

IN VITRO FERTILIZATION (IVF) GAMETE INTRAFALLOPIAN TRANSFER (GIFT)

Information for the Patient

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Welcome to the Fertility Associates of Memphis program for assisted reproductive technology (ART). Your doctor may have recommended one of the advanced assisted reproductive technologies such as in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT). These treatments can be overwhelming for some couples as the procedures are very involved and often quite technical. This information packet is designed to help guide the couple through all the steps of IVF and GIFT. Your doctor and nurse are available to answer any questions you may have. During normal business hours, you may reach us at 901-747-2229. Our nurse coordinators are available on weekends and holidays from 8:00 am - 4:00 PM by dialing 901-418-6353 and entering your phone number (with area code) after the beeps.

What is ART?

Simply explained, assisted reproductive technologies are fertility therapies in which both the woman's eggs and man's sperm are retrieved and treated outside the patient's body in order to increase the chance of pregnancy. The eggs and sperm may be cultured together in the laboratory to create embryos for transfer back into your uterus (IVF), or they may be combined and placed in the fallopian tube of the patient (GIFT).

The success of ART, in part, depends upon the patient's ability to provide enough eggs and sperm so that the chance of pregnancy is optimized. While even infertile men commonly provide an abundance of sperm, women require a series of medications to induce her ovaries to produce several mature eggs at one time.

For the sake of simplicity, most of the information in this document will refer to the IVF procedure. GIFT is identical to IVF except that the embryo transfer is replaced by an office laparoscopy procedure. For our patients undergoing GIFT, you should follow all IVF instructions and there is a section especially for you beginning on page 8.

Testing Required Prior to ART

Since we wish to optimize the conditions in which ART is performed, there are several important investigations that are required prior to starting treatments.

Assessment of Uterine Cavity

Although many couples have had extensive evaluations by the time they are ready to start therapy, it is essential that a normal uterine cavity (womb) be documented, as there are several abnormalities that may prevent pregnancy or implantation. We recommend that you have either an in-office hysteroscopy, sonohysterogram (SHG) or a hysterosalpingogram (HSG) to evaluate the cavity prior to your procedure. The HSG, commonly known as the "dye test" is performed by instilling dye into the uterus while taking x-rays to see the contour of the uterine cavity. In contrast, the SHG is performed by instilling a little fluid into the uterine cavity during a transvaginal ultrasound. Again, this allows the contour of the uterine cavity to be assessed. Alternatively, hysteroscopy allows direct visualization of the cavity by inserting a small, flexible telescope into the uterus. Hysteroscopy can be performed in our office as an outpatient procedure with very little patient discomfort. If you have had an HSG performed by another physician within two years preceding IVF and, if there has been no intervening event such as surgery, your doctor will request the x-ray films for review. If the uterine cavity appears normal, this test may be omitted.

Clomiphene Citrate Challenge Test

To help us determine how your ovaries will respond to stimulation, we will be performing a clomiphene citrate challenge test (CCCT). On the third day of your menses, we measure two blood hormone levels – FSH and estradiol (E2). These tests must be drawn on cycle day 3 (remember, cycle day 1 corresponds to the first day of your menstrual flow) and it is important that these tests are performed at our offices since values vary considerably between laboratories. You will also have a transvaginal ultrasound examination on this day so that we may assess the appearance of your ovaries. You will then take a course of clomiphene citrate (Clomid, Serophene), 2 tablets a day from cycle day 5 through 9 (10 tablets in all). On cycle day 10, we will measure another FSH hormone level.

The result of your CCCT is very important in the management of your ovarian stimulation and determines your proper medication dosage. This information will also be used to determine certain modifications from the basic IVF cycle. It is best performed immediately prior to your down regulation cycle (see below).

Some of our patients do not experience a normal menses on their own and need to take hormones to start a menses. For these patients, it may not be possible to perform a proper CCCT and we will need to rely on other methods. You must inform us if you have been taking any medication or supplements up to 3 weeks prior to the CCCT.

Blood Tests

Prenatal tests including your blood type and your blood count ensure a good start for your pregnancy. We also test for such diseases as AIDS, cytomegalovirus, syphilis, and hepatitis. A rubella titer is obtained to make sure you are immune to rubella (also known as German Measles). If you are not immune and become pregnant, the virus can cause severe birth defects in the developing fetus. If you are not immune, we will recommend that you receive the rubella vaccine prior to becoming pregnant.

Husband Investigations

We ask your husband to schedule two sperm tests prior to IVF. The first is the IVF semen analysis, which is an essential and required test. Many men have had semen analysis, either here or elsewhere, and may wonder why they

have to repeat it. The IVF semen analysis differs in that the embryologist will test different methods of sperm preparation to determine which results in the best sperm performance and can observe how well the sperm survive over 3 days in laboratory culture. The second is a test for anti-sperm antibodies, which are abnormally-produced proteins from the immune system that attach directly to the sperm and interfere with fertilization. If these antibodies are present on the sperm, we may recommend either intracytoplasmic sperm injection or a pre-treatment of the sperm with an enzyme called chymotrypsin that may help with fertilization.

Trial Transfer

This test usually applies to our patients undergoing IVF but may also be performed in our GIFT patients. It is a 'practice run' for the embryo transfer. An empty transfer catheter is passed into the uterus just as it will be when your embryos are ready to be returned to you. It allows us to plan your transfer so that there are no surprises on that day. The trial transfer is usually scheduled with the doctor that will be performing the actual embryo transfer and may be repeated if any difficulty is encountered.

Getting Started

Once you and your doctor have agreed to proceed with one of the assisted reproductive techniques, your first step is to contact our IVF nurse coordinator. The nurse will review the procedure, risks, costs and schedule in detail. Many of your required tests, if not already performed, can be scheduled at this time. Your husband's semen analysis and sperm antibody test are scheduled through our andrology department and can be arranged by calling 901-747-2229 and asking for the Andrology Lab. The nurse will also arrange for you to go through injection teaching – a self-learning process where you will learn and practice to mix and give yourself an injection. Since it is critical that these medications be correctly administered, injection teaching is mandatory before IVF can begin.

It is vital that we have a reliable way of contacting you so that important instructions can be communicated. Through our experience, a working home answering machine or voice mail is the best method and you must have either before getting started. Please check it at least once a day around 4:00 PM for our messages.

The IVF process is dependent on your menstrual cycle and takes several weeks to complete. You will be kept busy with tests which must be completed before we can start. When your results are available, our IVF team of doctors, nurses, and embryologists meet to determine the exact instructions and dosages of medications. If something is missing or an abnormality found then it may delay your start date. However, if all goes according to plan, approximately 6 - 8 weeks after the start of your menses, you can expect to be undergoing embryo transfer.

The preparatory work is vital to the success of ART and cannot be avoided. Your nurse or doctor will be happy to help you understand your instructions.

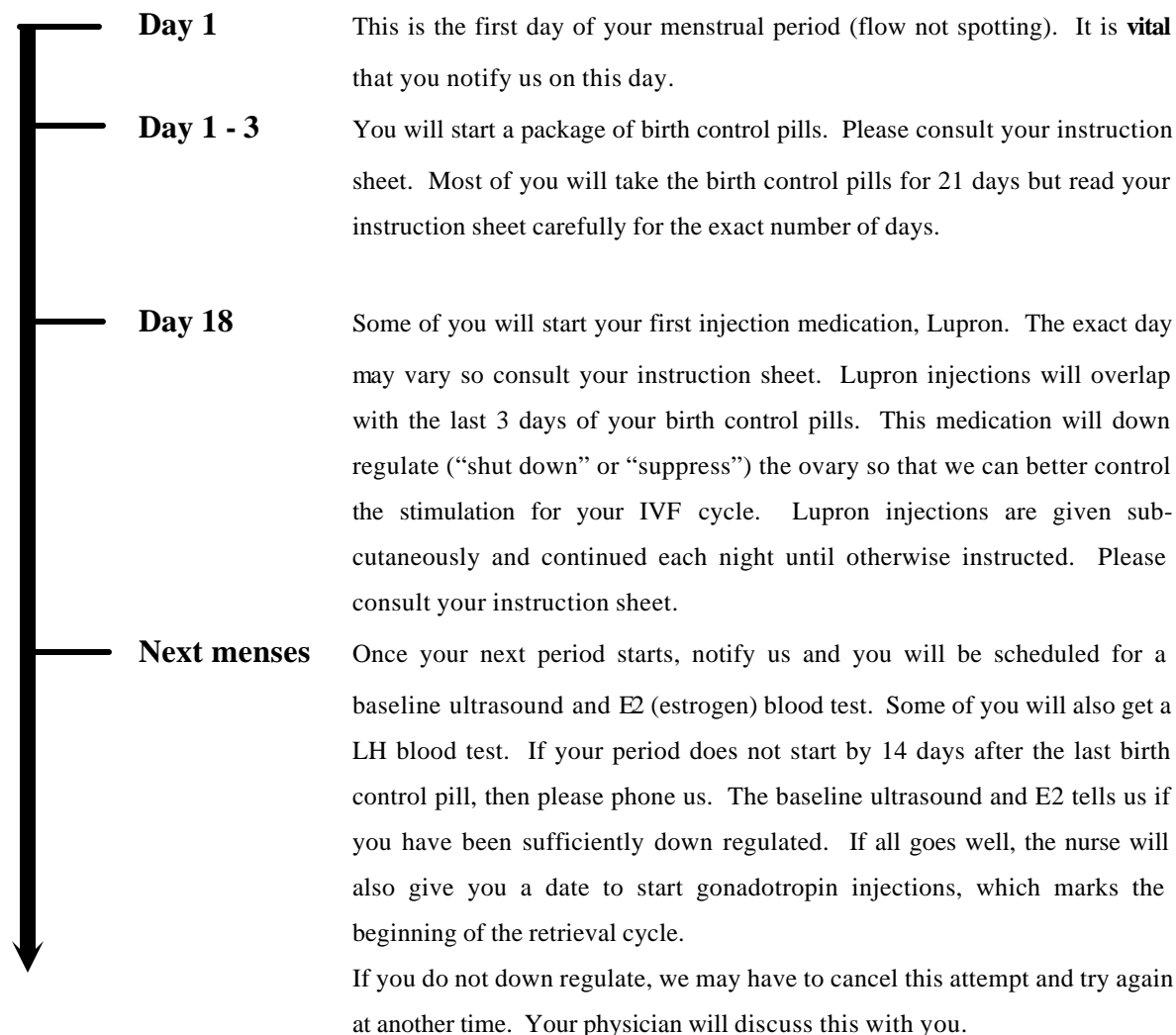
Ovarian Stimulation

We are now ready to start IVF with ovarian stimulation. This process takes a while and allows the maturation of several eggs from your ovaries. When it is complete, the eggs are ready for retrieval.

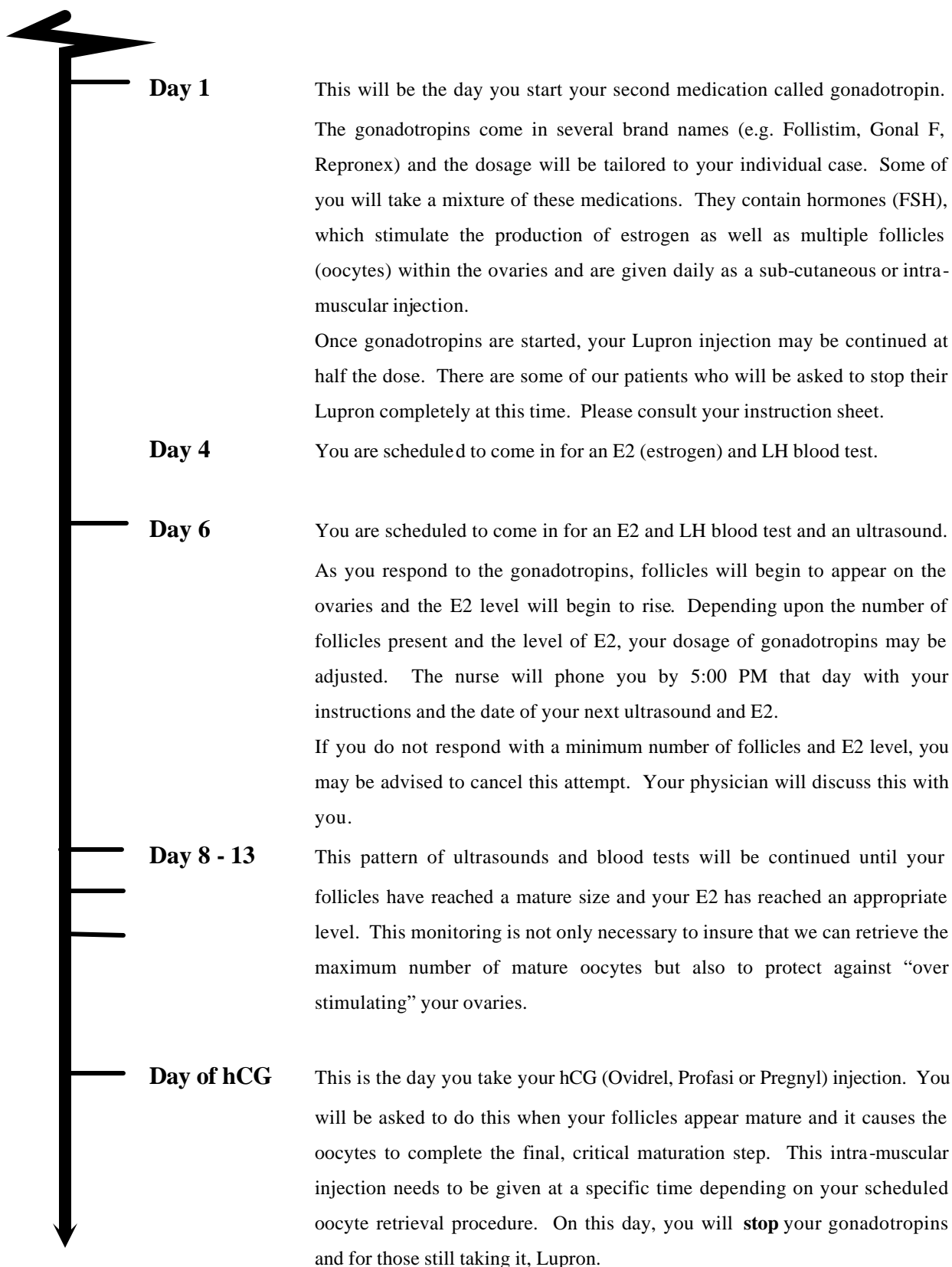
We utilize several different ovarian stimulation protocols. Before you start, you will be given a sheet with personalized instructions based on your menstrual dates and the protocol we have chosen for you. Keep this sheet handy as you will refer to it several times during IVF and we often will give you new instructions to add to it as the stimulation proceeds.

Most protocols span two menstrual cycles with medications started near the end of one and usually continued through a menses to the next. The first cycle often is referred to as the down regulation (pre-IVF) cycle, and is very important in maximizing success rates during the following cycle. The second is referred to as the retrieval cycle.

Down Regulation Cycle



Retrieval Cycle



Oocyte Retrieval

Oocyte (Egg) Retrieval

Forty hours after the hCG injection, the eggs will be mature and may start to ovulate so we schedule the oocyte retrieval (aspiration) just prior to expected ovulation. The retrieval will be performed at East Memphis Surgery Center. The morning of the retrieval, your husband will need to provide a semen sample at our office and an intravenous line (IV) will be started on you. The oocyte retrieval procedure can be performed under conscious sedation, which means you will be awake for the procedure but are kept comfortable with short-acting narcotics and sedatives. You can elect to go to sleep with general anesthesia for the procedure. Under general anesthesia, you will not feel the procedure at all and you will wake up in the recovery room. However, the cost of general anesthesia is extra and you may extend your recovery time by a few hours.

To retrieve your eggs, the doctor will use transvaginal ultrasound guidance to place a needle through the vaginal wall into the ovaries. You may experience some cramping, but most patients tolerate it very well. The entire procedure typically takes 20 - 35 minutes depending on the number of oocytes. After the retrieval, you will remain in our recovery room for approximately two hours for observation. You will need someone to drive you home after the oocyte retrieval.

Clearly, most couples wish to get the largest number of oocytes. An attempt will be made to aspirate all the follicles that can be safely accessed but not all of them will contain an egg. A satisfactory number of eggs retrieved corresponds with your final E2 level and ultrasound measurements of mature follicles. Remember, more important than the number of eggs, is the quality.

Because of down regulation, your ovaries may not be able to produce enough progesterone to allow implantation and maintain a pregnancy. For this reason, you will need to take supplemental progesterone beginning the night after the retrieval. Progesterone is usually given as an intra-muscular injection once each night.

Fertilization and Embryo Growth

Six hours after the oocyte retrieval, your husband's sperm will be incubated with your eggs. The natural process where a single sperm broaches the outer egg covering and delivers its' genetic material is termed fertilization and occurs overnight in our laboratory. The eggs will be examined microscopically to look for fertilization the next morning. Fertilization is confirmed when two pronuclei are visible in the egg cytoplasm. One pronucleus originates from the egg and contains the maternal chromosomes while the other originates from the sperm and contains the paternal chromosomes. The fertilized egg is now referred to as an embryo.



Two Pronuclei Embryo



Four-cell Embryo

Over the next 72 hours, the embryos will be checked for cell division or cleavage, a critical step in their development. The embryos are transferred back to you on the third to fifth day after the retrieval. We determine the day of transfer by the ability of the embryos to thrive in a laboratory environment. If it appears that the embryos will perform better in the uterus than in the laboratory, then we will transfer earlier. By the third day, they usually will have divided (cleaved) to at least a four-cell embryo. By the fifth day, they have often reached a very advanced stage called a morulae or a blastocyst. On the day of transfer, the embryos will be graded based on the number of cells that have now formed (morulae and blastocysts are not graded), as well as the appearance of cells themselves. Many couples are anxious regarding the quality of their embryos but grading is a subjective and imperfect process. We have noted many pregnancies with grade 1 (perfect) as well as grade 3 (average) embryos.

Not all of the eggs retrieved will complete this process. Of all the retrieved eggs, 60 - 80% will normally fertilize. Of those, 60 - 85% will divide and only 20 - 40% will make it to the blastocyst stage

The Embryo Transfer

The embryo transfer is usually a painless procedure and will be much like the "trial transfer" that you had during one of your initial visits. During the embryo transfer, a speculum is placed into the vagina, a small catheter will be placed through the cervix into the uterus, and several embryos will be transferred into the uterine cavity. The decision of how many embryos to transfer will be made based on several factors:

- 1) the endometrial thickness and pattern;
- 2) the embryo stage and grade;
- 3) the age of the patient; and
- 4) your tolerance and acceptance of the risks associated with multiple births.

After the transfer, you will stay on the bed with the feet slightly elevated for approximately 30 minutes. You are invited to bring your favorite cassette tapes or CDs to listen to during this resting period. After leaving the office, you should then restrict your activities to bed rest at home with bathroom privileges for the next 72 hours.

The progesterone injections are continued each night to help support implantation and pregnancy. In one week you will have a blood test to check your progesterone level and, if needed, adjustments will be made. You will be scheduled for a pregnancy test approximately 2 weeks after transfer.

Cryopreservation of Embryos

Embryo cryopreservation (freezing and storage in liquid nitrogen) is available for any viable embryos that are not transferred at the time of IVF. This situation exists when multiple eggs are fertilized resulting in more embryos than are needed for transfer. You may want to consider cryopreservation if a second pregnancy is desired or, as an opportunity for a later, second transfer if the initial IVF attempt is not successful, without having to go through another ovarian stimulation and oocyte retrieval. While the pregnancy rate is not as high as the initial IVF cycle, transfer of thawed embryos is a simpler therapy, involving less medication, at less cost and without an oocyte retrieval procedure. Clearly, there are not always extra embryos to cryopreserve. If this is your case, do not be alarmed, as this does not affect your chances of getting pregnant during the actual IVF cycle.

Pregnancies following transfer of thawed embryos result in normal babies with no higher risk of birth defects or disease than the general population. Pregnancies have occurred after thawing embryos cryopreserved for up to 7 years. Because of the theoretical risks involved in long-term embryo storage, we highly recommend that you thaw and transfer any embryos within 5 years of cryopreservation.

You will be offered cryopreservation before the beginning of your IVF cycle. If you choose **not** to cryopreserve, our laboratory will only fertilize enough eggs to allow for embryo transfer - typically 4 to 6. Since there is no reliable method of determining egg quality, the eggs chosen for fertilization are largely at random. This may lead to less than optimal embryos for transfer. If you choose to cryopreserve your extra embryos, you and your husband will need to make some decisions regarding the disposition of your embryos in the event of any unforeseen circumstances. Please read our consent form carefully and if you feel it necessary, consult your attorney before making your decisions. Our staff is happy to answer any questions you may have.

Gamete Intrafallopian Tube Transfer (GIFT)

The GIFT protocol is identical to IVF up to and including the oocyte retrieval. The difference occurs after retrieval with the transfer of the eggs and sperm together (gametes) into the fallopian tube through office laparoscopy. Thus, fertilization occurs in your fallopian tube and not in our laboratory. GIFT is appropriate for certain women with unexplained infertility with at least one normal fallopian tube and where there are normal sperm parameters. Your physician will help you make the decision about whether to perform a GIFT or IVF cycle. Since laparoscopy is involved, we perform office-based GIFT to help control costs for our patients. However, not all of our patients will be a candidate for GIFT.

The procedure is again accomplished under conscious sedation. Shortly after oocyte retrieval, local anesthesia is injected into your navel area and a small (1/4 inch) incision is made. A small laparoscope (fiber optic telescope) is inserted through this incision so the doctor can visualize your uterus, fallopian tubes, and ovaries. One or two additional, small incisions will be made in your abdomen in order for the doctor to place needed instruments. The fallopian tube is gently held so that a special catheter containing a few eggs with sperm can be directly injected into the fallopian tube. All the instruments are then removed and the incisions closed with a few stitches. Afterward you will remain in the office for approximately two hours for observation. Your care at this point is identical to that of IVF patients. Extra eggs can be fertilized by your husband's sperm in our laboratory with any resultant embryos being cryopreserved (see above).

Intracytoplasmic Sperm Injection (ICSI) and Assisted Hatching

In certain situations, we may recommend either ICSI and/or assisted hatching during your IVF cycle. ICSI will be recommended in cases with:

- 1) very low sperm counts or poor motility,
- 2) high levels of sperm antibodies,
- 3) or a previous cycle with poor or no fertilization.

With the ICSI procedure, a single sperm is loaded in a microscopic needle and then directly injected into the egg. In cases of severe male factor, this allows sperm which previously could not penetrate the outer covering of the egg to now fertilize the egg.

Assisted hatching is performed on your embryos if you:

- 1) are over the age of 39,
- 2) have an elevated FSH level,
- 3) previously failed implantation,
- 3) have embryos with a thick outer shell, or
- 4) have highly fragmented embryos.

In addition, patients who have not succeeded in a previous ART attempt may be counseled to undergo assisted hatching in another attempt. The hatching process involves thinning the outer layer of the fertilized embryo so that the embryo can literally hatch from this outer layer and implant. The hatching process occurs naturally in all embryos, but studies have shown, as women get older, this process is impaired due to an increased thickness in the shell. If you undergo ICSI or assisted hatching, we will prescribe steroids and antibiotics for you to take around the time of transfer in order to prevent any inflammatory response in your uterine lining from affecting the embryos.

Final Comments

This packet is intended only as an overview of the IVF and GIFT protocol. Your exact protocol will be individualized and the treatment prescribed for you may differ from the ones described here. Specific instructions on mixing and injecting medications, as well as for the retrieval and transfer, are provided at the IVF teaching session. The IVF nurses and physicians will be happy to discuss the process further with you at any time.

Remember, to schedule tests, notify us of your period or contact the nurse:

Call our office at (901) 747-2229 during normal business hours. Leave your name, phone number, date menstrual cycle started and the reason why you are calling. If you phone before 2:00 PM, we will call you back that day. Otherwise, we may not phone you until the next day.

On weekends or holidays, please call the weekend pager between 8:00 AM and 4:00 PM. Dial (901) 418-6353 and wait for the beeps. Enter your phone number with area code. The nurse will return your call.

If your menstrual flow starts after 4:00 PM, we will consider the next day as cycle Day 1. Simply call us the next day to schedule any tests or procedures.