicates approximately 10%-12% of pregnancies. Its incidence is increased in multiple pregnancies. Premature labor can result in premature delivery of an infant unable to survive without some assistance. Premature birth is the single greatest cause of death or disability of newborns. Treatment of premature labor could include a hospitalization with extended bed rest and medical therapy.

Route of Delivery

Most deliveries can be accomplished via the vaginal route. However, in approximately 25% of cases there will be the need to perform a cesarean section. In cases of a multiple pregnancy, there is an increased chance of the need for a cesarean section. Delivering the baby through incisions made in the lower abdomen and the uterus is known as a cesarean section. It can be performed under general, epidural or spinal anesthesia. Following a cesarean section, a two to five day hospitalization will be necessary. After discharge recovery may take up to six weeks. Complications from delivery could include infection, hemorrhage, blood clots in the legs (deep vein thrombosis) or lungs (pulmonary emboli) and other complications that may necessitate additional surgery (i.e., D&C, hysterectomy) or medical treatment.

Postpartum

Generally, it may take up to one to two months following delivery before a woman is able to return to her normal activities. The average weight gain during pregnancy is 25 pounds. Some women do not return to their pre-pregnancy weight. Some of the other physical changes of pregnancy that may not reverse themselves include the development of stretch marks in the abdomen, change in the shape and texture of the breast tissue and vaginal relaxation which can

cause protrusion of the colon, bladder or intestines into the vagina that could produce symptoms and require surgery. Following the delivery of the infant you may also experience feelings of depression or anxiety.

General Wellbeing

Pregnancy affects women in different ways. While some women feel fine during the pregnancy, others have complaints of nausea, fatigue, loss of energy and may develop various discomforts (i.e., lower abdominal aching, back pain). These symptoms and others may affect a woman's sense of well-being and ability to function at home or at work. Depending on the nature and degree of the symptoms a woman may not be able to function at the work place and therefore may experience lost income. Following a delivery, between 50%-70% of women experience the "post-partum blues" characterized by mood swings, depression, fatigue, anxiety, confusion and difficulty with concentration. Less than 10% of women experience the more severe symptoms of postpartum depression that may necessitate medical intervention.

Time Commitment

Pregnancy lasts an average of 280 days, but may be shorter or last longer depending on the circumstances. During the pregnancy the woman will make frequent visits to her obstetrician to monitor the pregnancy. It may be necessary to remain in the vicinity of your local obstetrician during all or part of the pregnancy. In some cases of premature labor bed rest could be prescribed.

Mortality Rate

The overall mortality rate associated with pregnancy is 0.01% (1 in 10,000). Some of the reasons for death include the following: embolism, hypertensive disease, bleeding, ectopic pregnancy, infection, stroke and complications from anesthesia.

III. 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**

Overall Risks

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

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one

wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under five 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%. In IVF babies the birth defect rate may be 6%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects. ICSI may be performed which carry some additional risks, the ICSI consent will inform you of additional information on risks associated with the ICSI procedure.

Some birth defects are identified at the time of an ultrasound performed around 11-16 weeks of pregnancy. If a congenital anomaly is identified, the option to terminate the pregnancy can be accomplished with medications to induce labor and/or a dilation and evacuation (D&E). This is performed in the operating room under anesthesia. In a multiple pregnancy fetal reduction may be an option.

Potential Risks in Singleton IVF Pregnancies

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

In the table above, 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.

Imprinting Disorders

These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies approximately 4% of children with the imprinting

disorder called Beckwith-Weidemann Syndrome were born after IVF, which is more than expected. A large Danish study however found no increased risk of imprinting disorders in children conceived with the assistance of IVF. Since the incidence of this syndrome in the general population is 1/15,000, even if there is a 2 to 5-fold increase to 2-5/15,000, this absolute risk is very low.

Childhood Cancers

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

Currently, due to the extremely low number of cases reported it cannot be definitively stated whether any or all of the assisted reproductive technologies or associated procedures are or are not associated with these disorders, but it is important to understand that an increased risk may exist. The Practice can make no guarantee of a healthy and genetically normal child(ren).

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 (four fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

Risks of Multiple Pregnancy

When more than one embryo is transferred; the possibility of multiple pregnancies exists. The chance of a multiple pregnancy increases with the number of embryos that are transferred. This is a function of the number and quality of embryos transferred into the uterus as well as the age of the donated egg.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Of note, IVF twins do as well as spontaneously conceived twins. Triplet (and greater) pregnancies deliver before 32 weeks (seven months) in almost half of cases.

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks of Pregnancy). Others include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. 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 perinatal morbidity and mortality 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 for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus 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 have additional risks. Twin-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. Abruptio 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) 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. 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 risk of chromosomal abnormalities increases with the age of the woman who provides the egg. A chorionic villi biopsy or a genetic amniocentesis can assess the chromosomal status of the fetus(es).

IV. Additional Information

The Option of Selective Reduction

Pregnancies that have more than two 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 options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, 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 and emotional distress are the main risks 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 5% to 10%. Complicated issues can emerge regarding the decision to keep all the embryos or to reduce the pregnancy to twins can produce anxiety, depression and grief for couples.

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%).

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.

Undergoing treatment with IVF is stressful. Anxiety and disappointment may occur at any of the phases of treatment. Significant commitment of time and emotional energy is required. The physicians at the Practice encourage patients to meet with the mental health team before undergoing treatment if the procedure induces stressors that impede your normal daily living.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany infertility.

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:

- * Decreased ability to appropriately manage disappointments/stress loss of interest in usual activities
- * Depression that does not 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

In some instances, it may be advisable to meet with a mental health counselor or psychologist before, during and after the treatment cycle. I/We understand support groups are available should we need additional support.

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 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). 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.

Alternatives to IVF

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 issues relating to disposition of any cryopreserved embryos. Sperm freezing, but not egg freezing, has been an established procedure for many decades. Egg freezing is considered an experimental procedure at this time; however, the Practice has had several successful pregnancies.

Acknowledgment of Informed Consent and Authorization

I/We have voluntarily consented to participate in the Practice's IVF program in attempt to achieve a pregnancy. This consent form describes procedures and medications that will be performed.

By signing this document I/we acknowledge that we have read the consent form; had an opportunity to ask questions and receive answers to our satisfaction; and had an opportunity to obtain an independent legal opinion.

When the partner of the patient signs this form (if applicable), he/she acknowledges that he/she has read the consent; had an opportunity to ask questions and receive answers to his/her satisfaction; and had an opportunity to obtain an independent legal opinion.

Furthermore the partner of the patient acknowledges that any language in this document that states "she" also means "he/she"; that "I" also means "we"; that "my" also means "ours"; that the singular tenses in sentence construction also means the plural tense and that; except where the interchange of these terms would refer to an act that is not possible biologically.

I/we understand that medical information concerning my treatment may be analyzed and could be used in a publication. In accordance with federal law, identifying information and information concerning my treatment will be submitted to a national data registry that publishes statistics on treatment outcomes. I understand that no publication resulting from these or other information that would allow us/me to be identified will be created by the Practice.

I/we request that one or more viable embryos be transferred to my uterus for the purpose of making me pregnant.

I/we have read and understand the sections in this consent form-describing embryo transfer I/we request that the Practice assist me/us in achieving a pregnancy by transferring one or more embryos or gametes (sperm and donated eggs) to my body.

By participating in the program, I/we accept the responsibilities, conditions and risks involved as set out in this document and as explained to me/us by the staff of the Practice. In addition, I/we consent to the techniques and procedures required to be a patient as they have been described in this document and as they have been explained to me/us by the Practice. I/we acknowledge and agree that my acceptance into treatment and my continued participation is within the sole discretion of the Practice.

I/we understand that the ability to participate in another cycle of treatment, should this cycle be unsuccessful, will be determined by the physicians at the Practice. I/we understand that I/we can withdraw from the program at any time, but will remain financially liable for those services provided to us and expenses generated by the egg donor if applicable.

I/we have read this document, understand the purpose, risks and benefits of this procedure, and I/we have been given the opportunity to ask questions which have been answered to my/our satisfaction by the Practice physician and/or nurse coordinators.

Print Patient Name

DOB _____

Signature of Patient

Date _____

Print Spouse/Significant Other Name

DOB _____

Signature of Spouse/Significant Other

Date _____

Witness/Practice Representative

Date _____



Gestational Carrier IVF: Embryo Transfer Agreement

Definitions

The following defined terms are utilized throughout the following document:

Practice - CCRM Minneapolis is referred to herein as the "Practice."

When the document refers to either the "Practice" it is referring to the defined entity above.

Intended Parents:

_____ and _____
(Spouse) (Spouse)

and IVF Gestational Carrier:

_____ and _____
(Gestational Carrier) (Gestational Carrier's Spouse, if applicable)

agree as follows:

1. Ova shall be removed from

(Intended Parent, Anonymous Donor, or Known Donor)

and fertilized utilizing in vitro techniques with the sperm of

(Intended Parent, Anonymous Donor, or Known Donor)

2. The embryo transfer shall be performed by a Practice physician, each being licensed in the state of Minnesota. The Practice is located at 6565 France Avenue South, Suite 400, Edina MN 55435. The parties to this Agreement have undertaken as well as requested these procedures for the purpose of Intended Parents conceiving a child to be carried by the Gestational Carrier, with, if she is married, the knowledge and consent of her spouse.

3. The child or children born through this means shall be, in all respects, the legal and natural child or children of the Intended Parents, and not of the Gestational Carrier and, if she is married, her spouse.
4. All embryos belonging to the Intended Parents which are not transferred to the Gestational Carrier belong to them and they may do with them as they wish.
5. If the Intended Parents do not wish to retain and maintain the viability of the embryo(s) not transferred for gestational purposes, they may donate their embryo(s) or may elect to have them destroyed.
6. The Court and the parties to this Agreement may rely upon the recitations in this Agreement. They signify, by signing below, that they have received complete explanations of this process, and that they voluntarily agree and consent to participating in this process, and further agree that any child or children born through this process shall be legally the children of the Intended Parents.

Dated: _____

Intended Parent

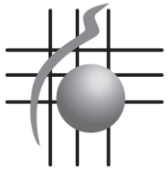
Gestational Carrier

Intended Parent

Gestational Carrier's Spouse, if applicable

CCRM Minneapolis

(Physician)



Consent Form for a Gestational Carrier

Definitions

The following defined terms are utilized throughout the following document:

Practice - CCRM Minneapolis is referred to herein as the “Practice.”

Lab - Fertility Lab Sciences of Minneapolis, LLC is referred to herein as the “Lab.”

When the document refers to either the “Practice” or the “Lab” it is referring to the defined entities above.

Introduction

I voluntarily give my consent to and authorize the Practice physicians and their technical assistants to perform transfer of embryos into my uterus, as the gestational carrier, and the necessary procedures to achieve this. In vitro fertilization (IVF) is a treatment that helps infertile couples to achieve a pregnancy. A woman’s fertility is compromised making her unable to utilize her own egg (oocytes) or her own uterus, which requires the couple to utilize the uterus of another woman. The In Vitro Fertilization technique involves four steps: 1) developing eggs in the woman’s ovaries; 2) removing the eggs from her ovaries; 3) placing the eggs and sperm together in the laboratory to allow fertilization to occur, and 4) transferring fertilized embryos into the gestational carrier’s uterus for the establishment of pregnancy. The existence of the embryo outside of a woman’s body creates the possibility of placement of the embryos into a second woman (gestational carrier) who then carries the pregnancy. The intention following the delivery, are to unite the baby or babies with the couple who will be the intended rearing parents. The main goal of this voluntary gestational carrier procedure is to allow couples to have a child. This is an elective procedure designed to result in a pregnancy when other treatments have failed or are not appropriate or medically not feasible.

Indications for gestational carrier treatment include situations in which a woman has no uterus, a congenitally deformed uterus, or a uterus that is unable to support a pregnancy, or another medical condition that precludes her from successfully caring a pregnancy. In such situations, she still is capable of becoming a “genetic mother” or mother with “genetic father.” Treatment with In Vitro Fertilization is a process where eggs are removed from the ovaries of either the intended parent or through the use of a donor. The eggs are then fertilized with sperm in the laboratory. The fertilized eggs (embryos) are then transferred into the uterine cavity of the gestational carrier for implantation and the establishment of pregnancy. Following the delivery, the intention is that the intended parent(s) will be the rearing parent of the offspring. The intention following the delivery is to unite the baby or babies with the intended parent(s) who will be the rearing parents.

This consent reviews the IVF gestational carrier process from start to finish, including the risks that this treatment might pose to you. This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed. While best efforts have been made to disclose all known risks, there may be risks of the IVF/gestational carrier cycle, which are not yet clarified or even suspected at the time of this writing.

Purpose of Procedures

The purpose of these procedures is to allow couples to achieve a pregnancy and have a child, which is only feasible through the use of a gestational carrier. I understand that while IVF is a relatively new procedure, some aspects of the procedure are considered routine in the delivery of health care. The intended parent will sign consents for egg retrieval (laparoscopy or ultrasound directed aspiration), Cryopreservation, Donor Egg, Donor Sperm (if applicable), and preimplantation genetic testing/screening (PGS) will be obtained separately for each of those procedures.

This document explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed.

Pre-treatment Recommendations

The gestational carrier should avoid any activity, behavior, or medication during treatment that would reduce the chances of conceiving or increase the risk to an unborn child. Below are recommendations for the woman participating in this treatment:

1. The gestational carrier should take a prenatal vitamin on a daily basis. These vitamins contain folic acid, which reduces the chance of neural tube defects (e.g. spina bifida).
2. Smoking must be avoided before and during treatment.
3. Recreational drugs are absolutely contraindicated.
4. Ingestion of aspirin or aspirin-like products (e.g. Motrin, Advil, Anaprox, Naprosyn, Aleve, etc.) should be avoided during treatment. Tylenol is a suitable alternative.
5. The use of alcohol should be eliminated during the treatment cycle and pregnancy.
6. The use of all prescription and over-the-counter medications should be discussed with the treatment team.
7. You will not obtain a tattoo or piercing during the cycle and will inform the treatment team when you had last had one done.
8. Caffeine should be eliminated during the entire cycle.
9. Avoid ALL herbal supplements.
10. Avoid intercourse during the cycle preparation until the pregnancy test, you may discuss with the treatment team when intercourse can be resumed.

Description of Treatment

The IVF cycle is performed in conjunction with the gestational carrier treatment, which involves several steps. Success cannot be guaranteed during any or all of these steps. If optimal results are not appreciated at any step, it may be recommended that the treatment be stopped and the cycle canceled. The steps of the treatment are discussed below.

1. **Ovulation induction:** In most cases, the “genetic mother” or egg donor will take medications to stimulate the development of multiple ovarian follicles (fluid-filled cysts in the ovary that contain eggs).
2. **Egg Retrieval:** The genetic mother or egg donor will have the eggs removed from her ovaries.

3. **Insemination of the Eggs:** The eggs and sperm will be placed together in the laboratory and incubated in an effort to achieve possible fertilization and growth of the embryos.
4. **Culture:** Culture of any resulting fertilized eggs (embryos).
5. **Preparation of the Endometrium:** The uterine lining (endometrium) of the gestational carrier woman must be hormonally prepared prior to the embryo transfer to allow implantation to occur.
6. **Embryo Transfer:** One or more embryos will be transferred into the uterus of the gestational carrier.
7. **Uterine Lining Support:** Support of the uterine lining with hormones to permit and sustain pregnancy.
8. **Embryo Freezing:** Following the embryo transfer, any remaining embryos of suitable quality may be frozen (cryopreserved) and stored for future embryo transfer(s). The patient and spouse/significant other may decide later to donate unused embryos to another infertile couple or discard unused embryos.

The gestational carrier participates in steps 5, 6 and 7. The couple will participate in 1,2,3,4, and 8. If an egg donor is being used she will undergo steps 1 and 2; the intended parents will undergo 3, 4 and 8; while the gestational carrier will undergo 5, 6 and 7.

The menstrual cycle of the two female patients will be carefully coordinated, so that when the follicles (eggs) are mature, the lining of the gestational carrier is ready to receive an embryo, and this is done with medications that will mimic a woman's normal menstrual cycle. During a woman's menstrual cycle, usually one mature follicle develops within the ovary, which results in the ovulation of a single egg. The growth of the ovarian follicle during the first half of a woman's cycle is influenced by several hormones, including follicle stimulation hormone (FSH) and luteinizing hormone (LH) which are produced in the pituitary gland at the base of the brain. FSH is the main hormone that stimulates the growth of the follicle, which produces a form of the hormone estrogen called estradiol. When the uterus is exposed to the increasing levels of estradiol the lining begins to thicken. When the follicle is mature, a large amount of LH is released by the pituitary gland. This "LH surge" helps to mature the egg and leads to ovulation 36-40 hours after the initiation. Once ovulation occurs the follicle creates a corpus luteum, which then begins to secrete a hormone called progesterone. Progesterone and estrogen exposure is essential for uterine stability and implantation of an embryo. Egg retrieval occurs when the follicles reach maturity, the patient is given medication (HCG) to create an LH surge and the retrieval is scheduled for 35 hours after that injection occurs. The eggs retrieved will be inseminated or fertilized with the male's partner's sperm (or donor sperm) to create embryos. The embryos created will continue to develop in the embryology lab for three to five days at which point the embryos will be transferred into the prepared uterus of the gestational carrier.

Preparation of the Endometrium

Medications

Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical significance, but it is at least possible that use of fertility drugs may indeed cause some increased risk of uterine cancer.

Oral contraceptive pills: The birth control pill allows coordination of the cycles of both women. Many of the treatment protocols include oral contraceptive pills to be taken for two to four weeks before gonadotropin injections and before the initiation of estrogen is started, in order to suppress hormone production and to coordinate the two patient's cycles. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or stroke.

GnRH-agonists (Leuprolide acetate) (Lupron®): This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for one to three 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 and to suppress the gestational carrier from ovulating. After a few days of treatment with a GnRH-agonist, the brain decreases production of both FSH and LH through depletion of the receptors.

Though leuprolide acetate is an FDA (US Food and Drug Administration) approved medication, it has not been approved for use in IVF. However 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. Since GnRH-agonists are oftentimes administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception (condoms) the month you will be starting the GnRH-agonists. GnRH-agonists **have not** been associated with any fetal malformations. However, you should discontinue use of the GnRH-agonists as soon as pregnancy is confirmed.

Gestational carriers will be prescribed estrogen to assist in building the uterine lining, once the lining has been established and carefully timed with embryo development progesterone will be added to maintain the uterine lining for an embryo to implant: Progesterone and estradiol are hormones normally produced by the ovaries. The gestational carrier will not have ovarian stimulation and her ovaries will not be producing these hormones naturally, therefore the

support will be provided by estrogen and progesterone supplementation to assist in the development of the uterine lining and will continue until about the 12th week in pregnancy. Accordingly, supplemental progesterone and estradiol, are given to ensure adequate hormonal support of the uterine lining and pregnancy. Progesterone is usually given by intramuscular injection (progesterone compounded in sesame, olive, cottonseed, or other oil base) or by the vaginal route (Endometrin[®], Crinone[®], Prochieve[®], Prometrium[®], or pharmacist-compounded suppositories) after egg retrieval. Progesterone and/or estradiol 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, transdermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the injection site if given by the intramuscular route and the risk of blood clots or stroke.

Steroids: Steroid medications (dexamethasone, prednisone, or methylprednisolone) may be used during your gestational carrier treatment cycle. Steroids are oral medications used to suppress the immune system. The most common side effects with short term usage of steroids include headache, sleep or mood disturbances, weight gain, nausea, and fatigue. Other side effects can occur with long term usage and will be discussed if your treatment requires prolonged use.

Aspirin: Aspirin 81 mg (baby aspirin) may be used during the gestational carrier cycle to decrease potentially undiagnosed blood clotting abnormalities and improve pregnancy implantation. If successfully pregnant, we recommend taking aspirin through the 12th week of pregnancy. Side effects are uncommon but may include fever, allergic reaction, heart burn, stomach ulcers and/or bleeding, and easy bruising.

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 heparin, low molecular weight heparin or other medications may also be included in the treatment protocol and the risks associated with these will be discussed separately if their use is indicated.

Monitoring

During the endometrium development phase of treatment, monitoring uterine lining development is performed with periodic blood hormone tests and vaginal ultrasound exams. The development of the lining will be monitored beginning on or about the tenth through the twelfth day of the cycle and will be repeated depending on the physician's recommendation. Monitoring helps the physicians to determine the appropriate dose of medication and development of the uterine lining as well as the timing of the embryo transfer. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and possibly bruising, bleeding, infection or scarring at the needle sites. The need for

repeated ultrasound examinations and blood drawing on a frequent basis requires the woman's presence in the vicinity of the Practice office (or one of the satellite monitoring sites).

Embryo Transfer

If embryo(s) are to be transferred, the physician will perform the embryo transfer procedure. Generally, the embryos transfer into the gestational carrier is performed three or five days after the egg retrieval. Transfer of one or more embryos to the uterus is ordinarily painless. Transfer of embryos to the uterus involves the passage of a thin tube through the vagina and cervix into the uterine cavity.

The gestational carrier is asked to drink fluid and fill her bladder prior to embryo transfer. Typically an abdominal ultrasound is used to observe the placement of the embryos. The patient may experience a mild amount of cramping during the transfer procedure. Following the transfer the patient will rest for up to one hour prior to going home. We understand that there is a remote chance of infection as a result of embryo transfer. The most common symptoms associated with infection are pain and fever. If fever, vomiting, abdominal pain or any other symptoms develop following embryo transfer, you should contact a physician at the Practice. Following the transfer procedure, the patient will be required to remain on bed rest for up to one hour's time at the clinic and then at home for a total of thirty-six hours bed rest. If remaining embryos are of good quality they may be cryopreserved for future use; if embryo quality is poor, the remaining embryos will be discarded or used for research. If there is no evidence of fertilization after seventy-two hours of incubation, the oocytes (incompletely developed eggs) and sperm will be disposed of.

Uterine Lining Support

- **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**
- **Estrogen, given by patch, tablet or injection is also given for the purpose of lining development.**

Successful attachment of embryos to the uterine lining depends on adequate hormonal development and support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. The gestational carrier will not have ovarian stimulation and her ovaries will not be producing these hormones naturally, therefore the support will be provided by estrogen and progesterone supplementation to assist in the development of the uterine lining and will continue until about the 12th week of pregnancy. This additional hormone support (estrogen and progesterone) will be administered in the form of patch, pill, injections or suppositories. The use of these medications (estrogen and progesterone) can cause side effects such as nausea, vomiting, hot flashes, headaches, mood swings, joint pains and visual symptoms. Some women may have allergic reactions to the drugs. A rare risk of estrogen administration is development of blood clots, which can compromise the blood supply to vital organs, causing serious

problems. Additional problems described with estrogen usage include breast cancer, stroke or heart attack. Any of these conditions may cause death or serious long-term disability. Hormone testing for early pregnancy detection will be done by a blood sample (hCG) two weeks from the egg retrieval. Following a positive result the patient will follow-up with an ultrasound two and a half weeks later to indicate a pregnancy has been achieved. Additional blood draws and ultrasound exams may be necessary.

As a patient voluntarily requesting the IVF/gestational carrier procedure, we understand there are a number of steps involved in this procedure and that beginning this process does not guarantee that we will complete the process or become pregnant.

Success Rate

There are many complex and sometimes unknown factors that may prevent the establishment of pregnancy and delivery of a live born infant. Known factors, which may prevent the establishment of pregnancy, include, but are not limited to the following:

1. The ovaries may not respond adequately to the medications.
2. Technical problems including inadequate visualization or the position of the ovaries may prevent retrieval of the eggs.
3. There may be failure to recover an egg because ovulation has occurred prior to the time of the egg retrieval.
4. The eggs may not be recovered.
5. The eggs may not be normal.
6. The male partner may be unable to produce a semen sample or the semen sample may be of insufficient quantity or quality.
7. Fertilization of the eggs and sperm to form embryos may not occur.
8. Cell division of the embryo may not occur.
9. The embryos may not develop normally.
10. Embryo transfer into the uterus of the gestational carrier may be technically difficult or impossible.
11. If implantation occurs, the embryo(s) may not grow or develop normally.
12. Equipment failure, infection, technical problems, human errors and/or other unforeseen factors (natural disasters) may result in loss or damage to the eggs, semen sample and/or embryo.
13. The gestational carrier's uterine lining may not develop normally.
14. Pelvic adhesions may prevent access to the ovary with the follicles, thus making the procedure to obtain the egg from the patient's ovary not possible.
15. Implantation of the embryo(s) in the uterus after embryo transfer may not occur.
16. The embryo(s) may become infected due to infection in the semen or bacteria from the vagina.
17. The age of the patient.

Post transfer care

We understand that in conjunction with the transfer of embryo(s), the gestational carrier will be given natural progesterone by intramuscular injection and/or vaginal suppository along with estrogen to increase the chances for successful implantation. Should pregnancy result, we

understand that no harmful effects to the mother or the fetus are presently known to medical science from the use of this natural progesterone. Subsequent to the embryo transfer, we understand that blood hormone levels will be evaluated weekly if not more frequently to wean the patient off of the hormones. We understand that it will be necessary to continue taking the estrogen and progesterone until there is clear evidence that the placenta of the developing pregnancy is making sufficient amounts of these hormones to maintain the developing pregnancy. Nine to eleven days after the embryo transfer, a blood pregnancy test will be performed. If this test is found to be positive, a repeat pregnancy test may be performed two days later. If the test results are encouraging, another blood test to evaluate the estrogen and progesterone levels will be performed. Approximately two weeks later a vaginal ultrasound will be performed to determine the status of the pregnancy. Because of the potential complications following the embryo transfer, the gestational carrier should have access to medical care up to the time of the pregnancy test and beyond if pregnancy is established. If travel is absolutely necessary, it should be discussed with the physician. If the pregnancy test is negative all the hormone support is stopped and a menstrual cycle will follow.

Risks of Pregnancy

Pregnancies that occur with an IVF/gestational carrier are associated with increased risks of certain conditions (See Table "Potential Risks in Singleton IVF Conceived Pregnancies" 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.

Miscarriage

If pregnancy occurs; there is a risk of miscarriage. The risk of miscarriage in the general population is 15%-20%. The risk of miscarriage increases with the age of the woman who is utilizing her eggs. The risk of miscarriage in women who conceive with IVF is not felt to be higher than the risk of miscarriage in women who conceive spontaneously with their own eggs. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. Antibiotic therapy may be recommended. In some cases, however, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilation and curettage (D&C). This procedure is usually performed under anesthesia in the operating room and involves placing a suction tube into the uterine cavity to remove the pregnancy tissue. In other circumstances, medications may be given to bring about passage of the tissue. This approach may help avoid a surgical procedure, but this cannot be guaranteed.

Ectopic Pregnancy

While embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone (<5%) or concurrently with a normal intra-uterine pregnancy (heterotopic pregnancy, <1%). These abnormal pregnancies often require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy. Side effects of

methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding and injury to any internal organs. Surgery, which includes removing of the ectopic pregnancy and potentially an affected surrounding structure such as the fallopian tube is a standard alternative. No baby will result from these treatments. Frequently, in the case of a heterotopic pregnancy, the ectopic pregnancy can be surgically removed without compromising the intrauterine pregnancy, although this cannot be guaranteed.

Bleeding

Bleeding can occur early in pregnancy and is often diagnosed as a subchorionic separation (partial separation of the pregnancy from the uterine lining) which is typically treated with bed rest until the separation heals. Bleeding occurring later in the pregnancy can be a sign of a placenta previa, which is a low-lying placenta that covers the cervix or placental abruption, which is a detachment of the placenta from the wall of the uterus. Both of these conditions may result in premature labor and delivery. Uterine bleeding can also occur following a delivery. Management of the bleeding during pregnancy could include bed rest emergency cesarean section and/or a possible hysterectomy depending on the circumstances.

Maternal Complications- Women who carry a child are at risk of developing a pregnancy related illness. The most common pregnancy induced diseases are pregnancy-induced, hypertension (pre-eclampsia) and pregnancy induced diabetes (gestational diabetes).

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
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)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

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.

All pregnancies may develop the following conditions, but women over age 35 and those with a multiple pregnancy have a higher than normal risk of developing one of these conditions.

Infection

Infections may occur in the bladder, kidneys and the uterine cavity or at other sites during a pregnancy. Infections could necessitate the use of oral antibiotics. In some cases, hospitalization may be necessary with the administration of intravenous antibiotics. In rare cases, an infection in the uterine cavity following a delivery could result in clot formation in the pelvic vessels that may require heparin treatment.

Gestational Diabetes

Hormonal changes during pregnancy put a woman at risk for developing diabetes. It is estimated that between 1%-12% of women develop diabetes during pregnancy. This risk increases with multiple pregnancy. Management may include daily blood sugar monitoring, adjustment of the diet and possible insulin injections. Diabetes can have a detrimental effect on the fetus. Testing of the fetal well-being may be indicated and may include ultrasound examinations and recording of the fetal heart rate.

Pre-eclampsia

Pre-eclampsia (formerly called toxemia) is a condition that develops during pregnancy and results in high blood pressure, fluid retention and loss of protein in the urine. It occurs in up to 10% of pregnancies. It occurs more frequently in women during their first pregnancy. Other factors that put a woman at risk for the development of toxemia include a history of high blood pressure, kidney problems, diabetes or a multiple pregnancy. Initial treatment includes bed rest. In some cases, hospitalization and/or early delivery may be indicated. In rare cases convulsions may occur as a result of this problem.

Premature labor

The initiation of labor with uterine contractions generally occurs between weeks 37-42 of the pregnancy. The onset of labor may be considered premature if it occurs before the 37th week of pregnancy. Premature labor complicates approximately 10%-12% of pregnancies. Its incidence is increased in multiple pregnancies. Premature labor can result in premature delivery of an infant unable to survive without some assistance. Premature birth is the single greatest cause of death or disability of newborns. Treatment of premature labor could include a hospitalization with extended bed rest and medical therapy.

Route of Delivery

Most deliveries can be accomplished via the vaginal route. However, in approximately 25% of cases there will be the need to perform a cesarean section. In cases of a multiple pregnancy, there is an increased chance of the need for a cesarean section. Delivering the baby through incisions made in the lower abdomen and the uterus is known as a cesarean section. It can be performed under general, epidural or spinal anesthesia. Following a cesarean section, a two and five day hospitalization will be necessary. After discharge recovery may take up to six weeks. Complications from delivery could include infection, hemorrhage, blood clots in the legs (deep vein thrombosis) or lungs (pulmonary emboli) and other complications that may necessitate additional surgery (i.e., D&C, hysterectomy) or medical treatment.

Postpartum

Generally, it may take up to one to two months following delivery before a woman is able to return to her normal activities. The average weight gain during pregnancy is 25 pounds. Some women do not return to their pre-pregnancy weight. Some of the other physical changes of pregnancy that may not reverse themselves include the development of stretch marks in the abdomen, change in the shape and texture of the breast tissue and vaginal relaxation which can cause protrusion of the colon, bladder or intestines into the vagina that could produce symptoms and require surgery. Following the delivery of the infant you may also experience

feelings of depression or anxiety.

General Well Being

Pregnancy affects women in different ways. While some women feel fine during the pregnancy, others have complaints of nausea, fatigue, loss of energy and may develop various discomforts (i.e., lower abdominal aching, back pain). These symptoms and others may affect a woman's sense of well-being and ability to function at home or at work. Depending on the nature and degree of the symptoms a woman may not be able to function at the work place and therefore may experience lost income. Following a delivery, between 50%-70% of women experience the "post-partum blues" characterized by mood swings, depression, fatigue, anxiety, confusion and difficulty with concentration. Less than 10% of women experience the more severe symptoms of postpartum depression that may necessitate medical intervention.

Time Commitment

Pregnancy lasts an average of 280 days, but may be shorter or last longer depending on the circumstances. During the pregnancy the woman will make frequent visits to her obstetrician to monitor the pregnancy. It may be necessary to remain in the vicinity of your local obstetrician during all or part of the pregnancy. In some cases of premature labor bed rest could be prescribed.

Mortality Rate

The overall mortality rate associated with pregnancy is 0.01% (1 in 10,000). Some of the reasons for death include the following: embolism, hypertensive disease, bleeding, ectopic pregnancy, infection, stroke and complications from anesthesia.

III. 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**

Overall Risks

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

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do

not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under five 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%. In IVF babies the birth defect rate may be 2.6%-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects.

ICSI may be performed which carry some additional risks, the ICSI consent will inform you of additional potential risks associated with the ICSI procedure.

Some birth defects are identified at the time of an ultrasound performed around 11-16 weeks of pregnancy. If a congenital anomaly is identified, the option to terminate the pregnancy can be accomplished with medications to induce labor and/or a dilation and evacuation (D&E). This is performed in the operating room under anesthesia. In a multiple pregnancy fetal reduction may be an option.

Potential Risks in Singleton IVF Pregnancies

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

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

Imprinting Disorders

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

Currently, due to the extremely low number of cases reported it cannot be definitively stated whether any or all of the assisted reproductive technologies or associated procedures are or are not associated with these disorders, but it is important to understand that an increased risk may exist. The Practice can make no guarantee of a healthy and genetically normal child(ren).

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 (four fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

Risks of Multiple Pregnancy

When more than one embryo is transferred; the possibility of multiple pregnancies exists. The chance of a multiple pregnancy increases with the number of embryos that are transferred. This is a function of the number and quality of embryos transferred into the uterus as well as the age of the donated egg.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Of note, IVF twins do as well as spontaneously conceived twins. Triplet (and greater) pregnancies deliver before 32 weeks (seven months) in almost half of cases.

The most important pregnancy complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Others include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Pregnancy of

triplets and above increases the risk to the mother of more significant complications including post-partum hemorrhage and transfusion.

Prematurity accounts for most of the excess perinatal morbidity and mortality 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 for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus 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 have additional risks. Twin-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. Abruption 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) 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. 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 risk of chromosomal abnormalities increases with the age of the woman who provides the egg. A chorionic villi biopsy or a genetic amniocentesis can assess the chromosomal status of the fetus(es).

Additional Information

The Option of Selective Reduction

Pregnancies that have more than two 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 options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, 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 and emotional distress are the main risks 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 5% to 10%. Complicated issues can emerge regarding the decision to keep all the embryos or to reduce the pregnancy to twins can produce anxiety, depression and grief for couples.

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%.)

Psychosocial Effects of Infertility Treatment

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

Undergoing treatment with IVF as a gestational carrier is stressful. Anxiety, disappointment and second guessing your decision to be a gestational carrier may occur at any of the phases of treatment. Significant commitment of time and emotional energy is required. The physicians at the Practice encourage patients to meet with the mental health team before undergoing treatment if the procedure induces stressors that impede your normal daily living.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany infertility.

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:

- * Decreased ability to appropriately manage disappointments/stress loss of interest in usual activities
- * Depression that does not lift
- * Strained interpersonal relationships (with partner, family, friends and/or colleagues)
- * Difficulty thinking of anything other than the treatment of IVF
- * 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
- * Regret or second guessing your decision to be a gestational carrier.

In some instances, it may be advisable to meet with a mental health counselor or psychologist before, during and after the treatment cycle. I/We understand support groups are available should we need additional support.

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 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). We encourage the gestational carrier who so desire to consult with trusted members of their religious or ethics community for guidance on their decision to be a gestational carrier and the treatment involved.

Alternatives to IVF

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 issues relating to disposition of any cryopreserved embryos. Sperm freezing, but not egg freezing, has been an established procedure for many decades. Egg freezing is considered an experimental procedure at this time; however the Practice and the Lab have had several successful pregnancies.

Acknowledgement of Informed Consent and Authorization

I acknowledge that I, the undersigned, am voluntarily participating in the Practice In Vitro Fertilization and Gestational Carrier Program in order to carry a pregnancy for an infertile couple. That the child born is intended for the recipient couple to parent and rear the child (ren) conceived through this process. I authorize the Practice physicians and designated assistants to perform the procedure described herein.

By participating in this program, I accept the responsibilities, conditions and risks involved as set out in this consent and as explained to me by the Practice. In addition, I consent to the techniques and procedures required to be a gestational carrier for the intended parents as they have been described in this consent and as they have been explained to me by the physicians and staff at the Practice.

I believe that I am a low-risk candidate for sexually transmitted disease (STD's) such as hepatitis, genital herpes, HIV virus (AIDS), etc. I agree to be screened for STD's including HIV antibodies and I understand that I will be informed of positive results. I agree to inform the Practice if I engage or have engaged in any activities that puts me at risk for STD's (i.e., new or multiple partners or needle sharing) I understand that my spouse or significant other will be asked to be tested for the same communicable disease tests and they will be informed of any positive result.

I acknowledge that I have read and fully understand this written material and that all my questions concerning the treatment have been fully answered to my satisfaction.

I realize that the couple also participating in the treatment has other alternatives including adoption or continuing their relationship without children.

I am aware that there are other centers in the area that offer this treatment and I have agreed to have the treatment at the Practice.

I am aware that sometimes a donor egg is used instead the egg of the intended mother. I understand sometimes a woman's eggs are deemed unsuitable and the use of a donor egg is the couple's only option.

I have been given the opportunity to undergo medical, psychological and legal counseling, which have met with my satisfaction. I understand that the Practice requires all gestational carriers to obtain a legal contract and I have completed a contract with an attorney, which is acceptable to me. I understand I have the right to independent legal counsel and can obtain counsel at my will.

We understand that we will be asked to have communicable disease testing as well as the egg source and sperm source. We understand that the sperm source as well as the egg source whether donor or recipient using her own eggs, will be required to have communicable disease testing as well as be required to complete a communicable disease risk assessment. They have indicated that they believe that they are a low risk candidate for sexually transmitted diseases (STD's), such as hepatitis, Chlamydia, HIV, CMV etc. We agree to be screened for STD's

including HIV, Hepatitis B, Hepatitis C and syphilis and understand that we will be informed of positive results regarding either of us. We are fully aware that the donor of the egg cannot contract the diseases by giving the eggs for the procedure, but the Gestational carrier may be at risk. The gestational carrier may contract a communicable disease through the use of the sperm or egg source. We agree to inform the Practice if we engage or have engaged in any activities that put us at risk for STD (i.e. new or multiple partners, sharing needles, tattoo, piercing, blood transfusions and travel abroad having received medical treatment). We understand that both the sperm and egg source have also been given these instructions. We each agree that any and all information, including any otherwise privileged information that either of us provides to the Practice, or that is obtained by the Practice, may be shared by the Practice with our gestational carrier as well as the intended parents as it pertains to the health and welfare of the unborn child. We understand that both the sperm source and egg source will be required to have a second set of communicable diseases tested seven days prior to the egg retrieval. If these tests results are positive we understand that no embryos will be transferred into the gestational carrier and that these embryos will be discarded.

As the gestational carrier, I agree to have any pertinent medical history sent to the center for review. I will discuss any pertinent health issues with the physician at the Practice.

I understand that that all donors are screened and show that they are free from risk factors for, and clinical physical evidence of, infection due to relevant communicable disease agents and are free from communicable disease risks. Both the egg source and sperm source have tested negative for HIV, Hepatitis B, Hepatitis C, West Nile Virus and syphilis. I understand that the egg and sperm source have been asked to complete a risk assessment questionnaire and interviewed to assess for risks. However, unfortunately, no test or screening process in medicine is perfect or 100% accurate. This includes the unintentional transmission of a genetic characteristic, trait, and disease from donated egg or sperm. Furthermore, some communicable diseases of the egg source and sperm source (donor couple and/or donor egg), depending on the incubation period, may escape detection during the screening process and be transmitted to the recipient of the embryo. The Practice has never experienced the transmission of disease from donor to recipient. Fortunately, it is estimated that such transmission would be extremely rare. We also understand that the Practice cannot be responsible for donors' answers to risk assessment interview. The Practice educates all tissue donors on communicable disease risk behaviors and instructs the egg or sperm source donors to stay away from those behaviors during the donation cycle. The Practice will not be responsible for unknown risk behavior that the donor has not openly shared with us.

By undergoing this treatment, we accept the responsibilities, conditions and risks involved as set out in this document and as explained to us by the Practice.

I/we acknowledge and agree that my acceptance into treatment and my continued participation is within the sole discretion of the Practice.

I/we understand that the ability to participate in another cycle of treatment, should this cycle be unsuccessful, will be determined by the physicians at the Practice. I understand that I can withdraw from treatment at any time.

I/we understand that medical information concerning my treatment may be analyzed and could be used in a publication. In accordance with the federal law, identifying information and information concerning my treatment will be submitted to a national data registry that publishes statistics on treatment outcomes.

I/we, the undersigned, consent to undergo gestational carrier treatment with IVF. I/we have read this document, understand the purpose, risks and benefits of this procedure and have been given the opportunity to ask questions which have been answered to my satisfaction by the Practice.

We understand that the Practice, physicians and staff can not be held responsible or liable for any legal disputes that arise between the intended parents and the gestational carrier or any intermediate parties.

I/we have read this document, understand the purpose, risks and benefits of this procedure, and I/we have been given the opportunity to ask questions which have been answered to my/our satisfaction by the Practice physician and/or nurse coordinators.

Signature of patient

Date _____

Spouse/Significant other

Date _____

Witness/Practice representative

Date _____

Acknowledgement, Agreement and Assumption of Risks, Release and Hold Harmless Informed Consent and Option for Embryo Quarantine and Retesting for Communicable Disease

Definitions

The following defined terms are utilized throughout the following document:

Practice - CCRM Minneapolis is referred to herein as the “Practice.”

Lab - Fertility Lab Sciences of Minneapolis, LLC is referred to herein as the “Lab.”

When the document refers to either the “Practice” or the “Lab” it is referring to the defined entities above.

NOTE: THIS WRITTEN CONSENT IS AN IMPORTANT DOCUMENT AND THE COPY PROVIDED TO YOU SHOULD BE RETAINED WITH OTHER VITAL RECORDS FOR FUTURE REFERENCE.

(Print gestational carrier full name)

DOB

(Print gestational carrier partner’s full name)

DOB

The Federal Food and Drug Administration (FDA), as well as the Practice require communicable disease testing for egg donors, sperm donors, donors of embryos and couples using a gestational carrier. The communicable disease tests include HIV testing, HTLV (male only), syphilis, hepatitis B core antibody, hepatitis B antigen, and hepatitis C, CMV, West Nile Virus, gonorrhea and chlamydia. A risk assessment physical and exam will be completed to identify the presence of infectious disease. All testing must be completed according to FDA regulations at the time of tissue retrieval by both the egg source and sperm source and must be negative. However, depending on the incubation period some communicable diseases from the egg/sperm source may escape detection during the screening process, which could potentially be transferred to the recipient of the embryo. A second screening at six months from the time of creation, freezing and quarantine of the embryos is beneficial to further decrease the risk of an unintentional transmission of a communicable disease. Should an unintentional transmission occur, it is important for the gestational carrier and her spouse/significant other to understand that there is a possible risk of exposure to the baby, gestational carrier, as well as to her significant other through sexual contact, should the gestational carrier become infected by the embryo.

This document is to inform you as the gestational carrier and your spouse/significant other, that there is an option to have the embryos created and cryopreserved (frozen) for a six month time period and retest the egg source and sperm source for communicable disease prior to having an embryo transferred; should you as the gestational carrier or your partner desire (quarantine of the embryos). This will further decrease the risk of a potential infectious disease.

The cryopreservation of embryos procedure has been in practice by IVF centers for many years and is a viable option. With that said, the statistics for successful pregnancy for a frozen embryo transfer are slightly decreased in comparison with a fresh embryo transfer, so many patients elect for a fresh embryo transfer. There is new published data that freezing techniques, such as vitrification, which is utilized by the Practice has minimal impact on implantation rates.

Sexually transmitted infection (STI's) affect millions of men and women each year. Many of these STI's initially cause no symptoms, especially in women. Symptoms, when they do develop, may be confused with those of other diseases that are not transmitted through sexual contact. STI's can still be transmitted from person to person even if they do not show symptoms.

STI's can cause gynecologic cancers, chronic hepatitis, pelvic inflammatory disease, infertility, and other complications. Many STI's in women are silent; that is, without signs or symptoms.

A pregnant woman with an STI may also have early onset of labor, premature rupture of the membranes surrounding the baby in the uterus, and uterine infection after delivery. STI's can be passed from a pregnant woman to the baby before, during, or after the baby's birth. Some STI's (like syphilis) cross the placenta and infect the baby while it is in the uterus (womb). Other STI's (like gonorrhea, chlamydia, hepatitis B and C, and genital herpes) can be transmitted from the mother to the baby during delivery as the baby passes through the birth canal. HIV can also cross the placenta during pregnancy, infecting the baby during the birth process, and unlike most other STIs, can infect the baby through breastfeeding.

The harmful effects of STI's in babies may include stillbirth (a baby that is born dead), low birth weight (less than five pounds), conjunctivitis (eye infection), pneumonia, neonatal sepsis (infection in the baby's blood stream), neurologic damage (such as brain damage or lack of coordination in body movements), blindness, deafness, acute hepatitis, meningitis, chronic liver disease, and cirrhosis. Most of these medical complications can be prevented if the mother is screened and appropriate treatment is implemented, early in pregnancy and repeated close to delivery, if necessary. If infections occur at the time of birth, treatment can be initiated to minimize the risk of medical complications. Information obtained from: <http://www.cdc.gov/std/STDFact-STDs&Pregnancy.htm>

The Practice and Lab, the physicians and staff want to inform you of your options as a gestational carrier, please select one of the options below:

Initial

Female Partner

By initialing here, I/we are requesting to proceed with my IVF Gestational Carrier cycle **without** the six month quarantine of the embryos and are electing a fresh embryo transfer.

Initial

Female Partner

By initialing here, I/we are requesting to proceed with my IVF Gestational Carrier cycle **without** the six month quarantine of the embryos and are electing a frozen embryo transfer.

Initial

Female Partner

By initialing here, I/we are requesting to proceed with my IVF Gestational carrier cycle **with** the six month quarantine of the embryos and retesting prior to having embryos transferred.

I/we have had an opportunity to discuss this document with my/our physician and/or the treatment team and all of my/our questions have been answered to my/our satisfaction. I/we feel fully informed about the potential risks and unintentional transmission of a communicable disease is possible by transferring fresh embryos created by the intended parents, which may be unaware of an active infection. I/We understand that the



Gestational Carrier for International Intended Parent

Agreement Acknowledgement Assumption of Risk, Release and Hold Harmless

Definitions

The following defined terms are utilized throughout the following document:

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(Print Gestational Patient's full name) _____ DOB _____

(Print Partner of Gestational Carrier full name) _____ DOB _____

I have voluntarily accepted to be a gestational carrier for _____ and _____ (Intended Parents). I _____ (GC) and _____ (partner of GC) understand that the intended parents are non-U.S. citizens and are requesting the Practice, physicians and staff assist them with an IVF/ Gestational Surrogacy (with their own reproductive tissue or the use of a donor egg) in hopes to achieve a baby.

It has been explained to us that many countries have laws and legal restrictions applicable to Assisted Reproductive Technology (ART) procedures. To ensure the legal issues surrounding the treatment and the child(ren) born through these procedures are addressed and protected, the Practice has advised the Intended Parents to seek independent legal counsel from an experienced reproductive attorney in their home country, to assure all legal agreements for which they have entered into will be legally recognized and upheld in their country. I/we understand that the legal agreements which are agreed upon, signed and considered legal in the United States, can be superseded by laws in the Intended Parents home country. I/we understand that the Practice, its physicians and staff have required the Intended Parents to obtain legal counsel from an experienced specialized reproductive attorney from their home country, to assure that all legalities of the procedure are agreed upon, between all applicable parties (i.e. gestational carrier, intended parents, oocyte donor and the recipients) and to help protect the welfare of the potential child(ren) born through these procedures. This discussion must also address resolution of custody of embryos and any resulting children, as well as legal citizenship and rights for any potential children. The Practice, physicians and staff encourage me/us

(GC and partner of GC) to have all international legal contracts reviewed by our attorney to limit potential conflicts regarding any legal contracts, created by a U.S. attorney and the international contract. I/We understand that if this is not completed the child(ren) born through the process of ART with gestational surrogacy and/or donor egg may not be recognized as a legal citizen, may not be allowed to enter the country and legalities surrounding parentage may be in question. As the gestational carrier, I understand there may be risks in regards to participating as a gestational carrier for an international patient. I understand that there may be risks for the child(ren) born outside of their home country in regards to legal citizenship and reentry into their home country. I/we understand obtaining legal agreements from both countries will decrease, but not eliminate risks to the child born through this process.

I/we understand that the consents signed at the Practice and the Lab, do not address parentage, legal relationships and/or laws in regards to Assisted Reproductive Technologies and protection for child(ren) born through this process. I/We understand that the Practice requires us to obtain a letter from our attorney that agreements are in place prior to initiation of treatment.

On behalf of myself/ourselves/ child(ren) born through this process and anyone claiming by, through or under us, hereby release the Practice and the Lab, its directors, employees including but not limited to the Practice Physicians, from any and all claims, losses, liabilities and demands (either known or unknown) and to any claims that may arise in the future due to our decision to proceed with our ART/Gestational Carrier cycle to an international couple. I/we understand that participation in the gestational carrier program is purely voluntary. By signing this document we take full responsibility for the outcome and consequences of our decision and accept all risks, known or unknown associated there within. I/we are requesting to proceed with our ART treatment with the Practice and the Lab.

Print Patient Name

DOB _____

Signature of Patient

Date _____

Print Spouse/Significant Other Name

DOB _____

Signature of Spouse/Significant Other

Date _____

Witness/Practice Representative

Date _____

Guidance for Industry

Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Small Entity Compliance Guide

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit written comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact the Office of Communication, Training and Manufacturers Assistance at 1-800-835-4709 or 301-827-1800.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
August 2007**

Contains Nonbinding Recommendations

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Guidance for Industry

Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Small Entity Compliance Guide

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The Food and Drug Administration (FDA) has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). It is intended to help small entity establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps) better understand and comply with the comprehensive regulatory framework for HCT/Ps, set forth in Title 21 of the Code of Federal Regulations, Part 1271 (21 CFR Part 1271). Title 21 CFR 1271.3 provides definitions for important terms used in 21 CFR Part 1271.

Previously, FDA issued questions and answers regarding the regulations in 21 CFR Part 1271. These questions and answers, along with other guidances and rulemakings pertaining to 21 CFR Part 1271, can be found at <http://www.fda.gov/cber/tissue/docs.htm>, and will not be covered in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Historically, the approach to regulating human cellular and tissue-based products (now called human cells, tissues, and cellular and tissue-based products or HCT/Ps) was highly fragmented. In 1997, FDA proposed a new approach to the regulation of HCT/Ps.¹ This approach would

¹ 62 FR 9721, March 4, 1997.

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establish in 21 CFR Part 1271 a comprehensive regulatory program for HCT/Ps. In accordance with the tiered, risk-based approach that FDA proposed, some HCT/Ps would be regulated only under those new regulations and section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264), while others would be regulated as drugs, devices, and/or biological products under section 351 of the PHS Act (42 U.S.C. 262) and/or the Federal Food, Drug, and Cosmetic Act (the act). FDA requested written comments on the proposed approach and, on March 17, 1997, held a public meeting.²

FDA published three final rules and two interim final rules, outlined below, to implement the proposed approach.

1. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (registration final rule) (66 FR 5447, January 19, 2001). These provisions:
 - set forth 21 CFR Part 1271, Subpart A (general provisions pertaining to the scope and purpose of 21 CFR Part 1271, as well as definitions), and 21 CFR Part 1271, Subpart B (registration and listing procedures);
 - became effective in two stages:
 - the first effective date, April 4, 2001, applied to establishments whose products were already regulated under section 361 of the PHS Act and the regulations in 21 CFR Part 1270.
 - the second effective date was originally January 21, 2003, and applied to establishments that manufacture HCT/Ps currently regulated as biological products, drugs, or devices; hematopoietic stem cells from peripheral and cord blood; and reproductive cells and tissues. However, FDA delayed the second effective date until January 21, 2004.³
2. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing” (interim final rule) (69 FR 3823, January 27, 2004).
 - Excepted human dura mater and human heart valve allografts from the scope of the definition of HCT/Ps until the rulemaking for all of 21 CFR Part 1271 was completed.
 - Effective date – January 23, 2004 (compliance date – March 29, 2004).
3. “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products” (donor eligibility final rule) (69 FR 29786, May 25, 2004).
 - Set forth 21 CFR Part 1271, Subpart C (provisions for the screening and testing of donors to determine their eligibility).
 - Effective date – May 25, 2005.

² Id.

³ 68 FR 2689, January 21, 2003.

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4. “Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments, Inspection and Enforcement” (CGTP final rule) (69 FR 68612, November 24, 2004).
 - Set forth 21 CFR Part 1271, Subpart D (CGTP requirements), Subpart E (additional requirements for establishments described in 21 CFR 1271.10), and Subpart F (inspection and enforcement provisions for establishments described in 21 CFR 1271.10).
 - Effective date – May 25, 2005.
 - Subparts D (with some exceptions) and E do not apply to reproductive HCT/Ps at this time.
5. “Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling” (interim final rule) (70 FR 29949, May 25, 2005).
 - Revised certain regulations regarding the screening and testing of HCT/P donors and related labeling.
 - Effective date – May 25, 2005.

On June 19, 2007 (72 FR 33667), FDA adopted as a final rule, without change, the provisions of the May 25, 2005, interim final rule.

FDA believes that these regulations will increase the safety of HCT/Ps, and public confidence in their safety, by preventing the introduction, transmission and spread of communicable disease. The agency’s actions are intended to improve protection of the public health while minimizing regulatory burden, which in turn would encourage significant innovation.

III. QUESTIONS AND ANSWERS

A. GENERAL

1. Where can an establishment find the criteria to determine how their HCT/Ps will be regulated?

Title 21 CFR 1271.10(a) sets out the criteria that form the foundation of FDA’s tiered, risk-based approach to regulating HCT/Ps. HCT/Ps that meet all of these criteria are subject only to regulation under section 361 of the PHS Act and the regulations in 21 CFR Part 1271. (An HCT/P that falls into this category is referred to as a “361 HCT/P”). No premarket approval is required.

If the HCT/Ps do not meet the criteria in 21 CFR 1271.10(a) for regulation solely as 361 HCT/Ps, and the establishment does not qualify for any of the exceptions listed in 21 CFR 1271.15, the HCT/Ps are regulated as drugs, devices, and/or biological products (21 CFR

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1271.20). These HCT/Ps are subject to section 351 of the PHS Act and/or the act, and applicable regulations in Title 21 of the CFR.⁴

2. For establishments that manufacture a drug, device or biological product that is considered an HCT/P, what must the establishment do if a requirement in 21 CFR Part 1271 conflicts with a requirement in 21 CFR Parts 210, 211, or 820?

In the event that a regulation in 21 CFR Part 1271 is in conflict with a requirement in 21 CFR Parts 210, 211, or 820, the establishment must follow the requirements that are more specifically applicable to the product, rather than the more general requirements (21 CFR 1271.150(d)).

3. What are examples of some 361 HCT/Ps that meet the criteria in 21 CFR 1271.10(a)?

- Amniotic membrane when used alone or without added cells
- Bone
- Cartilage
- Cornea
- Fascia
- Ligament
- Pericardium
- Peripheral or umbilical cord blood stem cells (for autologous use or use in a first or second degree blood relative)
- Sclera
- Skin
- Tendon
- Vascular graft
- Heart valves
- Dura mater
- Reproductive cells and tissues (e.g., semen, oocytes, embryos)

All of the above are minimally manipulated, intended for homologous use only, and not combined with another article, with some exceptions.

4. For HCT/Ps recovered before May 25, 2005, which subparts of 21 CFR Part 1271 apply?

All HCT/Ps recovered before May 25, 2005 are subject to certain regulations in 21 CFR Part 1271, Subpart A (General Provisions) and Subpart B (Procedures for Registration and Listing), as appropriate. In addition, such HCT/Ps are subject to the regulations in 21 CFR Part 1270. The regulations in 21 CFR Part 1271, Subparts C through F do not apply to HCT/Ps recovered before May 25, 2005.

⁴ Applicable regulations include, but are not limited to, 21 CFR 207.20(f), 210.1(c), 210.2, 211.1(b), 807.20(d), and 820.1(a), which require establishments to follow the procedures in 21 CFR Part 1271, Subparts B, C, and D.

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5. For HCT/Ps recovered after May 25, 2005, which subparts of 21 CFR Part 1271 apply?

For 361 HCT/Ps, the subparts of 21 CFR Part 1271 apply as follows:

- Subparts A through C apply to all 361 HCT/Ps.
- Subpart D applies only to nonreproductive 361 HCT/Ps, with the exception of 21 CFR 1271.150(c) and 1271.155, which apply to all 361 HCT/Ps.
- Subpart E applies only to nonreproductive 361 HCT/Ps.
- Subpart F applies to all 361 HCT/Ps.

For HCT/Ps regulated as drugs, devices, and/or biological products, the subparts of 21 CFR Part 1271 apply as follows:

- Subparts A through D apply to all such HCT/Ps.
- Subparts E and F do not apply.

B. REGISTRATION AND LISTING

1. Which establishments are required to register and list their HCT/Ps?

All establishments that manufacture 361 HCT/Ps must register and list their HCT/Ps with the Center for Biologics Evaluation and Research (CBER) (21 CFR 1271.1(b)(1); see 21 CFR 1271.10(b) and 1271.21). In addition, all establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act must register and list their HCT/Ps with CBER (21 CFR 1271.1(b)(2)).⁵

FDA does not require establishments that manufacture drugs and devices under an investigational new drug application (IND) (21 CFR Part 312) or an investigational device exemption (IDE) (21 CFR Part 812) to register and list their HCT/Ps with CBER until the products are approved; or, cleared for premarket notifications. Therefore, establishments that only manufacture HCT/Ps currently under an IND or IDE do not have to register and list their HCT/Ps until the investigational HCT/P is approved through a biologics license application (BLA), a new drug application (NDA), or a premarket approval application (PMA); or cleared through a premarket notification submission (510(k)).

2. When must new establishments register and list their HCT/Ps?

New establishments must register and list their HCT/Ps within 5 days after beginning operations (21 CFR 1271.21(a)). The establishment should also appoint a Reporting Official who will be responsible for registration and listing updates and/or changes and who will serve as the contact for all registration related communication.

⁵ Specifically, 21 CFR 1271.1(b)(2) states that if an establishment manufactures HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act, 21 CFR 207.20(f) and 807.20(d) require such an establishment to register and list its HCT/Ps with CBER, following the procedures in 21 CFR Part 1271, Subpart B.

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3. Which establishments are exempt from HCT/P registration and listing?

If an establishment qualifies for any of the exceptions listed in 21 CFR 1271.15, the establishment does not have to register and list their HCT/Ps with CBER.

4. What else will establishments have to do after the initial registration?

Establishments must update their registration annually in December and submit changes in HCT/P listing within 6 months of the change (21 CFR 1271.21). Even if there are no changes or updates to an establishment's HCT/P listing, the establishment must still register annually. We recommend that establishments keep a record on file containing the field establishment identifier number (FEI #) and validation date of the registration as this information is necessary to make changes and updates electronically. If the ownership or location of the establishment changes, the establishment must submit an amended registration form within 5 days of the change (21 CFR 1271.26). FDA currently notifies the Reporting Official listed on Form FDA 3356 in November regarding the annual registration.

5. What would happen if an establishment does not register or forgets to submit the annual registration?

The establishment is in violation of the regulations.

6. How will an establishment know when it is officially registered with FDA?

FDA considers the establishment to be registered and in compliance with 21 CFR Part 1271 requirements as soon as FDA receives the Form FDA 3356 (registration form). After FDA processes the establishment's registration form, FDA will send to the Reporting Official a validated form, which includes the registration number (FEI #). If the establishment already registered under 21 CFR Parts 207, 607, or 807, the establishment will retain the same FEI #.

If the establishment has not received its validation form confirming its "registered" status and needs to know its registration status as "pre-registered", the establishment may contact FDA at tissureg@fda.hhs.gov or access the Public Query Application (<http://www.fda.gov/cber/tissue/tissregdata.htm>). The status will change to "registered" when the FEI # has been generated. An establishment may also use the Public Query Application to access a list of other establishments that are registered with the FDA.

When an establishment updates the registration form from "registered" to "inactive", FDA considers the status changed as soon as FDA receives the form.

7. Where can an establishment find more information on how to register and list HCT/Ps?

- <http://www.fda.gov/cber/tissue/tisreg.htm> – provides access to the establishment registration form (Form FDA 3356), instructions for completing the form (paper and electronic form), and other information on the Electronic Human Cell and Tissue Establishment Registration (eHCTERS).

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- <http://www.fda.gov/cber/tissue/tisregcontact.htm> – provides contact information for the CBER Tissue Establishment Registration Coordinator.

8. Must an individual or company register if it only obtains blood samples from donors and sends the samples to a registered establishment (e.g., an independent laboratory or a recovery establishment) for testing?

No. If an individual or company is simply obtaining a blood sample from a donor and sending the blood sample to a registered testing laboratory or to a registered recovery establishment, then the individual or company is not required to register. Obtaining a blood sample is not considered part of manufacturing.

9. Must an establishment (laboratory) register if it only performs speciation of microorganisms already detected in an HCT/P culture specimen?

Yes. By definition, manufacture includes processing, and processing includes testing for microorganisms (21 CFR 1271.3(e) and (ff)). Testing for microorganisms generally includes sampling, culturing and identifying the microorganisms present in the sample (speciation). FDA is aware that HCT/P manufacturers use this information in a number of ways, including determining whether an HCT/P may be processed and/or distributed. If an establishment (laboratory) only performs speciation of microorganisms, the establishment (laboratory) must register as it is performing a processing step (21 CFR 1271.1(b)).

10. What is the process to cancel registration if the establishment no longer manufactures HCT/Ps?

The Reporting Official listed on the Form FDA 3356 may submit a revised Form FDA 3356 (paper or electronic form), marking “inactive” in box 2, to inactivate the registration.

11. Must a hospital that manufactures more than one type of HCT/P (e.g., hematopoietic stem/progenitor cells, reproductive cells) and/or that performs different manufacturing functions (e.g., recovery, processing, donor testing) have multiple registrations?

Each physical location will generally have only one registration number (FEI #) for any combination of HCT/P types and/or functions unless the individual establishments are under different corporate entities. An establishment means a place of business under one management, at one general physical location, that engages in the manufacture of HCT/Ps (21 CFR 1271.3(b)). One general physical location could be reasonably construed to include separate buildings within close proximity provided that the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and capable of being inspected at the same time. For example, a hospital administrator could facilitate one registration of multiple laboratories under the same management. However, we recommend separate registrations for two or more business enterprises that are separate legal entities with different management even if both use the same facility or the same address.⁶

⁶ See http://www.fda.gov/ora/inspect_ref/fmd/fmd130.html.

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12. Must hospitals that surgically remove and temporarily store autologous HCT/Ps prior to implanting the HCT/Ps register and list such HCT/Ps?

No. We consider this to be the same surgical procedure, even though the storage time and future replacement surgery may be a number of days apart. Therefore, such hospitals would qualify for the exemption listed in 21 CFR 1271.15(b) as long as they do no additional manufacturing to the HCT/Ps.

13. Must hospitals that receive, store, and routinely share qualified HCT/Ps with other hospitals register and list such HCT/Ps?

Yes. An establishment is not required to comply with the requirements of 21 CFR Part 1271 if the establishment does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/Ps solely for implantation, transplantation, infusion, or transfer within its facility (21 CFR 1271.15(d)). Hospitals that receive HCT/Ps and make them available for distribution to other hospitals are performing the manufacturing steps of storage and distribution and therefore must register and list such HCT/Ps with CBER (21 CFR 1271.21; see 21 CFR 1271.3(e)).

14. Must foreign establishments that import HCT/Ps for distribution in the United States register and list such HCT/Ps?

Yes. All foreign establishments importing or offering for import HCT/Ps into the United States must register and list such HCT/Ps with CBER.⁷ If such HCT/Ps are 361 HCT/Ps, the foreign establishment should indicate the name, address, and phone number of its U.S. agent (someone located in the United States as a contact for inspection purposes) on the initial and updated registration form. If such HCT/Ps are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act, the foreign establishment must submit the name, address, and phone number of its U.S. agent on the initial and updated registration form; the U.S. agent must reside or maintain a place of business in the United States (see 21 CFR 207.40(c) and 807.40(b)). Foreign establishments may submit Form FDA 3356 via mail, facsimile, or electronically.

⁷ Foreign establishments manufacturing 361 HCT/Ps must register and list such HCT/Ps with CBER (21 CFR 1271.10(b); see 21 CFR 1271.1(b)(1) and 1271.21). Foreign establishments importing or offering for import drugs and/or devices into the United States must comply with the registration and listing requirements in 21 CFR Part 207, Subpart C, and Part 807, Subpart B (21 CFR 207.40(a) and 807.40(a)). Foreign biological establishments would also be subject to 21 CFR 207.40(a) and 807.40(a) because biological products meet the definition of “drug” or “device” under the act. As discussed in footnote 5, 21 CFR 207.20(f) and 807.20(d) require drug, device, and biological establishments to register and list their HCT/Ps with CBER, following procedures in 21 CFR Part 1271, Subpart B. Therefore, foreign establishments whose HCT/Ps are regulated as drugs, devices, and/or biological products and are imported or offered for import into the United States must register and list such HCT/Ps with CBER.

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C. DONOR ELIGIBILITY

1. How do the donor eligibility requirements under 21 CFR Part 1271, Subpart C, differ from the donor suitability requirements under 21 CFR Part 1270?

Title 21 CFR Part 1270 applies only to certain human tissue intended for transplantation (musculoskeletal, skin, and ocular), recovered before May 25, 2005, and requires donor screening and testing for only certain diseases (HIV, hepatitis B, and hepatitis C). Title 21 CFR Part 1271, Subpart C, applies to donors of additional cells and tissues, recovered on or after May 25, 2005, and requires screening and testing of these donors for additional relevant communicable diseases. For example, 21 CFR Part 1271, Subpart C, applies to donors of hematopoietic stem/progenitor cells derived from peripheral and umbilical cord blood (e.g., cord blood), reproductive cells and tissue (e.g., semen, oocyte, embryo), human dura mater, and human heart valves, in addition to donors of musculoskeletal, skin, and ocular tissue. Title 21 CFR Part 1271 also applies to HCT/Ps regulated as drugs, devices, or biological products, whereas 21 CFR Part 1270, does not.

2. Where can an establishment find more information on donor eligibility?

An establishment can find more comprehensive information on donor eligibility by accessing FDA's "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" and "Guidance for Industry: Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donors Who Were Tested For Communicable Diseases Using Pooled Specimens or Diagnostic Tests" at <http://www.fda.gov/cber/tissue/docs.htm>.

D. CURRENT GOOD TISSUE PRACTICE

1. What are current good tissue practice requirements?

Current good tissue practice (CGTP) requirements are the requirements in 21 CFR Part 1271, Subparts C and D, that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packing, and distribution (21 CFR 1271.150(a)).

2. What is the purpose of the CGTP requirements?

The requirements aim to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps by reducing the risk that the HCT/Ps contain communicable disease agents (e.g., viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents), and by preventing contamination during manufacturing.

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3. If an establishment only performs certain activities in the manufacture of HCT/Ps, must the establishment follow all CGTP requirements?

An establishment need only comply with those requirements applicable to the operations that it performs (21 CFR 1271.150(c)(1)(i)). For example, a laboratory that performs communicable disease tests but does not store HCT/Ps would not have to meet HCT/P storage requirements.

4. What are “core CGTP requirements”? Is an HCT/P establishment only required to follow core CGTP requirements and not other CGTP requirements?

Core CGTP requirements (21 CFR 1271.150(b)) are those requirements that directly relate to preventing the introduction, transmission, or spread of communicable diseases by HCT/Ps. They include requirements for facilities, environmental control, equipment, supplies and reagents, recovery, processing, process controls, labeling controls, storage, receipt, predistribution shipment, distribution, and donor screening and testing. Other CGTP requirements support the core CGTP requirements (e.g., requirements for procedures and recordkeeping). An establishment must follow all of the CGTP requirements applicable to the operations that it performs, whether or not they are considered core requirements. See 21 CFR 1271.150(c)(1)(i).

5. What if one establishment engages another establishment (e.g., a contract establishment) to perform certain steps in manufacture, under a contract, agreement, or other arrangement?

The contract establishment must comply with those CGTP requirements applicable to the manufacturing step(s) that it performs under a contract, agreement, or other arrangement (21 CFR 1271.150(c)(1)(ii)). The establishment that is contracting for outside work must ensure that the contract establishment complies with applicable CGTP requirements before entering into the contract, agreement, or arrangement (21 CFR 1271.150(c)(iii)). If, after entering into the contract, agreement, or arrangement, that establishment becomes aware of information suggesting that the contract establishment may no longer be in compliance, the establishment that is contracting for outside work must either: (a) investigate and take reasonable steps to ensure that the contract establishment complies, or (b) terminate the contract, agreement, or arrangement with the non-compliant firm (21 CFR 1271.150(c)(1)(iii)). For further information, see “Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements” available at <http://www.fda.gov/cber/tissue/docs.htm>.

6. What does an establishment do if it has questions about the CGTP regulations?

FDA previously issued questions and answers regarding the regulations in 21 CFR Part 1271, which include the CGTP regulations. These questions and answers can be found at <http://www.fda.gov/cber/tissue/docs.htm>. If an establishment has specific questions about the CGTP regulations, please contact the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852, 1-800-835-4709 or 301-827-1800. Questions may also be submitted via email to: matt@cber.fda.gov (industry) or octma@cber.fda.gov (consumers and health care professionals).

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E. FDA INSPECTION AND ENFORCEMENT OF ESTABLISHMENTS DESCRIBED IN 21 CFR 1271.10

1. What does an FDA inspection involve?

An FDA inspection will be conducted as necessary in the judgment of FDA to determine compliance with the applicable provisions in 21 CFR Part 1271 (21 CFR 1271.400(a)). The FDA inspection may include, but is not limited to, an assessment of the establishment's facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers and controls required to be maintained under 21 CFR Part 1271.

FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel as necessary to determine compliance with the provisions of 21 CFR Part 1271 (21 CFR 1271.400(c)). FDA representatives may take samples, may review and copy any records required to be kept under 21 CFR Part 1271, and may use other appropriate means to record evidence of observations during inspections (21 CFR 1271.400(d)). Financial records and personnel records are not required records under 21 CFR Part 1271.

For reproductive establishments, inspections will be limited to determining compliance with applicable provisions contained in 21 CFR Part 1271, Subparts A, B, and C; and 21 CFR 1271.150(c)(1) and 1271.155 of Subpart D. For information about compliance and surveillance activities relating to 361 HCT/Ps, see the Compliance Program Guidance Manual, Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), 7341.002, at <http://www.fda.gov/cber/cpg/7341002tis.htm>.

2. When will an FDA inspection be performed?

An FDA inspection will ordinarily be performed during regular business hours and may be made with or without prior notification (21 CFR 1271.400(a)). The frequency of inspection will be at FDA's discretion (21 CFR 1271.400(b)).

3. What enforcement actions can FDA take to prevent the introduction, transmission, or spread of communicable diseases for 361 HCT/Ps?

For 361 HCT/Ps, the advisory, administrative and judicial actions include an Untitled Letter; Warning Letter; Orders of Retention, Recall, Destruction, and Cessation of Manufacturing; and Prosecution.⁸

An Untitled Letter is a correspondence with regulated industry that cites violations that do not meet the threshold of regulatory significance for a Warning Letter. A Warning Letter is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other

⁸ See FDA's Compliance Program Guidance Manual, Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 7341.002, Part V – Regulatory/Administrative Strategy.

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activities to be in violation of statutes or their implementing regulations. Warning Letters are only issued for violations of regulatory significance (i.e., those that may lead to an enforcement action if the documented violations are not promptly and adequately corrected).

Under 21 CFR 1271.440, FDA may issue orders for retention, recall, destruction, and/or cessation of manufacturing. FDA may take one or more of these actions upon an agency finding that there are reasonable grounds to believe the following: (a) an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in 21 CFR Part 1271 and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or (b) the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or (c) an establishment is in violation of the regulations in 21 CFR Part 1271 and, therefore, does not provide adequate protections against the risks of communicable disease transmission.

FDA may pursue prosecution for gross, flagrant or intentional violations, fraud, danger to health, or a continued or repeated course of violative conduct.⁹

4. When would an FDA order for cessation of manufacturing go into immediate effect?

The FDA order for cessation of manufacturing will go into immediate effect only when FDA determines that there are reasonable grounds to believe that there is a danger to health if the establishment continues to manufacture (see 21 CFR 1271.440(a)(3)).

5. Are there any exceptions to the enforcement provisions in 21 CFR Part 1271, Subpart F?

Yes. In 21 CFR 1271.440(f), FDA will not issue an order for the destruction of reproductive tissue, nor will it carry out such destruction itself.

6. What are the requirements for importing 361 HCT/Ps?

With two exceptions (certain reproductive HCT/Ps and peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act), when an HCT/P is offered for import, the importer of record must notify, either before or at the time of importation, the director of the FDA district having jurisdiction over the port of entry through which the HCT/P is imported or offered for import. Additionally, the importer of record must provide sufficient information for FDA to make an admissibility decision (see 21 CFR 1271.420(a)). For additional information, see http://www.fda.gov/ora/inspect_ref/iom/IOMORADIR.html and <http://www.fda.gov/cber/cpg/7342007tis.htm>.

⁹ Sections 3559 and 3571(c) of Title 18, U.S.C., and section 368 of the PHS Act (42 U.S.C. 271) are the applicable statutes when pursuing prosecution for violating regulations promulgated under section 361 of the PHS Act. Under section 368(a) of the PHS Act, any individual who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Additionally, individuals may be punished by a fine of up to \$100,000 if death has not resulted from a violation of the regulations or up to \$250,000 if death has resulted.

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7. What are the exceptions for 361 HCT/Ps offered for import?

The import provisions in 21 CFR 1271.420 do not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in 21 CFR Part 1271, and donated by a sexually intimate partner of the recipient for reproductive use (21 CFR 1271.420(c)). In addition, such import provisions do not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in 21 CFR Part 1271, except when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission. In such circumstances, 21 CFR 1271.420(a) and (b) apply (21 CFR 1271.420(d)).