wisconsin fertility
INSTITUTE

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 the stress by providing a safe, comfortable environment. We also have a number of 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.

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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 by definition 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 multiple 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 particular 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 25% (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 carries 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.

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 technique 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.

PRE-CYCLE TESTING FOR IVF

Tests	Description	Female Partner	Male Partner	Egg Donor	Egg Donor's Partner	Surrogate	Surrogate's Partner
AMH	Blood test done to check the ability of the ovaries to respond to fertility medication and to determine the ovarian reserve	X		X			
TSH	A test to check on thyroid function	X		X		X	
HIV	Test for infection	X	X	X	X	X	X
HTLV-1 & II	A virus that can cause leukemia and neurologic disease					X	X
VDRL/RPR	Test for syphilis	X	X	X	X	X	X
Hep B S Ag	Test for Hepatitis B	X	X	X	X	X	X
Hep C Ab	Test for Hepatitis C	X	X	X	X	X	X
CMV-IgM	Test for Cytomegalovirus that can cause fetal damage if a woman is pregnant with active infection					X	
Rubella/Varicella	Check for rubella/varicella immunity	X				X	
ABO/Rh	Blood type	X		X		X	
Hysteroscopy/ Sonohysterogram/ Hysterosalpingogram	Test to check on the status of the uterus	X				X	
Semen Analysis	A test to check sperm count, motility and morphology		X		X		

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 meet with a member of the nursing staff who will review which tests are required prior to beginning the IVF treatment. 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 a number of 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 or Gonal F is begun on this day and continued for 9-14 days. It is 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. You will also begin Novarel at this time, either once or twice daily, depending upon your protocol. After about 13 days of egg growth, Ovidrel/Lupron or a combination of both (trigger shots) is administered to allow the retrieval of the eggs. These drugs are given 36 hours before harvesting your eggs, and is 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 or Gonal F 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 or Gonal F 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 or Gonal F are added at a dose of 450 units daily. We may also recommend adding Growth Hormone or Omnitrope to improve 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 Ovidrel, Lupron or a combination of both, 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 this drug for 5 days.

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 either 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.

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.

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 are able to 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 (attached), 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, nd 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 embryos look 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) grows 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 in order 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 less. 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 2 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.