In-Vitro Fertilization

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Welcome to the Wisconsin Fertility Institute and thank you for your interest in our *In Vitro* Fertilization program. This packet is designed to act 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 sincerely hope to help you build the family of your dreams, and we are honored to have the privilege of working with you.

The following is a list of steps to complete before beginning an IVF cycle:

1. Call the clinic (608-824-0075) to schedule a consultation with one of our doctors.

2. Obtain lab orders to complete the necessary testing for your IVF cycle.
    - AMH
    - TSH
    - Blood Type*
    - Rubella and Varicella Titer*
    - Sonohysterogram (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 faxed or sent over to our office as soon as they are completed.

    All labs must be 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 schedule the following appointments:

        Treatment Plan visit with your doctor, in person.

        IVF Lecture and Injection Training Class. This class is required and takes place in our office every Monday, Tuesday, Thursday, and Friday at 2:00pm. There is no additional cost for this class.

Once all the above steps have been completed, you are ready to begin your IVF journey.

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

The Doctors and Staff of Wisconsin Fertility Institute

A BRIEF HISTORY OF *IN-VITRO* FERTILIZATION

Robert Edwards, a Ph.D. physiologist, and Patrick Steptoe, a gynecologist, pioneered IVF in Great Britain during the 1970's. Edwards had spent the 1960's working with bits of human ovaries removed at surgery and had achieved the first fertilization of a human egg outside the body in 1967. During these same years, Steptoe was helping to develop the new surgical technique of laparoscopy. By 1971 the two men had met and begun to collaborate. Initially they retrieved eggs from the ovaries of volunteers by laparoscopy and focused on improving the timing of egg retrieval and *in-vitro* culture conditions. By the mid-1970's they felt ready to attempt pregnancy. Their initial pregnancy was, unfortunately, a tubal pregnancy (ectopic) in 1976. Then came true success and the first IVF baby, Louise Brown, was born in July 1978.

Steptoe and Edwards' original group of patients had undergone "natural IVF", meaning they were not given fertility drugs. Instead, they were monitored closely and when ovulation appeared imminent, even if it was 3:00 AM, a laparoscopy was done and an attempt made to aspirate the single mature egg. As might be suspected, they didn't always obtain the egg. Two Australian groups were only two years behind in achieving IVF pregnancies, but they chose a different route. They stimulated their patients with fertility drugs in hopes of recovering more than one egg. As their initial success rates, about 5% per attempt, were higher than that of Steptoe and Edwards, all subsequent new IVF programs also used "stimulated IVF". Eventually Steptoe and Edwards adopted this approach as well.

The 1980's saw continued improvement in embryology culturing techniques, refinements in fertility drug protocols, and the ability to retrieve eggs with a vaginal ultrasound probe instead of laparoscopy. As a result, IVF success rates began to climb slowly but steadily, reaching 20-25% per attempt for women under the age of 40 by the end of the decade.

The 1990's have seen additional improvements in the process, such as better treatment protocols for women 40 years of age and older and the development of ICSI (Intracytoplasmic Sperm Injection), a revolutionary treatment for severe male factor problems. With ICSI, a single sperm can be injected into an egg and thereby achieve fertilization. For women 35 years of age and older, a technique called Assisted Hatching and the ability to grow embryos longer (3 to 5 days before transfer) have helped improve the odds. Also, the process of egg donation (IVF using eggs donated by a younger woman) was perfected, producing high pregnancy rates in previously hopeless situations.

WHY 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 ARE THE CHANCES OF SUCCESS WITH IVF?

Everyone considering IVF clearly needs to know the success rates achieved by the program they plan to work with, and yet correctly estimating anyone's chances is quite difficult due to the many variables involved such as age, cause of the infertility, health of the woman’s uterus, and quality of the sperm.

Similarly, judging a program based on its pregnancy rate can be fraught with error. Programs can improve their pregnancy rates by refusing to treat older women or poor candidates. They can turn away couples with previous failures. They can also transfer large numbers of embryos, inflating the pregnancy rate but also producing a dangerously high multiple (and high-order multiple) pregnancy rate. Since policies vary from program to program, it is virtually impossible to determine the quality of program based upon pregnancy rates.

Nevertheless, a reasonable benchmark for all programs is an ultrasound proven pregnancy rate of at least 35% (although our rates are much higher). This should be highest among younger patients and is usually quite a bit lower in the patient over 40 (10% or less). The highest pregnancy rates are usually seen in young couples (under 30) with severe male factor infertility: these rates can approach 50-70%. Note that for no type of patient is the chance 100%, nor is it 0%.

One of the great difficulties with IVF is that it is very hard to know when to stop. *We can not with certainty predict who will ultimately succeed with IVF and who will not.* A poor prognosis patient may conceive in the

first IVF cycle, and a supposedly good prognosis patient may still be unsuccessful after their third or fourth cycle. Random chance (plain old luck) has a lot to do with how soon success will come. Clearly though, there must be a point at which we can no longer blame bad luck for continued failure.

Unfortunately, we don't know everything there is to know about fertility and there are almost certainly a host of rare problems that may prevent successful embryo implantation. Finding this break point between chance and pathology is enormously important and is therefore the focus of a great deal of current research.

The best evidence we have currently is that the "point of diminishing returns" is reached after IVF cycle number 3 or 4. This applies in cases where IVF has produced a reasonable number of good quality embryos for transfer. If, on the other hand, only unhealthy embryos result from the first IVF cycle, then the chances of success are much lower than normally found and the decision may be to stop IVF at that point.

WHAT ARE THE RISKS ASSOCIATED WITH IVF?

The track record of safety for IVF over the years has been very good. Nonetheless, there are risks that you should be aware of:

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) is 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 very 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 your getting very sick. The hospital stay can sometimes be several weeks, particularly if you are pregnant.

Excessive stimulation of the ovaries is called ovarian hyperstimulation. Ovarian hyperstimulation occurs in a small percentage of patients when too many follicles develop in the ovary. The ovary then grows to a large size and leaks fluid, resulting in nausea and bloating, dehydration, and, if severe, fluid collection around the abdominal organs, or ascites. In very severe cases, fluid collects around other organs, such as the lungs and heart, and blood clots and strokes can occur. If the ovary enlarges too much, rupture of the ovary and abdominal bleeding can occur. In rare cases, hospitalization and removal of abdominal fluid may be required to regulate fluid balance.

Fortunately, serious cases of ovarian hyperstimulation are quite rare and your doctor can predict and prevent hyperstimulation by monitoring the ovaries with ultrasound and blood estrogen levels. If we believe your risk is higher than most patients, a cycle may be cancelled. Although this is a rare event, cancellation provides complete safety, in that hyperstimulation almost never occurs after a cancelled cycle. If a cycle proceeds to egg retrieval, the risk of severe hyperstimulation is reduced by freezing all embryos and transferring them in a later cycle, after the risk has subsided You may be asked to take a drug called Cabergoline around the retrieval time or use different types of "trigger" injections before the retrieval. These steps will also decrease the risk of OHSS.

What to do:

- *Drink plenty of electrolyte-rich fluids like Pedialtyte*
- *Increase protein and salt intake*
- *You can take Tylenol for discomfort.*

What happens:

- *Your belly may swell; sometimes a bigger pant size/elastic pants becomes necessary.*
- *Symptoms may become worse before they get better.*
- *You may need come into to the clinic for a blood draw panel and/or ultrasound.*
- *Hospitalization may be necessary if symptoms persist or become more severe.*

Please contact the clinic right away if you experience:

- *Shortness of breath*
- *Reduced urination or if urine becomes dark in color.*
- *Calf pain or chest pain*
- *Extreme lower abdominal pain*
- *Vomiting or diarrhea*

We minimize the risk of severe OHSS by carefully monitoring your progress during drug treatment and adjusting the drug doses as necessary.

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 a possible increase in the risk of ovarian cancer in women who took the fertility pill clomiphene citrate (Clomid) for a long period of time (12 or more months). Clomid is rarely used in IVF, and no studies to date have indicated any increased risk for other IVF medications, but perhaps studies in the future will. However, given the difficulty of demonstrating an increased risk of ovarian cancer despite nearly 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 substantially lowers the risks of cancer of the breast, ovary and uterus.

THE IVF CYCLE: A COMPLETE GUIDE

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 is 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 in everyone, and occasionally a poor response to medication may necessitate a discontinuation of treatment, with resumption later using a different drug combination. In this center, three approaches are used primarily, although small variations may sometimes occur for individual patients:

(1) ***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.

(2) ***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.

(3) ***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.

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 then 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.

Embyro Freeze-All

Often during the IVF cycle, the follicles or eggs that are growing will secrete extra progesterone. When the uterine lining is exposed to those hormones in the cycle then the uterus and embryos are out of sync, making your chances of getting pregnant during that cycle very low.

We routinely freeze all viable embryos with a plan to transfer the embryos in subsequent menstrual cycles.

When transferring frozen embryos, the issue with synchronizing embryos and uterus is not a problem, because we provide all the hormones you will need, but at a lower dose than during the egg growth.

Information about Embryo freezing

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. You will be asked how you would like them frozen either as 1 embryo or 2 embryos per "straw".

Please be aware of how many "straws" you paid for as the provider calling you will not know this information as it is different for each patient. If you have insurance, please confirm if your insurance covers the freezing cost. If you are doing PGT-A or PGS your embryos must be frozen as a single embryo so we can identify each embryo with their genetic result.

- ***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?***
  Yes.

- ***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.

- ***If I freeze 2 embryos per straw does that mean I have to transfer both embryos?***
  No. We can thaw both embryos and re-freeze the additional embryo. However, this may result in additional costs to you. This also puts additional stress on the embryo as it must undergo the freezing and thawing process an additional time.

- ***How much does a straw cost?***
  Each straw is $200.

- ***When do I need to have the answer to how I would like my embryos 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 (ie 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.

Embryo Transfer

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.

Embryos are usually transferred either at three days old (cleaved embryo) or at five - six days old (blastocyst). Five days is preferred, but occasionally day three is chosen due to issues with embryo number or growth. For more information, see the discussion, "Choosing Your Day of Transfer".

Post-Transfer

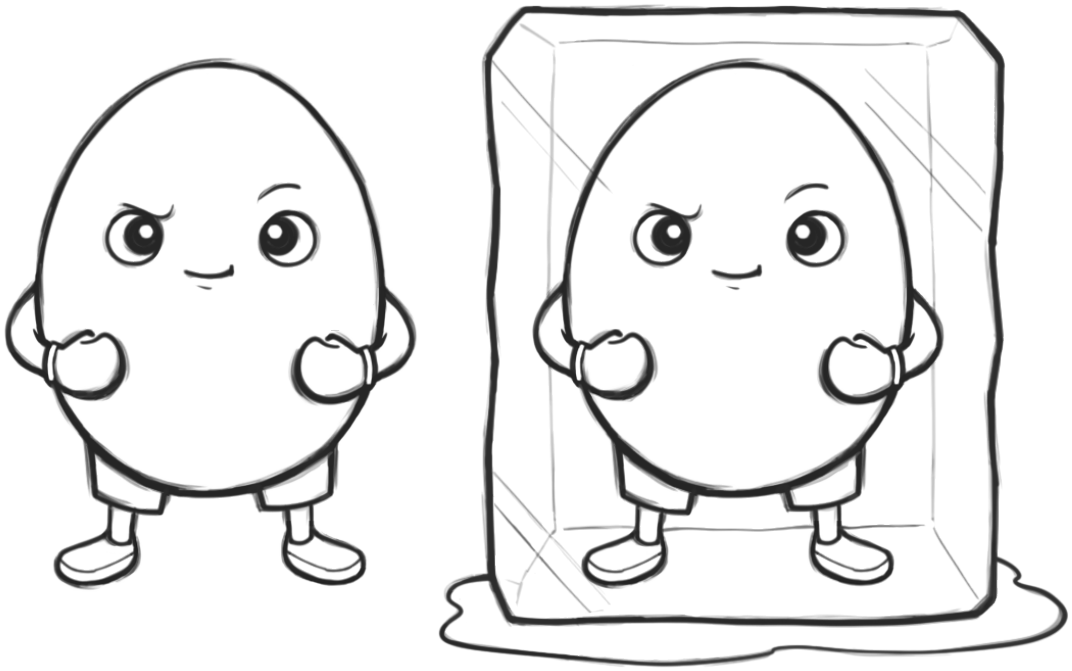
Bed rest after the transfer is discouraged. Do anything that brings you great peace and joy. Scheduled your pregnancy test on the given date.

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.

A note about storage fees…

Once your embryos are frozen at WFI, you will be responsible for the 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.

- Yearly - $400/per year. Should you discontinue storage before the year ends, you will NOT be given a refund.



INTRACYTOPLASMIC SPERM INJECTION (ICSI)

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 very poor semen samples, the laboratory still requires several normal appearing motile sperm for injection (at least one for each good egg).

ASSISTED HATCHING

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.

CHOOSING THE NUMBER OF EMBRYOS TO TRANSFER

The number of embryos transferred to your uterus will have a significant impact on your chances of conceiving. It is clear that 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. The American Society of Reproductive Medicine has provided recommendations for transfer numbers, but they are merely guidelines.

Note that they are designed to produce a reasonable pregnancy rate with a minimal multiple pregnancy rate, without considering embryo reduction.

In general, when fresh embryos are transferred on day 5 or 6 (blastocyst stage) it is advisable to transfer one or two. However, more may be replaced for older patients, prior IVF failures, or poor-quality blastocysts.

Day 3 embryos are more problematic, and while low numbers are recommended for young patients with excellent-looking embryos, there are many factors that might cause us to recommend transferring 3, 4, or even more embryos in some circumstances.
The final decision as to the number of embryos to transfer is yours. Please read and consider this information and discuss it with each other and your doctor. You will be asked to make a final determination on the day of your embryo transfer.

CHOOSING YOUR DAY OF TRANSFER

When a healthy embryo is created, it grows at a fairly predictable rate. 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 2 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 as well as with 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.

MICRO IN VITRO FERTILIZATION (MicroIVF)

It may occasionally be the case that a woman may need or wish to undergo in vitro fertilization but cannot devote sufficient resources to the standard approach to IVF. An alternative to routine IVF is called MicroIVF. This technique uses fewer and less expensive medications, less monitoring, and less laboratory embryo work. The advantage of the technique is that it is about half the price of standard IVF. The disadvantage is that there is no ICSI, assisted hatching, or cryopreservation of excess embryos.

Who is a candidate for MicroIVF?

The best candidates are young couples with no fertility issues aside from damaged or absent fallopian tubes (for example, women who have had a tubal ligation). Other good candidates include couples who conceive easily but have had multiple ectopic pregnancies.

How is MicroIVF done?

On day 3 of your menstrual cycle, you will begin stimulation of the ovaries an oral medication for a few days, then add injectable medications. About 2-3 ultrasounds will be performed during a 12–14-day period to ensure you are growing enough eggs, and to monitor their maturity. When the eggs are mature, an egg retrieval is performed by passing a needle across the vagina and aspirating up to four eggs. The eggs are then placed in a dish, sperm added, and the next morning fertilization checked. We usually transfer up to 3 embryos on the third day after the retrieval but prefer to transfer only 2. We don’t freeze any extra embryos, and do not inject the sperm into each egg (a procedure called intra-cytoplasmic sperm injection or ICSI).

How successful is MicroIVF?

In couples that fit the profile stated above, pregnancy rates are as high as 30% per attempt.

How can I elect to have MicroIVF?

Simply ask your doctor about this when discussing treatment options for IVF. This can occur at any time prior to establishing your IVF treatment plan.

IVF 101: A Primer

The following information is intended to give you an overview of the IVF process at Wisconsin Fertility Institute.

Medications 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.

Omnitrope: 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 has the potential to increase implantation rates by slightly 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.

Timing of Medications in IVF Process:

On day 1 of your menstrual cycle, you will call the office to set up your baseline visit for day 3. If it is a weekend or after hours, call the office and leave a message in the general voice mail, if you don't get through to us, just show up on day 3 at 8:30 am.

On day 3 of the cycle, you will come in for your baseline visit. At this 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.

If your estrogen level is low, 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 perhaps 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.**

The Retrieval (Day 0):

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

If you are undergoing MicroIVF, then we will use a single intramuscular shot of drugs to make you a bit sleepy and use local shots at the vagina to keep you comfortable. You will not use conscious sedation.

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 of the eggs we find if you are undergoing standard IVF and remove up to four eggs if you are undergoing Micro IVF.

All eggs will be passed to the Laboratory Director who will look at each egg and place each one in a Petri dish. A few hours later, the sperm is either placed with each egg in a Petri dish or a single sperm is injected into a single egg (via ICSI: Intracytoplasmic Sperm Injection).

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 for day 3. If it is a weekend or after hours, call the office and leave a message in the general voice mail, if you don't get through to us, just show up on day 3 at 8:30 am.

On day 3 of the cycle, you will come in for your baseline visit. At this 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 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 4^{th} or 6^{th} 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.

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 of 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 to know for some people 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 will 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 lOOmg 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.

Progesterone in Oil for Injection - Store at room temperature. Do not refrigerate.