Fertility Center of Miami

The A.R.T. of Fertility
A Patient Guide

The A.R.T. of Fertility

The physicians and staff of the Fertility Center of Miami understand how overwhelming and complex Assisted Reproductive Technology (ART) can be to patients. The purpose of this booklet is to familiarize you with the In-Vitro-Fertilization (IVF) process.

This booklet will discuss the following topics:

- Pre-cycle screening
- In-vitro Fertilization:
  1. Follicular Recruitment
  2. Oocyte harvesting or egg retrieval
  3. Fertilization and Incubation
  4. Embryo transfer
- What is ICSI?
- What are blastocysts?
- What is TESA/PESA?
- What is Assisted Hatching?
- Potential complications of IVF
- Embryo cryopreservation
- Frozen embryo transfer:
  1. Maturation of endometrial lining
  2. Thawing of cryopreserved embryos
  3. Embryo transfer
- Post pregnancy treatment
- Potential complications
- What is selective reduction?
- Pregnancy rates

Following your physician's consult you were given this guide to learn about IVF and a package of consents for IVF treatment. Once the pre-cycle screening is completed, you will meet with a nurse that will coordinate your particular IVF cycle and give you an opportunity to ask questions regarding this guide and the consents. Please bring the consents for treatment so that you may sign them at the time of the nursing consult.

Our staff is always happy to meet with patients to discuss new issues and answer further questions and concerns.

Pre-cycle Screening

The pre-cycle evaluation is an essential part of the IVF process that can identify factors which may contribute to a poor outcome. All testing on both members of the couple must be completed in preparation for a cycle of treatment. Once the screening is completed, you will meet with your physician to discuss the results and their impact on treatment. The following is a list of the basic evaluation:

Female Testing	Male Testing
HIV I and II antibody	HIV I and II antibody
Hepatitis panel	Hepatitis panel
RPR	RPR
Varicella antibodies	Semen Analysis
Rubella antibodies	Anti-sperm Antibody
FSH, LH, and Estradiol on the 3rd day of menses	Cystic Fibrosis
Cystic Fibrosis	Hemoglobin electrophoresis
Hemoglobin electrophoresis	
Hysteroscopy or Hysterosalpingogram	
Cervical cultures: Gonorrhea, Chlamydia, Ureaplasma, Mycoplasma, and routine	
Blood group and Rh factor	
Complete blood count and Chemistry panel	

WHAT IS IVF?

An understanding of natural conception is important in order to understand in-vitro-fertilization (IVF). Normally, a woman will produce one egg (oocyte) each month. The egg is released from the ovary at the time of ovulation and transported to the fallopian tube. Usually, it is in the fallopian tube that it will encounter sperm and be fertilized. The fertilized egg develops into an embryo that will travel to the uterus (womb) where it attaches and grows.

In IVF, the egg is collected directly from the ovary before ovulation and is fertilized with sperm in the laboratory. The fertilized egg is incubated for a period of 3 to 5 days. The resulting embryo is then transferred into the uterus passing through a small canal, called the cervix, which can be accessed through the vagina.
How is IVF performed? The following are step by step descriptions of the IVF process.

1. Follicular Recruitment

A harvest of several mature eggs is needed in order to perform IVF. When naturally a woman would produce only one egg monthly, the use of gonadotropins (fertility hormones) make possible an increased production of eggs. This translates into higher fertilization and pregnancy rates.

Down-regulation

In order to begin the egg production (follicular recruitment) the pituitary gland, which controls the ovary, must be "quieted", so as not to "interfere" with the fertility hormones. There are two types of medications used for this purpose: Lupron (Gonadotropin-Releasing Hormone agonist) and Ganirelix Acetate (GnRH antagonists).

Lupron

Lupron is an injectable drug that creates this state of suppression, medically termed "down-regulation". Lupron's immediate action is to stimulate the pituitary gland to release hormones that regulate the ovary, called follicle stimulating hormone (FSH) and luteinizing hormone (LH). With continued use of Lupron, the pituitary exhausts itself and a state of suppression is created.
Patients start daily injections of Lupron about 7 to 10 days before their expected period. To avoid an unexpected pregnancy while taking Lupron, it is very important to abstain from intercourse or use protection the month before starting medications. Often times the physician will prescribe oral contraceptive pills to be taken the same month that Lupron is started in order to avoid an inadvertent pregnancy.

Depending on the stimulation technique that is best for you, the physician may begin Lupron on a different day ("Flare up" protocol) or prescribe a different dosage of Lupron (Microdose Lupron). In all cases, Lupron is continued daily in conjunction with gonadotropins until the follicular recruitment phase is over.

GnRH antagonists

An alternative method of down-regulation involves the use of GnRH antagonists (Ganirelix Acetate). Shortly after the initial injection of Ganirelix Acetate, a state of down-regulation is immediately achieved, in contrast with Lupron which takes several days to produce this effect. Therefore, GnRH antagonists are started after initiating stimulation of the ovaries with fertility hormones, rather than prior to menses. GnRH antagonists block the potential premature release of LH, which precipitates ovulation, thus allowing the gonadotropins to continue to stimulate the follicles to grow. Often, an oral contraceptive is utilized in the month prior to initiating a GnRH antagonist.

Follicular Recruitment and Monitoring

The cycle of IVF treatment begins with the onset of the menstrual flow. Patients attend the office for a baseline ultrasound and blood work. The ultrasound evaluation ensures the absence of cysts in the ovaries, and the blood work verifies low levels of the hormone estradiol. These results indicate to the physician that the patient is down-regulated.
Eggs develop within a small sac of fluid within the ovary, called a follicle. While eggs are so small that cannot be seen without a microscope, follicles are easily visualized with the use of ultrasound imaging. Once down-regulation is verified, daily injections of gonadotropins (fertility hormones) will begin in order to recruit follicles and stimulate their growth. Gonadotropins can contain a pure form of Follicle Stimulating Hormone (FSH) or a mixture of FSH and Luteinizing Hormone (LH). Examples of FSH only gonadotropins are Follistim and Gonal-F,and examples of mixed preparations are Repronex and Menopur. Follicles respond to FSH by growing and producing the hormone estradiol. Typically, patients use daily injections of gonadotropins for approximately 8 to 12 days.

The goal of fertility drugs is to recruit as optimal a number of eggs as possible without over-stimulation of the ovaries. Therefore, careful monitoring of the patient's response to the medications is required. Monitoring involves ultrasounds performed through the vagina to visualize the number and size of the follicles. Blood is also drawn to assess the level of estradiol. This information allows the physician to modify the medication dosage, if needed, and to determine the extent of stimulation. Such monitoring visits start on the fourth or fifth day of gonadotropin injections, and continue throughout the course of medications. Common side effects of Lupron, antagonists, and gonadotropins that patients may experience are listed below:

Medication	Possible side effect
Lupron	• Headache • Vaginal dryness • Hot flashes • Mood swings • Bruising at the injection site
GnRH Antagonist (Ganirelix Acetate and Cetrotide)	• Headache • Flue-like symptoms, muscle ache • Irritation at the injection site • Breast tenderness
Gonadotropins (Gonal-F, Follistim, Repronex, and Menopur)	• Ovarian hyperstimulation: abdominal bloating and discomfort, enlarged ovaries. • Mood swings, depression • Breast tenderness • Stinging at the site of injection • Multiple birth

Once the doctor determines that the follicles have grown sufficiently and estradiol levels are appropriate, Lupron and gonadotropin injections stop. In preparation for egg retrieval, the patient receives a single injection of a hormone called hCG (human chorionic gonadotropin), also called Novarel. This injection is given at a specific hour since egg retrieval must be coordinated approximately 36 hours later.

2. Oocyte harvesting or egg retrieval

Egg harvesting or retrieval is performed under sedation in a special suite in the Center. An anesthesiologist is present during the procedure to administer anesthesia into the patient's vein, similar to that which a dentist might use for wisdom teeth extraction. Once the patient is asleep, a needle, guided by an ultrasound, is inserted in the back of the vagina and into the ovary. All the visible follicles are aspirated, and the fluid obtained is taken to the laboratory. It is in the laboratory, that the embryologist examines the follicular fluid to identify the eggs, and place them in the incubator. After the procedure, the couple is informed of the number of eggs retrieved. Recovery from the sedatives usually takes approximately one hour depending on the individual.
There are special circumstances based on the patient medical history that necessitates the retrieval be performed in the hospital. Under rare circumstances, local anesthesia can be used instead of sedation. In cases where the ovaries are not accessible through the vagina, laparoscopy under general anesthesia may be required in order to harvest the oocytes. Usually, not every follicle contains an egg, and not every egg is fully mature and capable of undergoing fertilization.

That same morning of the procedure, the male partner provides the semen sample. He prepares by keeping a period of abstinence of at least 2 days but no more than 5 days. He provides the sample in the privacy of specially designed rooms in the Center furbished with printed material and movies. Once the semen sample is collected, it is analyzed, washed, concentrated, and later mixed with the eggs.

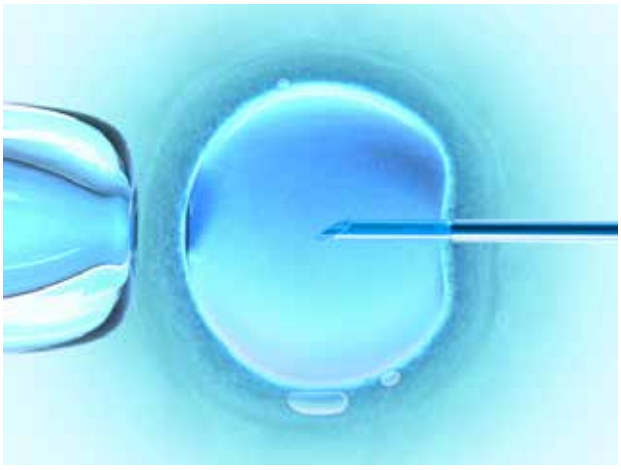
The interior of the uterus (endometrial lining) is prepared for the embryo transfer using intramuscular Progesterone injections. Progesterone is a steroid hormone that prepares and maintains the endometrial lining in optimal condition to receive an embryo, and support a pregnancy. The daily injections of Progesterone begin in the evening the next day following the egg retrieval and continue until the 10th or 12th week of pregnancy.

3. Fertilization and Incubation

The following day ("day 1"), the embryologist examines the eggs under a microscope to verify that fertilization has taken place. In general, not all eggs will fertilize, and not all embryos that result will continue to develop. The fertilized eggs are kept in a special fluid called culture media. They will remain undisturbed in the incubator where they grow and divide into many cells. In situations where there is a high suspicion that the sperm might not penetrate and fertilize the egg, intracytoplasmic sperm injection (ICSI) may be performed.

What is ICSI?

In some cases, including those of male infertility, the usual mixing of egg and sperm may not result in a fertilized egg. A technique termed ICSI (intracytoplasmic sperm injection) in which a single sperm is injected directly inside the egg with a microscopic needle, may offer a solution to those with male infertility. This technique is performed in the laboratory the day of the retrieval using mature eggs. We are unable to judge the genetic health of oocytes and sperm prior to fertilization, therefore, ICSI may result in the fertilization of an oocyte by an abnormal sperm. There are some reports of a less than 1% risk of abnormalities when ICSI is performed. In addition, if there is a genetic factor that is causing infertility, this may be transmitted to the offspring. Genetic testing of the developing embryo or fetus is recommended by the performance of either chorionic villus sampling or amniocentesis whenever ICSI is performed.



ICSI

On "day 3" (three days following the retrieval of the eggs), the embryologist will examine the embryos and check the degree of development. This information will help the embryologist and the physician determine whether to transfer the embryos that same day, or wait two additional days until the embryos reach the blastocyst stage.

What are Blastocysts?

Blastocysts are embryos that have developed for 5 to 6 days after fertilization. A healthy blastocyst is ready to hatch from its outer shell by the end of the 6th day and implant into the endometrial lining within 24 hours. Currently only about 20-40% of embryos mature into blastocysts, but those that do survive have a better chance to implant and develop into a baby. Why transfer blastocysts? Blastocyst culture can provide a natural selection of the best embryos instead of random selection among good quality embryos on "day 3". Blastocysts are a viable option whenever a good number and quality of embryos exist. When only a limited number of embryos are available on the third day, there is no advantage to continue culture to a blastocyst. Since blastocysts have a higher potential for implantation, fewer of them are transferred, generally two. Transferring fewer embryos translates into a lower risk for multiple pregnancy, and this is paramount for those couples that want to avoid selective reduction.

A human blastocyst

4. Embryo transfer

The embryo transfer takes place in a comfortable room while the patient lies on a special bed with stirrups. Anesthesia is not needed since only temporary, mild period-like cramping or no discomfort might be experienced. The partner or a family member can keep the patient company during the procedure. Use of perfumes should be avoided since it might be toxic to the embryos.
The morning of the transfer the embryologist and the doctor discuss with the patient the status of the embryos: the number of developed embryos, their quality, and number of cells of each one. A photograph of the embryos might be provided. At this point, the physician makes a final recommendation based on the patient's past history, age, stage of development of the embryos, and the patient wishes regarding selective reduction. Then the couple and the doctor make a joint decision regarding the number of embryos to be transferred. On the day of embryo transfer, the female partner is asked to sign the "Consent Form for Embryo Transfer and Disposition" confirming the number of embryos that the couple desires to transfer.

Prior to the transfer an ultrasound is performed through the vagina to chart the position of the uterus and measure the length of the cervix and the endometrial cavity. The doctor begins the transfer by placing a speculum in the vagina to help him/her visualize and thoroughly cleanse the cervix. First, a very thin catheter or tube is introduced through the cervix and into the uterus to assess any difficulties placing the catheter. This trial gives the doctor an opportunity to choose a technique for the smoothest transfer. Once the trial is completed, the embryos are brought from the laboratory inside a similar catheter and then placed gently inside the uterus.

Following the transfer, the patient lies for approximately one hour and then is sent home to rest for approximately 48 hours. Intense activities, strenuous exercises, and intercourse should be avoided until pregnancy tests results are known. Two weeks following the retrieval of the eggs a blood pregnancy test is performed. If pregnant, the patient continues Progesterone injections and returns for a pregnancy ultrasound two and a half weeks later. Once the ultrasound confirms a pregnancy inside the uterus, the patient is then referred back to their obstetrician for continued care and delivery.

After the delivery we will contact you to collect information regarding your health as well as the baby's and details of your delivery. We collect this data in order to track the outcome of the procedures we perform.

How many embryos do I transfer?

The goal of IVF is to provide couples the best possible chance for pregnancy with the lowest risk for multiple pregnancy. When transferring embryos that have developed for 3 days, the Center recommends transferring 3 embryos, based on the knowledge that pregnancy rates increase, up to a point, as the number of embryos transferred per cycle increases.

With the advent of blastocyst culture, it is possible to transfer a smaller number of embryos while maintaining excellent pregnancy rates. Typically, 2 blastocysts are transferred on day 5. It is important to understand that the number of embryos transferred may vary from couple to couple depending on the quality, quantity, and stage of their embryos, patient's age and medical history; as well as their stance on selective reduction.

Embryo disposition

When the transfer takes place on day 3, those embryos that are not transferred may be cultured for up to an additional two or three days until they reach the blastocysts stage. If they are of good quality, they may be frozen or cryopreserved if this option has been selected by the patient. When the transfer takes place on day 5, the embryos that are not transferred are cultured an additional day. The embryos that survive and continue to develop are cryopreserved. The embryos that do not continue to develop or degenerate are discarded. The physician and the embryologist will discuss embryo disposition for the embryos that remain. The patient may choose to cryopreserve surviving embryos of the extended culture or immediately discard any remaining embryos after the transfer.

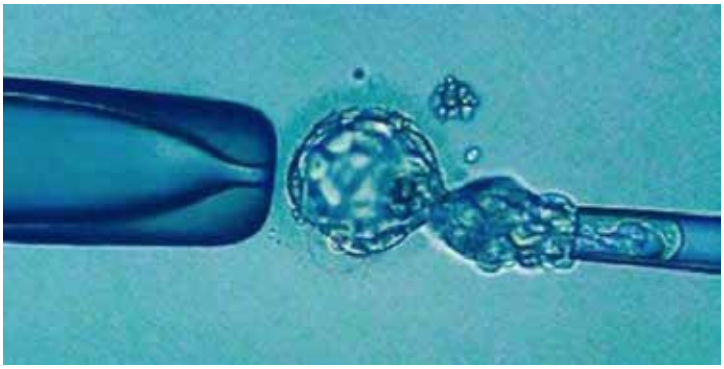
What is PESA or TESA?

PESA (percutaneous epididymal sperm aspiration) and TESA (testicular sperm aspiration) are procedures that are performed to obtain sperm in certain cases of male infertility. PESA or TESA can be performed on men that have zero sperm counts due to either a sperm production problem or a blockage in their reproductive tract, such as the result of a vasectomy, congenital absence of vas deferens, or infection. Once a diagnosis of azoospermia (zero sperm count) has been made, we work closely with a urologist with specialized training in male infertility who will retrieve the sperm. The urologist will first perform an exam and further testing which may involve blood work and/or a testicular biopsy. The result of these studies determine which procedure is more appropriate and more likely to yield sperm.

While PESA is usually performed in our Center the morning of the egg retrieval, TESA may be done the day prior to the egg retrieval to allow in vitro maturation of immature sperm. With PESA, a small needle is placed into the epididymis, which is a reservoir of sperm that sits atop each testicle, using local anesthesia. During TESA, sperm is obtained by means of a biopsy of the testicle. The sperm obtained from these procedures is then injected directly into the eggs (ICSI). The Fertility Center of Miami is proud to have announced on August 12, 1997, the birth of the first baby in Florida conceived with the aid of PESA.

What is Assisted Hatching?

When the embryo is ready to implant, it hatches out of the outer shell and begins to burrow in the uterus. Assisted hatching is a procedure performed by the embryologist under the microscope which involves making a small tear in the protective outer layer (zona pellucida) of an embryo to potentially increase the probability of embryo implantation. This would be recommended for embryos prior to day three transfer that have an appearance of a thickened outer layer when examined under the microscope. It may also be performed in women with a history of prior failed cycles of IVF, or in patients 37yrs. and older. It is commonly performed on thawed blastocyst embryos (in a cryopreserved embryo transfer cycle) prior to embryo transfer.



Assisted Hatching

Patients prepare for assisted hatching by taking antibiotics and steroid pills starting a day before the transfer and continuing for a total of 4 days. These measures are taken to protect the embryo from possible immune or bacterial assaults once they are transferred. Assisted Hatching as well as ICSI may damage the egg or embryo that may interfere with embryo development and implantation.

What is PGD?

Pre-implantation genetic testing is a procedure that allows the testing of embryos in order to rule out genetic diseases or to determine their sex before they are transferred into the uterus. With PGD (pre-implantation genetic diagnosis) usually a single gene mutation is evaluated. In contrast, PGS (pre-implantation genetic screening) refers to testing the embryo for aneuploidy. This is done by determining if there is an imbalance in the number of chromosomes present. It also identifies if the embryo is male or female based on whether there are two "X" chromosomes (female), or one "X" and one "Y" chromosome (male. Patients who elect to have either PGS or PGD will most commonly have ICSI performed to achieve fertilization and minimize DNA contamination.

Pre-implantation genetic testing is accomplished by obtaining a biopsy of the syncytial trophoblastic cells on the fifth or sixth day of embryo development. The embryos are cryopreserved after biopsy at the blastocyst stage of development. Once the results have been reviewed with the patient, acceptable embryos are available to be transferred back in a programmed frozen embryo transfer cycle (FET cycle).

POTENTIAL COMPLICATIONS OF ASSISTED REPRODUCTION TECHNOLOGIES

Ovarian Hyperstimulation Syndrome

Mild hyperstimulation can be seen in up to 10 to 20 % of women undergoing treatment. In most cases, the ovaries are slightly enlarged, causing mild abdominal tenderness and bloating. However, in a very low percentage of patients, severe hyperstimulation can occur. The ovaries can increase in size in some cases causing fluid to accumulate around the ovaries, dehydration, swelling of the abdomen, and tenderness. Rare cases of blood clots, ovarian twisting, chest and abdominal fluid collection have also been reported. Bed rest and hospitalization with careful monitoring of fluids is sometimes required when severe hyperstimulation occurs. Ovarian twisting or torsion may require surgical intervention. Complications of surgery may include the need for blood transfusion, loss of part of or all of an ovary, secondary adhesion (scar) tissue formation, and the compromise of future fertility. The increased risk of blood clots (thrombotic events) , although rare, can compromise the blood supply to vital organs, causing serious problems including strokes, heart attack, and long term disability.

Hyperstimulation symptoms tend to resolve in 7 to 10 days, however if the patient becomes pregnant, the condition can last 4 to 6 weeks. The key to controlling the hyperstimulation syndrome is in its recognition and prompt medical intervention. Therein lies the importance of frequent office visits for ultrasounds and blood test throughout the stimulation period so that the physician may adjust medication dosages as needed and assess the patient.

Surgical Risks

Egg retrieval by ultrasound guidance is a minor surgical procedure that allows most patients to return to work the following day. Mild abdominal pelvic discomfort is common following oocyte retrieval, and usually relieved with over-the-counter analgesics. Removing the eggs with a special needle entails a slight risk of bleeding, infection, and damage to the bowels, bladder, or nearby blood vessels. Excessive bleeding may require a blood transfusion. Approximately 1 patient in 1,000 will require major surgery to repair damage from complications related to eggs retrievals. Surgical intervention could result in the removal of an ovary, or the development of scar

tissue that could limit future reproduction. Severe pelvic infection could result in scar tissue that could interfere with future reproduction. Ultrasound guidance, however, aids the highly skilled physician to visualize the ovaries and as well as surrounding organs to perform the retrieval with the outmost care. Our patients are carefully monitored after the procedure to promptly detect possible complications. All patients also receive intravenous antibiotics during the egg retrieval to reduce the risk of infection. The combined use of these preventative measures have been extremely effective at preventing the occurrence of pelvic infection.

Complications of pregnancy

Even when a pregnancy occurs as a result of IVF, there are risks of miscarriage, ectopic pregnancy, and genetic defects. Also, all risks usually associated with pregnancy are still present. In some studies, the use of IVF has been associated with an increase in preeclampsia, gestational hypertension, placental abruption, placenta previa, and risk of cesarean delivery. Although embryos are transferred into the uterus, ectopic (tubal) pregnancy can occur.

Multiple pregnancy

There is a potential for multiple pregnancy whenever more than one embryo is transferred into the uterus. Most of the multiple pregnancies are twins, but triplets, quadruplets, and more have been described. Increased risk of monozygotic twinning (splitting of a single embryo) has also been noted. Multiple pregnancies are much more complicated and often associated with an increased risk for miscarriage, premature labor and delivery, cesarean section, and other obstetrical and neonatal complications. When greater than a twin gestation occurs, selective reduction is highly recommended. The risks of performing a selective reduction procedure include infection, and potential miscarriage of the remaining fetuses. This risk needs to be balanced against the risk of preterm delivery and its complications such as mental retardation.

Birth Defects

The vast majority of babies conceived as a result of assisted reproductive technologies, such as ICSI, IVF and IUI are perfectly normal, healthy, and free of birth defects. The Center for Disease Control reports that about 3% of babies in the U.S. are born with birth defects. The scientific literature reports a two- to four-fold increase in birth abnormalities associated with assisted reproductive technologies when compared to spontaneously conceived babies from fertile couples. In this context, the word "associated", does not imply that the cause of birth defects are from the assisted reproductive technologies employed.

A recent study published in the New England Journal of Medicine in May 2012 based on the South Australia birth registry found "the risk of birth defects associated with IVF was no longer significant after adjusted for parental factors". This included fresh IVF cycles, and frozen embryo transfer cycles from both IVF and ICSI procedures. There was an increase noted in those patients who had fresh ICSI embryos transferred, but it was uncertain if this was a direct effect of the performance of ICSI, or differences in a male infertility factor that lead to the use of ICSI that underlies the association. Further studies are needed to better clarify the association and to potentially determine a cause and effect relationship.

So what are the causes of birth defects? While the causes of most birth defects are unknown, studies show that smoking, alcohol, certain medications, drug abuse, and obesity increase a mother's risk of having a child with a birth defect. In addition, couples with a history of infertility are at higher risk of having a child with a birth defect compared to the fertile population, and this risk is evident whether they conceive naturally or by assisted reproductive technologies. Some medical experts also suggest that because pregnancies from IVF are monitored much more closely than spontaneous pregnancies, subtle abnormalities may be detected that otherwise would have gone undetected.

Despite these findings, the absolute risk of any individual birth defect remains low. To date, there is no scientific evidence that any of the assisted reproductive techniques, including ICSI, IVF, IUI, and hormone stimulation, cause birth defects.

Psychological Risks

Couples undergoing assisted reproduction procedures have described the experience as an "emotional roller coaster". The treatments are time-consuming and costly. Couples may become frustrated, angry, and resentful in their quest for pregnancy. At times, these feelings can lead to depression and feeling of low self-esteem; especially in the immediate period following a failed attempt at pregnancy. The support of family members and friends is very important at this time, however some couples may wish to seek psychological counseling as an additional means of support. Our Center has available experienced psychologists specializing in infertility to help couples deal with the grief, tension, and anxieties associated with assisted reproduction treatment.

EMBRYO CRYOPRESERVATION

The number of eggs harvested often present the opportunity to produce more embryos than can be transferred at one time. Couples have the option to freeze (cryopreserve) and store these extra embryos for future use, in the event that the cycle of treatment should fail or additional children are desired. The use of cyopreserved embryos eliminates the need for another egg retrieval and the use of gonadotropins. Generally, embryos are frozen following an egg retrieval and embryo transfer, but in some situations the embryos may be frozen before an embryo transfer takes place. Embryos may be suitable for freezing at different stages of development. They may be frozen following initial fertilization at the pronuclear stage of development (soon after fertilization), following cleavage at the cell stage of development (days 1– 4), or at later stages such as the blastocyst stage. The embryologist evaluates each patient individually and makes the determination as to which embryos are suitable for cryopreservation, and at what stage to freeze them. In general, not all embryos are of good enough quality to freeze. Those embryos that are not suitable for cryopreservation are discarded. Embryos that are suitable for freezing are exposed to a special freezing medium called a cryoprotectant. They are placed in either small tubes or straws which are then cooled to subzero temperatures. They are then stored in liquid nitrogen until they are thawed at a later date.

Despite the fact that cryopreservation of human embryos is well established, it is possible that at the time of thawing, none of the embryos will survive and therefore no embryos will be available for transfer into the female partner's uterus. When thawed embryos are transferred into the uterus, pregnancy rates are lower than that of a fresh embryo transfer cycle. Studies of pregnancies resulting from the transfer of frozen human embryos have failed to demonstrate either an increased risk of complications during the pregnancy or birth defects in the offspring. However, the possibility of presently unforeseen risks cannot be completely eliminated. It is also unknown how long embryos can be safely stored prior to embryo transfer. Embryos are frozen and stored initially at our Center for a period of one (1) year, after which, they are transferred automatically to a facility for long-term storage, unless the couple chooses to utilized them to attempt a pregnancy or to discard them before the 12 month period has lapsed.

FROZEN EMBRYO TRANSFER

A frozen embryo transfer treatment involves thawing embryos and transferring them into the uterus. In most cases, embryos are cryopreserved at the blastocyst stage of development, while less often embryos are frozen at the pronuclear or cell division stage. Embryos in the pronuclear stage are better placed into culture for an additional few days after thawing. In this manner, embryos will either continue developing or degenerate, according to their quality, enabling the embryologist to select the best embryos for embryo transfer. In order for embryos to be able to implant, they must be transferred into the uterus during a specific time frame during which the uterus is receptive. Hormone replacement treatment prepares the uterus for transfer of the embryos at the most optimal time.

After the transfer, a pregnancy blood test is performed in the same fashion as a regular IVF cycle. Continued hormonal support with patches and injections are essential during this cycle of treatment. When a patient becomes pregnant, hormonal support continues throughout the 10th to the 12th week of pregnancy.

1. Maturation of the Endometrial Lining

In a natural cycle, growth of the endometrium results from estrogen stimulation from the ovary. In the first half of a menstrual cycle, while the egg is developing, the cells which surround the oocyte produce the hormone estrogen. At midcycle, following a Luteinizing Hormone (LH) surge, ovulation occurs and the ovary produces progesterone. Progesterone changes the endometrium so that it matures and produces substances critical to the embryo in preparation for its implantation. The optimal time to transfer a thawed embryo is based on coordinating the development of the dividing embryo with the appropriate maturational changes within the endometrial lining. The maturity of the endometrial lining is determined relative to the LH surge and the day of suspected ovulation. Since on a natural cycle, this is often difficult to identify, most embryo transfer procedures will be programmed with a medicated hormone replacement cycle.

The Hormone Replacement Cycle

Patients are usually placed on Lupron to down regulate the pituitary gland. This medication is given by subcutaneous injection and initiated one week after natural ovulation takes place or while the patient is on oral contraceptives. Patients that begin Lupron without the use of hormonal contraception are advised to use barrier contraception during the cycle to avoid an inadvertent pregnancy while taking this drug. The patient should expect a normal menstrual flow about seven to fourteen days after the initiation of Lupron. Lupron is continued daily until the middle of the hormone replacement cycle.

Estrogen in the form of a transdermal patch (Vivelle, Estraderm) is begun once a pelvic ultrasound and blood test are completed to confirm that the lining has shed and the ovary is suppressed. In some cases, estrogen is given by mouth (Estrace), or by intramuscular

injection. No matter the route of administration, the dosages will change in order to recreate similar blood levels of estradiol that would normally be seen naturally without the use of medications. After approximately two weeks, an ultrasound and blood test are performed to ensure that the lining has developed sufficiently to progress to the second phase of medications (luteal phase). If inadequate growth is seen, the dose and number of days of estrogen stimulation may be increased. Progesterone is then used to support the endometrial lining and produce its necessary changes. Progesterone is usually administered by daily intramuscular injections. If the use of progesterone in oil is contraindicated (i.e. allergy, infection, poor tolerance), consideration for using either a progesterone vaginal gel or tablets can be considered.

In most hormone replacement cycles, blastocysts will be transferred on the twentieth day of hormonal treatment. Blood tests for estradiol and progesterone are usually performed on two occasions in the luteal phase to ensure an adequate absorption and effect of the hormonal treatment. In most cases, patients are instructed to use baby aspirin throughout the cycle. In addition, an antibiotic and steroid are usually prescribed around the time of transfer to minimize the inflammatory response of the endometrium.

Side Effects of Hormonal Replacement

Most patients using low dose estrogen and the medications above do not experience side effects or complications. Reported side effects of these medications (Lupron, estrogen, and progesterone) include nausea, bruising or redness at the site of the injection, vomiting, hot flashes, headaches, mood swings, joint pains and visual symptoms. An allergic reaction to any of these drugs can occur, and would necessitate changing medications. A rarer complication of estrogen administration is the increased risk of hyper-coagulation with the formation of blood clots (thrombosis). Blood clots can compromise the blood supply to vital organs and increase the risk of stroke, heart attack and serious long-term disability. Infection in the skin (cellulitis, or abscess formation) can occur at the injection site requiring antibiotics.

2. Thawing of the Cryopreserved Embryos

On the day of embryo transfer, the cryopreserved embryos are removed from the storage tank and thawed. The thawed embryos are either transferred immediately or continued in culture for transfer at the equivalent of the cell stage or blastocyst stage of development. When thawed, each embryo is evaluated to determine whether the embryo is potentially viable and whether an embryo transfer procedure should take place. Those embryos felt un-suitable for transfer are discarded. Even though embryo cryopreservation is a well-established procedure, some or all of the embryos may not survive or may be lost during freezing, thawing or transfer. If embryos have been stored at a facility other than the Fertility Center of Miami, the patient must ensure that appropriate arrangements are made in a timely fashion to transfer the custody of those embryos from that facility to FIVF.

Number of Embryos to Thaw

In general, embryos are cryopreserved in either straws or vials, each containing between one and three embryos. The decision of how many to cryopreserve in each vial is dependent on embryo quality, and the number of embryos available for freezing. The chance of a successful pregnancy following the transfer of cryopreserved embryos is related to the number and quality of embryos which are transferred. In order to maximize the patient's chances of getting pregnant, it may be necessary to thaw multiple vials of cryopreserved embryos to obtain a few optimal embryos to transfer. In general, 95% of embryos survive the freeze/thaw events. On rare occasion, all the embryos within a single vial will not survive. The decision of how many embryos to thaw will be made by a physician in conjunction with the laboratory personnel of the Center and the patient.

Number of Embryos to Transfer

Increasing the number of embryos that are transferred will increase, up to a certain point, the chances of pregnancy, but also increase the risk of a multiple pregnancy (e.g. twins, triplets). On the day of embryo transfer, the physician will discuss with you the results of the embryo thaw and make a recommendation on the number of embryos to transfer. On the day of embryo transfer, the female partner is asked to sign the "Consent Form for the Transfer of Thawed Cryopreserved Embryos" confirming the number of embryos that the couple desires to transfer.

3. Embryo Transfer

Patients are requested to have a moderately full bladder at the time of embryo transfer. This helps to straighten the angle between the cervix and uterus making the actual transfer procedure a bit easier. In those patients who have a uterus which is retroverted (tilted back), this is less important. In some cases, assisted hatching will be performed on the embryo if it is not already beginning to "hatch" out of its shell. Assisted hatching is performed under microscopic guidance whereby using fine instruments, the zona pellucida (or shell) of the embryo is thinned by the application of a dilute acidic solution. While it is our belief that in select circumstances his may be helpful for the implantation of the embryo, it is still controversial whether performance of this technique increases the chance of a successful pregnancy following IVF treatment. An ultrasound is performed on all patients immediately prior to the embryo transfer. This allows the physician to recheck the endometrial length to determine where to place the embryos within the cavity. A speculum is then placed in the vagina, and the cervix washed and cervical mucus

teased from the cervical canal. A "mock" embryo transfer is then performed to ensure that the soft tip catheter can pass the junction between the cervix and uterus. This also helps the physician decide which catheter to select for the embryo transfer. In some situations, the physician may elect to monitor the transfer with trans-abdominal pelvic ultrasound. The embryologist brings the embryos to the embryo transfer suite and the actual embryo transfer is performed. This usually occurs without any patient discomfort or symptoms. The catheter is then returned to the laboratory for microscopic evaluation to ensure that all the embryos have been deposited in the uterus and none are stuck in the catheter. In the rare case of a retained embryo, a repeat transfer will take place. The patient is then returned to the supine position and asked to rest for about an hour before going home. Patients are advised to have minimal activity and remain in bed or similar environment for approximately forty-eight hours. Thereafter, patients can resume normal activity, but are asked to refrain from coitus. A pregnancy test is performed nine to eleven days later.

Post Pregnancy Test Treatment

If the pregnancy test is positive, the patient continues estrogen and progesterone medications. Depending on the level, a repeat test may be performed two to four days later. Blood tests are performed weekly to both insure that the patient is absorbing and taking her medications properly, and to assess the presence of placental hormone production. Between the ninth and twelfth week of gestation, a shift takes place in a normal pregnancy whereby the hormones that are needed to support the pregnancy (estrogen and progesterone) are made less by the ovary and more and more by the growing placenta. By the end of the first trimester, a woman's ovaries are no longer needed to support the continued development of the embryo. When using a programmed hormone replacement cycle, the ovaries have been "turned off". As such, the hormones estrogen and progesterone which are being given are acting in place of the ovaries. When there is evidence that these hormones are being produced by the placenta, the dosages prescribed are gradually decreased and then discontinued. Usually medications are discontinued by the fourteenth week of gestation.

An ultrasound is performed between the sixth and seventh week of pregnancy to ensure the location and number of gestational sacs. Once fetal cardiac activity is documented, the patient is referred back to their obstetricians for continued care. The obstetrical management of the patient is left to the obstetrician, but we will continue to monitor weekly hormone levels and make modification to the hormonal replacement regimen until all medications have been discontinued.

POTENTIAL COMPLICATIONS OF FROZEN EMBRYO TRANSFER

Complications of a thawed cryopreserved embryo transfer cycle include those outlined previously for the medications, and those outlined in the IVF section. In addition, embryos may not survive and be available for embryo transfer. The risk of a multiple pregnancy (including monozygotic twinning) is increased particularly when more than one embryos is transferred. Common events associated with pregnancy include the occurrence of miscarriage and less frequently a tubal (ectopic) pregnancy. In some inconclusive studies, IVF has been associated with an increase in preeclampsia, gestational hypertension, placental abruption, placenta previa, and the risk of cesarean delivery.

Most infants born as a result of a cryopreserved embryo transfer cycle are normal. The rate of congenital abnormalities is not different from those babies conceived with IVF or naturally. Genetic abnormalities, as well as mental retardation, and structural abnormalities may occur in babies conceived with IVF, in babies conceived as a result of cryopreservation and thawing, as well as in those conceived naturally.

WHAT IS SELECTIVE REDUCTION?

Selective reduction is a procedure that is used when multiple embryos have implanted as the result of assisted reproductive technologies. The procedure is usually performed between 9 to 12 weeks gestation to selectively abort the extra embryos. Selective reduction is performed by a perinatologist on an outpatient basis by inserting a needle guided by ultrasound either through the abdomen or vagina to inject potassium chloride into the fetus. The incidence of miscarriage associated with this procedure is felt to be 4 to 5 %.

The decision of whether or not to undergo selective reduction can be a traumatic one, and couples who have invested time and effort to achieve pregnancy may often be unprepared to make this choice. If this procedure is morally or ethically unacceptable, then the number of embryos transferred should be strictly limited. It is helpful for couples considering selective reduction to undergo professional counseling prior to the procedure.

PREGNANCY RATES

Each couple's pregnancy potential is determined by the physician based on a variety of factors. The patient's age, the fertility potential of the partner's sperm, and the medical reason for infertility, are all taken into account when evaluating the couple's pregnancy rate potential. You may see our most recent data on pregnancy rates according to age in our web site **fertility-miami.com.** You will discuss your individual pregnancy rate with the doctor at the time of consult prior to establishing a treatment plan.

RESOURCES

American Society for Reproductive Medicine
1209 Montgomery Highway
Birmingham, Alabama 35216-2809
Phone: (205) 978-5000
www.asrm.org

Resolve National Fertility Association
7918 Jones Branch Drive, Suite 300 McLean, VA 22102
Phone: 703.556.7172 www.resolve.org

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