Fertility Center of Miami

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

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.

The A.R.T. of Fertility

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
- What is ICSI?
- What are blastocysts?
- What is TESA/PESA?
- What is PGT?
- Embryo cryopreservation
- Frozen embryo transfer:
  1. Maturation of endometrial lining
  2. Thawing of cryopreserved embryos
  3. Embryo transfer
- Post pregnancy treatment
- Potential complications of ART
- Pregnancy rates

Following your physician's consult you were given this guide to learn about IVF. Once the pre-cycle screening is completed, you will speak with a nurse that will coordinate your particular IVF cycle and give you an opportunity to ask questions regarding this guide. 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 contribute to your outcome. All testing on both members of the couple should 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 or VDRL	RPR o VDRL
Varicella antibodies	Semen Analysis
Rubella antibodies	Anti-sperm Antibody
AMS, FSH, LH, and Estradiol on day 2-4 of menses	Genetic Carrier Screening
Genetic Carrier Screening	
Hysteroscopy, Hysterosalpingogram, Sonohysterogram	
Cervical cultures: Gonorrhea, Chlamydia, Ureaplasma, Mycoplasma	
Blood group and Rh factor	
Complete blood count and Chemistry panel	
TSH and Prolactin	

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 eggs are collected directly from the ovary before ovulation and are fertilized with sperm in the laboratory. The embryos are incubated for a period of 5 to 7 days.

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 the production of eggs. This translates into higher fertilization and pregnancy rates.

Follicular Recruitment and Monitoring

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 hormone levels.
Eggs develop within a small sac of fluid within the ovary, called a follicle. While eggs are so small that they cannot be seen without a microscope, most follicles are easily visualized with the use of ultrasound imaging. 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). An example of an FSH only gonadotropin is Gonal-F, and an example of a mixed preparation is Menopur. Follicles respond to FSH by growing (increasing in size) and producing the hormone estradiol. Typically, patients use daily injections of gonadotropins for approximately 10 to 14 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 injectable medication that patients may experience are listed below:

Medication	Possible side effect
GnRH Antagonist (Ganirelix Acetate and Cetrotide)	• Headache • Flu-like symptoms, muscle ache • Irritation at the injection site • Breast tenderness
Gonadotropins (Gonal-F, Follistim and Menopur)	• Ovarian hyperstimulation: abdominal bloating and discomfort, enlarged ovaries. • Mood swings • Breast tenderness • Stinging at the site of injection

Once the doctor determines that the follicles have grown sufficiently and estradiol levels are appropriate, injections stop. In preparation for egg retrieval, the patient receives a single injection of a hormone called hCG (human chorionic gonadotropin) or leuprolide acetate. This injection is given at a specific hour since egg retrieval must be coordinated approximately 35 hours later prior to ovulation.

2. Egg Retrieval

The egg retrieval i s performed under intravenous 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 patient 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 ICSI is performed. If donor sperm is used, the donor sperm sample is thawed the day of the egg retrieval.

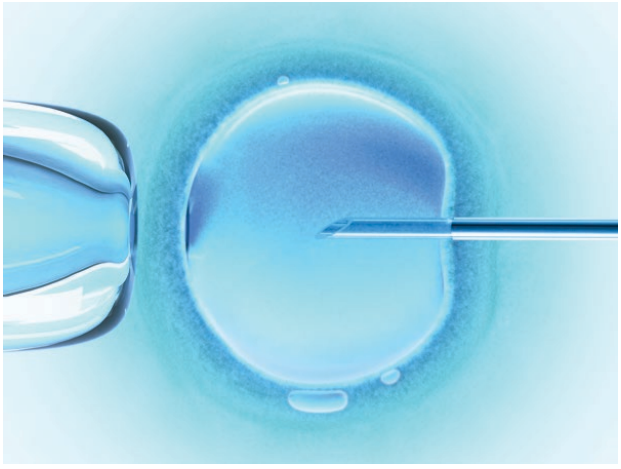
If oocyte cryopreservation is performed, the oocytes will be cryopreserved the same day of the egg retrieval. The purpose of oocyte cryopreservation or freezing is to save oocytes for a future attempt to establish a pregnancy.

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.

What is ICSI?

A technique termed ICSI (intracytoplasmic sperm injection) which is a single sperm injected directly inside the egg with a microscopic needle. 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. Genetic testing of the developing embryo is recommended by the performance of PGT-A.



ICSI

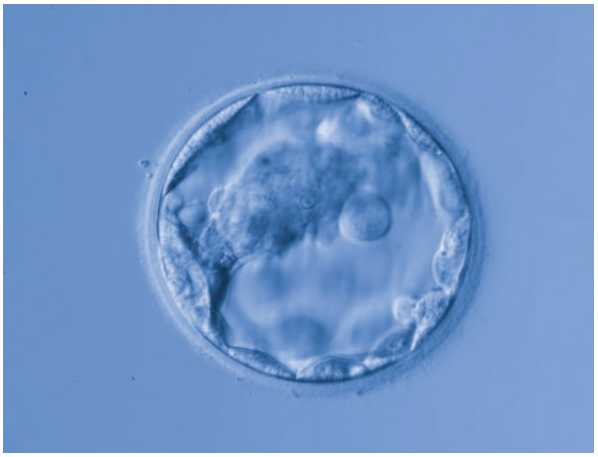
What is PESA or TESA?

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.

With PESA, a small needle is placed into the epididymis, which is a reservoir of sperm that sits atop each testicle, using local anesthesia or IV sedation. 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 are Blastocysts?

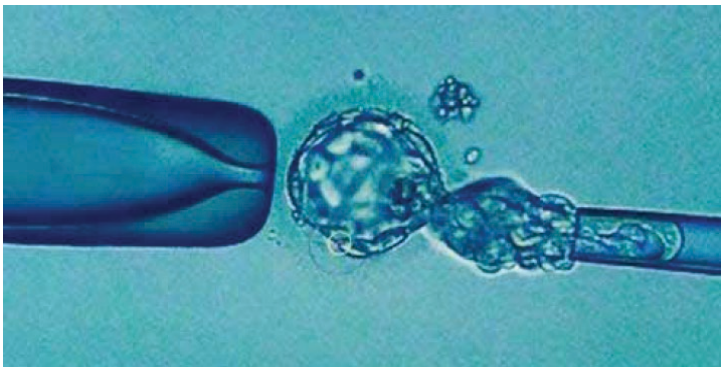
Blastocysts are embryos that have developed for 5 to 6 days after fertilization. The surface cells that surround the cavity (just under the outer shell) are called the trophectoderm and will later develop into the placenta. A more centrally located group of cells – the inner cell mass, will become the fetus. The goal of in vitro fertilization and embryo culture is to provide high quality embryos which are capable of continued development and result in live births. In general, under IVF culture conditions, about 25 to 60% of embryos progress to the blastocyst stage after 5 days of culture.



A human blastocyst

What is PGT?

Pre-implantation genetic testing is a procedure that allows the testing of embryos in order to rule out genetic diseases or to determine their chromosomes before they are transferred into the uterus. With PGT-M (pre-implantation genetic testing for monogenic single gene disease) usually a single gene mutation is evaluated. In contrast, PGT-A (pre-implantation genetic testing for aneuploidy) refers to testing the embryo for abnormal number of chromosomes. 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). 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).



Assisted Hatching

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 cryopreserved embryos eliminates the need for another egg retrieval and the use of gonadotropins. Generally, embryos are frozen following an egg retrieval. 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. 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. Embryos are frozen and stored initially at our Center, after which, they are transferred automatically to a facility for long-term storage.

FROZEN EMBRYO TRANSFER

A frozen embryo transfer involves thawing an embryo and transferring that single embryo into the uterus. In order for an embryo to be able to implant, it must be transferred into the uterus during a specific time frame during which the uterus is receptive. Hormone replacement treatment prepares the uterus for the transfer of the embryo at the most optimal time.

After the transfer, a pregnancy blood test is performed nine days later. Continued hormonal support with estrogen and progesterone 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 (or suppress) the release of FSH and LH. 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, when progesterone supplementation is started.

Estrogen in the form of a transdermal patch or tablet by mouth or vagina is begun once a pelvic ultrasound and blood test are completed to confirm that the lining has shed and the ovaries are suppressed.

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 of the endometrium is seen, the dose and number of days of estrogen stimulation may be increased or a different route of administration may be added. Progesterone is then used to support the endometrial lining and produce its necessary changes. Progesterone is usually administered by daily intramuscular injections or an oral and vaginal route. If the use of progesterone in oil is contraindicated (i.e. allergy, infection, poor tolerance), consideration for using either a progesterone vaginal gel and tablets can be considered.

In most hormone replacement cycles, a single blastocyst 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 aspirin 81 mg daily 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 embryo is removed from the storage tank and thawed. When thawed, the embryo is evaluated to determine it's viability and a picture is taken for the physician to discuss with the patient.

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. An ultrasound is performed on most patients immediately prior and during the embryo transfer. This allows the physician to recheck the endometrial length to determine where to place the embryo 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. The physician will monitor the transfer with trans-abdominal pelvic ultrasound. The embryologist brings the embryo 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 the embryo has been deposited in the uterus and not stuck in the catheter. In the rare case of a retained embryo, a repeat transfer will take place immediately. The patient is then returned to the supine position and asked to rest before going home. Patients are advised to have minimal activity for approximately forty-eight hours. Thereafter, patients can resume normal activity, but are asked to refrain from intercourse. A blood pregnancy test is performed nine 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 more and more by the growing placenta. As such, the hormones estrogen and progesterone which are being given will be reduced gradually 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 hormone levels and make modification to the hormonal replacement regimen until all medications have been discontinued.

Potential Complications of Assisted Reproduction Technologies

Ovarian Hyperstimulation Syndrome (OHSS) - Mild hyperstimulation can be seen in a small percentage of cases. 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, s welling 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 and 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. 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, 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 before, during, and 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. Although embryos are transferred into the uterus, ectopic (tubal) pregnancy can occur. There is a potential for multiple pregnancy whenever more than one embryo is transferred into the uterus. An 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, gestational diabetes, preeclampsia 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.

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.

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 embryo is transferred. Common events associated with pregnancy include the occurrence of miscarriage and less frequently a tubal (ectopic) pregnancy.
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.

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.

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

Fernando M. Akerman, M.D. | Farah S. Chuong, M.D. | Edward H. Illions, M.D. | Nicole Arencibia, A.P.R.N.

(305) 596-4013 info@fertility-miami.com

Miami
8950 N Kendall Dr
Suite 103
Miami, FL 33176

Miami Beach
4308 Alton Rd
Suite 760
Miami Beach, FL 33140

Administrative Office
9570 SW 107 Ave
Suite 203
Miami, FL 33176