

## **INFORMED CONSENT FOR ASSISTED REPRODUCTION**

### **INTRODUCTION**

In-Vitro Fertilization (IVF) has become an established treatment for many forms of infertility. The usual goal of IVF is to enable a patient to become pregnant using her own oocytes (eggs) and sperm from her partner. In some cases, donated sperm or oocytes may be used. Certain patients will require the participation of a gestational carrier (surrogate mother). IVF is an elective procedure designed to result in the patient's pregnancy when other treatments have failed or are not appropriate.

This consent reviews the entire IVF process, including the risks that this treatment might pose to you and your offspring. In addition to these known risks, there may be risks with IVF that have not yet been established or even suspected. This consent concerns only IVF procedures carried out by authorized medical personnel at Northwestern Medical Groups' division of Fertility and Reproductive Medicine, hereafter referred to as NMG.

IVF is generally administered in individual cycles. An IVF cycle typically includes the following steps or procedures:

- **Administration of medications** to stimulate the development of multiple follicles. A follicle is a sac in the ovary that contains an egg and produces hormones. An *unfertilized* egg is also known as an oocyte.
- **Retrieval** of oocytes from the follicles in the ovaries.
- **Insemination** (fertilization) of the oocytes with sperm.
- **Culture** (to grow in a small dish) of any resulting fertilized oocytes. A fertilized oocyte is known as an embryo.
- **Transfer** (placement) of one or more embryo(s) into the uterus
- **Administration of hormones** to promote the initiation and maintenance of pregnancy.

In certain cases, these additional procedures can be employed:

- **Intracytoplasmic Sperm Injection (ICSI)** – injection of the sperm into the oocyte to increase the chance of fertilization.
- **Assisted hatching** of embryos to increase the chance of embryo attachment (implantation).
- **Embryo cryopreservation** – freezing of embryos for later use

## **OUTLINE OF CONSENT FOR IVF**

The process of IVF includes many components. The following materials provide detailed information about each of the steps and topics related to IVF. You should read each section carefully and ask your physician any questions you may have. At the end of some of the individual sections, you must sign to indicate your specific wishes about certain treatments or actions, or to consent to specific treatment elements.

### A. Technique of IVF

1. Core elements and their risks:
  - a. IVF medications
  - b. Transvaginal oocyte retrieval
  - c. In-Vitro Fertilization and embryo culture
  - d. Use of abnormal or unused oocytes, sperm and embryos
  - e. Embryo transfer
  - f. Hormonal support of uterine lining (luteal phase support)
2. Additional elements and their risks:
  - a. Intracytoplasmic Sperm Injection (ICSI)
  - b. Assisted Hatching
  - c. Embryo Cryopreservation and disposition

### B. Additional risks to the woman

1. Ovarian Hyperstimulation Syndrome (OHSS)
2. Cancer
3. Risk of Pregnancy

### C. Risks to offspring

1. Overall risks
2. Birth defects
3. Risks of a multiple pregnancy

### D. Ethical and religious considerations in infertility treatment

### E. Psychosocial effects of infertility treatment

### F. Legal considerations and legal counsel

### G. Alternatives to IVF

## A. TECHNIQUE OF IVF

### 1. Core Elements and their Risks

#### a. **IVF MEDICATIONS**

The basic strategy of IVF relies upon the induction of the development of a large number of ovarian follicles simultaneously. FSH (follicle stimulating hormone) and/or LH (luteinizing hormone) injections are used for this purpose. These hormones are known as **gonadotropins**. Other medications are also used to prevent premature ovulation. The use of injectable gonadotropins requires careful monitoring in order to avoid either inadequate or excessive response.

Medications may include the following (this is a representative list and may not be complete):

- **Gonadotropins, or injectable “fertility drugs”** to stimulate the ovaries (Follistim®, Gonal-F®, Bravelle®, or Menopur®). These natural hormones stimulate the ovary in order to induce the simultaneous growth of several follicles over the span of eight (8) or more days. All injectable fertility drugs contain FSH, a hormone that will stimulate the growth of ovarian follicles that contain the oocytes. Certain fertility drugs also contain LH or create LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and follicle growth. Luveris®, a laboratory created LH, or a low-dose of hCG (a gonadotropin) can also be given as a separate injection in addition to FSH. These medications are given by subcutaneous injection (under the skin). Monitoring ovarian response through blood tests and ultrasound during ovarian stimulation is required to assure proper dosage of drugs and the timely recovery of oocytes.

As with all injectable medications – bruising, redness, swelling or discomfort can occur at the injection site. Rarely, these drugs may cause an allergic reaction. These medications are used to stimulate the maturation of multiple follicles. Many women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2% of women develop **Ovarian Hyperstimulation Syndrome (OHSS)**. Please see full discussion of OHSS in the “Risks to the woman” section that follows. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and rarely, clots in blood vessels.

Ovarian stimulation may result in only a few follicles developing. Should this occur, few or no oocytes may be obtained at retrieval. Prior to attempting retrieval, the treatment cycle may even need to be **cancelled**. Although pre-treatment evaluations of ovarian reserve may be reassuring, there is no guarantee that a satisfactory number of oocytes will be retrieved.

Some research in the past suggested that women who take fertility drugs over a long period of time, have a greater risk of developing ovarian tumors. Infertility in and of itself is a risk factor for ovarian cancer, however, recent studies have demonstrated that women who become pregnant after taking fertility drugs actually had a lower risk of developing ovarian tumors than did their infertile counterparts who took no fertility medication. This finding suggests that early reports may have falsely attributed the risk of ovarian cancer to the use of fertility drugs.

- **GnRH-agonists – Leuprolide acetate (Lupron®)**: This medication is injected subcutaneously and is one of the first given in a cycle. Lupron’s primary role is to prevent a premature surge of LH. If the LH level rises too early, oocytes may be released before they are ready to be retrieved. Because this category of drug initially causes the pituitary gland to release FSH and LH, they are sometimes used to start follicular growth or initiate the final stages of oocyte maturation. Though Lupron is an FDA (Federal Drug Administration) approved medication, it has not been approved by the FDA for use in IVF. However, it has been used routinely in this way for more than 20 years. In addition to the risks normally associated with injections, 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 this type of drug is commonly first administered after ovulation, it is possible that it will be taken early in a pregnancy. Although this drug category has not been shown to be associated with fetal abnormalities, it should be discontinued as soon as a pregnancy is confirmed. You may decrease the risk by using condoms (a barrier method of contraception) the month you will be starting Lupron or another drug in this category.

- **GnRH-Antagonists (Ganirelix Acetate or Cetroreliz Acetate) (Antagon<sup>®</sup>, Cetrotide<sup>®</sup>):** These medications are another class of drugs used to prevent premature ovulation. They are injected subcutaneously. They tend to be used for short periods of time in the late stages of ovarian stimulation. In addition to the risks normally associated with injections, the principal reported side effects include abdominal pain, headaches, skin reaction at the injection site and nausea. These side effects are not all inclusive but are the ones primarily reported.
- **Human Chorionic Gonadotropin (hCG) (Profasi<sup>®</sup>, Novarel<sup>®</sup>, Pregnyl<sup>®</sup>, Ovidrel<sup>®</sup>):** hCG is a natural hormone used in IVF to induce the oocytes to mature and, thus, become ready for fertilization. The timing of the injection of this medication is critical in helping to assure the retrieval of mature oocytes. In addition to the risks normally associated with injections, potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort.
- **Progesterone, and in some cases Estradiol:** Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. Progesterone and estradiol prepare the lining of the uterus to receive and nourish an embryo. After oocyte retrieval, the ovaries will not always produce adequate amounts of these hormones to fully support a pregnancy. Accordingly, supplemental progesterone, and in some cases estradiol, are given to ensure adequate hormonal support of the uterine lining. After oocyte retrieval, progesterone is usually given by intramuscular pharmacist-compounded suppositories). Progesterone has not been reported to be associated with an increase in fetal abnormalities. Side effects of progesterone include depression, sleepiness, or allergic reactions, and if given by intramuscular injection the risk of infection or pain at the administration site. Estradiol can be administered by oral, transdermal (skin patch), intramuscular, or vaginal route. Side effects of estradiol include nausea, irritation at the site of injection or skin patch and, rarely, the risk of blood clots or stroke.
- **Oral Contraceptive Pills:** in order to suppress hormone production or to schedule a cycle, oral contraceptive pills may be given for 2-4 weeks before starting hormonal injections. Side effects include irregular bleeding, headache, breast tenderness, nausea, swelling and, rarely, the risk of blood clots or stroke.
- **Other Medications:** Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with the either oocyte retrieval or embryo transfer. Antibiotic treatment may be associated with yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, and allergic reactions. Anti-anxiety medications or muscles relaxants may occasionally be recommended prior to the embryo transfer. The most common side effect is drowsiness. Depending upon the individual needs of the patient, other medications such as steroids, heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.

You should discuss any questions about individual drugs with your physician or pharmacist.

## **b. TRANSVAGINAL OOCYTE RETRIEVAL**

Oocyte retrieval is the removal of eggs from the ovaries. It is usually performed by inserting an ultrasound probe into the vagina. By means of the ultrasounds, the ovaries and the follicles containing the oocytes within the ovaries are visualized. The ultrasound probe contains a long needle that can be seen on ultrasound. The needle is guided into each follicle and the contents are aspirated (drawn into a test tube). The procedure is performed on each ovary. During the procedure the patient is provided with sedation and pain medication which is administered intravenously. Some women may experience some discomfort during the procedure. The aspirated material usually includes follicular fluid, oocyte, and granulosa (egg-supporting) cells. Rarely, the ovaries are not able to be reached by the vaginal route (trans-vaginally). In that situation, the oocyte retrieval will have to be performed through the abdominal wall (trans-abdominal). If trans-abdominal retrieval is necessary, your doctor will discuss the procedure and its risks with you. Risks of oocyte retrieval include but are not limited to:

- **Infection:** bacteria normally present in the vagina may be unknowingly transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other abdominal organs. The estimated incidence of infection after oocyte retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Rarely, infection may become severe enough to require hysterectomy and/or the removal of one or both ovaries. Oral antibiotics are used before and after the oocyte retrieval procedure to reduce the risk of pelvic or abdominal infection. Although the use of antibiotics reduces the potential incidence of infection, there is no way to eliminate this risk completely.
- **Bleeding:** the needle must pass through the vaginal wall into the ovary to obtain the oocytes. Both of these structures contain blood vessels. In addition, there are other blood vessels nearby. The needle may pierce a blood vessel. Small amounts of blood loss are common during oocyte retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding may require surgical repair and possible loss of the ovary. The need for blood transfusion is rare. Although very rare, review of the world literature with IVF indicates that unrecognized bleeding has led to death.
- **Trauma:** Although the procedure is directed by the use of ultrasound guidance, it is possible to damage other nearby organs during the oocyte retrieval. Reports in the medical literature have described damage to the bowel, appendix, bladder, ureters and ovary. Some women may develop adhesions (internal scarring). 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 estimated risk of such trauma is less than 0.1%.
- **Anesthesia:** The use of anesthesia during the oocyte retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting and, in rare cases, death.
- **Procedure Failure:** It is possible that the retrieval will fail to obtain oocytes. It is also possible that retrieved oocytes may be abnormal or of poor quality, and, thus, unable to produce a normal pregnancy.

## **c. IN-VITRO FERTILIZATION AND EMBRYO CULTURE**

After eggs are retrieved, they are transferred to the embryology laboratory where they are kept in conditions that support their growth. The eggs are placed in small dishes or tubes containing "culture medium," (special fluid that resembles the fluid found in the fallopian tube or uterus) that supports embryo development. The dishes containing the egg are placed in incubators that control the temperature and atmospheric gases.

A few hours after eggs are retrieved, sperm are either placed in the culture medium with the eggs (insemination), or, individual sperm are injected into each mature egg in a technique called Intracytoplasmic Sperm Injection (ICSI) (see below). The eggs are then returned to the incubator, to develop. Periodically over the next few days, the dishes are inspected so the development of the embryos can be monitored.

In the course of egg retrieval, a large number of eggs may be retrieved. In order to maximize the number of embryos available for transfer to initiate a pregnancy, NMG's policy is to attempt to fertilize all eggs retrieved.

Each day after eggs have been inseminated or injected with a single sperm (ICSI, Day 1), they are examined for signs of fertilization and development. If the egg is successfully fertilized, it will form an embryo. The cells of the embryo will then repeatedly divide, and the number of embryonic cells will increase.

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

Although every reasonable precaution is taken, any of the following may occur in the lab:

- Fertilization of the egg(s) may fail to occur.
- One or more eggs may be fertilized abnormally resulting in an abnormal number chromosomes in the embryo. Abnormal embryos identified as having chromosomal abnormalities will not be transferred.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Bacterial contamination or a laboratory accident may result in loss or damage to some or all of the eggs or embryos.
- Laboratory equipment may fail, and/or extended power losses can occur which could lead to the destruction of eggs, sperm, and embryos.
- Other unforeseen circumstances may prevent the performances of any step of the procedure, or prevent the establishment of a pregnancy.
- Hurricanes, floods, or other 'acts of God' (including bombings or other terrorist acts) could destroy the laboratory or its contents, including sperm, eggs, or embryos being stored.

#### **d. EMBRYO TRANSFER**

After three to five days of development, the embryos are examined. If they appear to have developed successfully, one or more embryos are selected for transfer to the uterus. Embryos are placed in the uterus through a thin tube inserted through the vagina and cervix. Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. The procedure is usually painless, although some women experience mild cramping. Although the possibility of a complication from the embryo transfer is very rare, risks include infection and loss of, or damage to, the embryos. In rare cases, insertion of the embryo into the fallopian tube may result in tubal pregnancy that may require surgery.

The number of embryos transferred influences the chances of pregnancy as well as the chances of a multiple pregnancy. The transfer of several embryos increases the probability of a successful pregnancy. However, it also increases the risk of a multiple pregnancy (twins, triplets, or other multiple births). The age of the woman and the appearance of the developing embryos have the greatest influence on the incidence of pregnancy and the change of multiple pregnancy. While it is possible, it is unusual to develop more fetuses than the number of embryos transferred. It is critical for you to discuss the number of embryos to be transferred with your physician well in advance of your transfer.

In an effort to help curtail the problem of multiple pregnancies, national guidelines published in 2006 recommend limits on the number of embryos to transfer (see Tables below, reprinted with permission from the Society for Assisted Reproductive Technology). These limits may be modified depending on the developmental stage of the embryos, the quality of the embryos, and the patient's personal history.

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

| <b>Embryos</b> | <b>Age &lt; 35</b> | <b>Age 35-37</b> | <b>Age 38-40</b> | <b>Age &gt; 40</b> |
|----------------|--------------------|------------------|------------------|--------------------|
| Favorable      | 1 or 2             | 2                | 3                | 5                  |
| Unfavorable    | 2                  | 3                | 4                | 5                  |

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

| <b>Embryos</b> | <b>Age &lt; 35</b> | <b>Age 35-37</b> | <b>Age 38-40</b> | <b>Age &gt; 40</b> |
|----------------|--------------------|------------------|------------------|--------------------|
| Favorable      | 1                  | 2                | 2                | 3                  |
| Unfavorable    | 2                  | 2                | 3                | 3                  |

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

**e. HORMONAL SUPPORT OF UTERINE LINING (LUTEAL PHASE SUPPORT)**

Successful attachment of embryos to the uterine lining depends on adequate hormonal support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. However, in IVF cycles, this support is not always adequate. Therefore, progesterone is routinely given, and sometimes estradiol is also prescribed. Estradiol is given by oral, vaginal (suppository), trans-dermal (skin patch) or intramuscular injection route. Progesterone is generally administered by intramuscular injection or vaginally. These hormones are usually given for a period of 2 to 10 weeks.

2. Additional Elements and their Risks

**a. INTRACYTOPLASMIC SPERM INJECTION (ICSI)**

The use of ICSI may provide an effective treatment for male factor infertility. If viable sperm are available ICSI can counter abnormal factors of semen, such as, motility and sperm quality because ICSI delivers or places a sperm directly into the egg. With ICSI, a single sperm injected into the interior of an egg using an extremely thin glass needle. ICSI may allow couples in which the male has normal sperm counts but has male factor infertility to achieve

fertilization and live birth rates close to those achieved with in-vitro fertilization (IVF) using conventional methods of fertilization. ICSI can be performed in men with no sperm in the ejaculate if sperm can be successfully collected from the epididymis or the testis.

Reports on the risk of birth defects associated with ICSI as compared to those associated with conventional fertilization in IVF cycles, have yielded conflicting results. The most comprehensive study thus far, based on data from five-year-old children, has suggested that ICSI is associated with an increased risk of certain major congenital anomalies (birth defects). However, whether this increased risk is due to the ICSI procedure itself, or to defects within the sperm could not be determined. Note that even if there is an increased risk of birth defects in children conceived with ICSI, the risk is relatively low (4.2% versus ~3% of those conceived naturally). The impact of ICSI on the intellectual and motor development of children also has been controversial. An early report suggested that development in such children lagged significantly behind that of children resulting from conventional IVF or those conceived naturally. However, more recent studies from larger groups have not detected any differences in the development or the abilities of children born after ICSI, conventional IVF, or natural conception.

The prevalence of sex chromosome abnormalities in children conceived via ICSI is high than observed in the general IVF population, (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). The reason for the increased prevalence of chromosomal anomalies observed in ICSI offspring is unknown. It may result from the ICSI procedure itself or the father's genetic makeup. Men with sperm problem (low count, poor motility, and/or abnormal shape) are more likely themselves to have genetic abnormalities and often produce sperm with abnormal chromosomes. The sex chromosomes (X and Y) in the sperm of men with abnormal semen appear especially prone to abnormalities. If sperm with abnormal chromosomes produce pregnancies, these pregnancies will likely carry these same defects. The prevalence of translocations (a rearrangement of chromosomes that increases the risk of abnormal chromosomes in egg or sperm) can cause miscarriage and appears higher in ICSI offspring (0.36%) than the general population (0.07%).

#### **b. Assisted Hatching**

The cells that make up the early embryo are enclosed within a flexible membrane (shell) called the zona pellucida. During normal development, a portion of this membrane dissolves, allowing the cells of the embryo to escape or "hatch" out of the shell. Only upon hatching can the embryonic cells implant in the lining of the uterus to form a pregnancy. Assisted hatching involves making a hole in the outer shell that surrounds the embryo. This procedure may make it easier for embryos to implant in (attach to) the uterine wall.

The hatching is usually performed on the day of transfer, before loading the embryo into the transfer catheter. The opening can be made by mechanical means (slicing with a needle or burning the shell with a laser) or chemical means by dissolving a small hole in the shell with a dilute acid solution.

NMG, like some other programs, uses assisted hatching as part of our treatment protocols. We believe assisted hatching may improve implantation rates, and ultimately, live birth rates. However, we do not have definitive evidence to support this belief.

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

#### **c. EMBRYO CRYOPRESERVATION AND DISPOSITION**

Freezing (or cryopreservation) of embryos is a common procedure. Since multiple eggs are often produced during ovarian stimulation, it is common for more embryos to be available than are appropriate for immediate transfer to the uterus. If a patient chooses to do so, these additional embryos can usually be frozen for future use. This can eliminate the expense and inconvenience of undergoing stimulation to obtain additional eggs in the future.

Furthermore, the availability of cryopreservation permits patients to choose to transfer fewer embryos during a fresh cycle. This option reduces the risk of high-order multiple gestations (triplets or greater). Other possible reasons for cryopreservation of embryos include the freezing of all embryos in an attempt to prevent severe ovarian hyperstimulation syndrome, or if a couple were concerned that necessary medical treatment (e.g., cancer therapy or surgery) might reduce their future fertility. The pregnancy success rates for cryopreserved embryos transferred in to the human uterus varies from practice to practice. Overall pregnancy rates at the national level with frozen embryos are lower than with fresh embryos. This, at least in part, [probably] results from the routine selection of the best-looking embryos for fresh transfer, reserving the 'second-best' for freezing. There is some evidence that pregnancy rates are similar when there is no such selection. These are the indications for embryo cryopreservation:

- To reduce the risks of multiple gestation (triplets or greater).
- To preserve fertility potential in the face of certain necessary medical procedures.
- To minimize the medical risk and cost to the patient of IVF by decreasing the number of stimulated cycles and egg retrievals.
- To temporarily delay pregnancy and the risk of OHSS by freezing all embryos when this risk is too high.

### **RISKS OF EMBRYO CRYOPRESERVATION**

There are several techniques for embryo cryopreservation. Research is ongoing. One traditional method includes "slow," graduated freezing in a computerized setting. The other traditional method involves "rapid" freezing methods, called "vitrification." Both these current techniques deliver a high percentage of viable embryos when thawed after cryopreservation. There appears to be no difference in embryo viability between embryos frozen by either method. However, there can be no certainty that cryopreserved embryos will thaw normally or divide and eventually implant in the uterus.

Cryopreservation techniques possibly could be injurious to the embryo. Extensive animal data through several generations as well as limited human data do not demonstrate that children born of cryopreserved embryos that have been thawed will experience a greater risk of abnormalities than those born of fresh embryos. It is not possible, however, to be certain that there is no difference in the rate of abnormalities until very large numbers of children who were born following embryo freezing and thawing have been studied.

### **EMBRYO DISPOSITION**

NMG will only maintain cryopreserved embryos for a period of two years from the last visit to the NMG IVF program. After that time, any cryopreserved embryos must be:

1. Thawed and transferred (you are responsible for the costs of these procedures)
2. Discarded
3. Transferred to another storage facility (you are responsible for any fees associated with retrieving and packaging the embryos for shipment, equipment rental, and shipping)

There are fees associated with maintaining embryos in a frozen state. Patients/couples who have frozen embryos must remain in contact with NMG on at least an annual basis in order to inform NMG of their wishes as well as to pay fees associated with the storage of their embryos. In situations where there is no contact with NMG for a period of two years or annual fees associated with embryo storage have not been paid for a period of two years and NMG

unable to contact the patient after reasonable efforts have been made, the embryos will be considered to be abandoned and may be destroyed by NMG in accordance with normal laboratory procedures and applicable law. Reasonable efforts may include phone calls and registered mail to the most recent phone number/address in your chart. You are solely responsible for notifying NMG of any changes in your contact information, including address changes if you move.

Because of the possibility of you and/or your partner's separation, divorce, death or mental incapacitation, it is important, if you choose to cryopreserve your embryos, for you to decide what should be done with any of your cryopreserved embryos that remain in the laboratory in such an eventuality. Since this is a rapidly evolving field, both medically and legally, the clinic cannot guarantee what the available or acceptable avenues for disposition will be at any future date. At the present time, the options are:

- 1) Discarding the cryopreserved embryos
- 2) Donating the cryopreserved embryos for approved research studies
- 3) Donating the cryopreserved embryos to another couple in order to attempt pregnancy

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

- a) In the event of divorce or dissolution of the marriage or partnership, NMG will abide by the terms of the court or settlement agreement regarding the ownership and/or other rights to the embryos
- b) In the event of the death or legal incapacitation of one partner, the other partner will retain decision-making authority regarding the embryos
- c) In the event both partners die or are legally incapacitated, or if a surviving partner dies or is legally incapacitated while the embryos are still stored at NMG, the embryos shall become the sole and exclusive property of NMG. In this event I/We elect to: (please select and initial your choice). Note: both the patient and the partner must agree on disposition; as with other decisions relating to IVF, you are encouraged to discuss this issue.

**Please indicate your choice on the last page of this consent**

In the event that both partners die and the choice of disposition is donation, either to research or to another couple, NMG will make every effort to carry out the couple's wishes. If, however, after two years from the time of the couple's death, such efforts have been unsuccessful, the embryos will be discarded by the lab in accordance with laboratory procedures and applicable laws.

**B. RISKS TO THE WOMAN**

**1. OVARIAN HYPERSTIMULATION SYNDROME (OHSS)**

The most serious side effect of taking fertility medications to stimulate their ovaries during IVF is ovarian hyperstimulation syndrome (OHSS). If the drugs stimulate the ovaries too much, the ovaries can suddenly swell and fluid can leak into the belly and chest area. Symptoms of OHSS can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure or death. A very small percentage of women who undergo in vitro fertilization (2% or less of all treatment cycles) experience a severe case of OHSS. Very severe cases represent an even smaller percentage of women. About 1.4 in 100,000 cycles has led to kidney

failure. OHSS occurs at two stages: the early stage at 1 to 5 days after egg retrieval as a result of the hCG injection, and the late phase at 10 to 15 days after retrieval as a result of the hCG produced when a pregnancy occurs. The risk of severe complications of OHSS is about 4 to 12 times higher if pregnancy occurs. Occasionally, when the risk of OHSS is thought to be unacceptably high following an oocyte retrieval, no embryo transfer is performed. In such cases the embryos can be frozen for use at a later time.

OHSS rarely occurs in women who take fertility medicines only by mouth. Other risk factors for OHSS include patient age of less than 35 years, very high estrogen level during fertility treatments, and polycystic ovarian syndrome.

## 2. **CANCER**

Many have worried that the use of fertility drugs could lead to an increased risk of cancer- in particular, breast ovarian, and uterine cancers. One must be careful in interpreting epidemiological studies of women taken 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 in to account the increased cancer risk due to in infertility per se, current evidence does not support a relationship between fertility drugs and an increased risk of cancer. No conclusive long term research on the use of fertility drugs on cancer rates exists. More research is required to determine the long-term risk of fertility drugs on breast, ovarian, and uterine cancer rates.

## 3. **RISKS OF PREGNANCY**

Pregnancies that occur with IVF are associated with increased risk of certain conditions (see Table below reprinted with permission from the Executive Summary of the National Institute of Child Health and Human development Workshop held in September 2005). Some of the risks stem from the higher average age of women who become pregnant by IVF. The underlying cause of infertility may also be the cause of the increased risk of pregnancy complications. There may be additional risks related to the IVF procedure itself, however there is no research to determine the relative causes.

### **Potential Risks in Singleton (single baby) IVF – conceived Pregnancies**

|                             | <i>Absolute risk (%) in IVF-<br/>conceived Pregnancies</i> | <i>Relative Risk (vs. non IVF-<br/>conceived Pregnancies)</i> |
|-----------------------------|--|---|
| <i>Pre-eclampsia</i>        | 10.3%  | 1.6 (1.2—2.0)   |
| <i>Placenta previa</i>      | 2.4%   | 2.9 (1.5—5.4)   |
| <i>Placental abruption</i>  | 2.2%   | 2.4 (1.1—5.2)   |
| <i>Gestational diabetes</i> | 6.8%   | 2.0 (1.4—3.0)   |
| <i>Cesarean delivery</i>    | 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.

Currently more than 30% of IVF pregnancies are twins or triplets or greater. About half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. Twins, triplets and other multiple birth children are at much higher risk of premature birth or low birth weight than are singleton children. Premature birth and low birth weight are associated with a number of serious health risks. IVF twins deliver on average three weeks earlier and weigh 1,000gm less than IVF singletons. Of note, IVF twins do as well after birth as spontaneously conceived twins. Triplet and greater pregnancies deliver before 32 weeks (7months) in almost half the cases.

Additionally while the intent of embryo transfer is to transfer embryos directly into the uterus, a known risk of embryo transfer into a fallopian tube, the cervix or the abdominal cavity. This may result in an ectopic (outside the uterus) pregnancy. In addition, abnormal intrauterine pregnancies have occurred after embryo transfer during IVF. These complications may occur either alone or at the same time as the methotrexate (a week chemotherapy drug) or emergency surgery to remove the abnormal pregnancy. Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headaches, skin rash, sensitivity to the sun and temporary abnormalities in the liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus that may result in infertility, infection, bleeding and injury to internal organs.

## C. RISKS TO OFFSPRING

### 1. OVERALL RISKS

Since the first IVF birth in 1978, more than 3 million children have been born worldwide as a result of IVF. Many studies have been conducted to assess the health of IVF children and the majority have been reassuring. As more time has passed and the dataset has enlarged, some studies have suggested that IVF babies may be at increased risk for various problems as compared to naturally conceived babies.

Because the infertile couples do not have normal reproductive function, they might have babies with more abnormalities than a group of morally fertile couples. Therefore comparing a group of infertile couples to a group of fertile couples is not the proper comparison to make if one wants to assess the risk of the IVF absolute risk of any abnormal outcome appears to be small.

IVF-conceived singletons tend to be born slightly earlier than naturally conceived singletons (39.1 vs. 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF baby weighing under 5 pounds 9 ounces (2500 grams) at birth is 9.5% vs. 5.3% in naturally conceived singletons.

### 2. BIRTH DEFECTS

The risk of birth defects in the normal population is 2-3%. In IVF babies the reported birth defect rate is 2.6%-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to establish a link between IVF treatment and specific types of birth defects.

**Imprinting Disorders.** These are rare genetic disorders having to do with whether a maternal or paternal gene functions inappropriately. In two studies, approximately 4% of children with the imprinting disorder called Beckwith-Weidemann Syndrome, a congenital overgrowth condition which may affect all systems of the body were born after IVF, which is more than expected given the fraction of infants born following IVF treatment. On the other hand, a large Danish study 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 (a fast growing but treatable eye cancer affecting the retina.) in one study in the Netherlands, five cases were reported after IVF treatment, which is 5 to 7 time more than expected.

**Infant Development.** In general studies of long-term developmental outcomes have been reassuring. However, these studies are difficult to do and suffer from limitations. A recent study with better methodology reported an increased risk of cerebral palsy (3.7 fold) and developmental delay (4 fold), but most of this risk stemmed from multiple pregnancy with the associated prematurity and low birth weight.

Potential Risks in Singleton IVF Pregnancies:

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

In this table, reprinted with permission from the Society for Assisted Reproductive Technology, 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 indicated that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the "Confidence Interval") indicates the range in which the actual Relative Risk lies.

### **3. RISK OF A MULTIPLE PREGNANCY**

The most important maternal complications associated with multiple gestation are preterm labor and delivery, preeclampsia, and gestational diabetes (see prior section on Risks to Women). Others include gallbladder problems, skin problems, excess weight gain, anemia, nausea and vomiting, and worsening of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum weakness of the abdominal-wall, and umbilical hernias also can occur. Births of multiple fetuses (triplets and above) increase the risk to the mother of more significant complications including post-partum hemorrhage (bleeding) and the need for blood transfusion.

Prematurity accounts for most of the increase in complications (morbidity) as well as infant and maternal deaths (mortality) associated with multiple fetuses. Singleton IVF pregnancies are associated with an increased risk of prematurity, independent of the mother's age. With multiple pregnancies, fetuses may have growth problems, and the fetuses may develop at different rates. These factors also result in increased perinatal morbidity and mortality.

If IVF and embryo transfer results in a multiple pregnancy, you have to option of multi-fetal pregnancy reduction (One or more fetuses are selectively terminated). Multi-fetal pregnancy reduction reduces but does not eliminate the risk of complications related to multiple births.

Fetal death rates for single, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 10,000 and 21 per 1,000, respectively.

The spontaneous death (vanishing twin) of or more of those fetuses in a multiple pregnancy may be observed in up to 25% of pregnancies after IVF. This complication is more common in the first trimester. Loss of fetus in the first trimmest is unlike to physically affect the surviving fetus or mother. Demise of a single fetus in a twin pregnancy

after the first trimester is more common when they share a placenta, which occurs in between 0.5% and 6.8% of twin pregnancies, and may cause harm to the remaining fetus.

Fetuses 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 when compared to pregnancies in which two placentas are present. The incidence of twins sharing the same placenta appears to occur more frequently in pregnancies resulting from IVF.

Placenta previa (an incorrectly located placenta that may cause severe vaginal bleeding) and vasa previa (abnormal location of fetal blood vessels that may result in their rupture) are more common complications in multiple pregnancies. Abruption placenta (premature separation of the placenta from the uterus) also is more common. Additionally, postpartum hemorrhage may complicate 12% of multi-fetal deliveries. Consequences of multiple fetuses include these major risks of prematurity: cerebral palsy, retinopathy (an eye abnormality that may cause blindness), chronic lung disease, fetal growth restriction, low birth weight, polycythemia (increase red blood cells), hypoglycemia (low blood sugar), and necrotizing enterocolitis (death of some or all of the bowel tissue). In the absence of these complications, it is unclear as to what extent multiple fetuses themselves affect their behavioral development.

Rearing of twins, triplets and other multiples may generate physical, emotional, and financial stresses. The incidence of maternal depression and anxiety is increased in women raising multiple offspring. At mid-childhoods, prematurely born offspring from a multiple fetus pregnancy have lower IQ scores. Also noted is that multiple children from the same pregnancy have an increase in behavioral problems when compared with that of the single birth pregnancy. It is not clear to what extent these risks are affected by IVF.

***The Option of Multi-fetal Pregnancy Reduction (MFPR):*** Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. The greater the number of fetuses within the uterus, the greater is the risk for adverse prenatal 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 of maternal and preterm delivery, but often creates profound ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggests that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%.

In general, the risk of loss following 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 when the final number of viable fetuses is one or two, the loss rate is higher in pregnancies reduced to three viable fetuses (triplets). Pregnancies that are reduced to twins appear to do as well as spontaneously conceived twin pregnancies. An increased risk of having a small fetus for its gestational age is increased when the number of fetuses prior to MFPR is over four. The benefit of MFPR can be documented in triplet and higher number fetal pregnancies 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 before 32 weeks when compared to twins in which the risk of birth prior to 32 weeks is 7 to 10%)

#### D. ETHICAL AND RELIGIOUS CONSIDERATIONS IN INFERTILITY TREATMENT

Infertility treatment can raise ethical and religious concerns and questions for some patients. 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.

## E. PSYCHOLOGICAL EFFECTS OF INFERTILITY TREATMENT

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

The clinical psychologists of our health care team are specially trained in infertility care and are available to address any emotional symptoms that result from your infertility or its treatment. While it is normal to experience emotional ups and down 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 (e.g., two weeks or longer), you may benefit from working with a mental health professional:

- Loss of interest in usual activities
- Depression that doesn't lessen
- 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, early morning awakening, sleep more than usual for you)
- Change in your appetite or weight (increase or decrease)
- Increased use of drugs or alcohol
- Thought about death or suicide (contact us immediately if having such thoughts)
- Social isolations
- Persistent feelings of pessimism, guilt, or worthlessness
- Persistent feelings of bitterness or anger

Our program has two psychologists on staff to assist you. They may be reached by calling our receptionists at 312-695-7269. Additionally, you may contact a national support group such as RESOLVE ([www.resolve.org](http://www.resolve.org), Tel. 888-623-0744) or The American Fertility Association (AFA), ([www.theafa.org](http://www.theafa.org), Tel. 888-917-3777).

## F. LEGAL CONSIDERATIONS AND LEGAL COUNSEL

The law regarding IV, embryo cryopreservation, subsequent embryo thaw and use, and parent-child status of any resulting child(ren) is, or may be unsettled in the state in which either the patient, spouse, partner, or any current or future donor lives, or in Illinois, the state in which NMG Program is located. NMG does not provide legal advice, and you should not rely on NMG to give you any legal advice. You should consider consulting with a lawyer who is experienced in the areas of reproductive law and embryo cryopreservation as well as the disposition of embryos, including any questions or concerns about the present or future status of your embryos, your individual or joint access to them, your individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.

## G. ALTERNATIVES TO IVF

There are alternatives to conventional IVF treatment such as using donor sperm, donor eggs, adoption or not pursuing treatment. 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 still considered an experimental procedure at this time.

**Reporting outcomes:** The 1992 Fertility Clinic Success Rate and Certification Act requires the Centers for Disease Control and Prevention (CDC) to collect cycle-specific data as well as pregnancy outcome on all assisted reproductive technology cycles performed in the United States each year. Further, the CDC is required to report success rates using these data. Consequently, data from your IVF procedure will be provided to the CDC, and to the Society of Assisted Reproductive Technologies (SART) of the American Society of Reproductive Medicine (ASRM). NMG's IVF Program is a member of SART. The CDC may request additional information from NMG or may contact you directly for additional follow-up. Additionally, your information may be used and disclosed in accordance with HIPPA guidelines in order to perform research or quality control. All information used for research will be de-identified prior to publication. De-identification is a process intended to prevent the data associated with your treatment from being used to identify you individually.

**NOTE:** This document provides reported outcome statistics of what are considered to be national averages for facilities using IVF treatments. These reported statistics include pregnancy rates, cesarean delivery rates and pre-term delivery rates. These numbers are not meant to indicate the rates of these outcomes at Northwestern Medicine or other individual practices offering IVF. Northwestern Medicine may at any time have a higher or lower pregnancy and delivery rate than these national averages, as well as higher or lower risks for certain complications. It is appropriate to ask your physician about our particular rates for a specific time period.

While this information is believed to be up to date at the time of publication (2009), newer reports may not yet be incorporated into this document. Ask your physician if you would like further information