Introduction

*In vitro fertilization (IVF)* is a technique in which egg cells are fertilized by sperm outside the woman's womb, *in vitro*. IVF is a major treatment in infertility when other methods of assisted reproductive technology have failed. The process involves hormonally controlling the ovulatory process, removing ova (eggs) from the woman's ovaries and letting sperm fertilize them in a fluid medium. The fertilized egg (zygote) is then transferred to the patient's uterus with the intent to establish a successful pregnancy.

In vitro fertilization and embryo transfer (IVF-ET) was first successfully used in humans over 25 years ago; since then, more than one million children have been conceived using this technology. IVF is a procedure designed to enhance the likelihood of conception in couples for whom other fertility therapies have been unsuccessful or are not possible. It is a complex process and involves multiple steps resulting in the insemination and fertilization of oocytes (eggs) in our laboratory. The embryos created in this process are then placed into the uterus for potential implantation.

IVF is an elective medical treatment. IVF may provide a couple who has been otherwise unable to conceive with a chance to establish a pregnancy.

Super ovulation Stimulates Egg Development

The controlled "super ovulation" techniques used in IVF are designed to stimulate the ovaries to produce several eggs (oocytes) rather than the usual single egg as in a natural cycle. Multiple eggs increase the potential availability of multiple embryos (fertilized eggs) for transfer and ultimately increase the probability of conception.

The medications required to boost egg production may include, but are not
limited to the following: Lupron (gonadotropin releasing hormone-agonist),
Antagon or Cetrotide (gonadotropin releasing hormone-antagonist), Follistim,
Bravelle or Gonal-F (FSH, follicle stimulating hormone), Reppronex (combination
of FSH and LH, luteinizing hormone), and Pregnyl or Novarel (hCG, human
chorionic gonadotropin). Each is administered by injection only. Most
medications are given subcutaneously (beneath the skin), though some are
intramuscular injections (into the muscle). Risks associated with injectable
fertility medications may include but are not limited to, tenderness, infection,
hematoma, and swelling or bruising at the injection site.

Risks associated with the medications may include, but are not limited to,
allergic reactions, hyperstimulation of the ovaries (mild, moderate or severe),
failure of the ovaries to respond and cancellation of the treatment cycle.

There are situations that can occur during a stimulation that may necessitate
canceling your IVF cycle and stopping treatment for a period of time. This occurs
because the ovaries produce either too many or too few eggs in response to
drug stimulation protocol. Although we realize that this can be a big
disappointment, at times it is necessary to discontinue the use of the
medications to avoid the possibility of complications and to afford you the best
chance of future success. If canceling the cycle becomes necessary, you will be
told to stop your injections. No hCG injection will be given and no egg retrieval
will occur. You will be asked to schedule an appointment with your physician to
make decisions regarding future treatment cycles.

When ovulation induction medications are used in fertility therapy, the ovaries
are coaxed to produce more than one egg to the point of maturity.
Consequently, hormone levels of estrogen and progesterone reach much higher
than normal values. When the estrogen level becomes mildly to moderately
elevated, side effects that may be experienced include, but are not limited to,
fluid retention with slight transient weight gain, nausea, diarrhea, pelvic
discomfort due to enlarged cystic ovaries, breast tenderness, mood swings,
headache and fatigue.

Ovarian Hyperstimulation Syndrome (OHSS)

If the estrogen level rises excessively and hCG is administered to trigger final
maturation of the eggs, the following more serious complications may result:

- Excessive fluid retention with fluid in the abdomen and/or chest cavity;
- Thrombosis of arteries and/or veins (formation of blood clots) which
  may lead to stroke, embolus, or potentially fatal complications;
- Abnormally enlarged ovaries, which have the possibility of rupturing or
twisting (a surgical emergency)

Any of the three problems listed above may require prolonged hospitalization.

Given the potential for such severe complications, it is important that we
carefully monitor your response to these medications. This monitoring also
allows your physician to determine when the eggs are ready for the next stage,
oocyte (egg) retrieval. Monitoring includes frequent blood drawing for estradiol
(estrogen) and possibly progesterone, LH and FSH levels. These blood tests will

Mashhad University of Medical Sciences
take place over approximately a twelve-day period. Risks associated with blood
drawing may include, but are not limited to:

- Pain at the site of needle stick
- Tenderness or infection of the skin
- Bruising or scarring of the site of blood draw
- Development of a blood clot in the vein (thrombosis, thrombophlebitis)

The second portion of the monitoring phase in IVF involves the use of
intravaginal ultrasound to track follicular growth. The eggs develop inside fluid-
filled cysts of the ovaries called follicles, which enlarge as the eggs mature.
Ultrasound studies usually begin after an estrogen response has been measured
and continue on a frequent basis until oocyte (egg) retrieval. The ultrasound
studies are performed using a vaginal probe. Vaginal sonograms carry no
appreciable risk but may cause slight discomfort, particularly as you near the
point of ovulation.

Ovarian stimulation with the fertility medications causes multiple follicles to
develop. This is desirable in IVF because as the number of eggs increases, the
chance for success increases. Multiple embryos can also increase the risk of
multiple pregnancy. Approximately 20-25% of pregnancies with IVF will be
multiple. Most of these will be twins, but triplets, quadruplets or even greater
multiple pregnancies can occur. A procedure called "selective reduction of
pregnancy" has been performed in several medical centers across the country in
selected cases of triplets or more. Selective reduction is not offered on site or by
GRS staff. More information on this procedure and recommended centers is
available on request.

**Retrieving the Oocytes (egg retrieval)**

For IVF, collection of eggs is usually performed under transvaginal ultrasound
guidance. To accomplish this, a needle is inserted (under IV sedation) through
the vaginal wall into the ovaries using ultrasound to locate each follicle. The
follicular fluid is drawn up into a test tube to obtain the eggs. Although patients
are given pain medications intravenously and are carefully monitored by an
anesthesiology staff, some women may experience some discomfort during the
procedure. Generally, the oocyte (egg) retrieval takes 20-30 minutes. Patients
are usually discharged home within hours after the retrieval. Risks of oocyte
(egg) retrieval may include, but are not limited to, the following:

- Potential reactions from the drugs and procedures used in the
  administration of anesthesia.
- Risks associated with the passage of the needle through the vagina
  into the ovaries (including infection, bleeding, inadvertent damage to
  adjacent structures including, but not limited to, the bowel, bladder,
  blood vessels, ureter, uterus or ovary(ies), and adhesion formation
  (internal scarring) following the procedure. Although uncommon,
  significant bleeding or damage to the bowel may occur, and surgery
  may be required to repair such damage; this is a very uncommon
  event. Rarely, infection may become severe enough to require
  hysterectomy and/or removal of one or both ovaries.
Collecting and Preparing the Sperm

A semen sample will be obtained from the partner by masturbation on the day of the oocyte (egg) retrieval. This is usually obtained while the retrieval is being performed. Abstinence from ejaculation for two to five days prior to providing this semen specimen is recommended. After the specimen is produced, the sperm will be prepared for inseminating the collected eggs in our laboratory. Because this can be a stressful time period for men, the man/partner may be unable to produce a specimen when needed. Men who feel that they may have difficulty producing a semen specimen have the opportunity to have their specimens frozen by our laboratory ahead of time for use in this situation. Testicular biopsy can also be performed as a method to extract sperm for IVF.

Insemination of Eggs and Embryo Culture

Following egg retrieval, the follicular fluid is immediately transferred to the adjacent laboratory for identification of eggs, evaluation, and preparation for insemination. In the process of collecting the follicular fluid, it is possible that a large number of eggs may be retrieved. It is strongly recommended that all of these eggs be inseminated to maximize the number of embryos available for subsequent transfer. Any objection(s) to this policy should be stated in writing and attached to the IVF-ET consent form with the understanding that pregnancy success may be reduced. Otherwise, the prepared sperm will be added to each egg and they will be allowed to incubate overnight under controlled laboratory conditions. The next day, each egg is evaluated for evidence of fertilization. However, it is possible that no eggs are fertilized. If this happens, the laboratory staff will re-inseminate the eggs or perform intracytoplasmic sperm injection (ICSI) in hopes of obtaining embryos for transfer. If fertilization still does not occur, the eggs will be discarded and the remainder of the procedure will be cancelled. In the case of severe male factor, the couple may be asked to consider the option of using anonymous donor sperm (obtained through a licensed sperm bank for use as a "backup" or secondary sperm source) if it is not possible to obtain sufficient sperm from the partner at the time of fertilization.

The eggs that have fertilized will be allowed to develop for two or more additional days under controlled laboratory conditions before they are placed inside the woman's uterus. Depending upon the couple's wishes, some fertilized eggs/embryos may be frozen and stored for future use.

After the embryos are transferred to the womb, the woman will continue progesterone supplementation that begins on the evening of your egg retrieval procedure. Progesterone can be taken as a combination of oral troches and rectal/vaginal suppositories or by injections. Administration of these medications after egg collection has been shown to create a more favorable uterine environment for the embryos, which therefore increases pregnancy rates. Side effects of progesterone may include, but are not limited to the following:

- Vaginal dryness;
- Bloating, breast tenderness;
- Depression, mood swings;
- Delay of menses.

Synthetic progesterone-like medications have been associated with certain birth
defects. By using only natural progesterone, the risk of drug-induced birth defects is significantly reduced. It is important to note, however, that birth defects occur in approximately 3% of spontaneously-conceived pregnancies in the USA. Therefore, use of natural progesterone does not guarantee a child without a birth defect.

Transferring Embryos to the Uterus

Embryos are transferred on either day three or day five of development. The embryologists at GRS are highly-skilled in identifying "healthy" embryos and in some cases will recommend that a patient extend embryo development to day five, known as the blastocyst stage. Blastocyst transfer has become quite common in IVF cycles as it can increase chances for success while decreasing the likelihood of multiples. Your physician will work closely with the embryologists to determine if a day three or day five transfer would be ideal for your cycle.

Embryos are transferred to the uterus through a small tube (catheter). This procedure is much like a pap smear and does not require any anesthesia and is usually painless. The embryos are placed in a small amount of fluid inside the catheter, which is passed through the cervix at the time of a speculum examination. The embryos are placed in a manner so they reach the top part of the uterus. The number of embryos transferred depends on individual circumstances of the couple, and this decision will be made collectively by you, your physicians and the embryologist. Typically, two to four embryos are be transferred in one treatment cycle.

Embryo transfer can cause mild cramping. Although unlikely, during the embryo transfer the embryo(s) may be displaced through the cervix (causing loss of embryos) or into the fallopian tubes (causing possible tubal pregnancy). There is a small risk of bleeding or infection as a result of the transfer procedure.

After transfer, the woman may get dressed and leave after a brief recovery period. A pregnancy test will be done twelve to fourteen days after the transfer, regardless of the occurrence of any uterine bleeding.

The transfer of several embryos increases the probability of success. A multiple embryo transfer also increases the risk of a multiple pregnancy. Any multiple pregnancy carries an increased risk of miscarriage(s), premature labor and premature birth as well as an increased financial and emotional cost. Pregnancy-induced high blood pressure and diabetes are more common in women pregnant with more than one fetus. Prolonged hospitalization may be necessary for these pregnant women and for the mother and babies after delivery. Tubal (ectopic) pregnancy is also possible, and a combination of normal pregnancy and ectopic pregnancy may occur. A tubal pregnancy is a condition that may require laparoscopy or major surgery for treatment. Like spontaneous (natural) conceptions, pregnancies that arise through IVF may result in miscarriage. In the event of a miscarriage, a dilatation and curettage (D&C) may be necessary.

Couples going through therapy must choose and formalize their choice in the appropriate GRS consent form by indicating one of the following options for handling of any remaining embryos:
• Freezing (cryopreservation) of remaining embryos for use by the couple in future treatment cycles
• Anonymously donating the embryos for use by another infertile couple(s), if the donating couple and the donated embryos meet the screening criteria (You will not receive any money for this donation, nor will GRS "sell" them. GRS reserves the right to cryopreserve (freeze) any donated embryos as well as the right to discard any donated embryos if a suitable woman cannot be identified to receive the embryos)
• Allowing the embryos to develop in the laboratory until they perish, at which time they would be disposed of in a manner consistent with professional ethical standards and applicable legal requirements (This usually occurs within six to eight days after egg collection)

Other Issues

Any assisted reproduction process or technique can be psychologically stressful. Significant anxiety and disappointment may occur. We encourage you to consider short-term supportive counseling during this time and we are happy to provide you with a list of psychiatrists, psychologists, counselors and social workers who may help you through this difficult time.

A substantial time commitment is required by both partners to complete an entire course of IVF therapy. It will be necessary for couples to adjust their schedules to undergo the required testing and therapies associated with IVF-ET. It is the responsibility of the woman to report to our office as scheduled for repeated ultrasound examinations and blood tests over several days or weeks before and after the expected time of egg collection. It is the responsibility of the man to be available at the time identified by the physician to provide sperm.

Theoretical Concerns & Potential for Success

Unfortunately, neither conception nor a successful outcome of pregnancy is guaranteed by the IVF-ET procedure. There are many reasons why pregnancy may not occur with the IVF-ET procedure. In fact, there are complex and largely unknown factors that limit pregnancy rates following assisted reproductive techniques. Some of the known reasons for failure may include, but are not limited to:

• There may be a failure to recover an egg because:
  - follicles that contain mature eggs may not develop in the treatment cycle
  - ovulation has occurred before time of egg recovery
  - one or more eggs cannot be recovered
  - pre-existing pelvic scarring and/or technical difficulties prevent safe egg recovery

• The eggs that are recovered may not be normal;
There may be insufficient semen to attempt fertilization of the recovered eggs because the man is unable to produce a semen specimen, because the specimen contains an insufficient number of sperm to attempt fertilization, because the laboratory is unable to adequately process the specimen provided, or because the option to use a donor sperm as a "backup" was declined;

Fertilization of the eggs to form embryos may fail even when the egg(s) and sperm are normal;

The embryos may not develop normally or may not develop at all. Embryos that display any abnormal development will not be transferred;

Embryo transfer into the uterus may be difficult/impossible, or implantation(s) may not occur after transfer, or the embryo(s) may not grow or develop normally after implantation;

Any step in the IVF-ET process may be complicated by unforeseen events, such as hazardous or catastrophic weather, equipment failure, laboratory conditions, infection, human error and the like.

In the event the couple should die before embryo transfer, the embryo(s) will be discarded unless other provisions are made in writing.

When pregnancy occurs following IVF, it will typically be a normal pregnancy. However, there is always a risk of abnormal pregnancy, miscarriage, blighted ovum, ectopic pregnancy or premature delivery. This is because the process of IVF-ET does not protect against such normal occurrences. Congenital abnormalities, genetic abnormalities, mental retardation or other birth defects which occur in approximately 3% of spontaneously-conceived pregnancies may still occur in children born following assisted reproductive techniques. A large review of a subset of children born following assisted reproductive procedures found the incidence of developmental anomalies similar to a control group of children spontaneously conceived. Women with multiple pregnancies have a much higher risk of complicated pregnancies, which may include the following: toxemia, pre-eclampsia, miscarriage, premature labor and delivery, stillbirth, birth defects, and other complications.

Alteratives to IVF-ET

Depending upon the individual and unique cause(s) of infertility for each couple, the chance of conception through alternative means, including intrauterine insemination (IUI) and medicinal therapy, other than IVF-ET may or may not exist. Possible success rates of these alternatives may vary depending upon the type and severity of the cause of the infertility. For some couples, it may even be possible to conceive spontaneously without a physician's help. You should discuss these alternative treatment methods with your physician before you proceed with IVF-ET therapy.

Potential Complications

The major complication of IVF is the risk of multiple births. This is directly related to the practice of transferring multiple embryos at embryo transfer. Multiple births are related to increased risk of pregnancy loss, obstetrical complications, prematurity, and neonatal morbidity with the potential for long term damage.
Strict limits on the number of embryos that may be transferred have been enacted in some countries (e.g., England) to reduce the risk of high-order multiples (triplets or more), but are not universally followed or accepted. Spontaneous splitting of embryos in the womb after transfer does occur, but is rare (<1%) and would lead to identical twins. Recent evidence suggest that singleton offspring after IVF is at higher risk for lower birth weight for unknown reasons.

Another risk of ovarian stimulation is the development of ovarian hyperstimulation syndrome.

**IVF Counselling**

Inevitably, the stakes are high with assisted conception and negative emotions can often be hard to deal with, as well as counter-productive. Keeping upbeat and positive is an important element in improving your chances of success. Which is why it can be an invaluable prop to have an experienced counsellor for you and/or your partner to talk to. Many of our clients use the counselling sessions that we offer as a way of avoiding, or at least minimising, the adverse effects that these stresses and strains might otherwise bring.

*If IVF fails*

For many couples, sadly, their first attempt at assisted conception will fail. Being able to go through this with someone who understands your particular case and what the implications might be, can be very helpful in coming to terms with the negative result and deciding what the next step should be. Our counsellors have lots of experience to offer in helping you to plan the best way forward.

Couples who choose IVF have long been on an emotional roller coaster of alternating hope and disappointment, both in each monthly cycle and with each new treatment. The IVF experience is similarly described, with hope and elation followed by letdown and sometimes extreme disappointment. Each step of the treatment brings new and increased stress and anxiety.

**What Helps?**

1. Know what to expect. Eliminating as many unknowns as possible reduces stress. Information increases feelings of being in control. With good understanding you'll know what questions to ask and you can be a more active partner in managing your treatment. You should know that at each step the treatment could be canceled. You should know that IVF might not succeed in the first attempt. Be realistic, based upon your age, diagnoses, treatment available and success rates. If pregnancy is not achieved a lot has been learned about you and what else might be tried in the next cycle, plus there is evidence that repeated attempts at IVF increases the overall chance for pregnancy. The first and last IVF cycles are the most stressful--the first because of the unknown, the last because so much is at stake when all current options for a biologic child
have been exhausted.

2. Cushion yourself with as many sources of emotional support as possible. We have a counselor available to you throughout the treatment cycle and after you leave. The medical and nursing staff expects to be sources of ongoing emotional support. Possibly the best support persons are other infertile friends or patients. Identify a support person near home that you can talk to after you leave.

3. Working through decisions before starting the treatment will decrease stress during the IVF cycle. Clarify the position you and your partner will take on fertilizing all eggs, freezing embryos, and multifetal reduction. Have an idea of how many treatment cycles you will do. Consider what you will do if treatment is not successful. Consider your feelings toward donor eggs, donor embryos and adoption. It is important that couples leave the program glad that they took the chance; confident that they have done everything they could to achieve a pregnancy, relieved that they have finished the task of infertility treatment. They can then go on with their lives, exploring the other alternatives to achieving parenthood or remaining childfree.