



Welcome to the Wisconsin Fertility Institute and thank you for your interest in our *In Vitro* Fertilization program. This packet is designed to function as a resource for you as you begin the journey through the complex world of assisted reproduction. We have attempted to provide as many answers to your questions as we could anticipate. However, this is not a stand-alone document meant to answer all your questions and concerns; rather, this packet is meant to provide an overview and to supplement information obtained from your doctor, the IVF nursing team, and other members of the Wisconsin Fertility Institute.

Here at WFI, we are firm believers in the partnership between medical team and couple to achieve a goal that is decided upon in a collaborative manner. We do not practice paternalistic directives; nor do we pretend to necessarily know what is always in your best interest. Instead, we will do our best to explain what we prefer to do and why we do it. If you feel confused or pressured, please speak up and let us know as this is not our intent. We strive to create an atmosphere of trust and cooperation, and we can only do that if you are an active member of the team voicing your concerns if you feel your needs are not being met.

We realize that creating a family is a serious endeavor, and that your decision to pursue IVF is a commitment to sacrificing considerable time and expense. We also understand how anxiety-provoking the process can be. To this end, we have attempted to minimize stress by providing a safe, comfortable environment. We also have several ancillary services available via local professionals, designed to aid in your ability to cope with the pressure of IVF. Please ask us about these services.

Once again, thank you for your interest in and support of the Wisconsin Fertility Institute. We hope to help you build the family of your dreams, and we are honored to have the privilege of working with you.

In Vitro Fertilization

In Vitro Fertilization is a treatment for infertility that removes eggs from a woman's ovary or ovaries to achieve a pregnancy either at that time or later. A patient can use sperm provided by her partner or from a donor for the insemination of her eggs, and have the resulting embryos transferred to her uterus or use a gestational carrier.

In Vitro Fertilization Process & Risks

An IVF cycle typically includes the following steps or procedures:

- Taking medicine to grow several eggs at once.
- Removing the eggs from the ovary or ovaries
- Mix eggs and sperm together so the eggs will be fertilized.
- Growing any resulting fertilized eggs (embryos) in the lab
- Placement ("transfer") of one or more embryo(s) into the uterus
- Taking hormone medications to help you have a successful pregnancy.

Sometimes, other IVF steps may be included:

- Injecting individual sperm into each egg, called intracytoplasmic sperm injection.
- Cryopreservation (freezing) of eggs or embryos that are not transferred to the uterus.
- Genetic testing of the embryos for abnormal genes or number of chromosomes.

Steps to Begin Your IVF Treatment

New Patient Phone Consult with Provider- You will discuss previous medical history and fertility treatment.

Lab orders to complete the necessary testing for your IVF cycle.

- AMH
- TSH
- Blood Type*
- Rubella and Varicella Titer*
- Sono hysteroogram (SHG), to be completed on days 5-12 of your menstrual cycle.
- Semen Analysis
- Infectious Disease Testing

The testing can be completed at LabCorp or with your own provider. Please call them to confirm how to best complete the testing within their system and to ensure the results are sent over to our office as soon as they are completed.

All labs must have been completed within the last year except for Rubella/Varicella Titer and Blood Type. If you have had any of the other tests completed within the last year, it is not necessary to repeat them. Simply have the results sent to our office.

Once labs are completed and received, you will receive a call from our IVF Coordinator to discuss the next steps. These include:

- *Treatment Plan visit with your doctor.*
- *Injection Training-Completed online through our website*

Please do not hesitate to call us or reach out through your patient portal if you have any questions or concerns along the way. We look forward to working with you!

Financial Counseling Appointment ***Required***

During your financial counseling appointment, you will meet with one of our finance team members to discuss your treatment cost, payment schedule, financing options and consent forms. We will also be able to answer any questions you may have during this time regarding cost and consents. Please understand that no medications will be ordered, and you will not be able to proceed with your treatment until this call is completed and consent forms are returned.

You will receive consent forms and your estimates **via your patient portal** after your New Patient consultation with the provider. Once you have received these you may schedule your financial consultation online through your patient portal.

Login to your patient portal

Choose Appointments

Click on the green Make an Appointment button at the top of the page

Continue to Select a Day

Simply choose the day and time you would like to have your call.

On the day of the call the Finance team will call you.

We look forward to joining you on this journey!



Gretchen Collins, MD



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The Need for IVF

Tubal Factor

IVF was developed specifically for women whose fallopian tubes had been injured by prior surgery or infection. Surgical repair of damaged tubes is sometimes a viable option, but for many types of injuries bypassing the tubes is less expensive and more successful. This can be achieved with IVF.

Male Factor

IVF is clearly the best treatment modality ever developed for low problems with sperm. Intracytoplasmic Sperm Injection (ICSI), in which a single sperm is placed inside each mature egg, has improved dramatically since 1990 and now offers hope even when very few sperm are present in an ejaculate. Sperm can sometimes even be withdrawn from the testes when there are none in the ejaculate.

Endometriosis

While not usually the first line of treatment for this problem, IVF works well for endometriosis. It is the therapy of choice for severe cases or when lesser treatments have failed.

Unexplained Infertility

Although we do not know the cause of unexplained infertility, IVF is a particularly successful method of treatment. It is assumed that whatever the cause in such couples, pregnancy is more likely due to the many natural steps that are bypassed by IVF. Data support this contention: pregnancy rates are very high with each attempt at IVF in unexplained infertility. However, the cost per pregnancy is higher than with many other treatments. For this reason, IVF is usually reserved for couples with unexplained infertility that have failed to conceive with several other, less involved therapies.

What Is the Risk Associated With IVF?

Multiple Pregnancies: The risk of multiples is directly linked to the number of embryos transferred. Multiple pregnancies carry with it the problems of greater discomfort, higher risks of miscarriage, pregnancy-induced hypertension, fetal growth and development problems, and cesarean section delivery compared to singleton pregnancies. The biggest threat, however, is prematurity. Premature infants can have a host of problems ranging from minor disabilities to major mental or physical impairment to even death. Two methods to minimize high-order multiple gestations (triplets or more) are to transfer no more than two embryos or to selectively reduce the number of embryos after multiple pregnancy occurs.

Ectopic Pregnancy: The world's first IVF pregnancy in 1976 ended up in the woman's fallopian tube instead of her uterus. Even though the embryos are placed in the uterus, they are incapable of embedding in the endometrium immediately and may drift into a fallopian tube. In women with normal fallopian tubes, 1-2% of all IVF pregnancies are ectopic. For those with damaged tubes, the risk can be as high as 4-5%. This is still considerably below the risk for ectopic pregnancies in women with abnormal tubes who conceive naturally. We can usually diagnose most ectopic pregnancies early in pregnancy, before any risk of rupture of the fallopian tube, which allows a choice between two forms of treatment: laparoscopic surgery to remove the ectopic pregnancy or an injection of a drug called methotrexate to dissolve it.

Ovarian Hyperstimulation: The fertility drugs used in IVF usually cause the ovaries to enlarge somewhat. Some women's ovaries are so sensitive to these medications that they enlarge 4- or 5-times normal size and cause discomfort and leakage of fluid from the blood vessels into the abdomen, a problem called Ovarian Hyperstimulation Syndrome (OHSS). Severe OHSS occurs in less than 1% of patients but usually requires hospitalization and careful treatment to avoid you getting sick. The hospital stay can sometimes be several weeks, particularly if you are pregnant.

Infection: There is a 0.1 percent (1 per 1,000) risk reported in the medical literature that a pelvic infection would occur after egg retrieval. These infections have been mild in some cases and severe, even to the point of requiring major surgery, in others. We always attempt to minimize this risk by using sterile techniques and treating you with antibiotics.

Cancer: A study in 1994 showed an increase in the risk of ovarian cancer in women who took the fertility pill clomiphene citrate (Clomid) for an extended period (12 or more months). Clomid is rarely used in IVF, and studies to date have indicated an increased risk for other IVF medications, but studies in the future will. However, given the difficulty of demonstrating an increased risk of ovarian cancer despite 30 years of IVF, it is likely that even if the risk is increased, it is a slight increase! Counterbalancing this theoretical risk is the known benefit of pregnancy, which lowers the risks of cancer of the breast, ovary, and uterus.

Risks of Pregnancy with IVF

Getting pregnant through IVF comes with certain risks. This is partly because women using IVF are often older than those who might get pregnant on their own. In addition, the cause of infertility itself may be to blame. There may be other risks linked to IVF that are not known at this time. Please see the table below for certain known risks.

About 25% of IVF pregnancies are multiple pregnancies (twins, triplets, or greater) in 2015, of which less than 1% are triplets or more. Identical twins occur in less than 5% of all IVF pregnancies. Identical twins may happen more often after blastocyst (Day 5 or 6) transfers. Multiple pregnancies in general have an increased risk of pregnancy problems. In addition to premature delivery, problems include pre-eclampsia (high blood pressure and protein in the urine), excess bleeding with delivery, and diabetes of pregnancy (gestational diabetes). Problems with the placenta (afterbirth) are also more common. Other problems more common with multiple pregnancy include gall bladder problems, skin problems, and the need for extra weight gain.

In IVF, embryos are transferred directly into the uterus. Still, tubal, cervical, or abdominal pregnancies can sometimes occur. These abnormal pregnancies may need to be treated with medication or surgery. Abnormal pregnancies within the uterus can also occur.

Risks to Your Baby

The first IVF baby was born in 1978. Since then, more than 5 million children around the world have been born through IVF. Studies have shown that these children are quite healthy. In fact, some experts believe having a child through IVF is now just as safe as having a child naturally. Still, one must be careful when making this claim. Infertile couples do not have normal reproductive functions. This means that a baby they have through IVF may have more health problems than a baby conceived naturally.

IVF single babies are often born about 2 days earlier than naturally conceived babies. They are about 5% more likely to weigh less than 5 pounds, 8 ounces (2,500 grams) than a naturally conceived single baby. IVF twins are not born earlier or later than naturally conceived twins.

The risk of birth defects through normal birth is about 4.4 %, and it is about 3% for severe birth defects. In IVF babies, the risk for any birth defect is about 5.3%, while the risk for a severe birth defect is about 3.7%. Most of the increased risk with IVF seems to be due to older mothers and to having infertility. No higher risk is seen in frozen embryo or donor egg cycles.

Imprinting Disorders. These are rare disorders caused by whether the genes from the mother or the genes from the father are working. Studies do not agree on whether these disorders are associated with IVF. Even if they are, these disorders are extremely rare (1 out of 15,000 people).

Childhood Cancers. Most studies do not suggest any extra risk, except for retinoblastoma (a cancer behind the eye). One study did report an increased risk after IVF treatment, but further studies did not find an increased risk.

Infant Development. Most studies of long-term developmental outcomes have been reassuring so far. Most children are doing well; however, these studies are hard to do, and they have some limitations. A more recent study using better methods shows an extra risk of cerebral palsy and developmental delay; however, this arose mostly from prematurity and low birth weight that was a result of multiple pregnancy.

Risks of a Multiple Pregnancy

More than 30% of IVF pregnancies are multiple pregnancies (twins, triplets, or greater). Identical twins occur in less than 5% of all IVF pregnancies. Identical twins may happen more often after blastocyst (Day 5) transfers, and with assisted hatching after cleavage stage (Day 3) transfers. Premature delivery accounts for most of the extra problems associated with babies from multiple pregnancies. IVF twins deliver an average of three weeks earlier than IVF single babies, and they weigh about 2 pounds less than IVF single babies. Triplet (and greater) pregnancies deliver before 32 weeks (7 months) in almost half of cases. Fetal growth problems and unequal growth among the fetuses can also result in perinatal illness and death before or shortly after delivery.

Multiple fetuses that share the same placenta, such as most identical twins, have additional risks. Twin-to-twin transfusion syndrome, where the circulation is not equal between the fetuses, may occur in up to 20% of twins who share a placenta. Twins sharing the same placenta have a higher frequency of birth defects compared to twins with two placentas. Death of one fetus in a twin pregnancy after the first trimester is more common with a shared placenta; this may cause harm to the remaining fetus. Other problems babies can face include cerebral palsy, retinopathy of prematurity (eye problems that result from premature delivery), and chronic lung disease. No one knows how much multiple pregnancies affect neurological or behavioral development, even when none of the other problems occur. Fetal death rates for single pregnancies are 4.3 per 1,000. For twins, that number is higher at 15.5 per 1,000; and for triplets, the fetal death rate is 21 per 1,000. The death of one or more fetuses in a multiple pregnancy.

Ethical and Religious Considerations in Fertility Treatment

Infertility treatment can raise ethical or religious concerns for some patients. IVF involves the creation of embryos outside the human body. It can also involve the production of extra embryos and can lead to a high number of fetuses (triplets or more). Patients who have concerns should speak with their counselor or religious leader, or with someone else they trust. This can be a helpful step in infertility treatment.

Psychosocial Effects of Infertility Treatment

Finding out that you or your partner is infertile or have a lower fertility can be very painful. Infertility and its treatment can affect your emotions, your health, your finances, and your social life. During treatment, you may feel anxious, helpless, depressed, or all alone. You may go through highs and lows. Be sure to notice if these feelings get severe. In some cases, you may want to seek the help of a mental health expert. Here are some of the warning signs you should watch out for:

- Losing interest in the things you usually like to do.
- Feeling depressed most of the time.
- Strained feelings with your partner, family, friends, or those with whom you work.
- Thinking about infertility always.
- Feeling extremely anxious or nervous.
- Having trouble finishing tasks.
- Finding it hard to focus or concentrate.
- Having changes in your sleep patterns, such as having a tough time falling asleep or staying asleep, waking up early every morning, or sleeping more than normal.
- Having a change in your appetite or weight (increase or decrease).
- Using drugs or alcohol more than before.
- Thinking about death or suicide.
- Staying away from other people.
- Feeling negative, guilty, or worthless much of the time.
- Feeling bitter or angry much of the time.

Reporting Outcomes

In 1992, the Fertility Clinic Success Rate and Certification Act was passed. This law requires the Centers for Disease Control and Prevention (CDC) to gather facts about IVF cycles and pregnancy outcomes in the U.S. each year. These facts and success rates are reported every year. Information from your IVF procedure will be reported to the CDC. It will also be reported to the Society of Assisted Reproductive Technologies (SART) of the American Society for Reproductive Medicine (ASRM), Wisconsin Fertility Institute is a member of this organization. The CDC may ask for more information from the treatment center or contact you directly for additional follow-up. Information about your cycle may be used for research or quality control according to HIPAA (Health Insurance Portability and Accountability) guidelines. Your name will never be connected to your cycle information in any research that is published.

Research Conducted by SART

Since 2006, the Society for Assisted Reproductive Technology has participated in a series of studies looking at the health of women and children after IVF. Many of these studies are still being conducted. The studies compare women who have not had trouble conceiving and their children with women who used IVF and their children. The studies also compare women who had trouble conceiving but did not do IVF, and their children, to women and their IVF children. IVF children who have siblings form another study group. They are compared with their siblings who were conceived with IVF, conceived with non-IVF fertility treatment, or conceived spontaneously. The items studied are problems related to pregnancy or birth, and the risk of birth defects.

Children are also followed to find out if they have developmental delays, problems in school, or increased risk of childhood or adult cancer. You can see the results of many of these studies in the information given below. Results can also be found on the SART website (www.sart.org) under “Research.”

Evaluation and Preparation Phase

You will begin the road to IVF by consulting with one of the doctors at the Wisconsin Fertility Institute. At that visit, the doctor will review all treatment options available to you, as well as their likelihood of success and approximate cost. The doctor may also suggest additional tests to further refine the likelihood of success with each option. If you should then opt for IVF, you will be given laboratory requisitions for these tests. Once these tests are completed and we have the results, you will again meet with your doctor and a nurse, review the test results and, if all are normal, proceed to treatment. If one or more tests are abnormal this will be discussed with you and treatment plans reconsidered.

Cycle of Treatment

There are several different approaches to drug administration for an IVF treatment cycle, and each has been found to be the best approach in some patients. However, no approach works for everyone, and occasionally a poor response to medication may necessitate a discontinuation of treatment, with resumption later using a different drug combination. All patients will start estrogen in the second half of the cycle prior to starting IVF. This prevents early follicular recruitment and may result in more eggs. In this center, three approaches are used primarily, although small variations may sometimes occur for individual patients:

Antagonist: This is the most common regimen that is currently used. With the beginning of the menstrual period, a baseline visit is conducted. This visit consists of 3 steps: (a) an ultrasound to show that nothing has begun to grow on the ovaries, (b) a blood estrogen level to confirm that nothing was missed on ultrasound, and (c) a check to make sure consent has been obtained. If the ovaries are quiet, the estrogen level is low, and consent forms are signed, we are ready to begin stimulation of the ovaries. Follistim/Gonal F/Menopur began on this day and continued for 9-14 days. These are all given subcutaneously (SQ), (small needle just under the skin). For women needing a little help with egg quality, Growth Hormone or Omnitrope may be added. Periodic ultrasound examinations and blood estrogen levels are performed. When the largest ovarian follicle (egg surrounded by fluid) measures 14 mm, daily injections of Cetrotide or Ganirelix are administered subcutaneously each morning to stop ovulation from happening too early. After about 13 days of egg growth, Ovidrel/Lupron/Novarel or a combination of these (trigger shots) are administered to allow the retrieval of the eggs. These drugs are given 36 hours before harvesting your eggs and are responsible for their final maturation and readiness to be mixed with sperm.

Agonist suppression: With this approach, women begin a drug called Lupron after a couple of weeks on oral contraceptives. The drug is administered daily by subcutaneous injection. When a subsequent period begins, the woman comes to the clinic for a baseline visit. The Lupron is continued, Follistim/Gonal F/Menopur is added each day for 9-14 days total. Once the eggs are mature you will take the trigger shots 36 hours before egg harvesting.

Microdose flair: In patients with a previous poor response to stimulation, who are age 40 or over, or an AMH less than 1.5, another approach to stimulating the ovaries is Microdose Flair. The idea behind this treatment protocol is to use the body's own FSH in combination with Follistim/Gonal F/Menopur to stimulate the ovaries to grow eggs.

The day after your period begins you have a baseline visit, and if all is acceptable you administer a low dose of Lupron subcutaneously twice daily. After the first 2 days of

Lupron, Follistim/Gonal F/Menopur are added at a dose of 450 units daily. We may also recommend adding Growth Hormone or Omnitrope to improve the quality of eggs. These drugs are continued, with periodic ultrasound examinations and blood estrogen tests, until a reasonable number of eggs have grown and matured (usually 9-14 days). The previous drugs are then discontinued and 2 Ovidrel (trigger shots) are administered to allow the eggs to be retrieved.

Medications Often Involved with IVF

Follistim/Gonal-F/Menopur: These drugs are used to help grow eggs. They are the same hormones that your own body makes to grow eggs. Your own body will secrete a small amount of this hormone during your menstrual cycle, so that you grow one mature egg. You will take high doses of these hormones to grow extra eggs in a cycle. You usually will take these drugs for 9-14 days during your treatment. These drugs are injected just underneath the skin in your belly or your thigh.

Omni trope: This drug is another shot taken just underneath the skin. It is used for women that may need a little extra help to improve quality of their eggs.

Ovidrel/Novarel/Lupron: These shots, taken just underneath the skin, are used as trigger shots to prepare the eggs for retrieval. The timing of these particular shots is CRITICAL.

Ganirelix/Cetrotide: These drugs are also given as shots, just underneath your skin in your belly or thigh. It is usually taken in the morning and is used to stop your eggs from ovulating too early.

Estradiol/Estrace: This drug is given by mouth and will begin once you start growing your lining for a frozen embryo transfer. You will continue it until week 11 gestation or until you have a negative pregnancy test.

Progesterone: This drug is after the lining check during your frozen embryo transfer. It helps keep the uterine lining thick and helps improve implantation of the embryo. You will continue it until week 11 gestation or until you have a negative pregnancy test.

Doxycycline: This is a drug taken by mouth that decreases infection rates. You will take it twice a day beginning the day of the retrieval.

Prednisone: This medicine can increase implantation rates by suppressing the immune system. This is used during the frozen embryo transfer cycle.

Valium: This medicine is taken at the time of the embryo transfer to help relax the uterine muscle.

Lovenox: This drug may be used in your embryo transfer cycle. It is given just under the skin as a subcutaneous shot to help with embryo implantation.

Transvaginal Oocyte (Egg) Retrieval

Thirty-six hours after the administration of the trigger shots, you will undergo a procedure called egg retrieval. You will be instructed not to eat or drink anything after midnight the night before the egg retrieval, and the morning of the retrieval, due to the anesthesia given. You will need a ride home that day. On the day of the retrieval, a fresh semen sample will be obtained for use in the fertilization process. In certain situations, a sample can be obtained earlier and cryopreserved or frozen. The specimen would then be thawed for use on the day of retrieval.

The egg retrieval procedure is done at our office under light anesthesia (intravenous sedation). A needle guided by ultrasound is passed through the top of the vagina and into the follicles in the ovary. It takes about 30 minutes to retrieve the eggs, and then 60-90 minutes to rest in our recovery room. The fluid we remove from the follicles is given immediately to our embryologists who use their microscopes to find the otherwise invisible eggs. The eggs are usually inseminated a few hours after retrieval with sperm from your husband, partner, or an anonymous sperm donor. This is done by our embryologists who are also responsible for culturing the fertilized eggs (now called embryos) until the time of transfer to your uterus. The day of retrieval you will begin an antibiotic called doxycycline (2 times daily) which will help decrease risk of infection. You will continue taking this drug for 5 days.

Risks of Egg Retrieval

Infection: Bacteria from the vagina may be transferred into the pelvis or ovaries by the needle. This can cause an infection of nearby organs. The incidence of infection after egg retrieval is small (less than 0.1%). If you do get an infection, you may be given antibiotics. Severe infections sometimes require surgery to remove infected tissue. Infections can reduce your chance of getting pregnant in the future. Antibiotics may be used before the egg retrieval to help reduce the chance of infection. Still, there is no way to remove the risk completely.

Bleeding: The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both structures contain blood vessels. There are also other blood vessels nearby. This means that tiny amounts of blood may be lost while removing the eggs. The risk of major bleeding is small (< 0.1%). Major bleeding may require surgery to

stop and could result in the removal of an ovary. Only rarely is a blood transfusion needed. If bleeding occurs and is not noticed (also rare), it can lead to death.

Trauma: Even with ultrasound guidance, nearby organs can be damaged. This includes damage to the intestines, appendix, bladder, ureters, and ovary. In some cases, a damaged organ may need to be fixed or removed through surgery. Still, the risk of damage during egg retrieval is extremely low.

Anesthesia: The use of anesthesia while removing eggs can cause an allergic reaction or low blood pressure. It can also cause nausea or vomiting. In rare cases, use of anesthesia has resulted in death.

Failure: Sometimes no eggs are found during the retrieval process. In other cases, the eggs are not normal or are of inferior quality. These situations can prevent you from having a successful pregnancy.

In Vitro Fertilization

After eggs are retrieved, they are transferred to the embryology laboratory where they are kept in conditions that support their growth. The eggs are placed in small dishes or tubes containing "culture medium," which is special fluid to support development of the embryos. The fluid is made to resemble the conditions in the Fallopian tubes and uterus. The eggs are then placed into incubators, which keep the temperature, humidity, gas, and light at just the right levels. Three to four hours after the eggs are retrieved, sperm are placed in the culture medium with the eggs. In some cases, individual sperm is injected into each mature egg in a technique called Intracytoplasmic Sperm Injection (ICSI). The eggs are then returned to the incubator, where they remain to develop and grow. They are inspected at intervals over the next few days to check their progress.

Intracytoplasmic Sperm Injection ("ICSI") is a new modality in the treatment of severe male factor infertility. ICSI is indicated where the partner has less than 10 million motile sperm per milliliter, where there is abnormal sperm morphology, sperm penetration, acrosomal reaction, or repeated failure to fertilize your or a donor's eggs in prior IVF attempts. ICSI might also be indicated in cases of egg defects, which limit or inhibit spontaneous fertilization *in vitro*. ICSI is a technique of gamete micromanipulation in which a single sperm is captured in a microscopic glass pipette and meticulously injected into the cytoplasm of a single egg. Harvested, mature eggs are selected to undergo this delicate procedure. Although we can use poor semen samples, the laboratory still requires several normal appearing motile sperm for injection (at least one for each good egg).

Assisted Hatching (“AH”) is a micromanipulation technique in which the shell around the embryo (the zona pellucida) is opened or thinned to facilitate the embryo hatching process. AH involves drilling the zona using a laser, the technique shown worldwide to produce the best results. The Wisconsin Fertility Institute is selective when choosing whether to use Assisted Hatching. AH is not performed in all cases, but is usually added when embryo quality is low, or when embryos that are only 2-3 days old are used for the transfer. We also use AH for ALL thawed embryos.

Embryo Culture

On day 3, 5 or 6 after your retrieval you will receive a call letting you know how many embryos have made it to the blastocyst stage. Each embryo is frozen separately in a straw.

- **What is a straw?**
A straw is a rigid tube, and the device used to store your embryos.
- **Can I choose to freeze some embryos as singles and some as doubles?**
No. We freeze each embryo separately.
- **If I freeze 1 embryo per straw does that mean I can only transfer 1 embryo at a time?**
No. You can thaw 2 straws and transfer 2 embryos.
- **How much does it cost per embryo to freeze?** *You will be charged \$200.00 per embryo that is frozen. We do cap the amount charged at \$1200.00*
- **When do I need to have the answer to how I would like my embryos to be frozen?**
You need to be ready to answer how you would like your embryos frozen by day 5 and again on day 6. We would like to freeze the embryos in the morning, so it is important to be ready to answer when we call.
- **Will I know my total number of embryos to freeze on day 5?**
No. We give embryos an extra day to make it to the blastocyst stage (i.e. Day 6 embryos). We will guide you on day 5 with how many additional embryos we think you may have on day 6 but we never know for sure how many additional embryos you will have to freeze.

Timing of Medications in IVF Process:

Please let the office know on day 1 of the month prior to starting IVF that you are interested in IVF the following month. They will schedule you for a luteal progesterone level (around day 21). You may do an IUI (intrauterine insemination) this cycle if that is part of your treatment plan. If your progesterone level is appropriate, you will be started on estrogen three times a day (estrace 3mg TID).

On day 1 of your next menstrual cycle, you will call the office to set up your baseline visit. If it is a weekend or after hours, call the office the following business day. You will stay on the estrace and this will prevent you from starting another cycle and keep all the follicles in the ready position for stimulation. Depending on your cycle you may be on the estrace for 1-14 days prior to starting the IVF stimulation medications.

The nurses will let you know when you will come in for your baseline visit. During this visit, we will perform 1) a blood test and 2) an ultrasound exam of your uterus and ovaries to make sure there are no cysts and that all the eggs are small.

If your lab levels are appropriate, your ovaries have no large eggs, and your uterus looks ready, you will be instructed, to start the first set of drugs to grow the eggs and some that will improve egg quality.

Over the next 12-14 days, you will come in for ultrasound examinations and blood draws. You will be seen somewhere between 4 and 7 times during this 2-week period. We will adjust your dosing of drug to grow the eggs during this process.

About midway in the cycle, you will add the drug that will stop you from ovulating (Cetrotide, Ganirelix). These drugs are taken in the mornings, for 5-7 days total.

When your eggs are mature, (at least two of them measure about 20 x 20 mm average size) you will be told to stop taking the previous drugs. That evening you will take your trigger injection(s): Ovidrel/Lupron/Novarel. The trigger will allow the eggs to mature even further.

You will be given a specific time to take this medication—the trigger injection(s) must be given within fifteen minutes of the time you are told to inject!

The next day is the day before your retrieval. It is a shot free day.

You may not have anything to eat or drink after midnight the day before the retrieval.

Retrieval Day

The retrieval is performed 36 hours after you have taken your trigger shot. You should not eat or drink anything after midnight the night before the retrieval. If you usually take medications in the morning, it is ok to do so with a tiny sip of water.

When you come to the clinic, we will place an intravenous tube into a vein in your arm. We will give you drugs for conscious sedation; you will be a little sleepy and won't feel any pain.

During the retrieval, an ultrasound is placed into your vagina, and we aspirate or extract the eggs by passing a small needle across the vagina and inserting it into the ovary while we watch with the ultrasound. We will remove all eggs found if you are undergoing standard IVF. Keep in mind that ultrasound is a guide, sometimes we get more eggs than expected and sometimes we get less. If we get a much lower number of eggs than expected, that can indicate poor egg quality. This can either be a contributing factor to your subfertility or may have been a bad batch of eggs. You will have sedation and thus will need someone to drive you home after the procedure.

Embryo development usually proceeds along the following schedule:

Day 1: This is the day that the eggs and sperm come together, and we can check for signs of fertilization. At this stage, the normally fertilized egg is still a single cell with 2 nuclei, called a 2PN or zygote.

Day 2: Normal embryos will divide into 2 to 4 cells.

Day 3: Normally developing embryos will continue to divide and contain 4 to 8 cells.

Day 4: The cells of the embryo begin to merge to form a solid ball of cells called a morula (named because it looks like a mulberry).

Day 5: Normal embryos now have 100 cells or more and are called blastocysts. It has an inner fluid-filled cavity and a small cluster of cells on the inside called the inner cell mass.

It is important to understand that many eggs and embryos are abnormal. This means that some eggs will not fertilize, and some embryos will not divide at a normal rate. Some embryos may stop growing. Even if your embryo(s) develop normally in the lab, you still may not get pregnant.

IVF Lab Quality Control

We take great care of all eggs, embryos, and sperm in the lab. Still, there are many reasons why pregnancy may not happen with IVF:

- The eggs may fail to fertilize.
- One or more eggs may fertilize abnormally. This can lead to an abnormal number of chromosomes in the embryo. These abnormal embryos cannot be transferred.
- The fertilized eggs may fall apart before dividing into embryos, or the embryos may not develop normally.
- Rarely, the eggs or embryos may be harmed by contact with bacteria in the lab.
- Despite having backup systems in place, lab equipment may fail, or power may be lost. Both can lead to the destruction of eggs, sperm, and embryos.
- A lab accident or human error can happen and can lead to embryo loss.
- Other unplanned events may prevent any step of the process from being performed or prevent a pregnancy from occurring.
- Hurricanes, floods, or other “Acts of God” including bombings or other terrorist acts, could destroy the laboratory or its contents, including any sperm, eggs, or embryos.

Quality control is the process of running tests to ensure that lab conditions are the best they can be to help embryos grow. Systems in the lab are frequently checked to make sure conditions are optimal. Sometimes immature or abnormal eggs, or embryos that have not developed normally, can be used for quality control checks before they are discarded. None of the material that would normally be discarded--blood, tissues eggs, sperm or embryos--will be used to create a pregnancy or a cell line.

Preimplantation Genetic Testing (PGT)

There are several reasons that some patients choose to have PGT-M or PGT-A testing completed. You will be asked to decide if this testing is something you want completed before your first baseline appointment for IVF. Please understand that this testing does not guarantee that a pregnancy will occur, even if the embryo is testing normal. Factors other than genes also influence pregnancy rates. Screening the embryo’s chromosomes or testing for one specific genetic disease does not guarantee that an embryo will be healthy and free of other disorders. For example, some common disorders that cannot be checked with PGT are autism and diabetes. Some birth defects can also occur even if chromosome screening is normal. An example of this would be a cleft lip or palate (failure of the lip and upper mouth to join properly). It is always a possibility that PGT will show that there are NO normal embryos available to transfer. There are several reasons that some patients choose to do PGT testing such as:

- Determining whether the embryo has the incorrect number of chromosomes.
- Determining whether the embryo has a structural rearrangement of its chromosomal material PGT-SR
- Determining whether the embryo has a specific disease-causing mutation PGT-M
- Determining the gender of the embryo.

Risk of Embryo Biopsy

- **Damage.** There is a small risk of damage to the embryo. This may result in no healthy embryos being available to transfer.
- **No result.** The test may not give a result. Sometimes, there is not enough genetic material retrieved to run the test. It may be possible to repeat the biopsy and try again to evaluate the embryo.
- **Misdiagnosis.** The test may give the wrong result, and say that a normal embryo is abnormal, or that an abnormal embryo is normal. The accuracy of testing is determined by the off-site lab.
- **Most testing is very accurate, so the chance of misdiagnosis is low.** Furthermore, since not all embryos are made up of cells with identical genetics (“mosaicism”), it is possible that accurate test result does not reflect the genetics of the entire embryo. Consequently, the current recommendation is to confirm the result in early pregnancy.

Cryopreservation

Sometimes there are normally developing embryos left after embryo transfer. Additional normal-appearing embryos can be frozen for future use. In some cases, it may be planned for all embryos from an IVF cycle to be frozen (for example, when PGS is used). On the other hand, some women may wish to freeze their eggs because they are not ready to conceive now, or because they are planning to have therapy such as cancer treatment that could damage their eggs.

Benefits of Freezing:

- Saves you from going through ovarian stimulation again if you need eggs or embryos in the future.
- Allows you to transfer fewer embryos in the fresh cycle and keep the others for a frozen cycle. This can reduce the risk of a multiple pregnancy (twins, triplets, or greater).
- Allows you to freeze all embryos in the fresh cycle to prevent over-stimulation of the ovaries.
- Allows you to freeze embryos while waiting for test results from PGS or PGD.
- Protects you if your future fertility is at risk because of surgery or other treatments such as cancer therapy.

There are different ways to freeze embryos. The most common are “slow” freezing and “rapid” freezing (called *vitrification*). You should know that embryos do not always survive the freezing and thawing process. There is always a risk that no embryos will survive. If this happens, the transfer will have to be cancelled. Studies of animals and humans indicate that children born from frozen embryo cycles do not have any greater chance of birth defects than children born after fresh embryo transfers; however, until very large numbers of children have been born from frozen embryos, it is not possible to be certain that there are no increased risks.

Storage Fees

Once your embryos are frozen at WFI, you will be responsible for the yearly storage fees. If you choose to freeze your embryos with us, you will need to fill out a credit card authorization form to set up automatic billing. Each time you freeze a new batch of embryos, you will be billed separately each year for that batch. The cost of embryo storage is \$400.00 per year. Should you discontinue storage before the year ends, you will not be given a refund. This storage fee will be charged yearly until all embryos have been used or discarded.

Embryo Growth and Quality

When a healthy embryo is created, it grows predictably. The day after sperm and eggs are mixed, the embryo generally is a single cell; it then divides and grows to approximately 6-8 cells by day 3 following egg retrieval. The growth continues, and by day 4 there are dozens of cells in a ball, called a morula. By day 5, the best embryos are greater than 200 cells and have a fluid filled space within their structure; this is called a blastocyst. For some slower growing embryos, this stage is not reached until day 6 following egg retrieval.

When embryos are formed following IVF, we are faced with the decision as to when to place them back into the uterus. This was originally done on day 1, then later day 2 or 3. Recently, many programs are transferring embryos on day 5 or 6. Why the tendency to transfer later in embryo development? The answer is simple: the longer we culture embryos in the laboratory, the easier it is to distinguish which are the best of the bunch! Virtually all day 1 embryo looks alike. Day 3 embryos may vary by cell number and appearance, but differences at this stage are not totally predictive of what will happen next. By contrast, a great day 5 embryo is easily distinguished from a mediocre or poor embryo. Understanding the quality of an embryo is vitally important as it is predictive of the chances of pregnancy. To give the best chance of conception, we would like to put back the best two embryos. We can do this on day 5 or 6, and in doing so provide a very good chance for pregnancy with no chance of triplets. To have the same chance of pregnancy with day 3 embryos, we would have to transfer 3 or 4 because it is not as clear

which are truly the best. Unfortunately, if they are all outstanding, there is a real risk of triplets or quadruplets! To avoid this risk, we could transfer only two embryos on day 3, but if they turn out to be mediocre then the chance of pregnancy is reduced. Thus, transferring on day 3 is trickier business than on day 5 or 6.

If this is the case, then why not always transfer on day 5/6? Some programs do just that. However, while over 80% of all embryos grow to day 3, only about 25% (1 in 4) grow to day 5. Thus, if you have relatively few embryos to start with, there is a very real chance that none will make it to day 5. If completing this process through the embryo transfer is critically important to you emotionally, such a failure to reach transfer could be devastating.

For this reason, our policy is to advise culturing embryos to day 5 or 6 whenever 8 or more embryos are formed on the day after retrieval. Our rationale is that since 1 in 4 embryos make it to day 5, you are likely to end up with at least 2 blastocysts for transfer. Conversely, if less than 8 embryos are made initially, we would suggest a day 3 transfer. Finally, if only 2 or 3 embryos are produced, a day 3 transfer is preferred by us to replace the embryos as soon as possible, since no selection needs to be made by laboratory personnel. After all, we assume that the uterus is at least as good an environment for the growing embryos as our incubators, and possibly even better.

However, these are merely our suggested policies. The decision will be yours. Please discuss the issues with each other and your doctor. A decision should be reached the day following retrieval, when we let you know how many embryos are formed. In any event, it is best to begin the discussion now, when the level of anxiety is lower. Please ask us if you would like us to facilitate or participate in this decision.

Choosing Number of Embryos to be Transferred

The number of embryos transferred to your uterus will have a significant impact on your chances of conceiving. The greater the number of embryos transferred, the greater the chance of a pregnancy. Unfortunately, the greater the number of embryos the greater the risk of multiple pregnancy, and when a large number are transferred there may be a substantial risk of high-order (triplet or greater) multiple pregnancy. How then do we determine the number to place back? The answer depends upon many factors, including the stage of embryo development, whether the embryos are fresh or thawed, the age of the patient, the reason for IVF, the appearance of the embryos, results of prior IVF attempts, and the acceptability of selective embryo reduction.

In general, when embryos are transferred on day 5 or 6 (blastocyst stage) it is advisable to transfer one embryo at a time. SART has guidelines for transferring embryos and as

a member of SART we need to follow their guidelines. Additionally overall pregnancy rates are higher with multiple single embryo transfers than two embryos transferred at one time. More embryos may be replaced for day 3 embryos, older patients, prior IVF failures, or poor-quality blastocysts. You may ask your provider if you qualify to put back more than one embryo, but they may say no to ensure we are following SART guidelines.

Timing of Medication in the Frozen Embryo Transfer Cycle

On day 1 of your menstrual cycle, you will call the office to set up your baseline visit. If it is a weekend or after hours, call the office and leave a message in the general voice mail.

When you come in for your baseline visit, we will perform 1) a blood test to make sure your estrogen level is low and 2) an ultrasound exam of your uterus and ovaries to make sure there are no cysts and that all of the eggs are small, and 3) do a mock embryo transfer to map the path through the cervix and an endometrial scratch to improve implantation rates.

If your estrogen level is low, your ovaries have no large eggs, and your uterus looks ready, you will begin Estrogen pills orally, a total of 3-4 per day, patches replaced every 3 days or injections taken each day. As early as day 10 of estrogen, you can come for a lining check, and if the lining is 7 mm or greater and has a triple layer architecture, the progesterone is added. You will continue the Estrogen until week 11 gestation.

Progesterone must be taken intramuscularly (big needle in the upper, outer quadrant of your bum). On the 4th or 6th day of Progesterone, the embryo(s) will be thawed and transferred. On this day you will need a full bladder and will be given valium which will relax the uterus for the rest of the day. The Progesterone is taken once daily and will be taken until week 11 gestation.

Both Prednisone and Doxycycline will be given for 5 days surrounding the transfer. These are taken orally. Sometimes, you will continue Prednisone through the pregnancy test or until the end of the first trimester. You will need to wean the Prednisone once you have been instructed to do so. You may also be asked to take an injection called Enoxaparin starting the day after the transfer, to continue through the pregnancy test or sometimes longer, depending upon your Doctor's recommendation. Prior to the transfer, you will be instructed to eat or drink lightly. The transfer itself is a very simple procedure and is nearly always completely painless. It is very much like a routine pelvic exam and involves the passage of a very small plastic catheter through the cervix. A tiny drop (10-20 microliters) of culture media with the embryos suspended within are deposited in the upper reaches of the uterus.

Post-Transfer

Bed rest after the transfer is discouraged. Do anything that brings you great peace and joy. Scheduled your pregnancy test on the given date.

If the pregnancy test is positive, you will be instructed to continue the Estradiol and progesterone. An ultrasound will be scheduled approximately 3 weeks after the positive test results to confirm a clinical pregnancy and determine the number of babies present.

In-Vitro Fertilization: Frequently Asked Questions

I have had all my lab testing done. Now what do I do?

If your testing was completed at the Wisconsin Fertility Institute, we will contact you when the results are in and have you set up an appointment with one of the providers to discuss your specific treatment plan. If your testing was done through your own health care provider, call us if you need our help getting the results sent or faxed to our office. Once we have received all the records, we will contact you to set up your treatment plan visit.

When is day one of my menstrual cycle?

This can be difficult for some people to know if they are spotting or bleeding stops and starts. Day one is considered the first day you see **flow**. Spotting does not count as flow. If you are not using a pad or tampon, then it is not day one yet. If you are unsure about what day counts as day 1, call us!

I need a refill on one or more of my medications. What do I do?

When we call in your original prescription, we also call in several refills. Simply contact the pharmacy from where you received your original prescription, and they will mail out more medications. Some pharmacies do not deliver on the weekends, so if you need more medication on Saturday or Sunday, you should have it delivered by Friday. If you need help, feel free to call us.

The flow sheet on the patient portal doesn't tell me which dose of medication to take tomorrow. What do I do?

When looking on the patient portal Flow sheet Tab, you will notice the medications are listed for each day you are to take them. You can look at the Patient Instructions tab to see when your next ultrasound and estrogen appointment should be scheduled. If you are still having trouble, call us!

What time of day should I take my medication?

- **Follistim/Gonal-f/Stimulation Drugs:** We usually prefer you take these in the afternoon/early evening.
- **Omnitrope:** this is also taken in the evening with the evening drugs.
- **Cetrotide/Ganirelix:** this medication is taken in the mornings, make sure you take it within 30 minutes of your scheduled time each morning. You will still take this medication the day that you trigger with Lupron or Ovidrel in preparation for the egg retrieval.
- **Lupron/Ovidrel/Novarel AS A TRIGGER:** These medications should be taken at the precise time that we tell you. Your egg retrieval time is based on when you took these trigger shots, so taking them on time is important. If you take your trigger shot at another time than we indicated (by more than 15 minutes) please call us right away.
- **Progesterone:** Should be at the same time each day, once daily, sometime in the morning.
- **Doxycycline:** Every 12 hours/twice daily with food.
- **Estrogen/Estrace:** This drug can cause nausea, so it is best to spread it out during the day. You can take it with meals or at bedtime. It will be taken 4 times daily.

Which medications should be refrigerated, and which ones should be kept at room temperature? When do they expire?

Please see the Medication Storage Fact Sheet in your IVF folder for a complete listing of medications and instructions.

What about herbs, supplements, or over the counter medications?

Any medications besides the ones we are prescribing should be cleared by one of our staff. Please review all medications you take with us. Tylenol and Benadryl products are ok to use during the cycle. Ephedrine based medications should be avoided.

Are there limitations on sexual activity?

There is no evidence to suggest that restricting intercourse is helpful.

MEDICATION STORAGE INFORMATION

Cetrotide 0.25mg - Store refrigerated. Store in original box. Use immediately after reconstitution/mixing.

Crinone 8% Vaginal Gel - Store at room temperature. It is acceptable to store at slightly lower or higher temperatures for very brief periods of time (as low as 59°F and as high as 86°F).

Endometrin 100mg Vaginal Inserts - Store at room temperature. It is acceptable to store at slightly lower or higher temperatures for very brief periods of time (as low as 59°F and as high as 86°F).

Follistim AQ Cartridge 300IU, 600IU, 900IU - Store refrigerated until the expiration date OR at room temperature for 3 months or until expiration date, whichever occurs first. Once the Cartridge has been pierced by a needle, it can be stored for a maximum of 28 days refrigerated or at room temperature. Protect from light. Do not freeze.

Ganirelix 250mcg Syringe - Store at room temperature. It is acceptable to store at slightly lower or higher temperatures for very brief periods of time (as low as 59°F and as high as 86°F). Protect from light.

Gonal-f 75IU Vial - Store at room temperature or refrigerate until expiration date. Do not freeze. Protect from light. After reconstitution/mixing: Use immediately. Discard unused material. Do not store drug in the syringe.

Gonal-f Pens 300IU, 450IU, 900IU - Before first use: Store refrigerated until expiration date OR at room temperature for up to 3 months or until expiration, whichever occurs first. After initial use: Store at room temperature OR refrigerate for up to 28 days. Protect from light. Do not freeze.

Leuprolide (Lupron) 14-day kit or prefilled syringe- Store refrigerated. Do not freeze. Protect from light.

Menopur 75IU Vial - Store at room temperature or refrigerated. Protect from light. Use immediately after reconstitution/mixing. Discard unused material.

Microdose Leuprolide/Leuprolide Dilution Vial - Keep refrigerated. Do not use after expiration indicated on vial.

Novarel 5,000- or 10,000-Units Vial - Store at room temperature. It is acceptable to store at slightly lower or higher temperatures for very brief periods of time (as low as 59°F and as high as 86°F). After reconstitution/mixing: Refrigerate and use within 30 days.

Ovidrel 250mcg Prefilled Syringe - Store refrigerated until expiration date OR at room temperature for not more than 30 days. Protect from light. Do not freeze.

Progesteronction - Store at room temperature. Do not refrigerate.

Important Information

Website- Patient portal and educational videos: <https://wisconsinfertility.com/>

Clinic Phone Number: 608-824-0075 **Fax Number:** 608-829-0748

Address: 3146 Deming Way Middleton, Wisconsin 53562

Clinic Hours: Monday, Tuesday, Thursday and Friday 7:30am-4pm
Saturday and Sunday 8am-9am

Clinical Staff:

Kelly, RN. Charge Nurse

Beth, RN. Egg Donor Coordinator, IVF Nurse

Hannah, RN. Embryo Donation/ Gestational Carrier Coordinator

Ashlee, RN. IVF Nurse