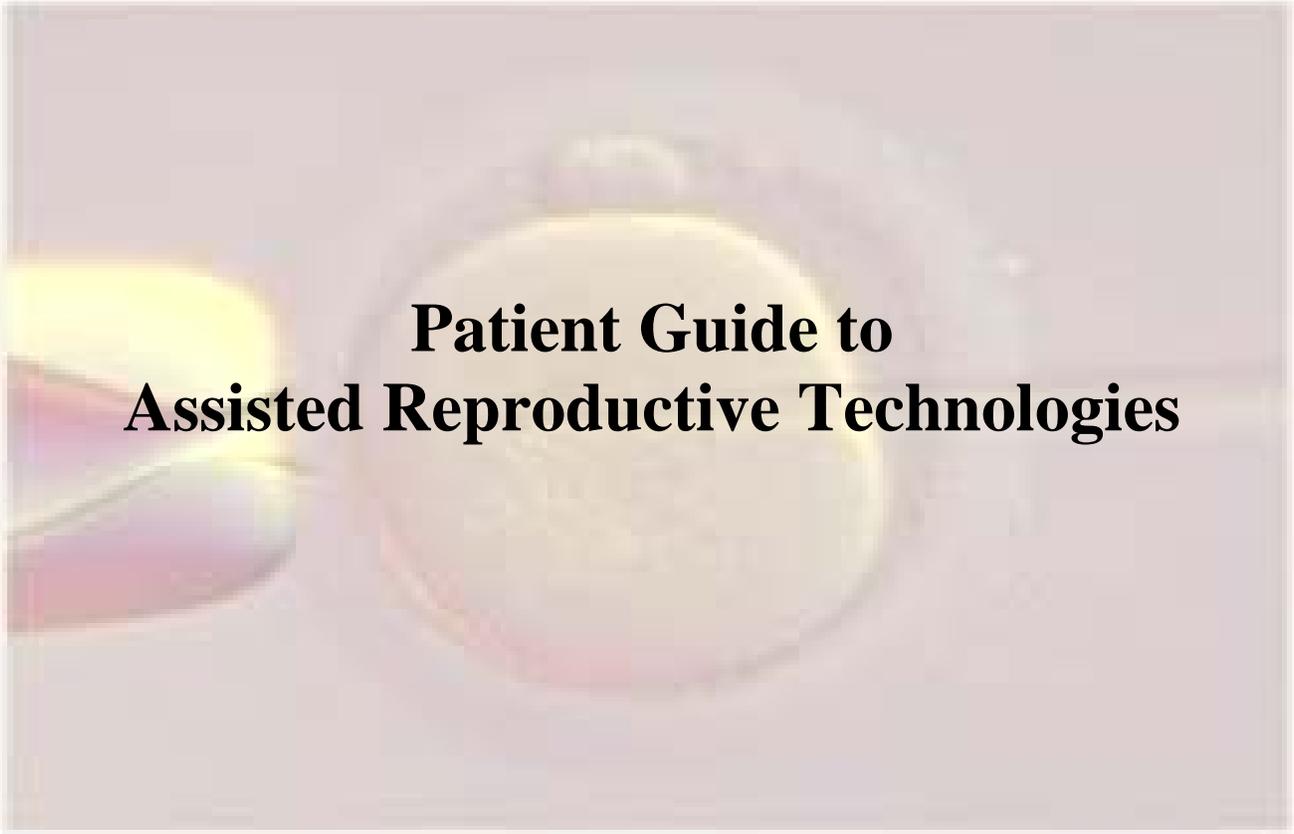




HEALTH SCIENCES

Center for Reproductive Medicine

A large, semi-transparent rectangular image showing a microscopic view of a cell, likely an oocyte, with a bright yellow nucleus and surrounding cytoplasm. The text "Patient Guide to Assisted Reproductive Technologies" is overlaid in the center of this image.

**Patient Guide to
Assisted Reproductive Technologies**

(336) 716-6476

www.wfubmc.edu/ivf

TABLE OF CONTENTS

		<u>Page</u>
I.	General Information	
	Advanced Reproductive Technologies/Introduction	3
	ART/IVF Candidates	4
	Getting Started.....	5
	In Vitro Fertilization	6-9
	Ovulation Induction and Monitoring.....	6-8
	Egg Retrieval	8
	Fertilization.....	8
	Embryo Transfer	8
	Luteal Phase Support	9
	Pregnancy Test.....	9
	Risks Associated with IVF	10-11
	Other Alternatives	11
	Additional ART Procedures.....	12
	Embryo Cryopreservation	12-16
	Micromanipulation.....	13
	ICSI (Intracytoplasmic Sperm Injection).....	13
	Assisted Hatching	14
	PreImplantation Genetic Diagnosis	14-15
	Oocyte Donation	16
II.	Cycle Instructions	
	Daily Instructions for Your Cycle.....	17
	Semen Specimen Collection.....	18
	Medications.....	19
	Gonadotropins (FSH, FSH/LH)	20-21
	HCG	22-23
	Progesterone for Luteal Support	24
	Injections.....	25-26
	Pre-Retrieval Instructions.....	27
	Egg Retrieval	29
	Embryo Transfer	30-31
	Pregnancy Tests	32
	Payment Policy	33
	Glossary.....	34-35
	Phone Numbers.....	36
III.	Additional Forms, Consents and Protocols	
	IVF Consents.....	Addendum A.

IVF Charges and Coding Information.....Addendum B.

ART
ADVANCED REPRODUCTIVE TECHNOLOGIES

Advanced Reproductive Technologies (ART) is a term used to describe a number of various technologies that have been developed to assist patients in becoming pregnant. These technologies include in vitro fertilization-embryo transfer (IVF-ET), frozen embryo transfer (FET), and micromanipulation. Micromanipulation refers to special techniques used by the ART laboratory to manipulate sperm, eggs, and/or embryos. These techniques include; intracytoplasmic sperm injection (ICSI), assisted hatching (AH), and preimplantation genetic diagnosis (PGD).

This booklet is divided into two sections. The first section is a general review of the different ART technologies employed here at the Wake Forest University Center for Reproductive Medicine. Section II, contains specific instructions related to the IVF cycle, as well a glossary. It is important that you read this booklet in its entirety and ask questions regarding any of the information presented.

ART/IVF CANDIDATES

Most patients who undergo ART have tried other less complex methods for treating their infertility. Although ART was originally developed to treat infertility caused by tubal disease or blockage; today it is an effective treatment for almost every cause of infertility. ART may be used as first-line therapy for patients with severe tubal disease, severe endometriosis, advanced age, or in couples with severe male factor infertility. It can also be used for patients who may be carriers for genetic disorders that may prevent them from having a healthy viable pregnancy.

Prior to proceeding with ART all patients and partners should have completed a basic infertility evaluation. ART candidates who will be using their own eggs should be under 44 years of age and should have:

no evidence of premature menopause

at least one accessible ovary, and

a normal uterus

Donor egg recipients should be under 50 years of age and have a normal uterus. All ART candidates should be in good health and have no medical conditions that would pose a serious health risk to themselves or the child they would carry.

GETTING STARTED

Before proceeding with any ART cycle, all patients and their partners must have completed the following:

Patient:

1. a sonohysterography or hysterosalpingogram within one to two years of ART cycle,
2. a day three FSH (follicle stimulating hormone), LH (luteinizing hormone), and estradiol level at least every year while active in the ART program,
3. hepatitis B, Hepatitis C, and HIV testing every year, and
4. documentation of rubella immunity and blood type, and
5. IVF payment/insurance verification through our financial counselor.

Partner:

1. hepatitis B, hepatitis C, and HIV testing every year, and
2. a semen analysis from an approved laboratory within the last year,

In addition, it is strongly recommended that all couples have the following tests completed to screen for genetic abnormalities:

Caucasians:	Cystic Fibrosis Screening
African-Americans:	Sickle-Cell Screening
Jewish descent	Jewish Panel including Tay-sachs and Cystic Fibrosis

Once the above tests have been completed, all patients will be placed on low-dose birth control pills to assist with the scheduling of their IVF cycle. While on birth control pills, they will be scheduled for an appointment with the IVF Nurse Coordinator to learn about their medications, injection techniques, and review the consents. All patients must have all medications purchased by this appointment.

IN VITRO FERTILIZATION (IVF)

In Vitro Fertilization is the process by which the female oocyte (egg) is allowed to be fertilized by the male sperm outside the human body. Once fertilization has taken place, the resulting embryo is transferred into the uterus (Embryo Transfer-ET) in order for implantation to occur. This technology has enabled many couples, who thought that pregnancy was impossible, to have children.

The first child born by this procedure was Louise Brown in 1978. Since that time, there has been a dramatic increase in the use and refinement of both in vitro fertilization (IVF) and embryo transfer. To date, there have been several thousand children born to couples who, without IVF-ET, had little or no hope of bearing children. IVF is well suited for patients who have damaged or no fallopian tubes, but it is also being used at most centers around the country for other causes of infertility (i.e., endometriosis, low sperm count and unexplained infertility).

Following the successful fertilization of the eggs in the laboratory, the embryos are placed back into the woman's uterus roughly 3-5 days after fertilization. Based on the success rates in established clinics in the United States and abroad, live birth rate per egg retrieval is 32.6% (*Assisted Reproductive Technology Success Rates*, CDC National Report, 2001).

IVF-ET consists of the following steps:

- 1) ovulation induction with a series of medications including, Lupron or Antagon and gonadotropins such as Follistim®, Gonal-F®, Repronex® and Bravelle®,
- 2) transvaginal ultrasound guided retrieval of eggs,
- 3) fertilization of eggs in the laboratory,
- 4) placement of fertilized eggs (embryos) into the uterus (ET),
- 5) luteal phase support with hCG and/or progesterone, and
- 6) pregnancy test.

1. OVULATION INDUCTION AND MONITORING

Ovulation Induction (IVF)

Ovulation induction is the term used for the stimulation of the ovaries to produce multiple eggs (follicles). The drugs used are all in the form of injection. One of two drugs will be used to prevent the premature release of eggs. This allows greater control over the IVF cycle. Depending upon the stimulation protocol, either Lupron® or Antagon®/Cetrotide® will be used to prevent the premature release of eggs. If Lupron® is used; this medication will be started two weeks prior to beginning the medications used to stimulate egg development. If Antagon®/Cetrotide® is used, it will not be started after ovarian stimulation with gonadotropins.

Medications called gonadotropins will be used to stimulate the ovaries to produce multiple eggs. There are several gonadotropin products on the market today (see page 13 for a listing of these medications). These drugs contain either the hormones FSH (follicle stimulating hormone) and LH (luteinizing hormone) or FSH alone. These hormones are responsible for the production and maturation of eggs.

The last medication prior to egg retrieval is human chorionic gonadotropin (hCG). HCG (Ovidrel®, Pregnyl®) allows for the final maturation of the eggs and the timing of the egg retrieval. It is given by injection into the deep muscle and will be administered when the follicles have reached appropriate size for retrieval (18-20mm in size).

All of these drugs have been used for many years in the treatment of infertility. Under proper supervision they are considered safe, and there is no evidence that they have any long term side effects in their users. The IVF nurse will review their dosage, administration, side effects and the necessary monitoring needed while on these drugs. This information is also included in the *Medication* section of this booklet.

Our protocols are modified to meet the needs of each individual patient. Approximately 15% of patients will not develop enough eggs for retrieval and will need to be canceled.

Timing of Egg Retrieval:

The human egg is susceptible to fertilization for a short period of time. In IVF, it is important that the egg be at the right stage of development when it is exposed to sperm. Evidence of egg maturity is derived from both ultrasound measurements of follicle size and serum levels of estrogen (developing eggs produce estrogen). Once the eggs are at the appropriate size, hCG will be given to trigger the final development of the egg. This is the last step in the egg maturation process. The hCG injection is given at night, and roughly 35-36 hours after the injection the eggs are ready for retrieval and subsequent fertilization. Therefore, women undergoing ovulation induction for IVF will be followed in two special ways (ultrasound and estrogen measurements) to assess the development of the eggs in their ovaries.

Ultrasound. A transvaginal ultrasound will give the physicians a visual description of the number of follicles developing, the rate of development, and to some extent the maturity of the eggs. Although one cannot visualize the egg by ultrasound, one can visualize the fluid filled sac (follicle) in which the egg is growing. The maturity of the egg correlates to the size of the follicle. Unfortunately, the ultrasound cannot always distinguish between a follicle containing an egg and a cyst; thus the estrogen level is very important in helping the physician distinguish between the two.

Ultrasounds will normally begin around the fifth or sixth day after the woman begins her ovulation induction. Ultrasounds will then be performed daily, or every other day, until egg retrieval. The follicles must reach at least 16-20 mm in diameter before they are considered to contain a mature egg. Most women need an average of 3-4 ultrasounds with each cycle.

Estrogen Measurements. Estrogen measurements will also be used to follow the growth of the eggs. Because the growing follicles produce estrogen, measurement of serum estrogen is used to guide adjustments in your medication dosage and to give an estimate regarding egg maturity. The test to measure estrogen in blood takes several hours to run; for this reason, blood is drawn in the early morning so that the results will be ready in the afternoon. Estrogen measurements will be obtained on the days that an ultrasound is scheduled. Both the ultrasound

and estrogen level will be used to determine the dose of medication and/or the timing of the hCG injection.

2. EGG RETRIEVAL

Unless special circumstances exist, the eggs will be obtained by a transvaginal ultrasound guided technique 35-36 hours after the hCG injection. This method of egg retrieval is accomplished by inserting an ultrasound probe with a needle guide into the vagina. Anesthesia, generally IV sedation, is required. Once the probe is lined up with the follicle (egg), the needle is advanced into the follicle and the fluid is removed. The probe is then redirected and the same method is employed until all eggs have been removed. One can expect that approximately 70% of eggs identified by ultrasound will be retrieved.

After the eggs are collected, they are taken to the lab adjoining the procedure room. While you are recovering from the procedure, the lab personnel will be identifying the eggs and preparing them for fertilization.

3. FERTILIZATION

In Vitro Fertilization (IVF):

The contents of each follicle that is aspirated will be examined for an egg. Each egg will be graded as to its state of maturity and placed in a separate dish. The dish is then transferred to the incubator which provides an environment suitable for fertilization and development of an embryo. The term embryo is used to refer to the developing individual, following fertilization until the end of the second month. Shortly after the eggs are retrieved, a semen sample will be obtained, and the sperm will be specially prepared in order to obtain the best sperm. A set number of sperm will be placed into each dish containing an egg and then returned to the incubator. If intracytoplasmic sperm injection (ICSI) is used, a single sperm will be injected into each egg. This technique is best suited when the sperm count or motility is low. Depending on the quality of the sperm and eggs, one can expect 50-70% of the eggs will fertilize. Cell division of the fertilized egg will begin about 24-36 hours after retrieval. When the embryos are at the 2-8 cell stage they are ready for transfer into the woman's uterus.

4. EMBRYO TRANSFER

Roughly 3-5 days following egg retrieval the embryos will be ready for transfer. At this time the dishes are removed from the incubator and each is examined for the presence of a viable embryo. Our laboratory director will make a decision regarding whether transfer will be done on day three or on day five when the embryos have reached blastocyst stage.

The embryo transfer will take place in a room next door to the ART laboratory. Prior to the procedure, the laboratory director will meet with each couple to discuss the number of embryos to be transferred and allow the couple to see the embryos under microscopic magnification.

5. LUTEAL PHASE SUPPORT

Progesterone, which is produced by the ovary after ovulation, is important for fostering early conditions suitable for implantation of an embryo. Progesterone levels in IVF cycles are usually more than adequate because of the stimulation of the ovaries involved in the first part of the cycle. However, since the process of egg retrieval removes some of the cells that are responsible for making progesterone, it is important to supplement with progesterone following the egg retrieval. This supplementation will be either in the form of progesterone injections, progesterone vaginal suppositories, progesterone capsules, or a combination of these products. These medications will increase the levels of progesterone during the time of early pregnancy. Patients will stay on progesterone until the results of their pregnancy test are known. If a pregnancy has occurred, the progesterone will be continued for an additional 3-4 weeks.

6. PREGNANCY TEST

Pregnancy tests are done between days 11 and 13 following embryo transfer. This blood level will be drawn in the morning and results will be called to the patient in the late afternoon of the same day.

RISKS ASSOCIATED WITH IVF

Hyperstimulation:

IVF is a fundamentally safe procedure. Every technique involved is already widely applied in the care of infertile couples. What is innovative is fertilization and early embryo development outside of the body. The major risk of ovulation induction is primarily hyperstimulation. Hyperstimulation results from too many eggs being developed in combination with a very high estrogen level. When eggs are aspirated from the ovary, as they will be in IVF cycles, hyperstimulation is rare. When it does occur, it consists of rapid enlargement of the ovaries during the latter part of the cycle which is accompanied by pain, fluid loss into the abdomen, and alterations in the circulation. When ovarian hyperstimulation is severe, individuals may become very ill and require hospitalization and major emergency measures to maintain their well-being. Such an event is extraordinarily rare, even under circumstances where egg retrieval is not performed.

Multiple Gestations:

When more than one embryo is returned to the uterus there is a risk of a multiple gestation. If pregnancy occurs, there is roughly a 25% chance of having twins with IVF and a 3-5% chance of triplets or greater. **Multiple births have an increased risk of miscarriage and premature delivery which can lead to death or a permanent deficit in prematurely born infants.**

Egg Retrieval:

The risks of vaginal ultrasound retrieval include the possibility of bleeding, injury to internal organs, or infection which might require antibiotic treatment. Although adverse reactions are very rare, you will be monitored closely during and following the retrieval. There may be some discomfort with the procedure; however, you will be given either IV sedation or spinal anesthesia.

Stress:

The last risk associated with IVF and related procedures are the possible trauma from stress. As IVF recipients, you may feel a great deal of pressure or anxiety created from by the emotional, financial and time demands of the program. After so much investment of yourselves and resources, disappointment may strike particularly hard. For this reason we may arrange an appointment with a counselor before beginning your IVF cycle. We hope you will find this helpful in dealing with the demands of our program.

Tubal Pregnancy:

All ART procedures can result in an ectopic (tubal pregnancy). The 1991 rate of tubal pregnancy per embryo transfer was 1.2%. All women with a positive pregnancy test will be followed carefully to facilitate early diagnosis of this condition.

Additional Concerns:

All couples have a 2-5% risk of having a child with a birth defect. For years, data obtained from IVF centers across this country have not shown an increase in birth defects in children conceived from IVF techniques. More recent studies have shown around 4% of children conceived through IVF have some birth defect. Other factors can contribute to birth defects including advanced age of the mother and chromosomal abnormalities in the couple. IVF and associated techniques may also increase this risk; however, at this time there is limited evidence as to the role IVF has in increasing risk.

Roughly 18% of all pregnancies will result in a miscarriage, and 1% of all pregnancies will end in a tubal pregnancy. While miscarriages often require no intervention, they occasionally need to be managed with a D&C. Tubal pregnancies can be life threatening if not diagnosed early and must be removed, usually by laparoscopy.

There is also some concern regarding the use of ovulation induction agents and the development of ovarian cancer. This is discussed in greater detail in the medication section.

OTHER ALTERNATIVES

The Assisted Reproductive Technologies are not viable alternatives for all couples. Many couples find that the stresses financially, physically and emotionally of ART are too great to continue on with medical therapy. Adoption and child free living are two options that many infertile couples have successfully chosen. It is important that each couple discuss these options. You may want to consider meeting with a counselor to discuss your feelings regarding ART as well as other alternatives. We encourage you to ask the ART team for information concerning adoption and child free living.

ADDITIONAL ART PROCEDURES

EMBRYO CRYOPRESERVATION

In the early to mid 1990's the technique of freezing embryos was developed and refined. Today, embryo cryopreservation is standard practice in many IVF centers. In embryo cryopreservation, eggs are fertilized with sperm and a portion of the resulting embryos are transferred to the patient. The remaining embryos are frozen and transferred at a later date. It is recommended that only two to three embryos should be transferred at one time; therefore, embryo cryopreservation allows the physician to fertilize all eggs and only transfer two to three at the time of the IVF cycle. If the couple does not become pregnant or they wish to have another child they can return to have the frozen embryos thawed and transferred without having to undergo ovarian stimulation and egg retrieval. This technology has increased the pregnancy rate for IVF by increasing the number of embryo transfers from one egg retrieval. The national live birth rate per transfer of thawed embryos is 23.4% (*Assisted Reproductive Technology Success Rates*, CDC National Report, 2001).

Although the delivery rate from embryo transfer with frozen/thawed embryos is lower, it has steadily increased over the years as laboratory techniques have been refined. Frozen embryos are thought to be viable indefinitely once they are frozen. The steps of embryo transfer with cryopreserved embryos are:

- 1) preparation of the endometrium (lining of the uterus) with estrogen, beginning day 1 of period, and progesterone injections, beginning day 14-15 of cycle,
- 2) thawing of embryos and transfer to the uterus after four-six days of progesterone therapy.

Although embryo cryopreservation is a good option for many couples, many women will not be able to produce enough eggs to allow embryo cryopreservation. To take part in embryo cryopreservation, all patients and their partners must sign a separate consent agreeing to this procedure.

MICROMANIPULATION

Advances in microscopic equipment and knowledge about eggs, sperm and embryos have led to the development of new techniques in ART. Micromanipulation refers to the handling and manipulation of individual eggs, sperm, or embryos in an effort to improve fertilization and/or pregnancy rates. These techniques require specialized equipment and personnel. Currently the most common micromanipulation techniques used are intracytoplasmic sperm injection (ICSI) and assisted hatching. ICSI is used to assist fertilization in cases of severe male factor infertility and assisted hatching is used to help the embryos attach themselves to the uterus (implantation). In addition, our facility also offers preimplantation genetic diagnosis (PGD). This procedure is available for couples who have a genetic disorder that they do not wish to pass on to an offspring or which impairs their ability to maintain a pregnancy.

Intracytoplasmic Sperm Injection (ICSI)

The ICSI technique has been developed over the past 10 years to treat cases of severe male factor infertility. This technique involves injecting a single sperm into the interior (cytoplasm) of an egg. Injected eggs are then returned to the laboratory incubator and are treated thereafter as in conventional IVF.

Candidates for ICSI may include patients with very low sperm counts or have sperm with poor motility. This technique is also used in couples with a history of failed fertilization with standard IVF techniques. ICSI may also be used to achieve fertilization using surgically extracted sperm from patients with anatomic or surgical conditions (such as vasectomy) that prevent sperm from entering the ejaculate. In all these cases, donor sperm or ICSI may provide the only options for conception.

Risks Associated with ICSI

ICSI differs dramatically from normal fertilization and standard IVF. In the latter two instances, the egg is surrounded by tens of thousands of sperm and only one sperm, through natural selection, is able to penetrate the egg. In ICSI, the lab personnel select a normal appearing sperm to be injected into the egg. The potential consequences of injecting a normal appearing sperm, which is in fact abnormal, include the development of a genetically abnormal embryo. Recent evidence suggests that some forms of severe male factor infertility are genetic and may be passed on to male offspring through the ICSI procedure. The incidence of congenital abnormalities (birth defects) following ICSI appears to 1-2% higher than that of the general population. This observation is based on the experience of several thousand babies born worldwide following ICSI.

Apart from the possible genetic consequences of selecting an abnormal sperm for injection, the physical trauma to the egg resulting from sperm injection can lead to degeneration of the egg, decreased fertilization rate, poor or arrested embryo development following fertilization, and reduced chance of a successful pregnancy outcome.

There is no guarantee that ICSI will result in either fertilization or pregnancy. A separate consent form and additional charge are required for ICSI.

The alternatives to ICSI for treatment of severe male factor infertility are limited. One option is the use of donor sperm. Using donor sperm normalizes the success of conventional IVF-ET in couples with severe male factor infertility. In cases where male factor is the only diagnosis, pregnancies with donor sperm can be achieved through timed intrauterine insemination, a treatment far less expensive and complicated than IVF-ET.

Assisted Hatching

Normally, embryos are transferred to the uterus three days after retrieval. Usually the embryos consist of six to eight cells at this stage. After transfer, the embryo must continue to develop to the blastocyst stage (a hollow ball of about 100 cells) before implantation can occur. This development takes several days. Immediately before implantation, the blastocyst must "hatch" from the coating (zona) which surrounds the embryo. To assist the hatching process, a special solution is used to dissolve the thick coating around the embryo. There is a small risk of damage to the embryos from the procedure. It is not clear which patients are the best candidates for assisted hatching. Currently, the laboratory uses assisted hatching on all patients who are 38 years of age or older and/or who have embryos with thick zonae. In order to perform assisted hatching on embryos, all patients must sign a separate consent. There are also additional charges for this procedure.

Preimplantation Genetic Diagnosis

Preimplantation Genetic Diagnosis (PGD) is a relatively new laboratory technique which is used in conjunction with IVF to screen embryos for genetic abnormalities. This procedure involves taking one cell from a developing embryo (cell biopsy) and analyzing the genetic material (DNA) for abnormalities.

PGD is offered to patients who are carriers of single gene disorders (diseases that can be traced to a specific location on a gene) and for patients who are at risk for chromosomal abnormalities due to an incorrect number of chromosomes in the cells (aneuploidies). Currently, Wake Forest University only offers PGD in cases of single gene disorders; however, PGD for aneuploidies will hopefully be offered in the near future.

For a couple to proceed with PGD they must first meet with Dr. Deaton and then be referred to our PGD clinic. The PGD clinic is staffed by genetic counselors who will review the PGD process, costs, risks and benefits of procedure, as well as alternatives. At the end of this visit the couple will be given an opportunity to sign the PGD consent.

Once the PGD consent has been obtained, the couple will be asked to pay a deposit for the PGD procedure. This deposit is separate from the IVF charges and is only for the genetic portion of the cycle. The couple will be sent to the lab to obtain blood samples. Once the deposit has been paid and blood samples have been obtained, it will take approximately 6-8 weeks before the couple will be scheduled for their IVF cycle.

Risks Associated with PGD

As in any conception, there is a risk of birth defects in children born following in vitro fertilization, cell biopsy, and PGD testing. This risk is generally 3-5%. There is also the risk that the PGD may not accurately detect those embryos which carry the disease in question or damage to the embryo may result from the cell biopsy procedure. This may result in embryos being transferred that carry the disease in question or having no embryos to transfer.

OOCYTE DONATION

For some women pregnancy with their own eggs is impossible. A few women carry a genetic defect which should not be passed on to their offspring; other women may not be able to produce eggs. This may happen due to premature failure of the ovaries (early menopause), surgical removal of the ovaries, or failure of the ovaries to respond adequately to ovarian stimulation. Advancing age also effects and contributes to lower pregnancy rates and higher fetal defects in women over the age of 35. Prior to IVF, these women had only the option of child-free living or adoption. Today, with IVF and related procedures, couples can request the use of donor eggs for their IVF cycle.

The major steps involved in IVF with donor eggs include:

- 1) ovulation induction of the donor with Lupron®, Antagon®/Cetrotide® or gonadotropins, and hCG,
- 2) stimulation of the uterine lining of the recipient female with estrogen and progesterone,
- 3) ultrasound guided egg retrieval of the donor,
- 4) fertilization of the donor's eggs with the sperm of the recipient's husband, and
- 5) transfer of the resulting embryos to the recipient's uterus.

Although IVF with donor eggs offers the hope of pregnancy to many couples, it is not an option for all couples. Egg donors are matched as closely as possible in regards to physical characteristics of the recipient couple. The recipient couple will not have access to identifying information of their donor. In addition, the donor will not have access to the identity of the couple receiving her eggs. The live birth rate transfer is roughly 28.7%-40% (*Assisted Reproductive Technology Success Rates*, CDC National Report, 2001).

It is also important to consider the psychological aspects of using donated eggs. Many couples may have fears that a child conceived with donated eggs or sperm may not look like them or they may fear that they will not be able to bond to the child as they would a child conceived with their own eggs or sperm. Although these concerns are very common, they do need to be dealt with before proceeding with an IVF cycle. If you are considering the use of donor eggs or sperm, you may be required to meet with a psychologist to discuss this option in detail and explore the psychological issues regarding donor gametes.

Currently, the Wake Forest University Program for Assisted Reproduction does not recruit egg donors. If you are considering anonymous donor eggs, we will be glad to refer you to a reputable program such as Duke University or University of North Carolina School of Medicine who have a number of available donors. We may be able to assist with your preliminary work-up and some of your monitoring.

DAILY INSTRUCTIONS FOR YOUR CYCLE

The following pages contain information and instructions for you to follow in relation to your IVF cycle. You will find it helpful to review this material each time you enter a new phase of your cycle. Please refer to your specific protocol to see which information is pertinent to you.

You may also find it helpful to keep a calendar of clinic appointments. Please bring your workbook to your appointments so that we can make notes or changes if necessary.

INSTRUCTIONS FOR SEMEN SPECIMENS

Prior to and during the IVF cycle, the partner may be asked to provide 1-2 semen specimens. The first one will be tested to ensure that the sperm count is adequate and that it can withstand the processing necessary for IVF. If adequate, this specimen may be frozen. The last specimen will be collected the day of egg retrieval and will be used to fertilize the eggs.

The IVF personnel will instruct you when you need to schedule your semen testing with the ART laboratory staff. The ART lab phone number is located in the back of the booklet. Below are instructions you should follow for each collection:

IT IS IMPORTANT THAT YOU PROVIDE THE SPECIMEN AT THE DESIGNATED TIME. FAILURE TO DO SO MAY REQUIRE POSTPONEMENT OF YOUR IVF CYCLE.

1. Do not have intercourse or ejaculate for three days before collection day; however, you should have intercourse or an ejaculation at least one week prior to the collection day.
2. Sterile specimen cups will be provided. They can be picked up in the *Center for Reproductive Medicine*, located on the second floor of the Comp Rehab Building.
3. Wash glans penis thoroughly, i.e.,
 - a. Pull foreskin back if uncircumcised.
 - b. Wash glans with soap and water.
 - c. Rinse and dry glans thoroughly.
 - d. Do not use lubricants.
4. Collect the entire ejaculate by masturbation. Do not use any lubricates or lotions. Use a sterile specimen cup.
5. The specimen must be in the office no more than one hour after collection. Keep the specimen at room temperature. If you live more than 1 hour away, you will be asked to collect your specimen in the office. A private area will be provided. You will be asked to show identification and fill out a form when you drop off the specimen. Please fill this form out completely. Please list any medications you are currently taking or have taken in the past six months.
6. The day of the egg retrieval you will be asked to collect the specimen at our office. Remember to bring proper identification. You may be asked to collect before, during or after your partner's egg retrieval. Occasionally, we may need your specimen the day before retrieval.

MEDICATIONS

IVF requires the use of several medications to achieve its goal. This booklet contains information on your medications including risks, side effects, preparation, and administration. You will also receive specific information on all medications from the IVF nurse.

Most patients will have their prescriptions sent to a mail order pharmacy. If your insurance requires that you use a specific pharmacy, you will be given prescriptions with refills for all necessary medications by the IVF Nurse Coordinator. **It is your responsibility to order refills for these medications.**

Medications used during the IVF cycle are as follows:

Common Name	Actual Name	Purpose
Antagon® Cetrotide®	GnRH antagonist	To prevent spontaneous release of eggs
Lupron®	GnRH agonist	Ovarian suppression/prevent spontaneous release of eggs
Follistim® Gonal-F® Bravelle®	Gonadotropins (FSH only)	Stimulate ovaries to develop multiple eggs
Repronex®	Gonadotropins (FSH and LH)	Stimulate ovaries to develop multiple eggs
Pregnyl® Ovidrel®	hCG	Final injection before egg retrieval, used to maturate eggs

GONADOTROPINS (FSH, FSH/LH)

There are a variety of gonadotropins available for ovarian stimulation. You will be prescribed one or a combination of the following: Follistim™, Gonal-F™, Bravelle™, and Repronex™.

In the IVF patient, gonadotropins are given to stimulate the ovaries to produce several follicles in one cycle. This allows the IVF team to retrieve more eggs and thus ensures a greater chance of fertilization.

Side Effects:

Side effects associated with these medicines include local irritation at the injection site and excessive ovarian stimulation. Other reported side effects include dizziness, nausea, headaches, irritability and hot flashes. These, however, are thought to be associated with the increase in estrogen levels from the stimulated follicles.

Risks:

Hyperstimulation of the ovaries is a potential risk when taking ovulation induction agents. Hyperstimulation occurs when the ovaries become enlarged. In mild to moderate cases of hyperstimulation, a person may experience abdominal distension and/or abdominal pain. Approximately 20% of patients will experience mild hyperstimulation. Symptoms usually resolve with the onset of menses, but in the case of pregnancy may continue for several weeks.

In severe hyperstimulation (less than 1% of patients in IVF programs), ovarian enlargement is accompanied by accumulation of fluid in the abdomen, nausea, vomiting, weight gain and a decrease in urine output. Women who experience severe hyperstimulation require hospitalization.

The symptoms of hyperstimulation usually do not occur until 4-5 days after your egg retrieval. If you notice any of the following symptoms please call the IVF office immediately: weight gain of over 5 pounds from your baseline weight, a decrease in your urine output, severe abdominal pain, dizziness upon standing, nausea or other discomfort which you find concerning.

There is also some concern that the use of ovulation induction agents may increase a person's risk of developing ovarian cancer. There is, however, no clear evidence that this is true. It is known that women who are infertile and who have never been pregnant are three times more likely to develop ovarian cancer than fertile women. Both pregnancy and past use of oral contraceptives appear to have a protective effect. If you have any further questions please ask the IVF nurse to give you further information.

Dosage and Administration:

You will be given specific instructions by the nurse on how to prepare the medication as well as the proper technique for administration. If needed, you or your spouse will practice the injection technique in front of the nurse. Most of our medications may be injected subcutaneously. The IVF coordinator will discuss with you the appropriate way to administer the drug you are taking.

You will be told by the IVF coordinator when to begin the gonadotropin injections. It should be given at the same time each day, usually in the late afternoon or the early evening. This ensures accurate measurement of your response when you come in for your ultrasound and estrogen measurement.

Preparation of Bravelle®/Repronex®/Gonal F®:

1. Assemble necessary items:
 - syringe with needle
 - injection needle (30G-1/2" needle)
 - alcohol wipes
 - gauze pad
 - band-aid
 - prescribed vial of Bravelle®/Gonal F®/Repronex®
 - 1 vial of diluent
2. Remove tops of diluent and medication (powder).
3. Remove needle cap from syringe, taking care not to touch or contaminate the needle.
4. Draw up 1/2 cc of diluent, inject into powder of Repronex®/Bravelle®/Gonal F®.
5. Gently rotate the vial to dissolve powder. After the medicine is dissolved, withdraw it back into the syringe. If using more than one vial of medication, inject this solution into the next vial, gently rotate and withdraw back into the syringe.
6. If there are any large air bubbles, hold the syringe upright and gently tap the syringe to force the bubbles to the top. Gently expel the air bubbles by pushing on the plunger.
7. Place the needle cap on the needle and change needles before giving injection.

NOTE: To dissolve Gonal-F®, Bravelle®, or Repronex®, use ½ cc diluent for one to three ampules of drug.

HUMAN CHORIONIC GONADOTROPIN (HCG)

HCG (Pregnyl®/Ovidrel®) is the last medication you will take prior to egg retrieval. HCG allows for the final maturation of the eggs and also enables the IVF team to time retrieval of the eggs. Chemically, hCG is similar to the hormone LH and, when given after Bravelle/Follistim/Gonal-F/Repronex mimics the body's own LH surge and triggers ovulation.

Side Effects:

The side effects caused by hCG are similar to gonadotropins. They include hyperstimulation of the ovaries, nausea, dizziness, headaches, and local irritation at the injection site. **See also side effects listed for gonadotropins.**

Dosage and Administration:

HCG must be administered into the muscle of either the hip or thigh (see Figure 1). It comes in a powder form and must be reconstituted with sterile water prior to administration. The usual dose of hCG for the timing of egg retrieval is 10,000 units. The nurse will instruct you on proper preparation of the medication as well as administration.

The IVF coordinator will tell you when you will take this drug. The timing of the hCG injection is critical, so please take it exactly when instructed to do so. This is based on both your follicle measurements and your estrogen level. **The night you take the hCG you will not take either, Follistim®, Gonal-F®, Bravelle®, Repronex® or Lupron®, or Antagon®/Cetrotide®.** You will be scheduled for egg retrieval approximately 35-36 hours after hCG administration.

Preparation of hCG:

1. Assemble necessary items:
 - syringe with needle
 - injection needle (27G-1-1/4" needle)
 - alcohol wipes
 - sterile gauze pad
 - band-aid
 - 10,000 unit vial of hCG
 - 10 cc vial of diluent
2. Remove top from both the medication and diluent vials. Wipe both with alcohol.
3. Remove needle cover from syringe and draw back the plunger to the 1 cc mark.

4. Inject air into the bottle of diluent. With needle still in vial draw back 1 cc of diluent into the syringe. (Keep needle below the level of diluent.)
5. Inject diluent into the bottle of hCG. Remove the needle and replace cover. Gently rotate the bottle to dissolve the powder.
6. With the vial upside down, draw up the hCG into the syringe. You should have 1 cc of hCG in your syringe. This is equivalent to 10,000 units of hCG.
7. Remove any large air bubbles and change needles.
8. You are now ready for injection. Please refer to the section on injections for proper technique.

PROGESTERONE FOR LUTEAL SUPPORT

Progesterone will be prescribed after egg retrieval or prior to embryo transfer for those going through either an IVF cycle or cryopreserved embryo transfer (CPET) cycle. Progesterone is the hormone responsible for preparing the lining of the uterus for implantation.

Side Effects:

The most common side effects of progesterone include breast tenderness, irritability, and nausea. Some women experience depression and acne while taking progesterone. If you do not become pregnant, you may have delayed menses because of the progesterone.

The progesterone used for injections is a thick oil based compound. Some women will develop soreness and irritation at the injection site. If you develop any irritation from the progesterone injections, please call our office. Some women may need to be switched to suppositories or gel if the irritation is severe. There is no association between the natural progesterone you will be prescribed and birth defects.

Dosage and Administration:

The usual dose for progesterone is 1cc each day until pregnancy test.

1. Assemble necessary items:
 - syringe with needle
 - injection needle (22G-1-1/2" needle)
 - alcohol wipes
 - sterile gauze pad
 - band-aid
 - 10cc vial of Progesterone in Oil
2. Remove top from the medication. Wipe with alcohol.
3. Remove needle cover from syringe and draw back the plunger to the 1 cc mark.
4. Inject air into the bottle of progesterone. With needle still in vial draw back 1 cc of progesterone into the syringe. (Keep needle below the level of diluent.)
5. Remove any air bubbles. Remove needle from syringe and replace with 22G 1-1/2" needle for injection.
6. You are now ready for injection. Please refer to the section on injections for proper technique.

INJECTIONS

You and your spouse will be taught by the IVF nurse how to administer your medications. Repronex®, Pregnyl®/hCG and progesterone are administered into the muscle, while Gonal-F®/Follistim®/Bravelle® and Lupron® are administered into the subcutaneous (fat) tissue. Below is a description on how to safely administer these shots. After reviewing this information with the IVF nurse, you will have an opportunity to practice your technique so that she can alert you of any problems.

General Information:

1. Remember to rotate injection sites daily to prevent discomfort.
2. To dispose of needles, it is recommended that you place them in the container a hard plastic container provided by the pharmacy. You may also use any hard plastic container, such as a laundry detergent container. In most counties, these may be discarded with your normal trash. However, it is recommended that you call your local sanitation office for advice on how to discard syringes.
3. Call the IVF nurse if you have any problems with either the injections or medications.

Intramuscular Injections (Pregnyl®hCG and Progesterone):

1. If your partner is giving the injection, the best location is the large muscle of the buttocks.
2. Either lie on your stomach or stand leaning on a chair for support. Your weight should be on the foot opposite the injection site.
3. To locate the correct site for injection, divide the buttocks into four quadrants (Figure 1.). The shot should be given in the upper outer region of the upper outer quadrant.
4. Wipe the area with the alcohol wipe in a circular motion from inside to outside.
5. The needle should be inserted completely into the site at a 90 degree angle (Figure 3.). This should be done in a darting motion.
6. While stabilizing the needle with one hand, gently pull back on the syringe to see if there is any blood return. If so, pull the needle out, change needles and repeat steps 3-6.
7. If there is no blood return, gently inject the medication into the muscle.
8. After all the medication is injected, pull the needle straight out and place a gauze over the area. Massage the area for approximately 30 seconds and place a band-aid on the site if needed.
9. If you will be giving the injection to yourself, the large muscle of the thigh may be used. The correct site for injection is in the area one hand breadth above the knee and one hand breadth below the hip (Figure 2.). You would then follow steps 4-8.

Figure 1.**Figure 2.****Figure 3.**

Subcutaneous Injections (Lupron®/Bravelle®/Follistim®/Gonal-F®/Repronex®):

1. Select the site for administration (Figure 3.).
2. Gently wipe the site with alcohol pad.
3. Tightly hold the medication-filled syringe and remove cap if necessary, being careful not to touch needle.
4. Hold syringe with needle pointing up and gently tap the syringe to move any air bubbles to the top of syringe.
5. If there is air in the top of the syringe, gently push the plunger up to remove air. Stop pushing the plunger when you no longer see air in the syringe.
6. Hold syringe with your dominant hand close to the base of the needle (hold syringe like a dart).
7. With the other hand, gently grasp a fold of skin at the injection site between your thumb and index finger (Figure 4.)
8. Quickly insert needle into the fold of the skin all the way to the base of the needle.
9. Slowly push plunger to inject all of the contents in the syringe.
10. Withdraw needle and place in sharps container.
11. If there is any bleeding at the injection site, place a dry cotton ball or bandage over site and apply gentle pressure for 1-5 minutes.

Figure 4.**Figure 5.**

PRE-RETRIEVAL INSTRUCTIONS

You will be scheduled for egg retrieval approximately 34-36 hours after your injection of hCG. Egg retrieval will take place either in the morning or early afternoon. You will go to the Minor Surgical Procedure Suite located next door to our office in the CompRehab building. You will be told by our staff at what time to report to the Surgical Suite. Below are instructions to follow prior to your retrieval.

The night before egg retrieval:

1. eat a good supper and have a late night snack,
2. remove any fingernail polish,
3. do not have intercourse, and
4. do not eat or drink anything after midnight.

The morning of egg retrieval:

1. take a shower,
2. remove any make-up, hair pins, jewelry, or contact lenses,
3. do not eat or drink anything, and
4. arrive in the Minor Surgical Procedure Suite at the designated time.

THE DAY OF EGG RETRIEVAL

On the day of egg retrieval you will be asked to report to the Minor Procedure Suite located on the second floor of CompRehab Plaza. Someone from the procedure suite will meet you and direct you to the holding room. You will be given a place to store your clothing and will then be placed on a stretcher. The nurse anesthetist will talk with you and discuss your sedation at that time. An IV will also be placed in your arm, and pre-operative vital signs will be taken. The lab will tell your partner where and when to go to collect his semen specimen.

Once all the pre-operative work has been completed, you will be wheeled to the procedure room and transferred to the procedure table. You will be draped with sterile sheets and towels. Dr. Deaton will also place a catheter in your bladder which will be promptly removed. Dr. Deaton will then clean your vagina with a sterile solution.

Prior to the bladder catheter, the nurse anesthetist will begin to administer your sedation. Please let him/her know if at any time you become uncomfortable. You will be drowsy through most of the procedure.

Once the vagina has been thoroughly cleaned, Dr. Deaton will insert the vaginal ultrasound probe. You should have minimal discomfort at this time. Dr. Deaton will then proceed to aspirate the follicles (fluid filled sacs containing the eggs). Lab personnel will be present in the OR room to transport the fluid to the lab for identification of the eggs. After all the follicles have been aspirated, the anesthesiologist will begin to withdraw your sedation.

You will then be transferred to the recovery room where you will stay for approximately one hour. Your partner or a friend will be allowed to sit with you in the recovery room until you are ready to leave. Dr. Deaton will meet with you and your partner before you are discharged to review your post-operative instructions and precautions.

After Your Egg Retrieval

Following the egg retrieval, you may experience some abdominal soreness, vaginal spotting, nausea and/or vomiting. These symptoms should resolve within a couple of days. **However, you should call the doctor if you experience excessive bleeding, difficulty breathing, severe pain, dizziness, or develop a fever.**

EMBRYO TRANSFER

Someone from our ART lab will call the day after your egg retrieval to discuss with you the number of eggs that were fertilized. You will also be told when to report to our office for embryo transfer. Embryo transfer will take place either three or five days after egg retrieval. The decision to have embryos transferred on either day three or five will be at the discretion of the ART lab director.

The day of embryo transfer you will report to our ART clinic. Please do not use the bathroom once you arrive to our office. You will need a full bladder for the embryo transfer procedure. Your partner will be allowed to be with you during the procedure as well as sit with you after the transfer.

At the time of transfer, the physician will discuss with you how many embryos he will place into the uterus. You will then be asked to undress from the waist down, lie down on the procedure table, and draped with a sheet. The physician will place a speculum in the vagina. The vagina and the cervix will be thoroughly cleansed with sterile water before transferring the embryos. The embryos will be transferred with the assistance of ultrasound. An abdominal probe will be placed on the abdomen, so that the uterus is can be visualized. Once this is done, the lab personnel will bring in the catheter containing the embryo(s) and the physician will place the catheter into the uterus using the ultrasound to help guide where the embryos will be placed into the uterus.

If the catheter is unable to be passed into the uterus, the embryos will be taken back to the lab and placed in the incubator. In rare instances your cervix may need to be dilated. It is felt that there is no damage done to the embryos if they are taken back to the incubator within five minutes.

No sedation is required for the embryo transfer. You may feel some mild cramping during the transfer; however this should resolve once the catheter is removed. After the embryos are transferred to your uterus, you will be asked to lie still with your hips elevated for approximately 30 minutes.

An ART team member will give you an appointment for your pregnancy test approximately 11-13 days after the embryo transfer. You will also continue with progesterone until the day of the pregnancy test.

For the next forty-eight hours after your embryo transfer, we encourage you to limit your activity. You may return to your normal activities after forty-eight hours. It is suggested that you refrain from any strenuous activity (i.e. weight lifting, running) until the results of your pregnancy test are known.

We realize that the time between your embryo transfer and the day of your pregnancy test is both long and frustrating. It is not unusual to be more emotional during this time. Be patient with yourself and realize this is natural. An ART nurse is available if you have any questions or concerns during this time.

YOUR PREGNANCY TEST

You will be scheduled for a serum pregnancy test between 10-12 days following the embryo transfer. The pregnancy test measures the amount of hCG (human chorionic gonadotropin) in your blood. HCG is a hormone that is produced by the developing placenta to sustain the pregnancy. During the first ten to twelve weeks of a pregnancy the level of hCG increases in a predictable manner.

We will not know the results of your pregnancy test until the afternoon of the pregnancy test. You will be notified as soon as this result is available.

If your hCG level confirms pregnancy, you will be asked to come back for a second hCG level. If that level is sufficient, you will be scheduled for an ultrasound around the fifth to sixth week of pregnancy. Once we have confirmed fetal heart motion by ultrasound, you will be referred to your obstetrician for care.

If your pregnancy test comes back negative the IVF team will be available to talk with you. IVF is a long and time consuming process. It is normal to be frustrated and upset if no pregnancy develops. You may find it helpful to meet with the counselor or the IVF coordinator to help put your feelings in perspective.

NOTE: If you do not become pregnant, you may be able to proceed with another IVF cycle after a two month waiting period. Dr. Deaton or an IVF nurse will be available to discuss this option with you and your partner.

PAYMENT POLICY

IVF can be an expensive endeavor especially if you do not have insurance coverage. We make every effort to keep the IVF and associated procedures affordable options for infertility patients.

It has been the policy of Wake Forest University Physicians and North Carolina Baptist Hospital to require payment of elective procedures and therapies prior to the initiation of treatment. If you have insurance coverage for IVF, you may be asked to pay the portion your insurance does not cover before initiating treatment.

All couples are asked to call Steve Tisdale in our Business Services Division to discuss payment of your IVF cycle. If you do not have insurance coverage for IVF, you will be asked to pay the cost of the cycle prior to beginning the stimulation medications. Steve Tisdale will assist you with this process.

GLOSSARY

ART (Assisted Reproductive Technology): The term used to refer to IVF, GIFT, ZIFT and other related procedures.

Aspiration: The use of light suction to withdraw the egg from the follicle.

Blastocyst: The term for an embryo with 100 cells at the stage prior to implantation.

D&C (Dilation & Curettage): A minor surgical procedure which expands the cervical canal of the uterus so that the lining of the uterus can be removed.

Egg Retrieval: The use of an ultrasound guided needle to aspirate the eggs from the ovary.

Embryo: The term given to the developing individual following fertilization until the end of the second month.

Embryo Transfer: The placement of the embryo(s) into the uterus following fertilization.

Estrogen: The female hormone produced mainly by the ovaries. As follicles grow, they produce increasing amounts of estrogen and this is measured in the IVF cycle to assess follicle (egg) maturity.

Fertilization: The process by which the sperm penetrates the egg.

Follistim®/Bravelle®/Gonal-F®: The brand name given to the drug containing FSH hormone. These stimulate the ovaries to produce eggs.

Follicle: The fluid filled sac which contains the maturing egg.

Follicle Stimulating Hormone (FSH): A hormone produced by the brain which stimulates the ovary to develop eggs for ovulation.

Gamete: A name referring to either the sperm or the egg.

Gestation: Another term for pregnancy.

GIFT (Gamete Intrafallopian Transfer): The combining of sperm and eggs outside of the body and by laparoscopy placing them in the fallopian tubes. Fertilization must then take place in the fallopian tubes.

HCG (Human Chorionic Gonadotropin): A synthetic drug which mimics the LH surge in the female cycle. It allows for final maturation of the egg and triggers ovulation.

ICSI: Intracytoplasmic sperm injection is the process whereby a single sperm is injected into the egg. It is often used in cases of poor sperm production.

Implantation: The embedding of the fertilized egg(s) into the lining of the uterus.

Lupron™: The medication used to "shut-down" the brain's release of FSH and LH, thus enabling the physician to better control follicle stimulation.

Luteinizing Hormone (LH): A hormone produced by the pituitary gland which triggers ovulation.

Oocyte: The medical term for the female egg. It may also be referred to as ovum.

Ovulation: The release of a mature egg from the ovary.

Ovulation Induction Therapy: The use of medications (Follistim®, Bravelle®, Gonalf®, Repronex®) to induce the ovaries to produce several follicles in a given cycle.

Preimplantation Genetic Diagnosis (PGD): the extraction of one cell from an embryo to test for genetic conditions.

Progesterone: The hormone which is secreted mainly during the second half of the female menstrual cycle and is responsible for the maturation of the uterine lining. This is necessary for successful implantation of the embryo(s).

Repronex®: Another brand name given to a drug containing FSH and LH. It stimulates the ovaries to produce eggs.

Ultrasound: A technique which utilizes sound waves to transmit pictures of internal body structures to a screen for visualization. In IVF, this technology is employed to visualize both the uterus and the follicles in the ovaries.

ZIFT (Zygote Intrafallopian Transfer): Eggs are retrieved from the stimulated ovaries and combined with sperm. Once fertilization takes place, the fertilized eggs (embryos) are placed into the fallopian tubes.

Zygote: A name referring to an embryo at the one cell stage.

IMPORTANT PHONE NUMBERS

*ART Office	716-6476 or 716-1369
Jeffrey L. Deaton, M.D.	716-6476
ART/Andrology Lab.	716-0161
Emergencies: after 5:00 p.m., weekends and holidays (Have the operator page Dr. Deaton).	716-2011
* Melanie Nguyen , R.N...	716-3778
*Lorraine Harris, R.N., BSN	716-0333
*Lori Ford	716-1369
Portland Professional Pharmacy	800-850-9122
WFUP Business Office (Steve Tisdale).	716-1269

Except for the emergency number, all other telephone numbers can be reached Monday-Friday 8:30 a.m.-4:30 p.m.

*You may leave a message on the automated system and your call will be returned as soon as possible.