PATIENT GUIDE
for
IN VITRO FERTILIZATION
(IVF) PROCEDURES

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What is In Vitro Fertilization?

In vitro fertilization refers to a procedure in which your eggs are removed and fertilized (usually with your husband's sperm) outside the body, in a laboratory dish, and then several days later the embryos are transferred back into your womb. The IVF procedure is, in fact, much more involved than that and involves a series of steps that lead up to the actual laboratory portion of the procedure. This booklet will describe those steps in detail, what is expected of you during each stage and discuss the risks and benefits of the IVF procedure. It is important that you read this manual thoroughly, and bring up any concerns with your doctor at the earliest possible opportunity.

Is IVF an experimental procedure?

No, IVF has been around for a number of years. The first child conceived by IVF is in her late twenties, and since than time the procedure has improved to the point that its success rates (per cycle) are higher than of natural conception. Tens of thousands of babies have been born as the result of IVF cycles. It is possible, though not certain that IVF, and particularly ICSI (where the sperm is injected directly into the egg) may be associated with a higher risk of birth defects. This is a very gray area in the medical literature. If a risk does it exist, it is relatively small.

Reasons for Doing IVF

Damaged, ligated or missing fallopian tubes
Endometriosis
Unexplained infertility
No success with injectable drugs/IUI
Poor sperm quality
Antibodies to sperm

Reaching the doctor and clinical staff

In order to have your questions answered during regular business hours, please call us at 609-896-4984. Routine clinical (not financial or insurance related) questions can be directed to our nursing line (option 3). Messages left on our voice mail before 2 PM on regular business days will be returned as soon as possible on that date. If you have call blocking, we may not be able to reach you. If you have an issue which is urgent and cannot wait, enter 5 and a member of our staff will locate the doctor. All insurance/ financial/ precertification issues should be addressed to Melissa in our business office (option 2). If you have questions about your embryos or storage issues, you will need to speak with Nick, the embryologist.

At night or on weekends, call Delaware Valley's main number 609-896-0777, and the answering service will put you through to the person on-call for infertility (either Dr. Derman or Hina Ahmed, Physician Assistant.) Please let them know that you are a patient of Princeton IVF, and that it is IVF related.

Our Laboratory

We pleased to be the first practice to offer in house IVF laboratory services in Mercer County. While our lab may be new, and the equipment state-of-the art, we are not new to IVF.

Our embryologists, Nick Yun and Brian Leonard are well reversed in IVF procedures. Our Embryology Laboratory is under the direction of Eduardo Kelly, MD, who has run some of the most successful IVF labs in California, Boston, and New Jersey.

Pre-IVF Checklist

*The following items **must** be completed prior to starting an IVF cycle:*
(instruction sheets for the first four items are available in the office or online)

(1) **Sonohysterogram (SHG)** must be performed at some point to check the lining of the uterus, and to give us a chance to figure out how best to replace your embryos. The procedure is done M-F in the early mornings. A trial (practice) transfer and cervical cultures will done be at the the time of your SHG. Please contact Raquel to find out if you need a authorization or referral for your insurance prior to this procedure.

(2) **Day 3 FSH/LH/E_2 level**- this blood test is drawn on the third day of bleeding or the next closest weekday in order to determine if you are a candidate for IVF and how best to stimulate your ovaries. It measures the "aging" of your ovaries. A good level is below 10. In some cases, we may do a clomid challenge test instead.

(3)**Semen analysis**- this is done after 3-7 days of abstention, and run in our office. Raquel can help set up the appointment. This is important to determine whether we can do standard IVF or require ICSI. You must contact Raquel to set up this appointment.

(4) **Endometrial Biopsy**- this is done within the week prior to the start of your fertility medications. In some patients, this may improve the effectiveness of IVF.

(5) **Injection Teaching**- this appointment will be scheduled within the week prior to the start of your fertility medications. Hina Ahmed, our physician assistant, will sit down with you to go over every medication individually and teach you how to administer these medications. You may wish to bring your partner to this visit if they are planning to help you with the injections. **Please bring in your box of medications to this appointment.** It is our hope that this appointment will alleviate any anxiety you may have in regards to the medication and will also assure us that you or your partner understand how to administer the medications. A date for this appointment will be given to you.

(6)You and your partner must have screening **bloodwork for sexually transmitted diseases**. You will also need a blood count and blood type.

(7) Review and **sign the IVF consent form and the cryopreservation (freezing) consent form**. We recommend embryo freezing whenever possible. Please make sure your partner signs where indicated, and that all pages are initialed. ***We must have this form by the day you start medications!*** The forms are available on the web site, but you must know the exact URL to get them. We can provide this for you.

(8) **Consultation with Dr. Fallick** - required only if the male partner has no sperm and TESA or MESA is required. He is a subspecialist urologist who will perform sperm aspiration procedures in his office in Voorhees. In some instances, the sample can be frozen and saved for the upcoming egg retrieval.

(9) **Financial clearance**- you must be cleared by Raquel at our business office before fertility injections can begin. It is your responsibility to make sure this happens. We cannot allow Follistim or any fertility drugs to begin until this are done.

(10) **Special arrangements**- If you are using donor sperm, Microsort sperm selection, preimplantation genetic testing or any non-standard procedures, all arrangement must be made well in advance.

The Steps involved in the IVF procedure:

(1) Shutting down the ovaries with birth control pills
(2) Stimulating the ovaries with fertility drugs
(3) Harvesting the eggs
(4) Fertilization in the laboratory
(5) Embryo transfer
(6) Support of the luteal phase
(7) The pregnancy test

Here is a description of each step:

1. **Shutting the Ovary Down with Birth Control Pills**

Birth control pills are started during the first week of the cycle before we do the IVF. This helps to balance out your hormone levels, improve the quality of your eggs and minimize the hot flashes if you are on lupron. You will take the pill, daily at the same time, and continuously. That means **no placebo/blank pills and no skipped pills until you are instructed to stop**. If you run out, you will start a new pack. In order to avoid confusion, you may wish to discard the placebo pills. Some women will experience nausea, bloating or irregular bleeding on the pills. If this happens, do not be concerned.

When you start the pills, be sure the doctor knows, so that we may give you a date to stop the pill. If you start your period and the pills over the weekend, you may wait until Monday morning to call us. The pill stop date will be after about 3-6 weeks, and is almost always on a Sunday. If you stop the pills too early or too late or take placebo pills instead, we may not be able to start your cycle when planned.

You will schedule and an appointment for ultrasound and bloodwork, on the Friday after you stop the pills. You will start your injectable medications on SATURDAY. We call this **"Day 3"** though it may not really be the third day of your period. Your period most likely will begin a day or two before "day 3," but do not be concerned if it has not begun.

Occasionally our patients with undergo a stimulation protocol that involves the use of Lupron or leuprolide, an injection that starts on day 20 of the cycle before the actual IVF cycle. Lupron is a GnRH antagonist, which initially stimulates and then suppresses the ovary. Along with the birth control, the Lupron will synchronize the egg development, and then later on, prevent premature ovulation. It can cause headaches and hot flashes. If you have been instructed to be on this protocol, you will come in by day 20 for injection teaching in order to start the medication. You will be given a Sunday to stop the pills and a Tuesday drop your Lupron dose to 5 units, you will come in for blood work and ultrasound that Friday and that Saturday will be your "Day 3."
Still other patients will undergo a lupron flare protocol in which lupron is started the day before the fertility drugs.

2. Stimulation of the Ovaries with Injectable Fertility Drugs

Human Menopausal Gonadotropins (**hMG**, **Repronex, Menopur**) and Follicle Stimulating Hormone (**FSH**, **Follistim, Gonal-F, Bravelle**): Repronex and Menopur are fertility drugs which contain equal amounts of FSH and LH and are extracted from the urine of postmenopausal women. FSH and LH are hormones that will stimulate multiple eggs in a given cycle, when given in higher than natural doses. Follistim and Gonal-F contains only FSH (synthesized in a laboratory), and are given by a specifically design pen that is similar to an insulin or epi pen. Bravelle also contains FSH (extracted from urine) is given by a small subcutaneous needle after reconstitution. The FSH-only drugs are generally given at night so we may adjust the dose as needed. In the morning you will use Repronex or Menopur, which you will need to reconstitute each day before injecting. In patients who respond poorly to the medications, the shots may be given by intramuscular injection.

At a predetermined point after stopping birth control pills you will be brought in for an ultrasound and blood work and will be started on the fertility medications. The start day is called **"DAY 3"** and may or may not coincide with the third day of your period. Most likely your fertility drugs will start on a Saturday. We will give you instructions on the timing and dosage of your injections. You should not start your fertility medications unless you have had blood work and ultrasound the day prior (Friday). During the stimulation, you will have ultrasounds and blood work 2-4 times a week until the follicles have reached a mature size, usually when the largest 2 are 17 mm in diameter. Maturation of the eggs typically takes 7-10 days.

IVF Timings for blood work and ultrasounds:

	Monday	Tuesday	Wednesday	Thursday	Friday
blood work	6-9AM	6-19AM	6-9AM	6-9AM	6-9AM
ultrasounds	6:45- 9AM	6:45- 9AM	6:45- 9AM	6:45- 9AM	6:45-9AM

In most instances, your blood work will be drawn first before preceding to the ultrasound. Please plan for spending one hour in our office for us to complete the blood draw and ultrasound process. Saturday visits are by appointment only, and usually at 7 AM.

Most patients receive their fertility injections twice a day. They may be subcutaneous (a small 25-30g needle or pen just under the skin) or intramuscular (a larger 22G needle in the buttocks). The doctor will make a determination on what will be the best mixture for you. The medications may include a mixture of Follistim, Gonal-F, Repronex, Bravelle and Menopur.

The major side effects include risk of ovarian hyperstimulation and multiple pregnancies. Although these preparations are considered generally safe, the long-term effects, if any (including concerns about the risk of ovarian cancer), from their use are currently unknown. Headaches and mood swings may occur as well.

Ovarian Hyperstimulation is one of the major, potential complications of treatment with injectable fertility drugs. Mild to moderate hyperstimulation is quite common and consists of a mild to moderate degree of ovarian enlargement and abdominal discomfort, and usually resolves on its own. Limited activity and Tylenol are normally all that are needed to alleviate symptoms. Severe ovarian hyperstimulation syndrome is far less common but is potentially life threatening. Severe ovarian hyperstimulation syndrome involves massive ovarian enlargement due to multiple ovarian cysts, accumulation of fluid in the belly and chest cavities and rarely blood clots (thromboembolism). This disorder is most common in women with polycystic ovaries, and those who produce more than 20 eggs or have very high estradiol levels. The best treatment is prevention. The disorder rarely becomes severe unless a cycle results in pregnancy. Ways of minimizing this problem from occurring include decreasing the doses of medications, taking Metformin, give intravenous albumin infusions, withholding hCG and canceling the cycle, and retrieving the eggs but freezing the eggs for transfer at a later time.

Signs that should alert you to the development of this syndrome include abdominal distention (bloating), rapid weight gain of more than 2 pounds in one day and difficulty taking a deep breath. When diagnosed, hospitalization may be indicated. In some patients, aspiration of the fluid with a needle may be helpful.

Multiple pregnancies occur in over 1/4 of IVF pregnancies and are mostly twins or triplets. If you have triplet or especially quadruplets or more, you should seriously consider a fetal reduction procedure to bring the number down to 2. As this may be a difficult moral dilemma for many couples, you should discuss this possibility with your partner in advance.

Unless you are on Lupron, on the Tuesday after you begin your fertility injections, you will start a third daily injection. **Ganirelix** is subcutaneous, comes in a premixed syringe and is taken each morning from the time you are instructed until the hCG shot (described below). It is a GnRH antagonist and is there to prevent your eggs from releasing prematurely. Side effects such as headaches are uncommon. If you do ovulate prematurely, your cycle will most likely be cancelled.

3. **Harvesting the Eggs**

When the eggs are of mature size, usually 17mm, you will receive instructions on when to take your hCG shot (**Novarel**, **Pregnyl, Chorionic Gonadotropin**). The box contains a vial of water and a vial of powder that says 10,000 IU. It is mixed as follows, draw up 3 cc of saline into the 22G needle/syringe and add it to the hCG powder, mix and inject intramuscularly in the buttocks. ***This injection must be given exactly at the time you were told to take it***. If you are more than 15 minutes off, you must let the doctor know first thing in the morning. On the day of hCG, you will also begin a short 6-day course of antibiotics (doxycycline) and steroids (Medrol).

Egg retrieval is performed transvaginally with ultrasound guidance under conscious sedation, and takes approximately 15 minutes. Dr. Derman will perform the procedure in our office. An ultrasound is performed at which time a needle is inserted into each

follicle and the egg and follicular fluid is aspirated. You will receive deep sedation given by an anesthesiologist. The anesthetic agents should be shipped to us in advance. If you have Aetna, we will order the medications ourselves. You will also bring in a vial of antibiotic (Doxycycline). If you have mitral valve prolapse and require special antibiotics, or have an allergy to Doxycycline, please let us know in advance.

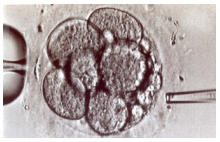
The risks of transvaginal aspiration of follicles include infection, bleeding and damage to the adjacent organs. Occasionally hospitalization, transfusion, intravenous antibiotics and/or surgery are required. Though exceedingly rare, deaths have been reported following the procedure.

4. Fertilization in the Laboratory

After the retrieval, the eggs are immediately handed over to our embryology lab. Your will provide a fresh semen sample shortly after you arrive at the office. and our staff will prepare the sperm. (If you are using donor sperm or microsort, you must arrange for the sperm to arrive at our office at least a week before retrieval) The eggs and sperm are placed together overnight and we will find out if the eggs have fertilized the following day. If you are having ICSI, the sperm are injected directly into the egg, but even then, fertilization is not always assured. Our laboratory staff will call to inform you about fertilization the day after retrieval.

Intra-Cytoplasmic Sperm Injection (ICSI) is a laboratory procedure in which a single sperm is inserted directly into the cytoplasm of an egg cell. This is done in cases of very poor sperm quality or failed fertilization in the past, or if the number of eggs is very small. It is performed on the day of retrieval. This is usually necessary in cases of sperm abnormalities. Some studies have suggested a slightly higher instance of abnormal sex chromosomes in infants conceived by ICSI while other studies have shown no risk to ICSI. In the case of a male child, this may cause your husband to pass on a gene that may cause his male offspring to be infertile.

PICSI is a sperm selection method for patients with highly fragmented sperm DNA who have failed previous IVF cycles. PICSI is used in conjunction with ICSI. This method will help to select a mature healthy sperm for injection.



Assisted hatching is a laboratory procedure in which an acid solution or laser is used to drill a hole in the zona pellucida, a protective coating around the egg. Women who are over 38, have embryos with thick zonas or have failed IVF in the past may benefit from this procedure.

If you have excess fertilized eggs, you have the option of **embryo cryopreservation** (freezing and storage). The extra embryos will be frozen and then stored for transfer at a later time, without having to undergo stimulation with the fertility drugs. **Choosing to participate in the freezing program will give you extra chances at IVF, at a lower cost, with less monitoring and with fewer medications.** If you wish to

participate in the cryopreservation program, you must tell us in advance, and sign the cryopreservation consent forms. The forms contain places where you indicate what you want done with your embryos should we be unable to find you in the future.

Embryo cryopreservation, assisted hatching, ICSI and PICSI incur extra charges which may or may not be covered by your insurance. If not, *any charges may be required up front, before you start your fertility drugs.*

During this time there are a number of events that may prevent you from reaching the next stage. The eggs may fail to fertilize or those that do fertilize may not divide properly or look grossly abnormal. A culture dish where the embryos are kept may become contaminated making the embryo(s) not suitable for transfer. Additionally, power outages, acts of g-d and other unforeseen events may occur.

5. **Embryo Transfer**

This procedure is usually performed three (or occasionally five) days after the egg retrieval and without the use of anesthesia. An abdominal ultrasound is used, so you will need to have a **full bladder**. You should drink one liter of water on the way in. Women who are younger or who have a large number of fertilized eggs may undergo a blastocyst transfer in which embryos are transferred at a later stage on day 5. This will minimize the risk of high order multiple pregnancies. The procedure is brief and lasts only a few minutes. A soft plastic catheter is introduced into the uterus through the cervix and the embryos injected, while we watch on the ultrasound. Rarely, it may impossible to pass the catheter. Side effects of the procedure include mild cramping and minimal bleeding. After a brief period of recovery you will be discharged and kept at home on bedrest for the next 24 hours.

6. **Support of the Luteal Phase**

The last part of the menstrual cycle is called the luteal phase, and during this time, large amounts of a hormone called progesterone is secreted to help maintain the early pregnancy. Since we will be removing some of the hormone producing cells, it will be necessary to replace it with medication.

Most patients will receive vaginal suppositories of progesterone. These suppositories will be taken three times a day which usually start 1day after the retrieval. The nurse will review with you how to take these suppositories on the day of your retrieval before you go home. You progesterone hormone level will be checked about 5 days after embryo transfer.

Some patients may need to start supplementation with progesterone in oil injections. The doctor will let you know if this is the case after reviewing your progesterone level results. Progesterone in oil injections require a 3cc syringe with a large 18G needle. The needle is used to draw up 1 cc of the medication. Warming up the oil may help in drawing the medicine up. You will then change to the 22G needle and inject high in the buttocks.

You will also be on Estrace (estradiol) 2 mg orally daily beginning the day after retrieval.

The progesterone shots and/or suppositories start the day after the egg retrieval and continue until the doctor clears you to switch to progesterone pills or you have a negative pregnancy test. Progesterone levels will be drawn several times to make sure the dosing is correct.

***Do not stop progesterone until you are instructed to do so by the doctor*.** Vaginal bleeding does not always mean the procedure has failed and may occur from vaginal suppositiories.

7. The Pregnancy Test

You will have a progesterone level drawn 4-5 days after the transfer. Then two pregnancy tests will be done, on *approximately* days 10 and 12 after the embryo transfer. Most of the time, results will be ready the same day. **You will not be given the results until the second beta (pregnancy test) is back**. That way we can give you an accurate assessment on what is going on. Once positive, it is essential we follow you closely will biweekly hCG and progesterone levels and ultrasounds as needed. As with all pregnancies, the risk of miscarriage and even ectopic (tubal) pregnancy exists with IVF pregnancies.

Cycle Cancellation

In some cases IVF cycles need to be canceled, and it is very important that you understand this. The following are some of the reasons:

-you do not respond adequately to the medication
-you over respond to the medication and the physician decides that it is too risky to your health to allow the cycle to proceed. In such a case, you may be given the option to go to retrieval and freeze vs. withholding the hCG shot.
-the LH or progesterone hormone levels rise prematurely indicating that the eggs are likely to release prematurely
-you do not take the hCG when instructed to do so
-egg retrieval procedure yields no eggs
-the eggs do not fertilize
-the fertilized eggs do not divide or look grossly abnormal

After cancellation, we can discuss if any additional testing is needed and make plans for a new IVF start if that is appropriate.

IVF and Stress

Infertility and its treatment are among the most serious sources of psychological stress you and your partner are likely to endure. It is important that the two of you are both strongly committed to doing IVF and are supportive of each other. If not, you may wish to consider counseling before beginning the cycle. **Reducing your stress levels will improve your chances for success.** We have a counselor to whom we can refer you if you need. Some of our patients find acupuncture to be helpful, and we can assist you with that as well.

Other sources for support include Resolve (a national network of infertility patients with a local chapter), books and internet chat sites.

Special Types of IVF

PGD

Patients who are carriers for know genetic diseases or have a history of recurrent miscarriages due chromosome abnormalities, may be candidates for **preimplantation genetic diagnosis** (**PGD**). On the day of the planned embryo transfer (see below), one of the eight identical cells that make up each embryo is removed and sent off for genetic testing. The lab can test for large chromosomal abnormalities such as Down Syndrome by a technique called FISH or single gene abnormalities such as cystic fibrosis using PCR. Two days later embryos are that are known to be normal after testing are transferred at the blastocyst stage. This procedure is expensive, usually not covered by insurance, may lower pregnancy rates and occasionally misses the abnormalities it is testing for. For PGD cases, we work in conjunction with Reprogenetics in Livingston, NJ whose scientists will perform the embryo biopsy and testing on the embryos. This procedure always requires advanced planning. Reprogenetics phone number is 973-436-5017.

Microsort ®

Currently this option is no longer available.

Many couples ask us about **sex selection** in order to improve your chances of having a boy or girl. If you are interested in such a procedure, we can make arrangements for sperm sorting procedure (**Microsort**), which is performed in Fairfax, VA. The sample is collected and then sorted for male or female sperm at their facility in Virginia. The procedure is done well in advance, frozen and shipped to our lab. In such cases, ICSI is always required. Please keep in mind that it is fairly expensive, not always effective and not yet FDA approved. The success rates for choosing the sex (not pregnancy rates) is 91 % for girls and 76% for boys. Plans for this must be made well in advance.

Frozen Embryo Transfer

As discussed above, we strongly encourage couples doing IVF to freeze any extra embryos. This will enable you to have extra chances for having a baby, with much less

hassle and cost than normally is associated with IVF. We use a mixture of hormones to simulate a natural unstimulated cycle.

The frozen embryo cycle works as follows: You will start a medication called Lupron (leuprolide) on day 20 of your cycle. Lupron is a GnRH antagonist, which suppresses the ovary and throws you into a temporary menopause. It can cause headaches and hot flashes. We will teach you how to do the injections at that time. The dose will start at 10 units daily (0.1 cc). When your period comes, the dose will drop to 5 units (0.05 cc) and you will schedule an ultrasound and blood work at the tail end of your period, during our morning hours. Please make sure you have filled out and returned to us the frozen embryo transfer consent pack (two pages) as soon as possible.

At that time, if your endometrium (the uterine lining) is thin enough and your estradiol level is low enough, will be begin a protocol of increasing doses of estradiol pills and eventually vaginal progesterone suppositories, and given a tentative date for transfer. You be instructed when to come in for one additional ultrasound, and if the endometrium is adequately thick at this time, your transfer date will be finalized.

When you show up for the transfer in our office, you may eat but please avoid caffeine and have a full bladder. You should drink a liter of water of water on the way in. The transfer is done under ultrasound guidance and is generally painless. You will be given a schedule for blood work as described above for “regular” IVF.

Donor Egg

Women who have failed multiple IVF cycles, have high FSH levels or are too old to be candidates for IVF, are usually advised to consider Donor Egg IVF. While a child born following such a procedure will not have any of your genes, the chances for having a child with this technique are extremely high, and minimally age dependent.

The first stage for egg donation is finding a suitable donor. You may have a friend or relative in mind, or we may put you in touch with an egg broker who can find a match for you. Using an anonymous donor can be very expensive, but the chances for personal and family conflicts are much lower, and the pregnancy rates are higher.

We work with the following egg brokerage agencies:

1. S.E.E.D.S 570-689-5755 www.seedscenter.com
2. Concieveabilabilities 877-201-7211 www.conceiveabilities.com
3. Tiny Treasures 781-279-1325 www.tinytreasuresagency.com

The donor is screened for genetic and sexually transmitted diseases, and counseled about the procedure she is about to go through. She then goes through the procedures described in steps 1, 2 and 3 above. Her eggs are then fertilized with your partner's sperm as described in step 4, and the embryos are transferred to your uterus as described in step 5.

Your uterus will be prepared with Lupron, and then estradiol and progesterone shots similar to what is described under the frozen embryo transfer section above. The

Lupron is started and dropped early on, so that you are ready to start the estradiol pills when your donor starts her fertility drugs.

Good luck

You and your partner are about to embark on an exciting, yet strenuous adventure. While you may at times feel overwhelmed, you should realize that you have an opportunity not available to earlier generations of women. Remember to set your sights on the goal at hand, but still try to be realistic about your chances.