



IVF PROGRAM PATIENT INFORMATION SHEET

Introduction

In vitro fertilization (IVF) and embryo transfer (ET) are procedures designed to enhance the likelihood of conception in an individual/couple for whom other techniques are not possible or have not been successful. The process involves multiple steps culminating in the insemination and fertilization of oocytes (eggs) in the laboratory. The resultant embryo(s) are placed back into the uterus to allow implantation and further growth. Each stage of the procedure has risks specific to that stage as outlined below. The specific steps are: 1) **Suppression** of a woman's own reproductive hormones followed by; 2) **Stimulation** of the ovaries with medications to produce multiple mature eggs; 3) Removal (**retrieval**) of the eggs from the ovary; 4) Collection and preparation of a sperm sample; 5) Combining the eggs and sperm in the laboratory to allow **fertilization** to take place; 6) Incubation in specially designed media in the **laboratory** to allow embryos to develop; 6) **Transfer (ET)** of the embryos back into the uterine cavity; 7) **Luteal phase** support with progesterone; and 8) determination of **pregnancy**.

IVF Procedure

Suppression of Reproductive Hormones: First, we turn off the production of a woman's natural hormones to allow us to most effectively stimulate multiple egg production by her ovaries. We may use oral contraceptives (OCP), gonadotropin releasing hormone (GnRH) agonists (Lupron/ Synarel) or antagonists (Antagon /Cetrotide) for suppression. Lupron, Antagon and Cetrotide are given as daily subcutaneous injections. Synarel is a nasal spray. The side effects with these medications may include:

Medications:

- hot flashes
- headache
- vaginal dryness and irritation
- decreased libido
- itching or irritation

Injections:

- lethargy
- swelling
- pain
- Bruising

IM injection may cause sciatic nerve injury if given in the wrong place.

Inhaled medications (Synarel) can cause nasal irritation. Other side effects have been reported but with very low frequency.

Ovarian Stimulation: The medications employed to stimulate multiple egg production include hMG (Pergonal, Repronex, Humagon), FSH (Follistim, Gonal-F) and hCG (Pregnyl, Novarel). hMG and FSH induce follicle development and hCG initiates the final stages of egg maturation just before retrieval. Follistim and Gonal-F may be given as subcutaneous injections but hMG and hCG must be given intramuscularly for best effect. The drugs themselves rarely cause significant side effects but the high levels of ovarian hormones that the stimulated ovaries produce can cause symptoms. These include:

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| • mild fluid retention with transient weight gain | • nausea | • diarrhea |
| • pelvic discomfort due to ovarian cyst formation and enlargement | • breast tenderness | • mood swings |
| • headache | • fatigue | |

More serious risks, though rare, can occur and include:

- Ovarian hyperstimulation syndrome (OHSS)-see OHSS Fact Sheet: excessive fluid retention with fluid in the abdomen (ascites) and chest cavity (pleural effusion); marked hemoconcentration (contraction of intravascular blood volume); thrombosis of arteries and/or veins which may lead to stroke or embolus; or transient renal dysfunction.
- Rupture of an ovarian cyst with or without internal bleeding.
- Torsion (twisting) of an enlarged ovary causing intense pain and, if untreated, permanent damage to the ovary.
- An allergic reaction to any of the drugs.

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Any of the above may require hospitalization, possibly prolonged, for monitoring, intravenous fluids or drainage of intraabdominal fluid until the condition resolves. Worldwide, there have been rare instances of death from severe OHSS. Internal bleeding and torsion may require surgical intervention. These complications may occur during or in the few weeks after treatment so it is important that you remain in contact with NCRS during this time. Ovarian stimulating medications have been implicated as a risk factor for ovarian cancer but more recent studies suggest that the risk may be from infertility itself rather than the medications. Successful pregnancy reduces the risk of ovarian cancer considerably. It remains uncertain whether these medications carry any long term risk.

NCRS staff **monitors** the ovarian stimulation closely. This entails frequent **blood hormone testing** and vaginal **ultrasound examinations**. The blood hormone levels allow us to determine the correct dose of stimulating medications while the ultrasounds allow us to determine the number and size of the developing ovarian follicles. This information allows the NCRS staff to determine the correct time for hCG injection and subsequent egg retrieval. Transvaginal ultrasound is quick and usually painless though some discomfort may occur as your ovaries become more stimulated. There is no known risk associated with transvaginal ultrasound and the FDA has approved the sale and manufacture of the machines used in our clinic. Blood draws (phlebotomy) may cause mild discomfort and bruising, bleeding, infection, redness, irritation or scarring at the needle sites. It is possible that the monitoring will show there is a low probability of successful egg retrieval and the cycle may be cancelled.

Egg Retrieval: We remove the eggs from the ovarian follicles under ultrasound guidance by passing a long thin needle through the vaginal wall and into the ovary. Rarely, we must insert the needle through the abdomen to get to the follicles. Each follicle is pierced, the fluid aspirated and sent to the IVF lab for evaluation. We hope to find one egg in the fluid from each follicle. We cannot, however, guarantee that the ovaries contain any mature or healthy eggs or that we will successfully retrieve them. The procedure is out-patient and performed under **Conscious Sedation** (see below) for pain control. Recuperation is prompt; patients usually leave for home within 2 hours of retrieval and return to work the next day. Risks include ovarian infection, bleeding, and possible damage to the intestines, bladder or other internal organs. All of these are quite rare.

Conscious sedation involves administration of sedatives through an intravenous line to induce light sleep. This is normally sufficient for pain control during egg retrieval. Some patients experience discomfort during the retrieval process despite the sedatives. Risks include respiratory inhibition and heart arrhythmias (irregular heart beats) which might require transport to the hospital for emergency care. Allergic reactions, including anaphylaxis, are possible.

Sperm collection: The male partner provides a semen specimen by masturbation one hour before the egg retrieval. We ask that you abstain from any ejaculation between 1 and 3 days prior to the retrieval but no longer than 5 days. Our andrology laboratory staff processes the sperm for insemination of the eggs. Each sperm specimen is carefully labeled with multiple identifiers including the name of each partner and chart number to insure that the correct sperm are introduced to the correct eggs. On occasion, you may be asked to produce a second specimen within one to two hours of producing the first sample. In some instances, the second sample has better sperm characteristics than the first. Rarely, no sperm will be found in the ejaculate.

Occasionally, a man is unable to provide a semen specimen within a reasonable time on the day of egg retrieval. If there is any concern that this might occur, we strongly recommend freezing a sample prior to the day of retrieval to use as back-up. But, when inability to collect occurs unexpectedly, a NCRS physician can aspirate the sperm directly from the testicle under conscious sedation (non-surgical sperm aspiration). Alternatively, we could use donor sperm or discard the eggs without insemination. Frozen samples and non-surgical sperm aspiration require intracytoplasmic sperm injection (ICSI) for reliable fertilization of the eggs.

IVF Embryology: At retrieval, our embryology staff rapidly identifies each egg and transfers it into a dish containing a culture solution. When an egg is removed from its follicle, it is covered by a layer of "nurse" cells called the "corona radiata". Blood and nurse cells are dissected from the egg after retrieval using needles and the eggs are placed into the incubator. Rarely, an egg may be damaged during the dissection procedure. Later in the day, the processed sperm are added to the dishes. The inseminated eggs are placed back into the incubator overnight to allow fertilization to occur. If preliminary tests determine that the sperm cannot naturally fertilize an egg, we will recommend intracytoplasmic sperm injection (ICSI-see ICSI information sheet). The eggs are inspected the day after retrieval to assess their quality and to see if successful fertilization has occurred. This is done by identifying two pronuclei within the egg. We cannot guarantee that all or any eggs will fertilize normally regardless of the technique used to inseminate the eggs. Some eggs degenerate or fertilize abnormally resulting in embryos that cannot be transferred. The culture solution is changed periodically to meet the changing needs of the growing embryos. Embryos are usually transferred back into the uterus 3 days after retrieval when they are between 6 and 10 cell stage. Under certain conditions, we may offer transfer 5 or 6 days after retrieval at the blastocyst stage (see **blastocyst transfer** information sheet). It is possible that none of the eggs fertilize or progress into embryos that can be transferred. Even embryos that appear normal on day 3 after transfer may not continue to develop into blastocysts.

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Equipment failure, infection, human error or other unforeseen factors may result in loss or damage to eggs, semen, and/or embryos. Unforeseen conditions (natural weather disasters, etc.) may make NCRS facilities or other medical or laboratory support unavailable at the appropriate time for egg recovery. No risk to the fetus is presently known arising from the material and methods used in the preparation and handling of eggs, semen and embryos in the laboratory.

Embryo Transfer: On the day of transfer, the embryos are inspected again. The embryologist will determine which, if any, embryos are best to transfer. We will discuss with you the embryologist's recommendations and decide how many and which embryos to transfer. Transferring multiple embryos increases the probability of conception but also confers a risk of multiple gestation. The embryologist may recommend **assisted hatching** (see Assisted Hatching information sheet) if he/she believes it will improve the implantation rate. High quality embryos that are not chosen for transfer may be cryopreserved (see cryopreservation information sheet). Excess poor quality embryos rarely produce pregnancy after cryopreservation and we do not freeze them.

We transfer embryos into the uterus using a small catheter (tube) inserted through the cervix. The embryo(s) are placed in the uterine cavity under ultrasound guidance. The procedure is usually painless and requires no anesthesia. Following the transfer, we ask that you remain lying down for 1/2 hour before returning home and then spend the remainder of the day resting. Rarely, technical difficulties prevent ET and you may elect to have the embryos cryopreserved for later transfer after the difficulty is rectified. In a small percentage of these cases, one or more embryos may be lost due to the difficult transfer. ET occasionally causes slight discomfort and there is a small risk of infection and/or bleeding. Despite placement of embryos into the uterine cavity, there is a small risk of tubal or cervical ectopic pregnancy which may require medical or surgical treatment. Not all embryos placed into the uterus will successfully implant and grow.

Disposition of excess embryos: High quality embryos that are not transferred may be frozen ("cryopreserved"- see **cryopreservation** information sheet), discarded or subjected to scientific study. Generally, those embryos that are viable and have a reasonable chance of resulting in a pregnancy will be cryopreserved for later use. Non-viable and poor quality eggs and embryos may be submitted for scientific observation or discarded. Under no circumstances will the unused sperm, eggs or embryos be used for fertilization or donation to other individuals, couples, corporations or institutions unless expressly requested by you. Embryos whose growth arrests after 1-6 days following retrieval, that are partially degenerate or for any other reason are considered unsuitable for embryo transfer or cryopreservation may be observed to determine cellular inclusions, genes, gene mutations, proteins and/or chromosomes. The studies use protocols that will cease the immediate growth of individual cells.

Luteal Hormone Support: Following ET, we provide progesterone supplementation until the pregnancy test is negative or for an additional 8 weeks if pregnancy occurs. Between retrieval and transfer, the progesterone is given as an IM (intramuscular) injection. After transfer, the progesterone may be given vaginally using either tablets or gel. Progesterone administration by injection often causes discomfort and swelling at the injection site which may last for some weeks after stopping the injections. Vaginal progesterone may cause local irritation, vaginal dryness and/or discharge. The package insert that accompanies progesterone may be confusing to patients because it indicates danger when taken during pregnancy. While this may be true of some progesterone-like medications (progestogens), it is not true of pure progesterone. The FDA requires "Class" labeling of some hormones, including estrogens and progestogens, even if they have been commonly and safely used for many years in clinical practice. Despite the product labeling, all progesterone products recommended by our clinic have been determined by multiple research studies to be safe and effective during pregnancy. However, only one of the products, Crinone® gel, has received specific approval by the FDA for use during pregnancy.

Pregnancy: We will have you get a blood pregnancy test done about 14 days after egg retrieval. It is not possible to identify a pregnancy prior to this as the hCG injection given before retrieval can interfere with the test. We cannot guarantee a successful pregnancy from any IVF/ET procedure. Pregnancy following IVF/ET may end in a miscarriage, ectopic (tubal) pregnancy, or stillbirth. Multiple pregnancies (twins, triplets, etc.) occur with greater frequency than natural conceptions. Some pregnancy complications may occur more frequently following IVF than natural impregnation such as preterm labor and early delivery but this remains unproven. Most infants born following IVF appear normal at birth. Congenital abnormalities, birth defects, genetic abnormalities, mental retardation, and/or other possible deviations from normal occur in children born following IVF at the same rate as they do in children resulting from natural fertilization.

The IVF process induces its own psychological stress. We refer patients for psychological counseling whenever requested or when we feel it would be useful. We encourage all patients to consider participating in our Mind-Body Wellness class.

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ALTERNATIVES TO IVF/ET

Alternative treatments to IVF exist for most infertility problems though the per cycle success rates from non-IVF treatments are usually lower. Success rates vary depending upon the type and severity of the cause for infertility. Most couples possess some possibility of spontaneous conception without a physician's help. On the other hand, some infertility disorders require IVF for treatment such as tubal disease.

Alternatives to participation in this IVF program may include:

- surgery (to correct abnormalities or diseases of the females reproductive tract),
- medical treatments (to induce release of one or more eggs from the ovary or change the characteristics of the cervical mucus),
- artificial insemination (to place sperm into the uterine cavity),
- adoption,
- expectant management (no treatment),
- remaining child free by choice.

Each of these treatment options has its own probability of success, risks and complications. You are encouraged to discuss all alternatives treatment with a NCRS physician.