BOSTON IVF

CONSENT FORM FOR
A COUPLE USING A GESTATIONAL CARRIER

INSTRUCTIONS:

This consent form provides a description of the treatment that you are undertaking.

- Read the consent completely. If you have any questions please speak with your doctor.
- Do not make any additions or deletions to the consent.
- Treatment **cannot** be started until all consents are signed.
- Consents must be signed in front of your nurse or physician.

INTRODUCTION

In Vitro Fertilization (IVF) is a treatment that helps an infertile woman achieve a pregnancy. The technique involves four main steps: 1) the development of eggs in the woman's ovaries; 2) the removal of eggs from her ovaries; 3) the placement of the eggs and sperm together in the laboratory to allow fertilization to occur, and; 4) the transfer of fertilized eggs (embryos) into the woman's uterus for the establishment of pregnancy. The existence of the embryos outside of a woman's body creates the possibility of placement of these embryos into a second woman (gestational carrier) who then carries the pregnancy. The intention following the delivery is to unite the baby (or babies) with the couple who will be the rearing parents.

This consent explains the treatment and describes the major risks. In addition, the responsibilities of those who participate in this treatment are discussed. This consent is valid for a period of one calendar year after it has been signed. Please make a copy for your records. It is recommended that you review the consent prior to each treatment cycle. If you have any questions about your treatment then it is your responsibility to speak with your physician.

Pre-treatment Recommendations

During treatment a woman should avoid any activity, behavior and medications that could reduce her chance of conceiving and having a healthy baby. In addition, the recommendations listed below should be followed.

1. A prenatal vitamin should be taken on a daily basis before the treatment is begun. This will reduce the chance that a baby will be born with a neural tube defect (e.g. spina bifida), which is a birth defect that affects the development of the spine.
2. Smoking must be avoided before and during treatment.
3. Recreational drugs are absolutely contraindicated.
4. Ingestion of aspirin or aspirin-like products (e.g. Motrin®, Advil®, Anaprox®, Naprosyn®, Aleve®, etc.) should be avoided during treatment. However, in certain circumstances your doctor may prescribe low dose aspirin (baby aspirin, 81 mg).

5. The use of alcohol should be avoided during treatment.
6. The use of all prescription and over-the-counter medications (including herbal remedies) should be discussed with a physician before starting a treatment cycle.
7. Ingestion of some fish, which contain higher amounts of mercury, can affect the development of the nervous system of a fetus. During the treatment you should avoid eating these fish- shark, swordfish, king mackerel, tilefish and canned tuna fish. You should limit the intake of all other fish to 12 oz. per week.

DESCRIPTION OF THE TREATMENT

Gestational carrier treatment is done in conjunction with IVF and involves several steps. Success cannot be guaranteed at any or all of these steps. If optimal results are not appreciated at any step, it may be recommended that treatment be stopped and the cycle cancelled.

I. **Ovulation Induction**: The 'genetic mother' will take medications to stimulate the development of multiple ovarian follicles (the fluid-filled cysts in the ovary that contain the eggs).

II. **Egg Retrieval:** The 'genetic mother' will have the eggs removed from her ovaries.

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

IV. **Preparation of the Endometrium:** The uterine cavity of the gestational carrier will be hormonally prepared prior to the embryo transfer to allow implantation to occur.

V. **Embryo Transfer:** One or more embryos will be transferred into the uterus of the gestational carrier.

VI. **Embryo Freezing:** Following the embryo transfer, any remaining embryos of suitable quality may be frozen (cryopreserved) and stored for future embryo transfer(s).

The gestational carrier participates in steps IV and V. The couple or the female partner of the couple ('genetic mother') will participate in steps I, II, III and VI. The steps of the treatment are described in greater detail below.

I. Ovulation Induction

The eggs are present in the ovaries within fluid-filled cysts called follicles. During a woman's menstrual cycle, usually one mature follicle develops, which results in the ovulation of a single egg. Several hormones including follicle stimulating hormone (FSH) and luteinizing hormone (LH) influence the growth of the ovarian follicle. These hormones are produced by the pituitary gland, which is located at the base of the brain. FSH is the main hormone that stimulates the growth of the follicle, which produces an estrogen hormone called *estradiol*. When the follicle is mature, a large amount of LH is released by the pituitary gland. This surge of LH helps to mature the egg and leads to ovulation 36-40 hours after its initiation.

The success of IVF is dependent on the number of eggs that are removed from the ovaries. Medications are administered to increase the number of follicles that develop, which will increase the number of eggs that are obtained at the egg retrieval, which will increase the number of embryos that will be available for transfer. By increasing the number of embryos that can be transferred, the chance of pregnancy increases. There are several medications that can be used for this phase of treatment.

1. *Gonadotropins* - these are injectable medications commonly prescribed to stimulate the ovaries of women undergoing IVF treatment. Two types of gonadotropins can be prescribed and are discussed below.

    a. FSH (Gonal-F®, Follistim®, Bravelle®) - These medications contain only FSH and are administered on a daily basis by injection.

    b. LH (Luveris®) – This medication contains only LH and is administered by injection. It is used in combination with FSH containing medications.

    c. Human Menopausal Gonadotropins (Menopur®, Repronex®) - These medications contain equal amounts of FSH and LH, and are administered on a daily basis by injection.

2. *GnRH Agonist (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 1-3 months. The primary role of this medication is to prevent a premature LH surge, which could result in the release of eggs before they are ready to be retrieved. Since GnRH-agonists initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. 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 are often times administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception (condoms) the month you will be starting the GnRH-a. GnRH-a have not been associated with any fetal malformations however you should discontinue use of the GnRH-a as soon as pregnancy is confirmed.

3. *GnRH Antagonist (Cetrotide®, Ganirelix®)* - GnRH antagonists are medications that reversibly bind to GnRH receptors in the pituitary gland and prevent release of FSH and LH. GnRH antagonists are administered in combination with gonadotropins. The major benefit of a GnRH antagonist is that it suppresses a LH surge thereby preventing ovulation.

4. *Clomiphene Citrate (Clomid®, Serophene®)* and letrozole *(Famara®)* - These medications are synthetic hormones that are taken orally for a period of five days and cause the release of FSH and LH, which stimulate the development of follicles. These medications are used in combination with injectable medications.

5. *Human Chorionic Gonadotropin [hCG] (Ovidrel®, Profasi® Pregnyl®, Novarel®)* - This medication contains the pregnancy hormone, hCG, which functions similarly to LH. It is administered 36 hours before the egg retrieval by injection and matures the eggs, which will allow them to become fertilized.

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

Note: Many of the medications that are used are administered by an injection. The patient or another person can be instructed to give these injections.

Side Effects

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 use of the above listed medications can cause side effects such as nausea, vomiting, hot flashes, headaches, mood swings, visual symptoms, memory difficulties, joint problems, weight gain and weight loss, all of which are temporary. 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.. Other possible side effects include the following:

- *Ovarian Hyperstimulation* - After the egg retrieval is performed, the ovarian follicles, which have been aspirated, can fill up with fluid and form cysts. The formation of cysts will result in ovarian enlargement and can lead to lower abdominal discomfort, bloating and distention. These symptoms generally occur within two weeks after the egg retrieval. The symptoms usually resolve within 1-2 weeks without intervention. If ovarian hyperstimulation occurs your physician may recommend a period of reduced activity and bed rest. Pregnancy can worsen the symptoms of ovarian hyperstimulation. Severe ovarian hyperstimulation is characterized by the development of large ovarian cysts and fluid in the abdominal and, sometimes, chest cavities. Symptoms of severe ovarian hyperstimulation include abdominal distention and bloating along with weight gain, shortness of breath, nausea, vomiting and decreased urine output. Approximately 2% of women will develop severe ovarian hyperstimulation and may need to be admitted to the hospital for observation and treatment. To help alleviate the symptoms of severe ovarian hyperstimulation an ultrasound-guided paracentesis can be performed which results in the removal of fluid from of the abdominal cavity. Rare, but serious consequences of severe ovarian hyperstimulation include formation of blood clots that can lead to a stroke, kidney damage and possibly death. Every woman who takes these medications can develop ovarian hyperstimulation. In some cases when there is concern that a woman is at significant risk for ovarian hyperstimulation, the cycle may be cancelled or the eggs will be retrieved and any embryos that result may be frozen.

- *Ovarian Torsion (Twisting*) - In less than 1% of cases, a fluid filled cyst(s) in the ovary can cause the ovary to twist on itself. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary.

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

- *Breast and Uterine Cancer*: More research is required to examine what the long-term impact of 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.

Monitoring

During the ovulation induction phase of treatment, monitoring of follicular development is performed with periodic blood hormone tests and/or vaginal ultrasound exams. Monitoring helps the physician to determine the appropriate dose of the medications and the timing of the egg retrieval. Vaginal ultrasound examinations are usually painless and generally considered to be safe. However, the possibility of harm cannot be excluded. Blood drawing may be associated with mild discomfort and, possibly, bruising, bleeding, infection or scar at the needle sites. The need for repeated ultrasound

examinations and/or blood drawing on a frequent basis requires the woman's presence in the vicinity of a Boston IVF monitoring site.

II. 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. Specimens normally discarded from this procedure may be used for future research purposes. If this is done all specimens will be anonymized and your name or medical information will not used. 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. Risks of egg retrieval include:

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

Bleeding*:* The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels. In addition, there are other blood vessels nearby. Small amounts of blood loss are common during egg retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding will frequently require 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.)

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

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

Anesthesia - For the egg retrieval, medications usually are administered by an anesthesiologist. The patient will have a consultation with the anesthesiologist before the procedure to review the risks and benefits of the anesthesia. In some cases the use of anesthesia on a specific patient may be associated with an increased risk. In such cases the physician may offer local anesthesia without the assistance of an anesthesiologist. It is mandatory that there is no oral intake after midnight prior to the egg retrieval. After the procedure is completed, the patient will be discharged home usually within one hour. Because of the anesthetic medications that are used a patient must be accompanied home by a responsible adult. Each patient is responsible for bringing a responsible adult with them on the day of the egg retrieval. Following the egg retrieval, vaginal spotting and lower abdominal cramping are normal. During the remainder of the day following the surgery, activities should be limited. If significant bleeding, vomiting, abdominal pain or any other symptoms develop, you should contact her physician. If you should have any difficulty in contacting your physician the patient or her caretaker should proceed to the emergency department of the nearest hospital.

III. Insemination of the Eggs

On the day of the egg retrieval, a sperm sample is obtained. Under some circumstances, sperm can be frozen prior to the day of egg retrieval for use on the day of egg retrieval. Reasons to consider sperm freezing would be if the male partner may not be available on the day of the egg retrieval or there has been difficulty in the past with the production of a semen sample. You are responsible for making arrangements to freeze sperm prior to the start of treatment if this applies to you. The source of the sperm can be from the male partner or in some situations the couple (patient) may choose to use donor sperm. The biologist processes the sperm sample and then the eggs are inseminated. There are two approaches to the insemination of the eggs that are discussed below:

1. ***Standard Insemination*** - If the sperm sample is adequate then a standard insemination of the eggs can be performed. After the sperm sample has been processed, a mixture of the sperm and eggs is placed in a plastic dish containing a nutrient culture media and then placed in an incubator in the laboratory to allow fertilization to occur. The nutrient culture media contains a serum additive, which is a blood product, and there is a rare chance of transmission of a viral infection. The morning after the egg retrieval, the eggs are examined to see if fertilization has occurred.

2. ***Intracytoplasmic sperm injection (ICSI)*** - ICSI is a laboratory procedure performed to increase the chances of fertilization.

   The ICSI procedure is a process, whereby, with the aid of a microscope and fine instruments, a single sperm is injected directly into the egg. Indications for ICSI include- a previous IVF cycle with poor fertilization, a previous semen analysis demonstrating significant abnormalities and in situations where surgical aspiration of sperm from the vas deferens or testicle is required. In most cases it is known at the start of the IVF cycle that ICSI will be performed. However, in other cases the sperm sample on the day of the egg retrieval may be unexpectedly inadequate for standard insemination and the ICSI procedure may be performed.

   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 (X and Y) 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 is increased with ICSI. The prevalence of de novo (not inherited) balanced translocations in offspring derived from ICSI is increased. The prevalence of these combined (0.36%) 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 (mutations) 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 also 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. If you would like additional information about the genetic issues surrounding IVF and the ICSI procedure talk to your physician about a referral to a genetics counselor.

The following additional risks are associated with the performance of the ICSI procedure:

1. The eggs may fail to become fertilized or may be damaged precluding their ability to be fertilized.
2. ICSI may yield presently unknown risks to the baby and/or mother.
3. Studies have shown that some cases of male infertility may be genetic. Therefore there is the possibility that infertility may be passed on to the offspring as stated above. Some studies show an increased risk of chromosomal and other abnormalities in babies born as a result of the ICSI procedure. If pregnancy is achieved testing can be performed to determine the chromosomal makeup of the fetus. If you would like additional information concerning genetics and inheritance, you should ask your physician to refer you to a genetic counselor prior to the start of your treatment cycle.
4. ICSI may compromise the protective effect of the membrane that surrounds the embryo, which may result in bacterial contamination and infection in the embryo that would render it non-viable.

On average, 60-70% of eggs will fertilize following the standard insemination or the ICSI procedure but in some cases none of the eggs fertilize. If fertilization is confirmed, plans are then made for the embryo transfer. In some cases of documented fertilization the embryos stop their development and the embryo transfer is cancelled.

IV. Preparation of the Endometrium

The gestational carrier is administered hormones, including estrogen and progesterone, to prepare the endometrium for implantation.

V. Embryo Transfer

After fertilization has been confirmed, the development of the embryos is monitored in the laboratory. If the embryos continue their development then plans are made for the embryo transfer. The embryo transfer is performed 3 to 6 days following the egg retrieval. Embryos transferred 3 days after the egg retrieval are generally at the 4 to 8 cell stage. Embryos transferred on day 5 or 6 are at a more advanced stage and may have developed into a blastocyst, which is made up of over 50 cells. Your physician will discuss with you the optimal time of the transfer. In the event that the embryos stop their development the embryo transfer is not performed.

At the time of the embryo transfer, a physician will review the fertilization results and the development of the embryos. A decision will be made regarding the number of embryos that will be transferred. Increasing the number of embryos transferred will increase the chances of pregnancy, but will also increase the risk of a multiple pregnancy (e.g., twins, triplets, etc). Remaining embryos that are not transferred will be examined and, if they are of suitable quality, may be frozen, stored and transferred at a later date. Alternatively, these "extra" embryos can be discarded.

Embryos which result from abnormal fertilization (i.e., polyspermy -when more than one sperm fertilizes an egg) will be discarded because they have no chance of developing normally. In addition, embryos that fail to develop properly (e.g., fail to divide, demonstrate other significant abnormalities of development) will also be discarded. Eggs and/or embryos, which have failed to develop (not viable), will not be transferred and will be discarded.

In order to perform the embryo transfer the woman is placed in the same position for a pelvic exam. A speculum is placed into the vagina and the cervix is visualized. The vagina and cervix are rinsed with a solution. In some cases an abdominal ultrasound is performed to help visualize the passage of the catheter. The biologist loads the embryos into a catheter, which the physician inserts through the cervical canal and into the uterine cavity. After placement of the catheter the embryos are injected into the uterine cavity. The catheter is examined by the biologist to confirm that the embryos have been discharged. Following the procedure the woman will be sent home. Activity should be limited on the day of the embryo transfer. Thereafter, normal activity should be resumed.

Very rarely, a uterine infection may occur after embryo transfer. The most common symptoms associated with infection are pain and fever. If fever, vomiting, abdominal pain or any other symptoms develop following embryo transfer, you should contact your physician.

Assisted Embryo Hatching

Your physician may recommend that assisted hatching be performed on the embryos just prior to the transfer. The zona pellucida is the outer protective membrane that surrounds the egg. After the sperm has penetrated the egg and fertilization has occurred, the embryo develops within the confines of the zona pellucida for a period of 5-7 days. Thereafter, an area of the zona pellucida thins out and the embryo "hatches" or is expelled out of the confines of the zona pellucida. It is only then that the embryo has the opportunity to implant into the uterine wall for the establishment of a pregnancy. It is possible that some embryos do not undergo this "hatching" process normally. A laboratory technique has been developed to facilitate the embryo with this "hatching" process and is referred to as *assisted hatching*. There is controversy as to whether the performance of assisted hatching increases the chance of a successful pregnancy following IVF treatment.

The assisted embryo hatching procedure- With the aid of a microscope and fine instruments, the zona pellucida (the outer membrane surrounding the embryo) is thinned by either the application of a dilute acidic solution or a laser. The embryos are then transferred back into the incubator until the embryo transfer is performed. Your physician may prescribe an antibiotic and a corticosteroid (methylprednisolone), which will be started on the day of the egg retrieval and continued for a period of four days.

The following risks are associated with the assisted hatching procedure.

1. The embryos may be destroyed or injured precluding their ability to implant.
2. There is an increased chance that an embryo splits and leads to a set of identical twins. This type of a multiple pregnancy is referred to as monozygotic twinning (MZT). The risks associated with MZT are described later in the consent. .
3. The procedure may yield presently unknown risks to the baby and/or mother.
4. Assisted hatching may not improve your chances of establishing a pregnancy.
5. There are risks associate with medications that may be prescribed
    a. Methylprednisolone- This medication has an anti-inflammatory action and modifies the immune response. The following side effects may occur but are more common when this drug is administered for a longer duration or at higher doses: mood swings, insomnia, depression, psychotic manifestations, muscle weakness, permanent hip replacement, impaired wound healing, increase sweating, headaches, vertigo, allergic reaction, loss of muscle mass, osteoporosis and abdominal distention. Other side effects include an increase in blood pressure, salt and water retention, increase excretion of potassium and calcium may occur. The use of methylprednisolone may mask the signs of an infection, make one susceptible to a new infection, and make it difficult to localize the source of an infection.
    b. The use of antibiotics may result in the following side effects which are dose-related: nausea, vomiting, diarrhea, loss of appetite, rashes, sensitivity to the sun, rare hypersensitivity reaction which may cause shock, blood diseases including reduced platelets or fractured blood cells which could result in anemia and/or bleeding.

VI. Embryo Cryopreservation of viable, high quality embryos (if any) not transferred:

I/We understand that to date, there are no known effects from long-term storage of cryopreserved (frozen) embryos. Although there are theoretical risks of congenital malformations, I/we understand that the best available research suggests that the rate of birth defects in children born following the cryopreservation of embryos is the same as the rate observed in an age-matched group of pregnant women who conceived without assisted reproduction:

1. **_____ Patient initials _____Partner initials I/We <u>AGREE</u> to embryo cryopreservation** (if **applicable**)

OR

2. **_____Patient initials _____Partner initials I/We <u>DO NOT AGREE</u> to embryo cryopreservation (if applicable)**

Disposition of Cryopreserved Embryos:
Any disposition of embryos requires the written authorization of both partners. If your embryos were formed using eggs/sperm from a third party donor, your instructions to donate these embryos must be in accordance with prior agreements with the egg/sperm donor or applicable law. Your instructions to donate the embryos may require separate consent from the egg/sperm donor.

I/We understand and agree that in the event of death or incapacitation of one partner, the embryo(s) will become the sole and exclusive property of the surviving partner, unless otherwise directed by law, a court order or as designated in my/our will. If the surviving partner, friends or family members wish to conceive with these embryos after your death, a legal document indicating this intent will be required.

I/We understand that the cryopreserved embryos will incur a charge according to the Fees for Embryo Cryopreservation and Storage policy of Boston IVF. Cryopreserved embryos will be maintained until specific directives and authorization for those directives are provided by me/us. Options for disposition are discussed in the Consent for Treatment Guideline and consent forms are required at the time of disposition. Boston IVF reserves the right at its sole discretion to make decisions regarding the final disposition of cryopreserved embryos if fee obligations are not met. In the event of divorce or dissolution of the relationship between patient and partner, embryos cannot be used, donated or discarded without the expressed, written consent of both parties or as directed by a court order, even if egg/donor sperm was used.

VII. Risks to the Woman

1. Ovarian Hyperstimulation Syndrome
To increase the number of eggs that develop, a series of hormone shots are given. The hormones used in this regimen are known to have, or suspected of having a variety of side effects, some minor and some potentially major. 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 *hormone* 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.

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 (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact of 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.

3. Risks of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions including pre-eclampsia, placenta previa, plancental abruption, gestational diabetes and cesarean section. 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.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater). 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 (2.2 pounds) 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.

Additionally, while embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone or concurrently with a normal intra-uterine pregnancy . These abnormal pregnancies often times require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy. Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding and injury to any internal organs.

A miscarriage is a failed intrauterine pregnancy. The risk of miscarriage in the general population is 15-20%. The risk of miscarriage increases with advancing maternal age. For women over 40 years of age, the risk may exceed 40%. Studies have shown that there is either no increase or a slight increase in the risk of miscarriage in women who conceive with IVF. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require surgical treatment. In some cases, removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilatation and curettage (D&C).

VIII. Risks to Offspring

1. **Overall risks**:

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

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

3. **Imprinting Disorders:**
These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. 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.

4. **Childhood cancers**: Most studies have not reported an increased risk with the exception of retinoblastoma:

5. **Infant Development**: In general, studies of long-term developmental outcomes have been reassuring so far; most children are doing well.

6. **Risks of a Multiple Pregnancy**: The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia and gestational diabetes (see prior section on Risks to Woman). Others include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Triplets and above increase the risk to the mother of more significant complications including post-partum hemorrhage and transfusion.
Prematurity accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations. Moreover, IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus or mother. No excess perinatal (mature fetus or newborn) or maternal morbidity has been described resulting from a “vanishing” embryo.

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

Monozygotic twinning (MZT) is a multiple pregnancy that results from the splitting of a single embryo, which will lead to a set of identical twins. The incidence of MZT is increased in pregnancies conceived following IVF and may occur between 1.5-5% of IVF pregnancies. In addition to the above stated complications associated with a multiple pregnancy with MZT there is a greater chance of twin-to-twin transfusion, which can affect the growth of the fetuses and increase the chance of other complications. Twins sharing the same placenta have a higher frequency of birth defects compared to pregnancies having two placentas. MZT occurs more frequently after blastocyst transfer.

Placenta previa and vasa previa are more common complications in multiple gestations. Abruptio placenta also is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries. Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity, and chronic lung disease) as well as

those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. Rearing of twins and high-order multiples may generate physical, emotional, and financial stresses, and the incidence of maternal depression and anxiety is increased in women raising multiples. At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons. It is not clear to what extent these risks are affected by IVF per se.

A multiple pregnancy may pose increased emotional and financial hardship for a couple. The risk of a multiple pregnancy can be reduced by decreasing the number of embryos that are transferred but this also reduces the overall chance of success. You are encouraged to have a discussion with your physician about the optimal number of embryos to transfer.

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

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

IX. 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.

X. Psychosocial Effects of Infertility Treatment

IVF can be psychologically stressful. Anxiety and disappointment may occur at any of the phases described above. Significant commitment of time and finances may be required. Patients are encouraged to consider meeting with a counselor. If you are interested in meeting with a social worker or psychologist please speak to your physician.

XI. Legal Considerations and Legal Counsel

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

XII. 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 my/our 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) (if my/our clinic is a member of this organization). The CDC may request additional information from the treatment center or contact me/us directly for additional follow-up. Additionally, my/our 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 my/our treatment being used to identify me/us as individuals.

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

1. The ovaries may not respond adequately to the medications.
2. Technical problems including inadequate visualization or the position of the ovaries may prevent the retrieval of the eggs.
3. There may be failure to recover an egg because ovulation has occurred prior to the time of the egg retrieval.
4. Eggs may not be recovered.
5. The eggs may not be normal.
6. The male partner may be unable to produce a semen sample or the semen sample may be of insufficient quantity or quality.
7. Fertilization of the eggs and sperm to form embryos may not occur.
8. Cell division of the embryos may not occur.
9. The embryos may not develop normally.
10. Embryo transfer into the uterus may be technically difficult or impossible.
11. If the transfer is performed, implantation may not result.
12. If implantation occurs, the embryo(s) may not grow or develop normally
13. Equipment failure, infection, technical problems, human error and/or unforeseen factors may result in loss or damage to the eggs, semen sample and/or embryos.

The foregoing general information is based upon the experience and knowledge of the Boston IVF physicians. It is based, in part, upon a review of the literature pertaining to Reproductive Medicine. This information is generally accurate and comprehensive, however, medicine is a dynamic discipline and reproductive medicine in particular is constantly evolving. Estimates of risks factors and the relative benefits of alternative treatment that have been discussed with you represent the best professional judgment of the physicians and caregivers of Boston IVF taking into account your specific needs and circumstances.

BOSTON IVF

ACKNOWLEDGMENT OF INFORMED CONSENT AND AUTHORIZATION

I/We acknowledge that we, the undersigned, are voluntarily seeking treatment with **In Vitro Fertilization (IVF) with the transfer of the embryos into a gestational carrier** in order to conceive a child. I/We will acknowledge our natural parentage of any child or children born through this treatment.

I/We have discussed this treatment in detail with a Boston IVF physician and caregivers in language that we understand. We understand the purpose, risks and benefit of the treatment. **I/We acknowledge that we have read all pages of this consent form and all of our questions concerning the treatment have been fully answered to our satisfaction.**

I/We are aware that there are other centers in the area that offer this treatment and we have freely chosen to have the treatment at Boston IVF.

I/We acknowledge that we have undergone medical, psychological and legal counseling that has been met with our satisfaction.

By consenting to treatment at Boston IVF I/we accept the responsibilities, conditions and risks involved as set out in this document and as explained by the staff of Boston IVF. In addition, we consent to the techniques and procedures used to accomplish this treatment described in this document and as explained by the physicians and staff of Boston IVF.

I/We understand and acknowledge that medicine is not an exact science and that in cases of doubt Boston IVF physicians and caregivers will exercise their best professional judgment.

I/We acknowledge and agree that acceptance into treatment and our continued participation is within the sole discretion of Boston IVF. We understand that should this cycle be unsuccessful, it may be determined that further treatment may not be indicated.

I/We acknowledge that it is our responsibility to notify Boston IVF in writing if we become aware of any information that Boston IVF should have in order to discharge its obligations under this agreement.

I/We agree to notify BIVF immediately in writing of any change in our marital status including separation or divorce.

I/We also understand that we are financially responsible for any medical expenses that are not covered by our insurance policy.

I/We understand that medical information concerning our treatment may be analyzed and could be used in a publication. In accordance with federal law, identifying information and information concerning our treatment will be submitted to a national data registry that publishes statistics on treatment outcomes. In order to obtain this information we give Boston IVF consent to contact any physicians who provided care during and after a pregnancy. I/We understand that no publication resulting from these or other scientific studies will contain our name or other information that would allow us to be identified.

I/We understand that Boston IVF complies with national recommendations for gestational carrier screening as outlined by the American Society for Reproductive Medicine. I/We understand that no test or screening process in medicine is perfect or 100% accurate. Furthermore, some infectious diseases of the gestational carrier, depending on the incubation period, may escape detection during the screening process and be transmitted to the fetus(es) during the pregnancy.

BOSTON IVF

By signing this document I/we acknowledge that we have had a thorough discussion with our Boston IVF physician and caregivers. This discussion included information on the risks, benefits, side effects and complications of the treatment. Furthermore, I/we acknowledge that the discussion with our Boston IVF physician provided sufficient information to allow us to make an informed decision whether or not to proceed with treatment. The discussion with our Boston IVF physician included alternatives including the option of having no treatment.

By signing this document I/we acknowledge that our Boston IVF physician and caregivers have obtained from us informed consent to proceed to proceed with In Vitro Fertilization (IVF) with the transfer of the embryos into a gestational carrier.

It is required that you have this document witnessed at Boston IVF, if unable because of distance the default is to have this document officially notarized.

Witness of Consent Form (if this form is completed no need to complete notarization form)

Patient Name (print) **Patient Signature** **Today's Date (**MM/DD/YYYY)

PATIENT- TYPE OF PICTURE IDENTIFICATION: ☐ Driver's License ☐ Passport ☐ Other: _____

ID NUMBER:_____ State/Country:_____ Expiration Date:___/___/_____
(MM/DD/YYYY)

Witness Name and Title (print) **Witness Signature** **Today's Date** (MM/DD/YYYY)

Partner Name (if applicable, print) **Partner Signature** **Today's Date** (MM/DD/YYYY)

PARTNER - TYPE OF PICTURE IDENTIFICATION: ☐ Driver's License ☐ Passport ☐ Other: _____

ID NUMBER:_____ State/Country:_____ Expiration Date:___/___/_____
Date (MM/DD/YYYY)

Witness Name and Title (print) **Witness Signature** **Today's Date** (MM/DD/YYYY)

Physician Attestation

The above mentioned patient and partner (if applicable) have been informed and counseled by me and other team members regarding the risks and benefits of the relevant treatment options, including non-treatment. The patient and partner (if applicable) expressed understanding of the information presented during the discussion.

Physician Name (print) **Physician signature**

Today's Date (MM/DD/YYYY)

BOSTON IVF

Notarization Form (This form is only needed if not able to have witnessed at Boston IVF)

Patient Name (print)	Patient Signature	Today's Date (MM/DD/YYYY)
		/ /

State of:_____ County of: _____

On this _____ day of _____ 20____, before me, the undersigned notary public, personally appeared

_____, proved to me through satisfactory evidence of identification,

which were_____, to be the person whose name is signed on the

proceeding or attached document in my presence.

ID NUMBER:_____ Expiration Date: ____/____/____
(MM/DD/YYYY)

____/____/____
Today's Date (MM/DD/YYYY)

_____
Notary Signature

_____
Title
My appointment expires: ____/____/____
(MM/DD/YYYY)

Partner Name (if applicable, print)	Partner Signature	Today's Date (MM/DD/YYYY)
		/ /

State of:_____ County of: _____

On this _____ day of _____ 20____, before me, the undersigned notary public, personally appeared

_____, proved to me through satisfactory evidence of identification,

which were_____, to be the person whose name is signed on the

proceeding or attached document in my presence.

ID NUMBER:_____ Expiration Date: ____/____/____
(MM/DD/YYYY)

____/____/____
Today's Date (MM/DD/YYYY)

_____
Notary Signature

_____
Title
My appointment expires: ____/____/____(MM/DD/YYYY)