Assisted Reproduction

In Vitro Fertilization
Intracytoplasmic Sperm Injection
Assisted Hatching
Embryo Freezing
Preimplantation Genetic Diagnosis
Egg Cryopreservation

Consent for Treatment

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Consent for Assisted Reproduction

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Intracytoplasmic Sperm Injection
Assisted Hatching
Embryo Freezing

INSTRUCTIONS:
Please read this document carefully. If you do not understand the information provided, please speak with your treating physician. This material is being presented so you can make an informed decision regarding the elements of IVF treatment you agree to undertake in your upcoming IVF treatment cycle.
Please bring the booklet with you to your appointment. You and your partner will also need to bring your photo ID. You will be asked to sign consents for treatment when you meet with the IVF New England physician.

OVERVIEW

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

This consent reviews the IVF process from start to finish, including the risks that this treatment might pose to you and your offspring. While best efforts have been made to disclose all known risks, there may be risks of IVF that are not yet clarified or even suspected at the time of this writing.

An IVF cycle typically includes the following steps or procedures:

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

In certain cases, these additional procedures can be employed:

- **Intracytoplasmic sperm injection (ICSI) to increase the chance for fertilization**
- **Assisted hatching of embryos to increase the chance of embryo attachment ("implantation")**
- **Embryo Cryopreservation (freezing)**

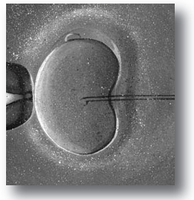
Please Note:

At various points in this document, rates are given that reflect what are believed to be U.S. national averages for those employing IVF treatments. These include items such as pregnancy rates, Cesarean delivery rates, and preterm delivery rates. These rates are not meant to indicate the rates of these outcomes within individual physician practices offering IVF, and are not to be understood as such. Specific physician practices may have higher or lower pregnancy and delivery rates than these national averages, and also higher or lower risks for certain complications. It is appropriate to ask the physician practice about their specific rates.

Also note that while this information is believed to be up to date at the time of publication (2014), newer reports may not yet be incorporated into this document.

Table of Contents

Revision Date: October 2014



Core Elements of IVF and Their Risk

Medications for IVF Treatment

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

Gonadotropins, or injectable "fertility drugs" (Follistim®, Gonal-F®, Bravelle®, Menopur®) These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (follicles are sacs which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. 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.

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 may be used to prevent premature ovulation

An overly vigorous ovarian response can occur, or conversely an inadequate response

As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to these drugs. The intent of giving these medications is to mature multiple follicles, and many women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2.0 % of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section 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.

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

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

GnRH-agonists: Leuprolide acetate (Lupron®)
This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for 1 to 3 months. It is the short-acting form that is used primarily in the IVF process. 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 (GnRH-a) initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way for more than 20 years. Potential side effects usually experienced with long-term use include, but are not limited to, hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. No long term or serious side effects are known. Since GnRH-a may be administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use contraception (either contraceptive pills or condoms) the month you will be starting the GnRH-a. GnRH-a have not been associated with any fetal malformations, however, you should discontinue use of the GnRH-a if pregnancy is confirmed.

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

Human chorionic gonadotropin (hCG) (Profasi®, Novarel®, Pregnyl®, Ovidrel®)
hCG is a natural hormone used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to, breast tenderness, bloating, and pelvic discomfort.

Progesterone, and in some cases, estradiol
Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg retrieval in some women, the ovaries will not produce adequate amounts of these hormones long enough to fully support a pregnancy. Accordingly, supplemental progesterone, and in some cases estradiol, are given to ensure adequate hormonal support of the uterine lining. Progesterone is usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories - see Compounded Medications on page 4) after egg retrieval. Progesterone is often continued for some weeks after a pregnancy has been confirmed. Progesterone use during an IVF cycle has not been associated with an increase in fetal abnormalities. Side effects of progesterone include depression, sleepiness, allergic reaction and, if given by intra-muscular injection, includes the additional risk of infection or pain at the application site. Estradiol, if given, can be by oral, trans-dermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the injection site if given by intramuscular injection and the risk of blood clots or stroke.

Oral contraceptive pills:
Many treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to

Continued on page 4

Oral contraceptive pills:
Many treatment protocols include oral contraceptive pills to be taken for 10 to 14 days before gonadotropin injections are started in order to suppress hormone production or to schedule a cycle. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or stroke.

Other medications:
Anti-anxiety medications or muscle relaxants may be recommended prior to the embryo transfer; the most common side effect is drowsiness. Other medications such as steroids, heparin, low molecular weight heparin or low dose aspirin may also be included in the treatment protocol.

Compounded medications:
Some of the medications that may be used in your fertility treatment, (such as micro-dose leuprolide acetate, micro-dose ovidrel, intramuscular progesterone in ethyl oleate, cotton seed or olive oil, progesterone vaginal suppositories) are "compounded drugs". This means that a licensed pharmacist (and not a drug manufacturer) has combined, mixed or altered the ingredients to create a medication tailored to the medical needs of a fertility patient. As such, these drugs have not been FDA-approved and therefore, not subject to the same testing and standards to determine their safety and effectiveness. These drugs have been prepared by a licensed pharmacist who is subject to the rules, regulations and sterile preparation guidelines of the State in which he/she practices and in which the pharmacy is located. These rules and regulations may or may not be as stringent as those for drugs approved by the FDA. As a result, compounded medications may carry certain risks and side-effects different from prescription medications supplied by a drug manufacturer. If you have questions about any medication that you are using that is compounded, please speak with your physician or contact the pharmacy directly.

Transvaginal Oocyte (Egg) Retrieval

Oocyte retrieval is the removal of eggs from the ovary. A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A long needle, which can be seen on ultrasound, can be guided into each follicle and the contents aspirated. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa (egg-supporting) cells. Rarely the ovaries are not accessible by the transvaginal route and laparoscopy or 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.

It is important to recognize that not all follicles contain eggs. In general, 50-70% of follicles are likely to provide an egg. Follicles 15mm and greater are the most likely to provide eggs.

Risks of egg retrieval include:

Infection:
Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are used before the egg retrieval procedure to reduce the risk of pelvic or abdominal infection in patients at higher risk for this complication. Despite the use of antibiotics, there is no way to eliminate this risk completely.

Bleeding:
The needle passes through the vaginal wall and into the ovary to obtion, 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 lead to death.) However, the risk of such trauma is low.

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

Anesthesia:
The use of anesthesia during the egg retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting and in rare cases, death. Complications are more likely to occur in those who have pre-existing
medical diseases such as obesity, asthma, high blood pressure and heart disease.

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

In Vitro Fertilization and Embryo Culture

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

A few hours after egg retrieval, sperm are placed in the culture medium with the eggs, or individual sperm are injected into each mature egg in a technique called Intracytoplasmic Sperm Injection (ICSI see page 6). The eggs are then returned to the incubator, where they remain to develop. Periodically over the next few days, the dishes are inspected so the development of the embryos can be assessed.

The day after the eggs have been inseminated or injected with a single sperm (ICSI), they are examined for signs that the process of fertilization is underway. At this stage, normal development is evident by the still single cell having 2 nuclei; this stage is called a zygote. Two days after insemination or ICSI, normal embryos have divided into about 4 cells. Three days after insemination or ICSI, normally developing embryos contain 6 to 8 cells. Five days after insemination or ICSI, normal embryos have developed to the blastocyst stage, which is typified by an embryo that now has 80 or more cells, an inner fluid-filled cavity and a small cluster of cells called the inner cell mass.

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

Sperm and eggs are placed together in specialized conditions (culture media, controlled temperature, humidity and light) in hopes of fertilization

Culture medium is designed to permit normal fertilization and early embryo development, but the content of the medium is not standardized.

Embryo development in the lab helps distinguish embryos with more implantation potential from those with less or none.

In spite of reasonable precautions, any of the following may occur in the lab that would prevent the establishment of a pregnancy:

- **Fertilization of the egg(s) may fail to occur.**
- **One or more eggs may be fertilized abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos 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 any step of the procedure to be performed or prevent the establishment of a pregnancy.**
- **Hurricanes, floods, or other 'Acts of God' (including bombings or other terrorist acts) could destroy the laboratory or its contents, including any sperm, eggs, or embryos being stored there.**

Quality control in the lab is extremely important. Sometimes immature or unfertilized eggs, sperm or abnormal embryos (abnormally fertilized eggs or embryos whose lack of development indicates they are not of sufficient quality to be transferred) that would normally be discarded can be used for quality control. You are being asked to allow the clinic to use this material for quality control purposes before being discarded in accordance with normal laboratory procedures and applicable laws. None of this material will be utilized to establish a pregnancy or a cell line unless you sign other consent forms to allow the clinic to use your eggs, sperm or embryos for research purposes.

Embryo Transfer

After a few days of development, one or more embryos are selected for transfer to the uterine cavity. Embryos are placed in the uterine cavity with a thin tube. Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. Although the possibility of a complication from the embryo transfer is very rare, risks include infection and damage to or loss of the embryos.

The number of embryos transferred influences the pregnancy rate and the multiple pregnancy rate. The age of the woman and the appearance of the developing embryo have the greatest influence on pregnancy outcome and the chance for multiple pregnancy. While it is possible, it is unusual to develop more fetuses than the number of embryos transferred. It is critical to discuss the number to be transferred before the transfer is done.

After a few days of development, the best appearing embryos are selected for transfer

The number chosen influences the pregnancy rate and the multiple pregnancy rate

A woman's age and the appearance of the developing embryo have the greatest influences on pregnancy outcome

Embryos are placed in the uterine cavity with a thin tube

Excess embryos of sufficient quality that are not transferred can be frozen

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

In an effort to help curtail the problem of multiple pregnancies (see Multiple Pregnancy on page 14), national guidelines published in 2009 recommend limits on the number of embryos to transfer (see Tables above). These limits differ depending on the developmental stage of the embryos and the quality of the embryos and take into account the patient's personal history.

In some cases, there will be additional embryos remaining in the lab after the transfer is completed. Depending on their developmental progress, it may be possible to freeze them for later use. (See Cryopreserved Embryo Storage on page 12).

Hormonal Support of Uterine Lining

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 some clinics also prescribe estradiol. Progesterone is given by the intramuscular or vaginal route. Estradiol is given by the oral, vaginal, trans dermal, or intramuscular route. The duration of this support is from 2 to 10 weeks.

Additional Elements of IVF and Their Risk

Intracytoplasmic Sperm Injection (ICSI)

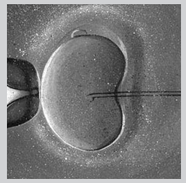
The use of ICSI provides an effective treatment for male factor infertility. The negative effects of abnormal semen characteristics and sperm quality on fertilization can be overcome with ICSI if viable sperm are available because the technique bypasses the shell around the egg (zona pellucida) and the egg membrane (oolemma) to deliver the sperm directly into the egg. ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle. ICSI allows couples with male factor infertility to achieve fertilization and live birth rates close to those achieved with in vitro fertilization (IVF) using conventional methods of fertilization in men with normal sperm counts. ICSI can be performed even in men with no sperm in the ejaculate if sperm can be successfully collected from the epididymis or the testis.

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

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

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

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



ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal

Overall success rates with ICSI are slightly lower than for conventional insemination

An increased risk of genetic defects in offspring is reported

ICSI will not improve oocyte defects

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 embryonic cells to escape or "hatch" out of the shell. Only upon hatching can the embryonic cells implant within the wall of the uterus to form a pregnancy.

Assisted hatching is the laboratory technique in which an embryologist makes an artificial opening in the shell of the embryo. The hatching is usually performed on the day of transfer, prior to loading the embryo into the transfer catheter. The opening 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.

Some clinics have incorporated artificial or "assisted hatching" into their treatment protocols because they believe it improves implantation rates, and ultimately, live birth rates although definitive evidence of this is lacking.

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

Assisted Hatching involves making a hole in the outer shell (zona pellucida) that surrounds the embryo

Hatching may make it easier for embryos to escape from the shell that surrounds them and improve likelihood of implantation

Genetic Screening Tests

Genetic carrier screening is done to determine if one or both parents may have abnormal genes that may increase the chance that their child will have a specific genetic disease. For many genetic diseases, if someone has an abnormal gene, that person is considered a carrier for that genetic disease. If this abnormal gene is passed to the child, the child will usually not be affected with that genetic disease, but will also be a carrier for that genetic disease. If both parents are carriers of the abnormal gene for the same genetic disease, there is a 25% chance that their child will inherit one abnormal gene from each parent and be affected with the genetic disease. Genetic screening is typically done on one parent first, and if the first parent tests positive, then the other parent is tested.

The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Geneticists (ACMG) recommend routine screening for certain genetic diseases and additional screening when indicated due to ethnicity, family history or other known risk factors. Two of the recommended standard genetic carrier screening tests are Cystic Fibrosis (CF) and Spinal Muscular Atrophy (SMA). There is no one genetic carrier test that detects all genetic diseases and, therefore, genetic carrier test may only be done for specified genetic diseases and are usually performed on a blood sample. During the course of your evaluation and treatment at the Reproductive Science Center if New England, your physician may recommend screening for specific genetic disease(s) which may be indicated based on your medical history and/or family history to determine whether or not you are a carrier for that specific genetic disease(s). You will be asked to sign a consent to be tested or a waiver declining testing for CF, SMA and any other genetic screening tests recommended by your physician.

Preimplantation Genetic Diagnosis (PGD)

The goal of PGD is to increase the probability that embryos which implant and create a pregnancy will be unaffected by the specific genetic condition being tested for. Embryos determined to be affected by the disease are identified at a very early stage so that transfer of these embryos is avoided, thereby decreasing the chances of the birth of an affected child. Below are examples of genetic abnormalities that can be evaluated using PGD. Each will be discussed specifically in the sections that follow:

1. Single gene mutations that can cause disease (e.g. Cystic Fibrosis, Spinal Muscular Atrophy, Tay Sachs)

2. Chromosome copy number, also known as aneuploidy (e.g. Trisomy 21 or "Down Syndrome")

3. Abnormalities in chromosome structure, such as translocations, circular chromosomes, inversions, duplications or deletions.

Embryos possessing any of the above abnormalities are considered to be "affected", whereas if the genetic makeup is normal, the embryo is considered to be "unaffected." The probability of becoming pregnant with an affected fetus is much less after PGD than it is after natural conception in couples at risk for passing on any of the above abnormalities to their offspring. **However, it is important to realize that even if an embryo has been tested and is determined to be genetically "unaffected," this does not guarantee the birth of a healthy child as there are many non-genetic factors that influence pregnancy outcome. In addition, the baby may be affected by a genetic condition which was not specifically tested for at the time of PGD.**

Description of Technique

During in vitro fertilization (IVF), eggs are fertilized by sperm leading to the development of embryos which may continue on to develop into blastocysts on the fifth or sixth day following egg retrieval. Biopsy can be performed either on the third day (blastomere biopsy) or on the fifth or sixth day (trophectoderm biopsy) after the eggs have been retrieved.

A small opening is made in the protein shell (zona pellucida) surrounding the embryo using a very precise laser beam after which one or more cells are removed from the embryo. The biopsied cells are transferred to a test tube in which they are dissolved, releasing the DNA for analysis. The biopsies from each sampled embryo will be transported to an outside genetics laboratory specializing in the analysis of the genetic material (the DNA) of the biopsied cells.

There are several techniques available, and the type of genetic diagnostic technique that is used depends on the genetic abnormality of interest and the laboratory performing the analysis. Some examples of these analytic techniques are described below.

A mutation (a change) in a gene that can cause disease can be detected using specific probes for the mutation plus DNA markers that identify sequences "linked" to the gene of interest. The testing will determine if the embryo has no mutations or has one or more mutations. Whether or not the embryo is determined to be an "unaffected," "carrier" or "affected" by the disease or genetic abnormality will depend upon the genetic disease of concern. There are many possible mutations that can occur in a given gene that could result in an

Continued on page 8

affected child. Which mutation or combination of mutations is present is often unique to the patient and her partner.

Customized probes may need to be designed and validated to identify these unique mutations and can often take up to 3 months to develop. This should be considered when planning the time line of your IVF cycle.

Another type of testing employs an array of thousands of molecular probes to detect the DNA and is, appropriately, called "microarray analysis". Comparative Genomic Hybridization-microarray (CGH-microarray) is a technique that compares the genetic readings from the biopsies with a standard reference DNA from normal cells. This comparison will provide information on whether the biopsies have the same chromosome copy number as the normal reference or have too few or too many copies, a condition called aneuploidy.

Potential Risks

1. Accuracy of Diagnosis using PGD

At present, PGD detects 95-99% of embryos affected with a genetic abnormality. This detection rate depends on the genetic condition of interest and the testing techniques used by the genetics laboratory that analyzes the biopsies prepared by RSC. Because this technology is not 100% accurate, there is a 1%-5% chance of mis-diagnosis, again, depending on the genetic abnormality being tested for and the techniques the genetics laboratory uses for the analysis. Therefore, it is strongly recommended that patients who become pregnant following IVF with PGD confirm the diagnosis with either chorionic villus sampling (CVS) or amniocentesis after pregnancy has been established. The risks and benefits of this procedure should be discussed with your obstetrician.

2. Inconclusive Diagnosis

Once PGD has been performed, the results are reported to the embryology team and your physician for review. The report will provide the result of the genetic analysis for each biopsied embryo. From this information, your physician can determine if the respective embryos are affected with the genetic condition of concern, or are unaffected. However, there are occasions where the analysis of the biopsy specimen yields inconclusive results because of technical reasons beyond the control of the individual performing the biopsy preparation or genetic analysis. Approximately 10% of biopsied embryos will not have a diagnosis. In this situation, a diagnosis of whether or not that embryo is affected with the genetic disorder cannot be made. In some instances, a re-biopsy of the embryo can be performed with freezing of the embryo and re-testing . Your physician will discuss your options with you and determine the best course of action.

3. Contamination

It is essential that the cell(s) biopsied from an embryo is the only source of DNA that is tested. If any other cells or DNA enter the test tube containing the biopsied cell(s), then the results of the analysis will be unreliable. One source of contamination is sperm adhering to the embryo from the insemination procedure. This is the reason why ICSI is done when PGD is planned - to ensure that there is no contamination with sperm. We make the maximal effort to ensure that contamination of the sample with extra cells or DNA does not occur. However, even the most careful procedures cannot entirely eliminate this possibility. Contamination usually affects less than 5% of cells tested during PGD. The genetic testing laboratory will perform a number of additional tests to assess whether or not contamination may be present in each sample, allowing most cases of contamination to be detected. If a biopsy is affected by contamination, the embryo from which it is derived cannot conclusively be determined to be free of genetic abnormalities. If such a case arises, your physician will discuss this with you.

4. Injury to the Embryo during the Biopsy Procedure

Embryo biopsy, the removal of cells from an embryo for testing, may have a negative effect on the embryo's development. If embryos arrest or develop poorly or abnormally, no embryo transfer will occur regardless of the embryo's genetic status.

5. No Suitable Embryos for Biopsy

Because embryo development is a product of sperm and egg quality which can vary from cell to cell, not all eggs and sperm have the ability to achieve fertilization, and not all fertilized eggs and embryos may develop to a stage allowing biopsy. If no embryos acquire the appropriate developmental stage, biopsy cannot be performed and PGD will not be possible.

Depending on the purpose of the PGD, if there are very few embryos suitable for biopsy, there is the option to not proceed with biopsy for PGD. Rather, these embryos may be cryopreserved to accumulate a reasonable number before proceeding with embryo biopsy in a subsequent IVF cycle.

6. No Genetically Unaffected Embryos Suitable for Transfer

It is possible that none of the embryos biopsied will be found to be unaffected. Embryos determined to be affected with a genetic condition are unlikely to result in a healthy pregnancy or live birth. Therefore, transfer of these genetically affected embryos will not be performed.

7. No Viable Embryos for Transfer

It is possible that the embryos found to be genetically unaffected do not develop normally. There may be other factors inherent to the embryos that do not allow development to proceed normally making these embryos unsuitable for transfer. Therefore, transfer of these embryos will not be performed.

8. No Extra Embryos for Freezing

If most of the embryos tested are found to be abnormal, there may only be one or two embryos suitable for transfer, and none are left for cryopreservation. This is very common.

9. Transfer and Confirmation of a Genetically Unaffected Embryo does not Guarantee a Healthy Child

There are many conditions that impact the health of a pregnancy and the resulting offspring that are not necessarily genetically predetermined. Factors such as environmental influences during pregnancy, delivery and other hereditable factors with no defined or identifiable genetic markers can result in having a child with developmental or other health issues.

Testing for Single Gene Diseases

There are many conditions that arise due to mutation or alteration within the DNA sequence of a specific gene. Such conditions include Cystic Fibrosis, Spinal Muscular Atrophy and Huntington's Disease, to name only a few. PGD for single gene diseases seeks to distinguish embryos that will be affected by the disease of concern between those that are unaffected, with the goal of increasing the chances of birth of a child free of the disease. Embryos that are affected possess the genetic mutations that result in the disease. Those that are "carriers" may possess one normal gene and one mutated gene. These "carrier" embryos are unaffected, however, these individuals may pass on their gene mutation to their offspring in the future. Embryos which are normal possess only normal (non-mutated) copies of the gene of concern.

Different diseases have different inheritance patterns - the manner in which a disease predisposition is passed through generations of a family. Your physician and/or genetics counselor will discuss with you the potential risks and benefits of PGD and how this testing applies to your specific situation.

Testing for Structural Chromosomal Abnormalities

Chromosomes are packages of DNA in string-like structures found in the nucleus of the cell. Chromosomes carry inherited information in genes made of DNA. During the process of cell division, occasionally, chromosomes may become fused to each other, or pieces of different chromosomes may interchange. This is known as a chromosomal translocation. This chromosomal translocation may occur in such a way that there is no extra or missing chromosomal material, or the break in the chromosome may not affect gene function and there is no effect on the individual. If there is no additional or missing chromosomal material, the translocation is considered to be "balanced". If there is extra or missing chromosomal material, the translocation is described as "unbalanced".

Individuals with balanced translocations typically have no medical problems, although some do have reduced fertility and suffer recurrent pregnancy losses. Although someone with a balanced translocation may otherwise be healthy, a problem can arise if the egg or sperm of that individual has an unbalanced chromosomal make-up that leads to an unbalanced translocation in the resultant embryo. The presence of an unbalanced translocation can lead to unsuccessful implantation of an embryo, a spontaneous miscarriage during pregnancy, or birth of a baby with mental and physical problems that may be incompatible with life. A child who appears to have the same balanced chromosomal translocation as his/her parent may have a subtle change in the chromosomal material which is sufficient to result in physical or mental problems. This new change may not be large enough to be detected by standard chromosomal analysis.

There are two types of chromosomal translocations: Reciprocal and Robertsonian. Reciprocal translocations involve any two chromosomes. Breaks occur in the chromosomes allowing pieces to be exchanged between them. Approximately one in 625 individuals carries a reciprocal balanced translocation. In contrast, Robertsonian translocations result from breaks in the middle of one chromosome and subsequent fusion of 2 bottoms of that chromosome, thus re-arranging the structure of that chromosome. Robertsonian translocations have been observed in chromosomes 13, 14, 15, 21 and 22. Approximately one in 900 individuals carries a Robertsonian translocation.

PGD for structural chromosomal anomalies seeks to identify embryos with a normal arrangement of chromosomal material. Your physician and/or genetics counselor will discuss with you how PGD can impact the chances of conceiving an unaffected child and the limitations of this technology depending on your specific situation.

Testing for Aneuploidy

There are 23 pairs of chromosomes in humans. Twenty- two pairs are called "autosomes" which are common to both men and women and the 23rd pair comprises the sex chromosomes. The normal male sex chromosome pair is XY and the normal female chromosome pair is XX. Problems arise when there are more or fewer chromosomes than the 23 pairs described above, a situation known as "aneuploidy". Extra or missing chromosomes can result from errors in cell division as the sperm and egg are forming in the testicle and ovary, respectively, or these errors can occur after the sperm fertilizes the egg and cells begin dividing as the embryo develops. The most common cause of miscarriage in the first 12 weeks of pregnancy is aneuploidy. As women age, the miscarriage rate increases, particularly after age 35 years and is largely due to an increasing proportion of eggs with an abnormal complement of chromosomes. Abnormalities of sperm may contribute to aneuploidy but are responsible for a small minority of cases. Some examples of aneuploidy include Down Syndrome, also known as Trisomy 21 in which there are 3 copies of chromosome 21 rather than two. Trisomy 16 is the most common trisomy found in spontaneous miscarriages in the first 12 weeks. Turner's Syndrome, also known as Monosomy X, is a condition in which the individual has only one X chromosome without a second X chromosome or Y chromosome. This is the most common genetic abnormality in spontaneous miscarriages in the first 12 weeks of pregnancy.

The utility of using PGD testing for aneuploidy is controversial. One of the challenges of performing this testing accurately is that all 23 pairs of chromosomes must be analyzed rather than limiting the test to a specific gene or piece of DNA involved in a translocation as described above. A second challenge is the phenomenon of "mosaicism", a situation in which an embryo may contain some normal cells and some aneuploid cell but later "correct" itself by excluding the aneuploid cells as the embryo develops. With rapidly advancing techniques in genetic analysis and embryo biopsy, these challenges have been surmounted, and the benefits of PGD for aneuploidy can be achieved. This testing can have up to a 5% misdiagnosis rate depending on the genetic analysis and embryo biopsy techniques that are used. PGD for aneuploidy has been used to address recurrent pregnancy loss, recurrent IVF failure and other situations where a couple may be at risk for a specific aneuploid event. Your physician and/or genetics counselor will discuss with you the risks and benefits of such testing in your specific situation.

Gender Selection and Family Balancing

PGD for determination of the gender of an embryo has multiple applications. There are certain genetic diseases that are caused by a mutation of a gene in the X chromosome. Because the normal male sex chromosome complement is XY, any gene mutation present on the X chromosome will result in the male individual being affected by the genetic disease, since there is not a complementary normal X chromosome to offset the expression of the mutated gene as there is in females (whose normal complement is XX). Hemophilia, which is a bleeding disorder, is an example of an X-linked disease. In this case, if a couple is at risk for passing Hemophilia on to their male offspring, they may choose to transfer only female embryos to avoid a male affected with the disease.

Another reason a couple may choose to determine the gender of their embryos is to balance their family. Couples who have one or more children of the same gender may wish to have a child of the opposite gender to balance their family. This application of PGD technology is controversial. For this reason, IVF New England (IVFNE) has taken a thoughtful approach to creating the guidelines below for performing PGD for family balancing:

1. The couple must have a medical indication for IVF.

2. The couple already has a child (or children) of one gender and they wish to balance their family with a child of the opposite gender.

3. If the couple is doing PGD for another medical indication and information about the gender is available, the couple may select the gender of the embryos among those available for transfer regardless of the status of their family dynamic.

4. It is strongly recommended that the couple meet with an IVF New England counselor or other appropriate psychological counselor prior to starting the treatment cycle.

It is important to recognize that PGD tests only for the disease of concern and does not seek to identify every possible genetic problem that may be present in a developing embryo. For example, PGD may be performed to identify if an embryo is affected with Cystic Fibrosis. The embryo may be correctly diagnosed as being unaffected with Cystic Fibrosis, but could potentially be affected with Down Syndrome. If PGD is being done for Cystic Fibrosis ONLY, then Down Syndrome will not be tested for. Your physician will discuss your testing options and recommendations with you.

Egg Freezing / Oocyte Cryopreservation

Egg freezing or oocyte cryopreservation may be discussed by your physician for the purpose of preserving your fertility through a process in which your eggs are frozen for later use. Egg freezing may be used in a variety of different scenarios depending on your unique clinical circumstances. Potential reasons for oocyte cryopreservation include freezing eggs for later childbearing, limiting the number of eggs to be inseminated during an IVF cycle to avoid creating surplus embryos, or for patients undergoing medical treatment that will negatively affect their future ovarian and reproductive functions (e.g. cancer patients or transgender individuals). Oocyte cryopreservation offers the benefit of being able to freeze eggs at one's current age for use in the future. Frozen eggs do not age with the passage of time and therefore may have a higher chance of pregnancy and a lower risk of miscarriage as compared to that individual conceiving later in life. This may allow some women the ability to preserve their reproductive potential even if their ovarian function has declined with advancing age.

The process of oocyte cryopreservation entails undergoing ovarian stimulation and monitoring followed by egg retrieval as described in the "Technique of In Vitro Fertilization (IVF)" section of this book. After the eggs are retrieved, mature, viable eggs are frozen and stored for future use rather than being inseminated for immediate use. Eggs which are, in the judgment of the embryology laboratory staff, found to be non-viable, immature, of poor quality or damaged will be discarded according to acceptable laboratory procedures. The process of freezing eggs for fertility preservation is done by a process called vitrification which allows the eggs to be frozen rapidly. The technologies used for egg freezing are relatively new techniques that continue to evolve. IVFNE uses protocols, methods and instrumentation that have been validated in other centers as well as our own center.

At the time pregnancy is desired, medications are administered to prepare the uterus for embryo implantation. Near the time the uterus is ready for embryo implantation, frozen eggs are thawed and inseminated by a process called intra-cytoplasmic sperm injection (ICSI) [See pages 6 - 7, *Additional Elements of IVF and Their Risk]* whereby a single sperm is injected into each egg. Eggs which fertilize successfully would continue to develop into embryos that are cultured in the laboratory until the time of the embryo transfer. At that time, one or more embryo(s) will be transferred to the uterus. Any remaining high quality embryos that are not transferred may be cryopreserved as blastocysts for future use.

As with traditional IVF, there is no guarantee of successful childbirth from freezing one's eggs. There are risks of damage to the egg during the process of oocyte cryopreservation and the eventual thaw, insemination and embryo transfer. Frozen oocytes may or may not survive the thaw, fertilize, form a viable embryo(s), or implant in the uterus. In addition, frozen oocytes and eventually created embryo(s) also have a risk of aneuploidy and miscarriage that is often related to the maternal age at which time the oocytes were retrieved for cryopreservation. To date, there is no long term data that suggests differences in the rates of birth defects or abnormalities in children born from cryopreserved eggs compared to fresh eggs. However, it is possible that, in the future, differences may become apparent that we are not yet aware of at this time.

It is also difficult to predict the number of oocytes one needs to freeze to result in successful childbirth in the future. Unlike a traditional IVF cycle where the outcome of egg retrieval, insemination and transfer are apparent in the near term, the outcome of the frozen eggs and their ability to result in a pregnancy is not known until much later in time. It is also possible that some women who freeze eggs may not end up using them as they may not have difficulty conceiving on their own in the future.

Deciding to freeze eggs is a decision that considers your individual medical, social, and ethical circumstances as well as a number of psychosocial aspects related to disposition of the eggs. IVF New England offers counseling resources to assist in navigating through these complicated issues. Your doctor will further discuss this with you at the time of your consultation.

Embryo Disposition

Freezing (or "cryopreservation") of embryos is a common procedure. Since multiple eggs (oocytes) are often produced during ovarian stimulation, on occasion there are more embryos available than are considered appropriate for transfer to the uterus. These embryos, if viable, can be frozen for future use. This saves the expense and inconvenience of stimulation to obtain additional eggs in the future. Furthermore, the availability of cryopreservation permits patients to transfer fewer embryos during a fresh cycle, reducing the risk of high-order multiple gestations (triplets or greater). Other possible reasons for cryopreservation of embryos include freezing all embryos in the initial cycle to prevent severe ovarian hyperstimulation syndrome (OHSS), or if a couple is concerned that their future fertility potential might be reduced due to necessary medical treatment (e.g., cancer therapy or surgery). The pregnancy success rates for cryopreserved embryos transferred into the human uterus can vary 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, 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. At IVF New England, embryos are routinely frozen at the blastocyst stage by vitrification on the 5th or 6th day following oocyte retrieval. Analysis of our internal data demonstrate comparable pregnancy rates achieved with our thawed vitrified blastocysts when compared to pregnancy rates achieved using blastocysts from a fresh IVF cycle that have not been frozen previously.

Indications:

- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures
- To increase the chance of having one or more pregnancies from a single cycle of ovarian stimulation
- To minimize the medical risk and cost to the patient by decreasing the number of stimulated cycles and egg retrievals
- To temporarily delay pregnancy and the risks of OHSS by freezing all embryos, when this risk is high.

Risks of embryo cryopreservation:

There are several techniques for embryo cryopreservation, and research is ongoing. Traditional methods include "slow," graduated freezing in a computerized setting, and "rapid" freezing methods, called "vitrification." Current techniques deliver a high percentage of viable embryos thawed after cryopreservation, but there can be no certainty that embryos will thaw normally, nor be viable enough to divide and eventually implant in the uterus. Cryopreservation techniques could theoretically be injurious to the embryo. Extensive animal data (through several generations), and limited human data, do not indicate any likelihood that children born of embryos that have been cryopreserved and thawed will experience greater risk of abnormalities than those born of fresh embryos. However, until very large numbers of children have been born following freezing and thawing of embryos, it is not possible to be certain that the rate of abnormalities is no different from the normal rate.

Because of the possibility of you and your partner's separation, death or incapacitation, it is important to decide on the disposition of any embryo(s), fresh or cryopreserved that remain in the laboratory. Since this is a rapidly evolving field, both medically and legally, the clinic cannot guarantee what the available or acceptable avenues for disposition will be at any future date. At the present time, the alternatives are:

- Discarding the cryopreserved embryo(s)
- Donating the cryopreserved embryo(s) for approved research studies.
- Donating the cryopreserved embryos to another couple in order to attempt pregnancy (You may be asked to undergo additional infectious disease testing and screening required by the FDA if you select this option.) This is often facilitated by an outside agency that coordinates embryo donation.

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

a. In the event of divorce or dissolution of the marriage or partnership, the ownership and/or other rights to the embryo(s) will be as directed by court decree and/or settlement agreement.

b. In the event of the death or incapacitation of one partner, the embryo(s) will become the sole and exclusive property of the surviving partner.

c. In the event of death or incapacitation of both partners or of a last surviving partner, the embryo(s) shall become the sole and exclusive property of the clinic unless legal documentation is in place stating otherwise.

Cryopreserved Embryo Storage

Options for cryopreserved embryo disposition provide that they can be:

1. Thawed and transferred;
2. Released to an outside embryo donation agency;
3. Donated to research;
4. Discarded; or
5. Transferred to another storage facility.

Additionally, maintaining embryo(s) in a frozen state is labor intensive and expensive. There are fees associated with freezing and maintaining cryopreserved embryo(s). Patients/couples who have frozen embryo(s) must remain in contact with the clinic on an annual basis in order to inform the clinic of their wishes as well as to pay fees associated with the storage of their embryo(s). IVF New England will maintain cryopreserved embryos according to the Fees for Embryo Cryopreservation and Storage Policy on the last page of the IVF Consent Book. Cryopreserved embryos will be maintained until specific directives and authorization for those directives are provided. When the disposition has been decided, IVF New England requires that a consent form specific to the method of disposition be signed and approved by the Laboratory Manager. IVF New England reserves the right at its sole discretion to make decisions regarding the final disposition of cryopreserved embryos if fee obligations are not met.

Donated or Research Embryo Fate

In certain situations, donating embryo(s) for research or to another couple may not be possible or may be restricted by law. While efforts will be made to abide by your wishes, no guarantees can be given that embryo(s) will be used for research or donated to another couple. In these instances, if after 5 years no recipient or research project can be found, or your embryos are not eligible, your embryo(s) may be discarded by the lab in accordance with laboratory procedures and applicable laws.

Risks to Female Patient

Ovarian Hyperstimulation Syndrome

To increase the number of eggs that develop in a given month, a series of injections containing hormones are given during the treatment cycle.

The most serious side effect of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). Its symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure, or death. The severe cases affect only a very small percentage of women who undergo in vitro fertilization -- 0.2 percent or less of all treatment cycles -- and the very severe are an even smaller percentage. Only about 1.4 in 100,000 cycles has lead to kidney failure, for example. OHSS occurs at two stages: early, 1 to 5 days after egg retrieval (as a result of the hCG trigger); and late, 10 to 15 days after retrieval (as a result of the hCG if pregnancy occurs). The risk of severe complications is about 4 to 12 times higher if pregnancy occurs, which is why sometimes no embryo transfer is performed to reduce the possibility of this occurring.

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk in IVF Pregnancies	Relative Risk in IVF 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.

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 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.

Risks of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions *(see Table at left 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.

Nationally, 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 (7 months) in almost half of cases.

Miscarriage and Ectopic Pregnancy

The goal of any assisted reproductive technology (ART) is to establish a pregnancy that develops into the birth of a healthy baby. This begins when the embryo, formed by the union of sperm and egg, successfully implants within the uterine cavity. As is true with natural conception, pregnancies achieved with assistance may not continue to develop normally.

A pregnancy may implant in the uterus, but develop abnormally and ultimately cease to develop. This is called a "miscarriage" or "spontaneous abortion". The most common time for miscarriages to occur is in the first 3 months (trimester) of pregnancy. The most common reason for these miscarriages is a chromosomal abnormality within the embryo that prevents development from proceeding normally. Miscarriages can also occur in the second and third trimesters, however this is less common.

A chromosomally and developmentally normal embryo sometimes implants outside the uterine cavity. This is called an "ectopic pregnancy". The fallopian tube is the most common place for ectopic pregnancies to occur. They can also occur on the ovary, in the cervix or in the abdomen, however these situations are very rare. They are first detected when hCG (human chorionic gonadotropin, the hormone detected by a pregnancy test) levels do not increase at the expected rate. When this occurs, levels are monitored very closely and pelvic ultrasound sometimes can visualize the location of the pregnancy. These pregnancies must be terminated because serious complications can develop if a pregnancy is allowed to progress in a location outside of the uterus. These pregnancies are most often resolved medically, however, in cases where medical treatment is unsuccessful or if the pregnancy is advanced, these pregnancies may need to be removed surgically.

To date there is no known direct causal relationship between the use of assisted reproductive technology and spontaneous abortion. However, the use of ART has been observed to be associated with an increase in the incidence of ectopic pregnancy. This increased risk may be due to the fact that many patients who require IVF to conceive may have pre-existing tubal disease causing their infertility which may or may not be apparent, and tubal disease is well-known to predispose to the development of tubal ectopic pregnancy. Transfer of multiple embryos simultaneously into the reproductive tract may increase the risk of "heterotopic pregnancy" which is the situation where one (or more) embryo(s) implanted in the uterus, but one (or more) embryo(s) also implanted in the fallopian tube(s) or elsewhere.

There are other potential factors that may increase the risk of miscarriage or ectopic pregnancy that are inherent to the couple's medical history. Your doctor will discuss with you what your particular risk factors are and any additional testing or precautions that are recommended.

Risks to Offspring

Overall risks

Since the first birth of an IVF baby in 1978, more than 3 million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. As more time has passed and the data set has enlarged, some studies have raised doubts about the equivalence of risks for IVF. A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

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

Potential Risks in Singleton IVF Pregnancies	Absolute Risk in IVF Pregnancies	Relative Risk in 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--2.2)
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.

Birth Defects

The risk of birth defects in the normal population is 2 to 3 %. In IVF babies the birth defect rate may be 2.6 to 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.

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 5 to 7 times more than expected.

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

Multiple Pregnancy

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-ecclampsia, and gestational diabetes (see prior section on Risks to Women). Others include gall bladder and skin problems, excess weight gain, anemia, excessive nausea and vomiting and exacerbation of gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias can also occur. Problems with the developing placenta are more common in multiple gestations and can lead to severe bleeding during pregnancy and in the post partum period. Maternal hemorrhage complicates 12% of multifetal deliveries. Triplets and higher order multiples further increase the risk of the above complications to the mother.

Prematurity accounts for most of the excess newborn complications associated with multi-fetal gestation. These potential complications include but are not limited to cerebral palsy, retinopathy of prematurity, chronic lung disease, fetal growth restriction and discordant growth, intracranial hemorrhage (bleeding surrounding the brain), necrotizing enterocolitis (a potentially fatal form of intestinal infection) and problems with cognitive and behavioral development. Multi-fetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications. It is also important to note that IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1000, 15.5 per 1000 and 21 per 1000, respectively. The death of one or more fetuses in a multi-fetal 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 additional complications to the mother or newborn have 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. The incidence of a shared placenta ranges from 0.5% to 6.8% and may cause harm to the remaining fetus. Twin to twin transfusion syndrome results when there is an imbalance of circulation between the fetuses and occurs in up to 20% of twins sharing a placenta. Excess or insufficient amniotic fluid may also result from twin to twin transfusion syndrome. Twins sharing the same placenta occurs more frequently after blastocyst transfer and these pregnancies have a higher frequency of birth defects compared to pregnancies having separate placentas.

Rearing of twins and high-order multiples may generate physical, emotional and financial stresses. The incidence of maternal depression and anxiety is also increased in women raising offspring from multi-fetal gestation. At mid-childhood, offspring born prematurely from multiple gestation have lower IQ scores and an increase in behavioral problems compared with singletons. It is not clear to what extent these risks are affected by IVF per se.

The Option of Multifetal Pregnancy Reduction: Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. The greater the number of fetuses within the uterus, the greater is the risk for adverse perinatal and maternal outcomes. Patients with more than twins are faced with the 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 complications to mother and fetus. Multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates profound ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggest that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%.

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

Ethical and Religious Considerations in Infertility Treatment

Infertility treatment can raise concerns and questions of an ethical or religious nature for some patients. The technique of in vitro fertilization (IVF) involves the creation of human embryos outside the body, and can involve the production of excess embryos and/or 'high-order' multiple pregnancy (triplets or more). 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.

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

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

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

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

Our health care team can assist you in locating a qualified mental health professional who is familiar with the emotional experience of infertility, or you can contact a national support group such as RESOLVE, (www.resolve.org, Tel. 1-888-623-0744) or The American Fertility Association (AFA), (www.theafa.org, Tel: 1-888-917-3777).

Legal Considerations and Legal Counsel

The law regarding embryo cryopreservation, subsequent thaw and use, and parent-child status of any resulting child(ren) is, or may be, unsettled in the state in which the patient, spouse, partner, or any donor currently or in the future lives. Patients are encouraged to consult a lawyer who is experienced in reproductive law about any questions or concerns about the present or future status of embryos, individual or joint access to them, individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.

Alternatives to IVF

There are alternatives to IVF treatment including use of donor sperm, donor eggs, donor embryos, adoption, or not pursuing any treatment at all. Gametes (sperm and/or eggs), instead of embryos may be frozen for future attempts to conceive in an effort to avoid potential legal issues relating to disposition of surplus cryopreserved embryos. Other interventions such as gamete intra-fallopian transfer (GIFT), zygote intra-fallopian transfer (ZIFT) and tubal embryo transfer (TET) were practiced in the 1990's, but are now mainly of historical interest. Through the years, the success rates for IVF have increased significantly such that these alternative techniques are now rarely practiced and are available at only a few centers around the country.

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 and requires them to report success rates using these data. Consequently, data from a patient's IVF procedure will be provided by IVFNE to the CDC, and to the Society of Assisted Reproductive Technologies (SART) of the American Society of Reproductive Medicine (ASRM). The CDC may request additional information from the center or may contact IVFNE patients for additional follow-up. Additionally, patients' information may be used and disclosed in accordance with HIPAA 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 a patient's treatment from being used to identify individual patients.

HIV (Human Immunodeficiency Virus) Screening

Tests for previous exposure to the HIV virus are performed on blood samples obtained from both male and female. HIV is the virus that causes AIDS (Acquired Immunodeficiency Syndrome). A positive test indicates that you have been infected with the HIV virus and are able to infect others.

It has been the policy of IVF New England to require that all individuals involved in infertility treatment be tested for the presence of HIV and other communicable diseases. The purpose of this testing is to prevent the occurrence of AIDS in a possible offspring, in accordance with the policies of the American Society for Reproductive Medicine. Women who harbor the virus, but have no symptoms of AIDS, may pass this serious disease to their offspring. Treating the pregnant woman may reduce the rate of transmission to the fetus. Men and women, whether or not they are symptomatic, may pass the virus to their sexual partners. Needle sharing with infected persons and blood products used medically are the other means of transmission of the AIDS virus.

Infected people may harbor the virus for many years (at least ten years in some cases) without manifesting any symptoms of AIDS. The fact that a person harbors the virus and is potentially contagious may be determined by a blood test. The blood test may not be accurate in the first weeks or even months after contracting the viral infection. It is not clear whether all persons with HIV will ultimately develop AIDS, but careful medical follow-up is required.

Each state regulates the performance of the test; most states mandate that individuals being tested be counseled about AIDS and about the implications of positive and negative test results. Copies of HIV test results are not sent out without the expressed written permission of the individuals.

In consenting to having testing for HIV, each member of the couple agrees to inform the other partner about the results of the test.

Couples who are using donor sperm, donor egg or a gestational carrier should be aware that the donor and/or carrier are tested for HIV, hepatitis, Chlamydia and other infections. Testing is performed in accordance with the U.S Department of Health and Human Services Food and Drug Administration regulations, which govern Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products. Despite this testing, we can make no guarantee that there will not be the transmission of HIV, or any other virus or illness.

References

General IVF overviews available on the internet

http://www.sart.org/
http://www.cdc.gov/art/
http://www.resolve.org/site/PageServer

Number of Embryos to Transfer

Guidelines on number of embryos transferred. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S51-S52.

Culturing Embryos to the Blastocyst Stage

Blastocyst culture and transfer in clinical-assisted reproduction. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S89-S92.

Intracytoplasmic Sperm Injection

Genetic considerations related to intracytoplasmic sperm injection (ICSI). The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology.
Fertil Steril 2006; 86 (suppl 4): S103-S105.

Embryo Hatching

The role of assisted hatching in in vitro fertilization: a review of the literature.
A Committee opinion. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S124-S126.

Ovarian Hyperstimulation

Ovarian hyperstimulation syndrome. The Practice Committees of the American Society for Reproductive Medicine. Fertil Steril 2006; 86 (suppl 4): S178-S183.

Risks of Pregnancy

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Risks to Offspring

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Multiple pregnancy associated with infertility therapy. The Practice Committees of the American Society for Reproductive Medicine Fertil Steril 2006; 86 (suppl 4): S106-S110.

Imprinting diseases and IVF: A Danish National IVF cohort study. Lidegaard O, Pinborg A and Anderson AN. Human Reproduction 2005; 20(4):950-954.

Patient Bill of Rights

IVF New England exists for the purpose of providing high quality care that consistently meets or exceeds the expectations of patients. We believe that each patient is worthy of respect and understanding, and has certain rights and responsibilities related to the care she/he receives.

As a patient of IVF New England you have the right to...

- **Be treated with dignity, courtesy, and respect.**
- **Access services regardless of race, religion, sexual preference or source of payment**
- **Be fully informed verbally or in writing, prior to services being rendered, of all financial obligations**
- **Participate in decision-making regarding your care**
- **Have access to the physician and nurse directing your care, and information regarding your treatment and treatment outcomes**
- **Have questions answered courteously and thoroughly**
- **Be communicated with in a way that you can reasonably understand**
- **Have the right to refuse treatments (as permitted by law) and to be informed of the medical consequences of such refusal**
- **Be assured of privacy and confidentiality in treatment**
- **Have the right to approve release of medical records to outside sources**
- **Have competent, qualified personnel carry out the services for which they are responsible**
- **Voice grievances about care that is not provided, recommend policy/service changes, and make complaints without fear of reprisal or unreasonable interruption of care**

Complaints, recommendations, or grievances should be reported to:
Rick Dietz, Executive Director, IVF New England
One Forbes Road, Lexington, MA 02421-7305 • 781.674.1215

Patient Responsibilities

Each Patient has the responsibility to...

- **Provide complete and accurate information regarding their health status and medical care to the best of his or her ability**
- **Make it known whether or not they understand the care and treatments to be performed, and take an active role in their treatment by being informed and prepared**
- **Update name, phone number, address and insurance information as changes occur**
- **Notify RSC staff of appointment cancellations at least 24 hours in advance**
- **Notify their physician or nurse of any hospital admissions related to their care**
- **Tell staff members of any concerns about quality of care**

IVF New England
Helping people become parents®

IVF New England

Fees for Embryo Cryopreservation and Storage

Many times a patient yields more healthy embryos from in vitro fertilization than would be wise to transfer. With your informed consent, these additional healthy embryos can be cryopreserved for your later use in attempting to establish a pregnancy.

Billing Policy – Embryo Cryopreservation

If embryos are cryopreserved after your embryo transfer, IVF New England will bill your insurance for the cryopreservation service. Typically, insurance will cover embryo cryopreservation if infertility treatment is covered; however, we suggest you contact your insurance company directly for coverage information on your specific policy.

Should you not have insurance coverage for treatment or should your insurance deny coverage for embryo cryopreservation, you will receive a bill for $325.

This $325 fee will cover the initial cryopreservation and the first three months of storage.

Billing Policy – Embryo Storage

For the fourth and subsequent months your embryos remain in storage a fee of $85 for each calendar month, or part thereof, will be billed on a monthly basis.
Billing for storage is effective as of the first day of the month.

At this time, Blue Cross Blue Shield of MA and Harvard Pilgrim are the only insurances that offer coverage for long-term storage of embryos. If Blue Cross Blue Shield of MA pays for embryo cryopreservation, there will be 2 years of storage included in that payment. If Harvard Pilgrim pays for the embryo cryopreservation, there will be 1 year of storage included in that payment. If there is no coverage for the initial cryopreservation, there is no coverage for any additional storage and you will be billed directly for storage fees.

Should you have any insurance other that Blue Cross Blue Shield of MA or Harvard Pilgrim you will be billed directly for storage services as long term storage is not a covered benefit.

If, at any time, you wish to remove your cryopreserved embryos from IVF New England, you will be required to complete a consent form and return the notarized consent to IVF New England. The forms are available on our website or can be obtained by calling our CryoBiology Laboratory.

If you have any additional questions please contact Financial Services at 781.674.1585.