

Treating Infertility



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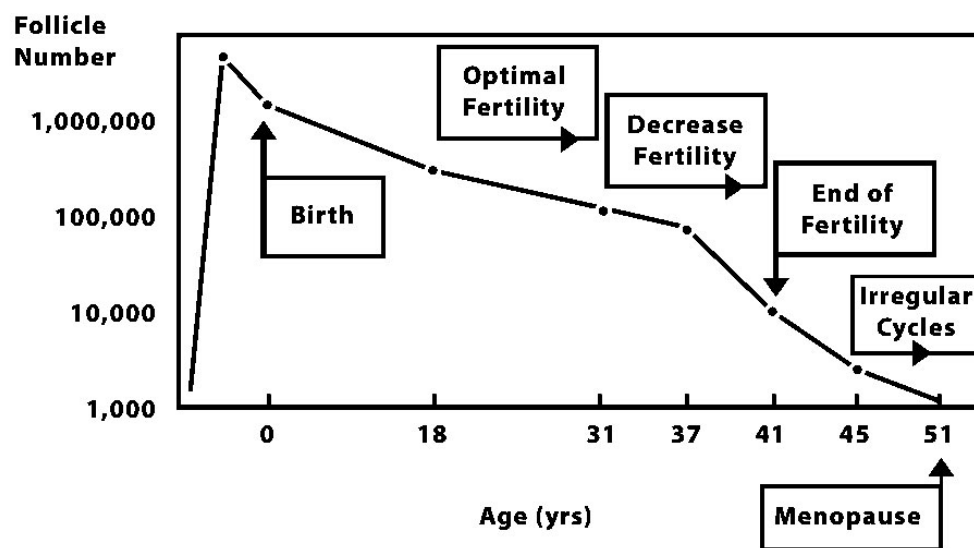
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The Infertility Epidemic

We are in the midst of a worldwide epidemic of infertility. Ironically, even in countries with severe overpopulation, one of the most common reasons for a visit to the doctor is the inability to have children. Twenty-five percent of modern couples in their mid-thirties everywhere in the world are infertile. From our teen years (when the last thing we really want is a child) to our midthirties (when we finally feel emotionally and financially secure enough to start a family), there is a twenty-five-fold decline in our ability to get pregnant. Let me explain.

Ironically, the incidence of infertility in teenagers is rare. For women in their early twenties, still only 1 to 2 percent are infertile. By their late twenties, however, 16 percent of women are infertile, and in their mid to late thirties, 25 percent are infertile. By age forty, more than half of women are infertile, and pregnancy beyond age forty-three is very uncommon. If you are in your thirties, have been working hard to establish yourself, and are now just casually thumbing through this booklet at your doctor's office because you're thinking maybe in a few years you might like to start a family, you should realize that there is a 25 percent chance you will not be able to do so without medical intervention. What accounts for this dramatic increase in infertility over the last forty years is just the woman's biological clock, which correlates with her declining store of eggs. Even by the time you are just in your midtwenties, there is a 10 percent chance



The decreasing follicle pool and age related decline in female fertility

you will have become infertile, even though five years earlier you would have had no problem at all getting pregnant. The biology of fertility in humans has not changed in the last forty thousand years. What has changed in the last few centuries is our life span and the age at which we first try to conceive.

Men and women are now able to obtain fuller educations, develop themselves in their careers, and contribute dramatically to the intellectual and economic prosperity of the modern world. This would not occur so readily if we were saddled with children as teenagers or in our early twenties. But this change in society is also the reason for the epidemic rise in infertility.

Nonetheless, with dramatic new technology, virtually any couple now (with a few exceptions) can have a child. But you must understand the myriad complexities of your reproductive system in order to get the right help instead of the wrong help, and to deal with the emotional and financial costs the process might cause if you are not savvy. Most important, you need to understand your biological clock and how to manage it. Our intention is (1) to teach you how to manage your biological clock so that you won't need technology to get pregnant, and (2) to explain how you can use technology safely to get pregnant if that is currently your only option.

The Importance of Understanding Your Biological Clock

In a *New York Times Magazine* article in December of 1989, a 41 year-old writer named Paulette conveyed her sense of loss at trying to have a child in her late thirties, not succeeding, and now finding herself a successful 41 year-old writer who, sadly, “will probably never have a baby.” It wasn’t until she reached age 38 that she first decided to stop using birth control pills and try to get pregnant. She had hoped she could get pregnant naturally after learning more about the timing of her cycle and the quality of her cervical mucus. She did not understand her biological clock. It wasn’t until she reached forty that she saw a local doctor who began fertility testing, including mucus testing, hormone testing, and two endometrial biopsies. None of this plodding got her any closer to getting pregnant. She then went through the many simple, old methods of treatment that sometimes work and might possibly make sense in a young woman trying to have a baby. But not for a 38 year old woman.

In fact, what Paulette went through is the conventional approach of trying to make a diagnosis and then using simple, old-fashioned methods to supposedly treat that diagnosis. The problem with this conventional view was that (1) many of these “diagnoses” are just normal variants that have nothing to do with why the woman is not getting pregnant, and (2) if a woman’s time has almost run out, fiddling around for too long with the old-fashioned approaches may waste the few precious years she has left.

As physicians, we simply have to admit that we often really don’t know why a couple isn’t getting pregnant except that the wife is nearing the edge of her biological clock. Of course, a low sperm count in the husband, tubal obstruction, lesions in the uterine lining, and poor ovulation can all contribute to infertility, and all of those problems can be solved. But the biggest problem for a 38 year-old woman is simply her age.

There is now simple testing that could have told her (when she was younger) just when her particular biological clock would expire and let her decide (while there was still time left) when to stop procrastinating. Some women lose their fertility in their twenties and others not until their forties. We can now explain to you how you can gauge your own biological clock at an earlier age, and indeed freeze that clock while you are still young. If you are too late for that, I will explain how you can still get pregnant if you get the proper treatment.

Years ago I celebrated New Year’s with our son’s high school biology teacher and his 39 year old wife, Pam, with their six-week old baby, who never would have existed without IVF. Pam told me to make sure to tell everyone how awful it is to go through the conventional series of “diagnostic” tests and ineffective treatments for years and years with one contradictory diagnosis after another. She had gone through seven years of this at the previous clinic she had used. She had been through literally hundreds of pills, shots, doctors’ visits, and tests, not to mention worthless and potentially damaging surgery.

When Pam and her husband came to us, I told her that I really didn’t know why she wasn’t getting pregnant. But she was in her late thirties and that was enough reason for them to be infertile; I recommended *no more tests*. She was thrilled when I suggested we proceed right to what was then the “new” technology of in-vitro fertilization (IVF). She was fed up with trying to figure out why she was infertile and getting nowhere. After seven years of wasted efforts, Pam finally conceived with the IVF procedure, and she and her husband had a healthy baby, who is now a healthy teenager. She has no idea why she was infertile and neither do I nor her original doctors. Fortunately, for Pam, it was not already too late.



A non-invasive ultrasound technique called “Antral Follicle Count”, as well as an isoteric blood test called “AMH”, can tell us just where you are on your age related biological clock, and when you should start to worry.

The Number of Antral Follicles and Approximate Reproductive Age

Antral Follicle Count (per ovary)	Median Years to Last Child	Median Years to Menopause
20	14.8	24.0
15	9.3	18.4
10	4.2	12.9
5	—	7.3

Achieving Pregnancy Without the New Technology

Do not misinterpret the focus of what I am saying. It is better to avoid the need for infertility treatment, and we want to give you tools for doing just that.

In one couple who had been infertile for many years, the wife ovulated perfectly on day fourteen of every twenty-eight-day cycle like clockwork. In fact, because her ovulatory cycle was so perfect and so regular, she always ovulated on Tuesday or Wednesday. Her husband, who was a traveling workaholic businessman, was only in town on the weekends. So for years they never got pregnant simply because they were having sex only on the weekends. A simple rescheduling of their intercourse resulted in her getting pregnant rather quickly without any high technology. But simple approaches like this only work if you have not yet reached the descending point in your biological clock.

One lady begged me to review her case even though she and her husband could not travel to our clinic in St. Louis. At that time, we were estimating the quality and time of ovulation from basal body temperature (BBT) charts (rather than ultrasound and simple leutinizing hormone [LH] urine testing). Her BBT charts clearly showed poor ovulation, but her doctor had insisted on not treating her because he felt the husband's low sperm count was the problem. In fact, the local urologist had put the husband on the male hormone testosterone, which would make his muscles bigger but would certainly lower rather than raise his sperm count. After her husband discontinued these steroids and she went on Clomid, she promptly became pregnant. I still receive a Christmas card every year from her despite the fact that we never met. There are countless similar stories in which very simple approaches work, but only if you learn about your own particular fertility clock.

However, the problem of infertility in our modern society is getting worse, and the simpler methods do not work well for many would-be parents. These simpler methods should be discontinued after they have been shown to be ineffective for a couple, and the newer technology should be used before too much time, energy, emotion, and money have been wasted on old-fashioned approaches. However, it is my hope that by knowing where you are on your own biological clock, you will be able to have your family naturally, without necessarily having to resort to high technology.

Misleading Diagnoses of the Cause of Your Infertility

The Simple, Unexplainable Effect of Age

In 1982, the French reported in the *New England Journal of Medicine* a large study of 2,193 “normal” women (whose husbands had no sperm whatsoever in their ejaculate) undergoing artificial insemination with fertile donor sperm. These were “normal” women, and they were being inseminated with completely normal sperm. There is no logical reason why they shouldn’t all have gotten pregnant. Yet it was very clear that the “normal” women under thirty had a high pregnancy rate, and the “normal” women over thirty showed decreasing pregnancy rates as they got older. A study from Ontario published seven years later in the *Journal of Fertility and Sterility* looked at more than two thousand couples with “unexplained” infertility. The chances of getting pregnant with simple, conventional methods of treatment were directly related to how young the woman was. No other factor studied was significant except for the age of the woman.

The decline in fertility as women get older is related to the aging of their eggs. You are born with all the eggs you will ever have, about two hundred thousand to four hundred thousand by the time of puberty, and every month about a thousand of them die. Thus as you get older, your eggs will decrease in both number and quality. Yet some women remain fertile into their forties, and others lose their fertility in their twenties. The table on the previous page shows you how to determine at what particular age you will lose your fertility, so that you can plan to avoid that dilemma.

A woman I first saw in 1990 is typical of many I see every week. Tammy got pregnant very easily as a young teenager after her first sexual experience and gave the child up for adoption. Five years later, again she got pregnant quite easily and kept this baby as a single mother. She continued to have completely regular, normal periods for six more years, got married, and then used condoms for birth control for three years until she and her husband were certain that their marriage was a stable one. By the time they finally decided to try to have children, she was thirty-three years old, and her menstrual cycles had become irregular, varying from twenty-five to thirty-two days. All of her tests were normal, but now she couldn’t get pregnant.

What happened to her subsequently is a terrifying story that exemplifies the pitfalls I am hoping to help you avoid. She saw a doctor who performed major surgery to remove “endometriosis” and release the adhesions. But he also cauterized a great deal of her ovarian surface. This only served to reduce her remaining supply of eggs even further, making it even harder for her to get pregnant.

As long as insurance companies require a “pathological diagnosis” in order to pay for treatment, and as long as major surgery results in no difficulty in getting insurance payment (whereas in vitro fertilization usually is not covered), women like Tammy run a good chance of having inappropriate surgery that could very well reduce rather than improve her egg supply.

The Endometriosis Myth

The most commonly overused “diagnosis” for infertility is endometriosis. Endometriosis is a condition whereby some of the lining of the uterus has leaked back into the abdominal cavity and has implanted in tiny nodules either in the abdominal wall, on the outside of the fallopian tube, or possibly in the ovary.

When doctors perform a laparoscopy as part of an infertility investigation to see if the woman has a normal uterus, tubes, and ovaries, most of the time the examination is normal. Nonetheless the diagnosis of “endometriosis” is frequently inserted in the operative note simply because the insurance company is much happier to pay for laparoscopy when they see a “pathological” diagnosis, and doctors feel more comfortable that way. The euphemism that avoids outright deception is to call it “minimal lesion” endometriosis. Doctors are often so eager to find a diagnosis to determine the “cause” of infertility (not to mention the desire for patients to get insurance reimbursement) that many couples walk out of their long series of expensive infertility tests thinking incorrectly that they now know why they haven’t gotten pregnant. This might be harmless if it weren’t for the fact that it may lead to unnecessary or improper treatment, and could delay further the proper treatment. With infertility in older women, any delay caused by trying inappropriate though harmless treatments can be devastating.

The Male Factor and Varicocele Myth

There are many other popular “diagnoses” that may lead to inappropriate treatment. The doctor may obtain a sperm count on the husband and find that it is “low.” The husband may then be put on all kinds of totally ineffective drug treatments such as Clomid, Pergonal, human chorionic gonadotropin, or testosterone. But worst of all, he may be given that all too common diagnosis of “varicocele.” Very few men escape seeing a urologist for infertility without suffering through this diagnosis.

A varicocele is a varicose vein of the testicle (usually on the left side) that is present in 15 percent of all males on the planet. It is just a common, normal anatomic variant, but it has been argued that 40 percent of infertile men have varicoceles, and it is implied, therefore, that varicocele is the cause of the infertility. But most of these so-called minimal lesion varicoceles are not really varicoceles at all, and are no different from what is found in a normal, fertile male population.

The varicocele has little to do with male infertility. A careful study from Australia of 651 infertile men with varicocele was published in the *British Medical Journal* in 1985 demonstrating absolutely no difference in pregnancy rate among couples in which the husband had the varicocele operated on versus those who did not have the varicocele operated on. Similar studies have been repeated in Belgium, Sweden, and Germany. Furthermore, 15 percent of men who request a vasectomy (because they already have had all the children they want) are found on physical examination to have an obvious varicocele, and in my experience, that is the same as the incidence of varicocele in infertile males.

What happens to infertile couples once the diagnosis of varicocele is made in the man? Typically, the men get operated on, sometimes on one side, sometimes on both sides, and then they wait six months to see if the sperm count improves. Since sperm counts, like the weather, vary from month to month around a mean average value, it only makes sense that if you get one or two sperm counts before this unnecessary surgery, and one or two sperm counts after this unnecessary surgery, at least half of the men will appear to have some improvement. But this is just an illusion created by the variability of sperm counts, and the failure to make equal note of those whose sperm counts seem to have actually gone down after varicocelectomy. Because of the intrinsic variability of sperm counts, half of the patients will appear to have reduced counts after treatment, and half will appear to have improved counts.

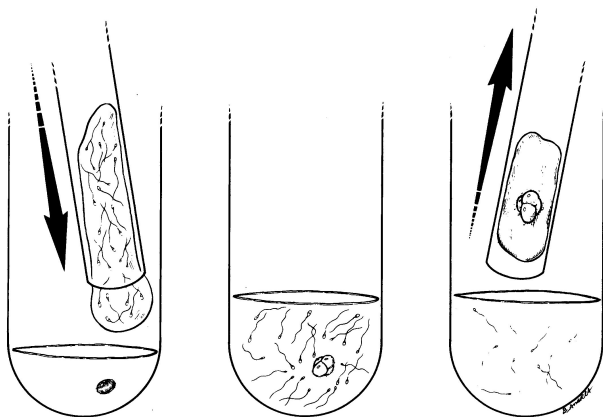
Furthermore, many couples can conceive naturally in spite of the husband’s very low sperm count. Manuel and Flora were a couple from South America who were married twenty-two years earlier, when she was only seventeen years old. Four years later she became pregnant and had a wonderful little baby boy, but she was never able to become pregnant again. A sperm count performed in their local city was zero. It wasn’t until eighteen years later, when Flora was thirty-nine years old and Manuel was forty-five, that they came to see me in St. Louis, and the enigma was solved. Manuel had zero sperm on the first semen analysis; however, after performing many semen analysis over a period of time, we finally found a few rare motile sperm on just one of those occasions. Testicle biopsy revealed that almost the entire testicle was non-functioning, except for a tiny island of normal sperm-producing tubules. Obviously, when Flora was very young, at age twenty-one, after four years of regular intercourse, a single sperm from Manuel was finally

able to fertilize one of her eggs, resulting in a baby boy. As she became older, however, Manuel's extremely severe infertility, compounded by the naturally decreasing quality of her eggs, made this couple infertile.

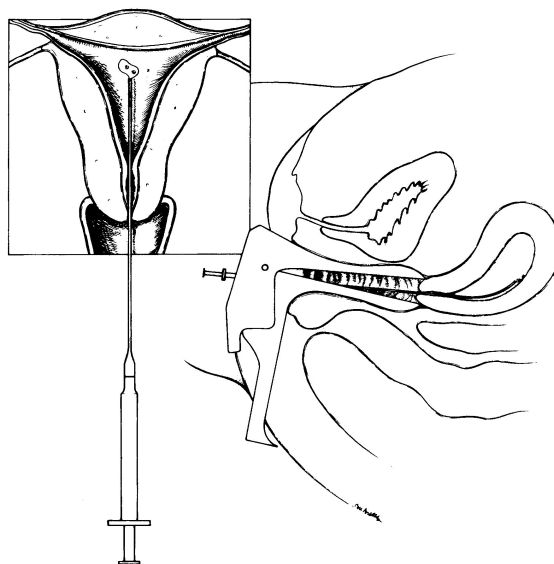
IVF and ICSI Bypass Everything That Can Go Wrong No Matter What the So-called Diagnosis Is

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) solve the quandary presented by our frequent ignorance of why couples are not getting pregnant. If the cause of infertility really is low sperm count, the sperm can be microinjected directly into the egg. If the cause of the problem is poor ovulation, the hormonal stimulation and aspiration of eggs from the ovaries removes the need for ovulation. If the issue is poor cervical mucus blocking the entrance of sperm into the womb, these new technologies can bypass that problem as well. If the problem is endometriosis (a highly questionable but very popular diagnosis), again IVF overcomes the unfavorable environment for fertilization that endometriosis supposedly creates in the woman's pelvis. If the problem is poor pickup of the egg by the fallopian tube from the surface of the ovary (a tricky feat in which the fallopian tube has to "reach over" and grab the egg by twisting back on itself), IVF, as well as gamete intrafallopian transfer (GIFT), once again bypasses this event.

Almost anything that can go wrong during the arduous process that sperm and eggs normally have to go through can be bypassed with IVF and ICSI. If the couple is committed to several treatment cycles, and the woman is not too far along on her biological clock, most will get pregnant no matter what the diagnosis and no matter how severe the problem.

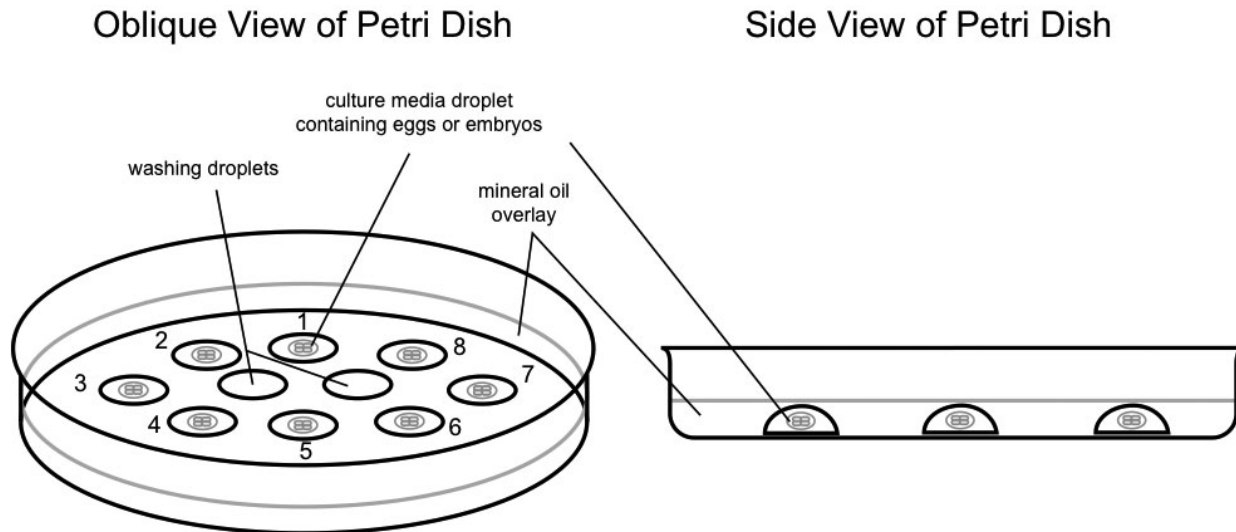


With IVF, your eggs are fertilized with your husband's sperm in a petri dish or a test tube, and the embryos are replaced back into your uterus two to five days later.



Improvements in the IVF Laboratory

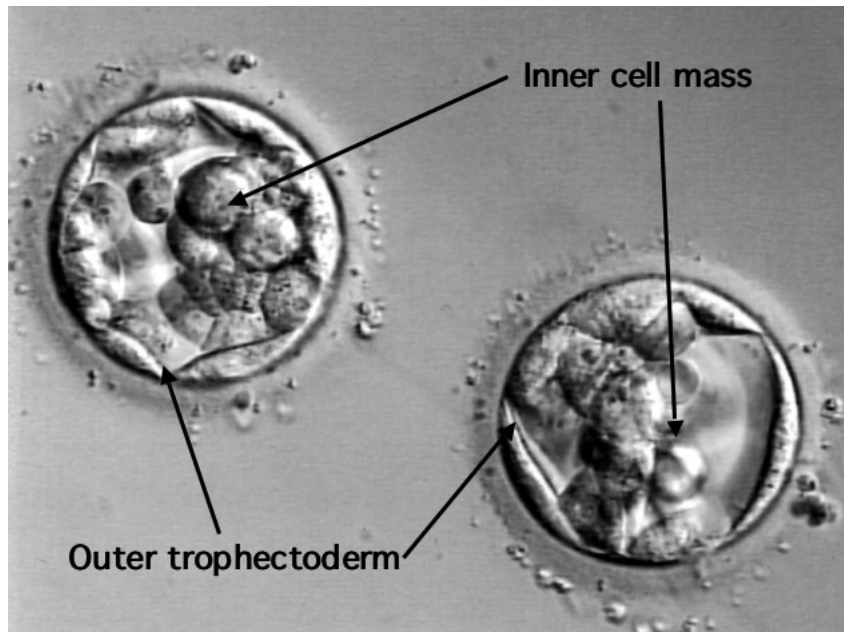
IVF is no longer a tenuous, last ditch effort to be resorted to after all else has failed. We can now create a completely safe environment in the IVF laboratory for the eggs and embryos, removing any possible downside to IVF over attempts at conventional treatment with its low success rates.



Petri dish set-up for IVF culture in microdroplets under perfect conditions that would ideally be found in your own fallopian tube and uterus.

For example, a major improvement in embryo culture in our lab was realizing that the oxygen content in the air we breathe is much too high for eggs and embryos. In fact, most cells in the body are exposed to a much lower concentration than the air we breathe. Too much oxygen delivered to these cells can, in a sense, overheat the cell. So it is much better to culture the embryos in only 5% oxygen (not the 20% that is in air). This is difficult to do. Large amounts of pure nitrogen gas have to be blown constantly through the incubator at a carefully controlled rate to lower the oxygen concentration in the incubator. But it is worth that extra effort to get higher pregnancy rates.

Classically, most IVF labs have cultured embryos at a pH (that means acidity) of 7.4 (the normal acid-base of your blood), and at an oxygen concentration of 20% (the same as in the air we breathe). However, these are not the acid or oxygen concentrations that are most favorable for embryo growth and development. In fact, the acid concentration inside the embryo is normally much greater than that, and the oxygen concentration is much lower. Conventional IVF culturing conditions, therefore,



Embryos (blastocysts) cultured in vitro before transferring back to patient.

are too alkaline and too oxygen-rich. In fact, oxygen concentration in the fallopian tube is only about 8% (not 20% as in air), and in the uterus, it is as low as 2%. So we now know exactly what are the correct conditions in the IVF lab to perfectly mimic what would be present in the fallopian tubes and uterus of a fertile woman. We can safely culture your embryos to day 5 or 6 without fear of harm.

This type of optimal culturing of embryos requires a lot of extra attention. To reduce the oxygen concentration in the incubator from 20% to 5% requires blowing through a huge amount of nitrogen (95%), and to keep the pH acid at 7.2 (but not too acid below 7.2), requires careful monitoring of the acidity of the media. This represent a lot of extra work, but it is well worth the effort.

Change in Thinking Since the Early 1980s

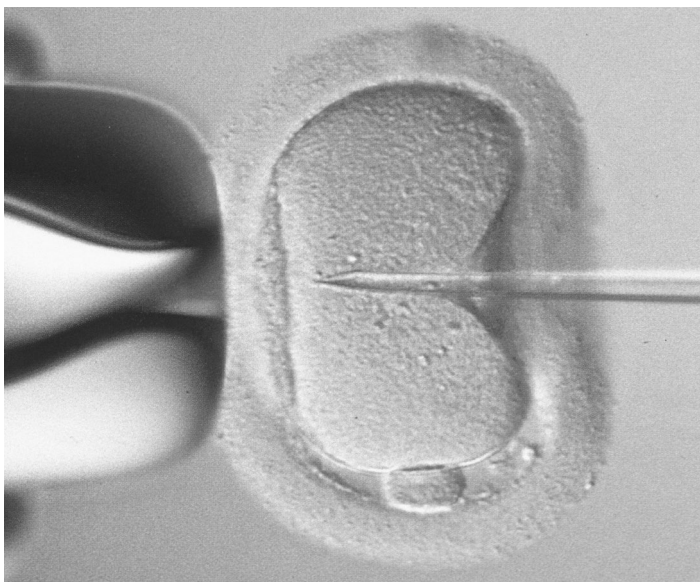
Much has changed since I wrote the first edition of *How to Get Pregnant* more than twenty-five years ago. We know now that it is a complete waste of time and money for the man to have surgery for varicocele or for the woman to endure a year of Lupron therapy to shrink her endometriosis. We know that treatment of the husband with Clomid or Pergonal and various other drugs will do nothing to increase his sperm count. We understand now more fully just how people do and don't get pregnant, and what is the best strategy for overcoming infertility.

Paulette does not have to waste her few valuable remaining years of potential fertility testing her mucus and wondering whether she's having sex at the right time. Tammy, who got pregnant easily as a teenager and now in her late thirties is happily married and wants a child, does not have to go through unnecessary surgery for endometriosis. We can avoid the emotional drain of literally years of fruitless testing and sling-shot-style therapy.

Very often, by the time a couple has gone through years and years of wasted, inappropriate infertility treatments, they're worn out, their funds are absolutely exhausted, and they can't even consider IVF, which would have been so much more likely to have helped them. Cynthia is a 32 year-old woman whose husband underwent two varicocelectomies and who herself was treated for infertility for ten years with Clomid, artificial insemination, several laparoscopies, and several operations to "lyse her adhesions," despite the fact that the cause of her infertility all these years had been completely idiopathic (that means we just don't know the cause). Although she would have a 60 percent chance for pregnancy with each treatment attempt with IVF, she is just too tired, frustrated, and emotionally depressed to go any further. Couples need the understanding and confidence to know whether they can safely temporize, or whether technology like IVF is more appropriate for them to utilize now, before they have exhausted their emotions, time, and resources.

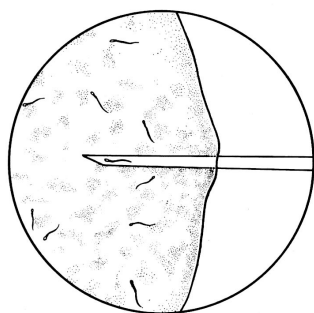
Progress in Male Infertility

In the early 1990s, the major stumbling block to treatment of infertile couples was the severely infertile male. In about 50 percent of infertile couples, there is a somewhat low sperm count, and in 10 percent the count is extremely low. In such cases, even IVF had routinely failed in the past. There was simply no effective treatment available for the infertile male. That all changed dramatically after 1993, thanks to the pioneering

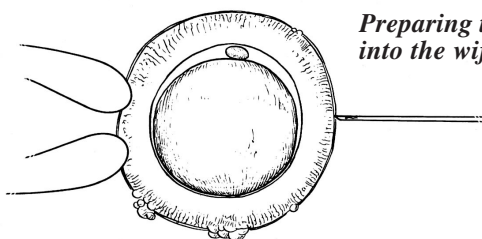


ICSI - The long sought solution to male infertility.

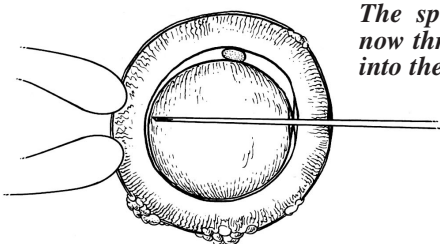
work on sperm retrieval and ICSI performed by Dr. Andre Van Steirteghem, Dr. Paul Devroey, and myself, shuttling back and forth between Brussels, Belgium, and St. Luke's Hospital in St. Louis. The work of this team has revolutionized the treatment of male infertility throughout the world and represents the single greatest advance in fertility treatment since the first IVF baby in 1978. Now it is possible to search for just a few sperm in the male ejaculate, and if there is no sperm in the ejaculate, often a few can be found in the testicle. We can then inject a single sperm into each of the female's eggs (ICSI). With this delicate technique, we achieve pregnancy rates for virtually sterile men that are no different from that of men with normal sperm counts. There are now very few cases of severe male infertility that cannot be successfully treated.



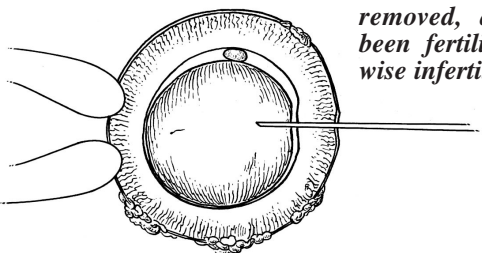
Picking up a weak infertile sperm with the micropipette.



Preparing to inject the sperm into the wife's egg.

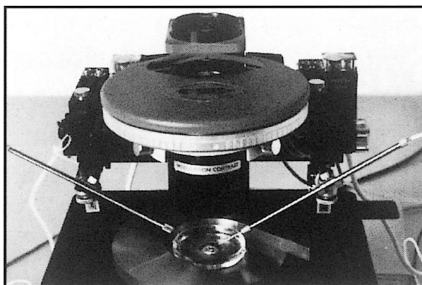


The sperm is being injected now through the micropipette into the egg.

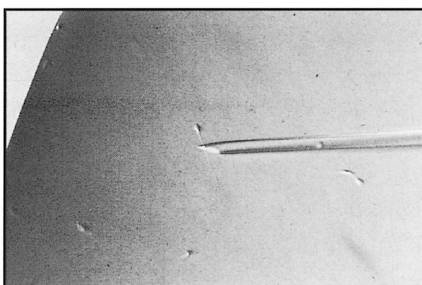


The micropipette is now removed, and the egg has been fertilized by the otherwise infertile sperm.

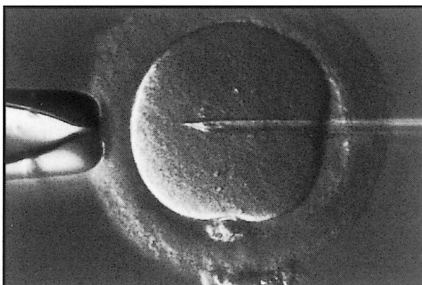
This is how the technique works: With ultramicromanipulative instruments attached to special microscopes, the woman's otherwise invisible egg can actually be held secure with a microscope "holding" pipette, and an even tinier micropipette can be used to inject a sperm through the hard outer shell of the egg so that this one sperm is literally forced to fertilize the egg. Can you imagine the delicacy of this type of manipulation? The sperm head is no more than 4 to 6 microns in diameter (that's approximately 1/4,000 of an inch), and an egg is approximately 130 microns in diameter (1/200 of an inch). It took years of painstaking research in Brussels and in St. Louis to perfect it.



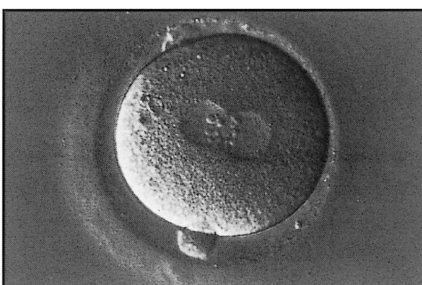
Micro-injection apparatus for ICSI



Picking up a single sperm from what was thought to be a sterile man.



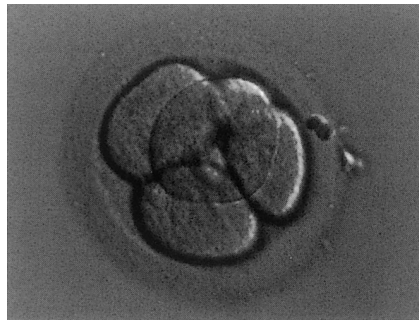
Injecting sperm into the wife's matured egg.



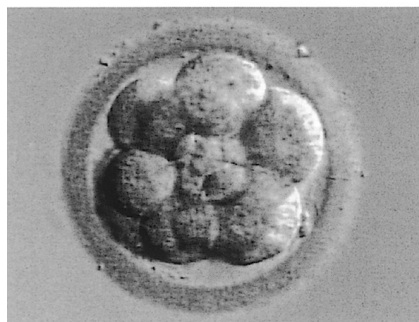
The next day, a normally fertilized egg which will become, in nine months, a happy, normal baby.

One of the biggest fears of those of us who were working on microinjection of sperm was that if the sperm couldn't get into the egg because of poor numbers, poor motility, abnormal shape, or poor maturation, then perhaps they weren't meant to get in. Perhaps it was naive to think that if such a poor sperm were injected into the egg, the chromosomes would be normal, and that a healthy baby could be obtained from such a procedure. Those fears proved to be completely wrong.

Even poor sperm have normal DNA sufficient for making a normal baby, and the only thing wrong with poor sperm (with an occasional exception) is simply that they cannot get into the egg. The incredible complexity of sperm physiology appears to serve no purpose other than to mechanically get the package of DNA that the sperm contains into the egg. Once that package of DNA is inserted into the egg, all the processes of fertilization and embryo formation leading to a baby can take care of themselves.



Beautiful 4 cell embryo two days after ICSI



Beautiful 8 cell embryo three days after ICSI

Even Men Who Don't Make Sperm Can Have Children

In 1985, a young couple, both 22 years of age, from New York, came to see me in St. Louis because he had azoospermia (no sperm in the ejaculate) and needed a testicle biopsy to see whether he had an obstruction that could be corrected with microsurgery. In those days, we always prayed that the biopsy would show normal sperm production, because our success rate with microsurgery to correct obstruction in male infertility was over 95 percent. But we could do nothing at that time for couples if the men weren't making sperm at all.

His biopsy revealed what we call "maturation arrest." This means that the early precursors for sperm production were present in the testicle, but there was no continuation of sperm production beyond these early stages. This man was by all definitions 100 percent sterile, and it was my unfortunate job to explain to this otherwise wide-eyed, cheerful young couple (who were looking forward so much to having a family) that they couldn't have children.

But this couple never gave up hope. Ten years later, they came back after they had heard about ICSI. By now we were having exciting success in using ICSI for men with extremely poor sperm counts, and in men with irreparable obstruction requiring retrieval of testicular sperm from a blocked but otherwise normally functioning testicle. But could it possibly work for men who were apparently not making any sperm at all? This determined couple helped us embark upon a new theory with startling consequences.

When I had looked back to my research from the early 1980s on quantitative testicle biopsy, I discovered a phenomenon that had previously eluded my attention. Even in men with zero sperm in the ejaculate, and apparently no sperm production, if one looked carefully throughout the testicular specimens, an occasional sperm precursor could be found that had the same number of chromosomes and the same basic appearance as a normal sperm. Based on this finding, this couple was our first case of a man who appeared to be making no sperm but in whom we were able to find just a few sperm "hiding" in his testicles. We injected these hidden sperm into his wife's eggs, and normal fertilization occurred. They had a happy baby girl who is now a healthy young woman who is having her own children now.

Another patient treated around the same time had, as a child, undescended testicles that were brought down surgically into the scrotum very late in his childhood. As is often the case with such men, he was clearly producing no sperm. When we operated on his testes to see if any sperm could be found (under the same theory, that any man with a testicle may have some sperm somewhere), indeed we were again able to find just a few sperm. We injected his wife's eggs with those testicular sperm and again obtained normal fertilization and pregnancy. This young man had been known to be sterile ever since he was a teenager. Yet during extensive exploration of his testicles, we found sufficient sperm to perform ICSI, and he could now have a normal family.

The question that might occur to every such couple is, will my baby be normal? The fear might arise that abnormal sperm in men with low sperm counts will cause a higher risk of producing abnormal babies. We have now studied this in over seven thousand such children born through the ICSI procedure as we performed it, and the news is great.

The children are normal, and there is no greater incidence of chromosomal or congenital abnormalities than in the children of normally fertile couples conceiving without any kind of reproductive treatment. There may be occasional exceptions, but they are related to the age of the wife, not the IVF or ICSI treatment. The offspring are more likely to be infertile (like their parents) but are otherwise normal, healthy children.

Poor sperm production represents up to half of the infertility cases in the world, and in the past it prompted couples to undergo billions of dollars's worth of ineffective, unscientific, and frankly stupid surgical and hormonal treatment. ICSI now solves that problem in most couples, but a genetic cure would still be preferable. Our research, in conjunction with the human genome project, the Howard Hughes Institute at MIT, the University of Amsterdam, and the Kato Clinic in Tokyo, thus far indicates that sperm production in men is controlled genetically by many different genes on the Y chromosome and elsewhere in the genome. We have now completely sequenced the Y chromosome and have located the areas on the Y chromosome where sperm production in these men is regulated, and we have identified many of the genes that

control spermatogenesis. This discovery means that in the future we may have a genetic cure for male infertility, i.e., replacing the missing gene (or genes) so that these men will be able to resume normal spermatogenesis, thereby in the future eliminating the need for ICSI.

Egg Donation

With the advent of ICSI, there is now only an occasional need for donor sperm, but there is still a strong need for donor eggs. It is my hope that women who read this will learn how to plot their own biological clock, and thereby will be able to avoid having to resort to egg donation by planning their life more knowledgeably. However, an older woman who has already run out of her own supply of fertile eggs can still get pregnant (using her husband's sperm, of course) with embryos derived from the eggs of a younger woman. Egg donation is much more readily accepted emotionally by couples than sperm donation, because the woman still gets to carry and deliver the baby. Because the woman carries the baby, emotional bonding is rarely adversely affected by its having been derived from a donor egg. Follow-up on the children who have resulted from egg donation, and on their parents, is wonderful. These are really happy families.

The question, whose baby is it? creeps into every aspect of egg donation, gestational surrogacy, and adoption controversies. Adopting eggs, i.e., using donated eggs, is much more secure for the infertile couple than struggling and traveling around the world to try to find a baby to adopt (a baby that could possibly be taken away in the future) at enormous cost. With donor eggs, which are legally recognized in every state, there is no risk (as with adoption) that the egg donor could ever interfere or lay claim to the child or to the embryos.

Even a woman without a uterus can have a child. It is possible for her mother, a very close friend, or a sister, to carry her biological child for her and then give that child back to her after the delivery. This is called gestational surrogacy. It is possible to arrange legal adoption from the surrogate even before the delivery. These procedures are medically and legally extremely safe and reliable.

In the mid-1980s, I saw a lovely woman who had undergone surgery by a well-meaning gynecologist for severe pelvic adhesions (scarring) caused by previous infections. The surgeon who explored her decided to try to release the adhesions on her fallopian tubes and ovaries. Unfortunately, the doctor performing the surgery got into some problems with bleeding that were beyond his ability to handle, and the only way he could solve the dilemma safely was by removing the woman's uterus (she was only twenty-five years of age). The doctor who removed her uterus did not feel the sense of tragedy he should have, because in those days, before IVF was so routine, with those diseased tubes she could not have had children anyway. He was not aware that this woman in the future could have gotten pregnant easily with IVF without the need for the hopeless operation to open her completely cemented-down tubes and ovaries. If this woman had only known that all she needed in order to get pregnant with IVF was a uterus, she might have avoided this foolhardy operation.

Miraculously, four years later, I called this woman back to tell her what, at the time, seemed absolutely incredible: that she could have a baby after all, even without her uterus. We could use her eggs and her husband's sperm and put the fertilized embryo into her own mother's uterus. Then, nine months later, her mother would give her newly delivered baby back to her. We now have helped so many women who have no uterus, or for whom pregnancy would be dangerous, have their babies this way. In many cases, their mother carried their baby, and in other cases, a sister, an aunt, or a close friend. Thus, a mother can give birth to her own grandchildren, and a sister can give birth to her own nieces and nephews. If you have no friend or family member who can carry your baby, we can, nonetheless, find you altruistic gestational surrogates who can do this for you.

You Can Save Your Eggs for Later: Egg Freezing & Banking

There are many couples in their twenties and early thirties who are married and committed to each other, but just don't want children yet. But they are afraid to put off having children into their late thirties or early forties for two reasons: (1) They are afraid that with their biological clock ticking, they will not be able to have children if they wait another ten years, and (2) they are afraid that if they do get pregnant later they will be in an age category where this poses a high risk of abnormal embryos and chromosomal defects in their children. These couples can undergo IVF while they are still young and have their embryos successfully frozen and stored. At a later date, the embryos can be thawed, and the wife can get pregnant even when she is older, with no increased risk of Down syndrome.

Although human embryos can be successfully frozen and thawed, and can result in happy, healthy babies, eggs, until very recently, could not be successfully frozen and thawed. The success rate in freezing eggs had always been extremely low, but this has all changed now. For young female cancer patients, whose ovaries would surely be destroyed by heavy chemotherapy and radiation, we can now remove an ovary, freeze it, and save it to be grafted back to the woman after she has been cured of the cancer. We can do the same with her individual eggs, and save them for subsequent IVF.

Both egg and ovary freezing are now also available for women who just feel a need to delay childbearing until their late thirties and forties, by which time their egg supply will very likely have been depleted. These are wonderful options for the woman who wants her own genetic child but does not anticipate starting a family for many years.

For decades we have been able to use cryogenic technology to freeze and store embryos derived from IVF in order that women not have to risk having a dangerous multiple pregnancy. The embryos can be thawed safely at a later date, and the pregnancy rate with these frozen embryos is still very high. That is nothing new. We have been able to do this since 1983, and long-term follow-up shows no deleterious effect on subsequent offspring. In fact, for many years young couples who are happily married, but want to put off childbearing until later, could readily have their embryos (derived from the husband's sperm and the wife's eggs) frozen and saved for later so that they do not sacrifice their chances for later parenthood.

However, freezing embryos for a future date does not solve the problem for unmarried women who want to have children in the future but have not yet met the right man. For these women, freezing their eggs, or even an entire ovary, would be the ideal solution. Until very recently, this holy grail of IVF was unattainable. The reason is that in order for fertilizable eggs to be retrieved, they must be in a mature state of development, with a complex alignment of chromosomes, and this makes them susceptible to even the slightest ice-crystal damage. However, with a new technique of vitrification, recently refined in Japan, ice-crystal formation is avoided completely, and early results indicate that very high pregnancy rates can now be achieved with frozen eggs. Thus, a woman who knows that she is nearing a time when she will lose her fertility because of her biologic clock can now freeze her eggs, or a piece of one ovary, and have her babies later.

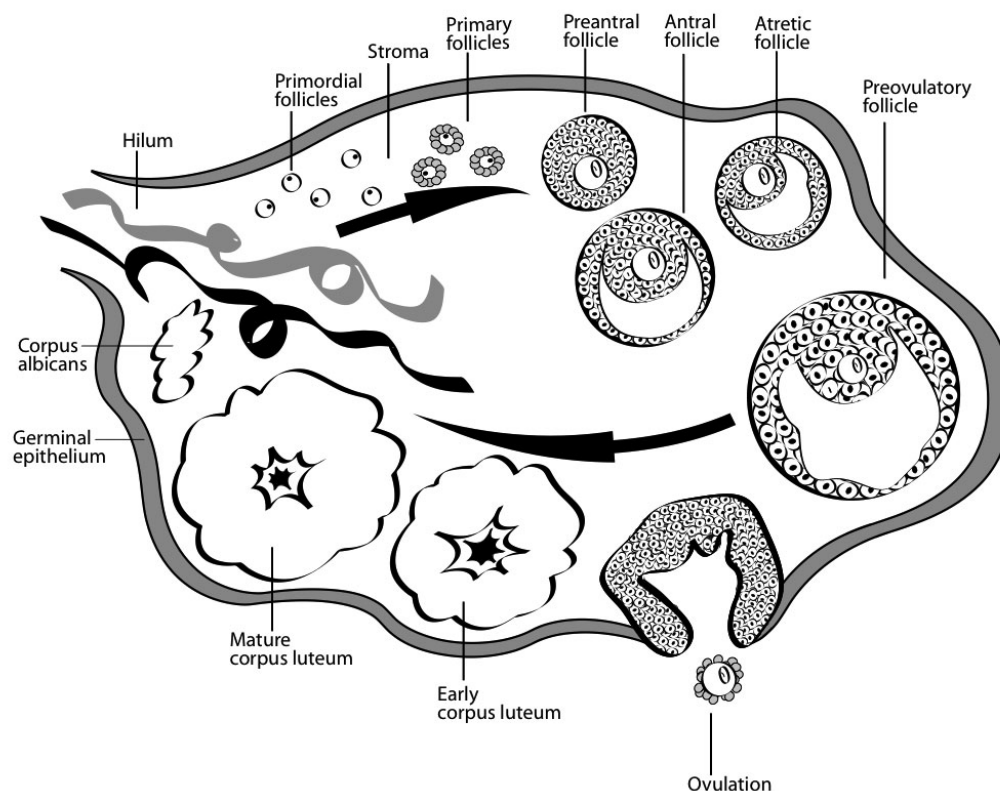
This new technique of freezing, called "vitrification," avoids the damage caused by ice forming inside the cell. With vitrification, you are not trying to pull every last molecule of water out, because it is impossible to do this 100%. In fact, 70% of the cell is water, and at best you can reduce that to 30%. So with the conventional controlled rate slow-freezing technique, there is always going to be some intra-cellular ice crystal formation, causing some damage to embryos, and severely damaging most eggs. Vitrification, on the other hand, uses a super high concentration of antifreeze (DMSO and ethylene glycol), and drops the temperature so rapidly that the water inside the cell never becomes ice. It just instantaneously super-cools into a solid with no ice crystal formation at all.

We can now freeze and thaw, and even refreeze and rethaw, with impunity, using this new protocol from Dr. Masashige Kuwayama from the Kato Clinic in Tokyo. With conventional "slow freezing," the temperature of the embryo goes down at precisely 0.3° C per minute. With vitrification (using four times the concentration of antifreeze, or cryoprotectant), the temperature is dropped at 23,000° C per minute, i.e., 70,000 times faster. At that speed of cooling, and at that concentration of antifreeze, ice crystals simply cannot form.

Of course, it is not quite as simple as it might sound. Such high concentrations of antifreeze, in a few minutes, could be toxic to cells. Therefore, the embryos (or eggs) must first be placed in lower concentrations of antifreeze (and sucrose to draw some water out), and then left in high concentrations only for less than a minute before instantaneous freezing. Then when the time comes to thaw the embryo, it must be instantaneously warmed, immediately taken out of the high concentration of antifreeze, and then placed into a solution with lower concentration, in order to avoid antifreeze toxicity. This requires more skill than conventional freezing, but it is faster, cheaper, and most importantly, avoids almost all freezing damage to either eggs or embryos. Such a reliable method of embryo freezing gives the IVF program much greater ability to avoid dangerous multiple pregnancy, and makes scheduling for procedures like egg donation simpler for the patient. Our frozen embryo pregnancy rates are extremely high with this technique and we can freeze embryos without hurting at all your chance of conception.

Using this vitrification technique for freezing, we can preserve eggs as well as embryos and sperm. This allows us to preserve the fertility of young women for the future in egg banks if they wish to delay childbearing. In St. Louis, we have demonstrated for the first time that an entire ovary can be removed and then grafted back after freezing and thawing so that even a menopausal woman can gain back her youthful fertility many years later. This new capability will be especially important to women undergoing treatment for cancer, because all the eggs that might have been lost to chemotherapy can be preserved by first removing, freezing, and storing her ovary for use later.

If you are considering freezing your unfertilized eggs, or one of your ovaries just because you want to put off childbearing until you are older, the best approach is to first determine just where you are on your biological clock so that you can know when it's time to worry. We can now monitor your biological clock from your early twenties on, so you know when you ought to try to have a baby naturally. If you find out that your biological clock is more advanced than you feel comfortable with, you now have the option of freezing an ovary or eggs and saving them until you are finally ready to have your child.



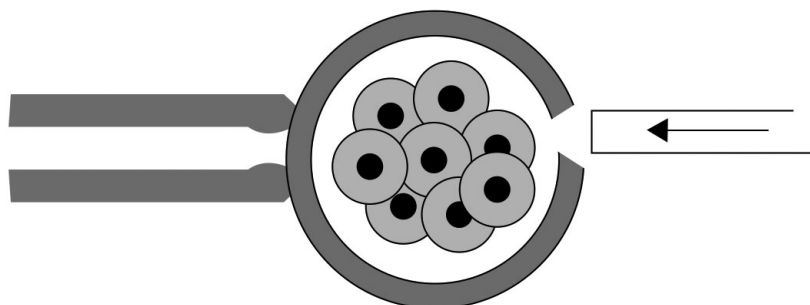
Various stages of follicles in the human ovary. The antral stage follicles can be counted with ultrasound and tell us how many more years you have left to conceive.

How Can I Be Sure My Baby Will Be Normal?

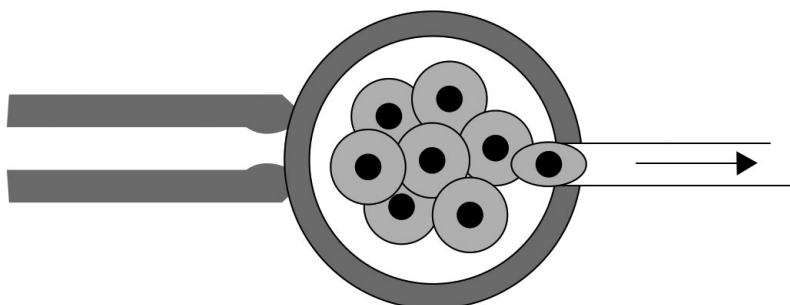
Why is the egg of an aging female less likely to result in a pregnancy and more likely to result in miscarriage or an abnormal baby than that of a younger woman? Why is it that a young egg placed into an older woman results in a high pregnancy rate, while an egg from an older woman results in an extremely low pregnancy rate? How can we now prevent Down syndrome, or other genetic diseases, without the need for amniocentesis and pregnancy terminations? It's all in the DNA.

With the emergence of DNA technology, we can help to ensure with IVF that you have a healthy baby. Otherwise fertile couples who are carriers of genetic diseases such as Tay-Sachs, cystic fibrosis, retinitis pigmentosa, hemophilia, Huntingtons, Marfans, and so on, can now use this technology to be assured that they will have normal children. We can easily screen couples for such genetic risks before they ever decide to have children, and if they have such a risk, preimplantation evaluation of the embryos can save them from having a child who would otherwise die or be handicapped with severe defects.

Embryo Biopsy



The 8-cell embryo is held by a holding pipette and a hole is made in the zona pellucida



A blastomere is aspirated into a biopsy pipette, and then can be genetically tested.

Several years ago, a 27 year-old woman with Marfan's disease (inherited from her father) came to my office with her fiancé. She was told quite correctly by her doctors that a pregnancy could easily be fatal to her because of her condition (which results in a weakened main blood vessel in the chest and leaky heart valves). She was about to be married the following year, and she came in with her mother and father, proposing that her mother be a surrogate and carry her baby via IVF. She was surprised when we told her that not only could her mother be a surrogate and carry her baby, but that as long as we were doing IVF anyway, we could test her embryos (derived from her eggs and her husband's sperm) before placing them into her mother, and transfer only the healthy ones. Thus, not only could we allow this woman to have a child safely via IVF and gestational surrogacy, but we could also assure her of having a baby that would not carry her disease.



Removing a polar body from the egg for genetic testing.

Most patients who had previously delivered a child with Down syndrome or had elected to have such a pregnancy terminated simply would not ever try again to get pregnant and undergo the risk of enduring this agony once more. Even patients with cystic fibrosis, who are managing to survive with modern medical treatment, tell us that they don't want their baby to have cystic fibrosis. Using IVF, we can test their embryos and put back only the healthy ones, thereby avoiding these heart-wrenching problems. For obvious ethical reasons, the unhealthy but viable embryos can be frozen and saved for a future date when gene therapy would be able to correct the genetic defect.

Japanese Minimal Stimulation Protocol (Mini-IVF)

When patients contemplate IVF, their first reaction is often the fear of daily injections of hormones for months, the incredibly high cost of the drugs, the risk of multiple pregnancy and consequent prematurity, side effects related to high levels of estrogen resulting from large numbers of eggs, hyperstimulation syndrome, and the prospect of painful daily progesterone injections for a full ten weeks even after the IVF procedure. Mini-IVF is a very unique approach developed by our colleagues in Japan to circumvent these problems in certain types of patients and reduce the cost while trying to maintain comparable success rates. We do not advocate this for all patients, but for many, it is worth trying.

Mini-IVF is designed to recruit only a few (but high quality) eggs, thus avoiding the risks of hyperstimulation, reducing the cost of drugs from an average of \$4,000 to closer to \$400, reducing the number of injections, and completely avoiding the painful progesterone injections. This approach is not just a simple-minded reduction in hormonal stimulation. It is an ingeniously conceived and completely different approach to IVF, that saves the patient much of the complexity and cost associated with more conventional IVF protocols. Here is how it works.

On Day 3 of the menstrual cycle, you start on a low dose of Clomid (50mgs), but you do not stop the Clomid in five days, as is usually the custom. You just keep taking the Clomid until ultrasound monitoring shows the follicles to be ready for ovulation. A very low "booster" dose of gonadotropin (just 150iu of FSH) is added on days 8, 10, and 12. Clomid not only stimulates your own pituitary to release FSH naturally (by blocking estrogen's suppressing effect), but by continuing the Clomid (a unique new approach), it blocks estrogen's stimulation of LH release, and thereby blunts premature ovulation. Thus, with this simple change in protocol, old-fashioned, inexpensive Clomid is able to stimulate the development of great quality eggs for IVF.

Another advantage of this protocol is that you do not have to go on Lupron first to suppress the pituitary. Staying on Clomid blocks estrogen from stimulating your pituitary to release LH, and then retards premature ovulation without your having to be suppressed. This means that you can be induced to ovulate with just a simple injection or nasal sniff of Lupron. This causes a more natural LH surge and avoids the luteal phase defect caused by HCG that would otherwise require months of progesterone injections.

The next step is to recognize that Clomid has a negative effect on the uterine lining (because it prevents estrogen from stimulating the endometrium). That is one reason why results in the past have been so poor with the use of Clomid for ovarian stimulation. The embryos are less likely to implant in such endometrium. But that problem is solved by using the Japanese protocol for embryo freezing, "vitrification," which I have discussed already. We can now freeze the embryos almost with impunity using this approach, with

only a 1% risk of loss. Then these embryos are transferred the next month in a “natural cycle” with no need for taking any hormones at all. Even if you do not naturally ovulate predictably, you can be given one injection of Lupron in the follicular phase (once your follicle reaches 1.5cm) to induce natural luteinization and still have a natural cycle embryo transfer with no hormones. The Day 3 frozen embryo would then be transferred five days later, and there is no need for taking any hormones at all.

Even for poor prognosis cases of older women with low remaining ovarian reserve, there is an advantage to mini-IVF over high dose stimulation. Such patients normally yield very few eggs anyway even with huge megadoses of gonadotropin. If they have any quality eggs remaining, mini-IVF is just as likely to yield as many eggs (very few, of course) as giving huge megadoses of gonadotropin. Even in the worst-case scenario, if there are no good eggs left at all, at least patients can discover this with less money spent on drugs.

Think of this simple parable: If you are sitting under an apple tree, and wish to eat the most ripe and ready apples, you have a choice. You can chop down the entire tree and look at every apple on the fallen tree to see which ones are ready, or you can simply try to shake the lower branches and eat the one or two that were ready to fall. That is the idea of mini-IVF.

It may not be appropriate for all patients, but for many, it will remove some of the aggravation and complexity associated with IVF, and also reduce the cost.

Where Do We Go for Help?

How do you decide where to go for help with infertility? When the U.S. Congressional Advisory Panel (of which I was one of five physician members) met back in 1988, we amassed figures that showed that of 150 IVF clinics in the United States, half of them had never achieved a pregnancy at all. Furthermore, of those that achieved pregnancies, the success rate varied from extremely low (less than 5 percent) to higher, but still not great, success rates. Evaluating the quality of the clinics was an extremely muddled mess. In 1984, it was reported at the World Congress in Helsinki, Finland, that of more than ten thousand women entering IVF cycles, there were only six hundred live births, for a success rate of only 6 percent. In the United States in 1987, out of a total of twelve thousand women undergoing IVF cycles, there were a little more than one thousand live births, for an overall success rate of about 9 percent. Such a low success rate would hardly be encouraging to a couple.

It was for this reason that the congressional bureaucrats who reported on the discussions of our advisory panel promulgated the claim that the success rate with this new technology was too low and the cost too high to consider it anything other than a last resort and that more resources should be spent on “conventional” therapy for infertility. The bureaucrats also refused to accept the recommendation of the advisory panel that infertility is a medical condition, which would have given strong weight to forcing insurance companies to pay for infertility treatment. The politicians were actually afraid that the female vote would be “offended” by referring to infertility as a medical condition and mandating insurance coverage. If they had not been so erroneously afraid of losing the female vote, IVF today might be affordable to more couples.

Today, your odds are very good that you’ll eventually get pregnant with IVF. But you must choose the right doctor and the right program. The Wyden bill, passed by Congress in the early 1990s, is not of much help. It requires that all IVF clinics report their pregnancy rates to the Centers for Disease Control (CDC). But this information doesn’t help infertile couples decide where to go for help. Some excellent clinics might have a lower pregnancy rate simply because they direct their attention to the most difficult cases with the longest duration of prior infertility, the greatest amount of scarring, the oldest women, the poorest sperm quality, or the lowest ovarian reserve. If the clinic had the kind of expertise that suited these difficult cases, it could easily have a lower pregnancy rate than a clinic that takes on more simple, routine cases.

In fact, since the Wyden bill became enforced by the Society for Assisted Reproductive Technology (SART) and by the CDC (the U.S. government’s main epidemiology arm), many clinics have simply “can-

celebrated" cases with low numbers of eggs because they don't want inclusion of such cases to lower their pregnancy rate. Pregnancy rates can easily be manipulated upward by selecting only those patients who have a large number of eggs, or by not recommending continued IVF to those who do not get pregnant in the first or second cycle. By law, these statistics are not supposed to be used for comparison shopping or marketing because they can be so misleading. But they always are.

We have seen many patients in St. Louis who were refused IVF treatment in their own communities because they appeared to have a dismal prognosis. Yet they were able to get pregnant with us and have children. I remember a 42 year-old woman from Canada who had gone through multiple IVF cycles when she was younger and failed to get pregnant. No IVF program in the United States would accept her because they were concerned about what that would do to their statistics. We warned her that her chance of pregnancy was extremely low, approximately 9 percent, because of her age and her very low ovarian reserve. Her first IVF cycle with us yielded only three eggs, and she failed to get pregnant. However, she insisted on coming back for a second cycle several months later, at which time we retrieved four eggs. This time she became pregnant and delivered a healthy little baby that has grown up to be a very fine young man. Similarly, we took care of a basketball executive and his wife who were both 42 years old and had gone through many failed IVF cycles elsewhere in good programs. When we put her through IVF, we obtained relatively poor-quality embryos with a great deal of fragmentation, and we felt quite sure she would not get pregnant. Nonetheless, she did get pregnant with healthy twins.

The only reason for citing these examples is to emphasize that even couples who are in a poor prognostic category can get pregnant but often they don't get the chance to undergo IVF because accepting such patients would lower the IVF program's statistics and impede their marketing efforts.

Some clinics have become so commercialized that they publish misleading advertisements in local newspapers and magazines, and even in the New York Times and the Wall Street Journal. These advertisements promise high pregnancy rates based on carefully selecting only the youngest, most fertile cases and offer money-back guarantees after overcharging for every cycle to cover the cost of rebates. Indeed, many unnecessary and expensive tests, which can cost as much as ten thousand dollars or more, are sometimes insisted upon before the first IVF cycle is even performed, thus guaranteeing hefty revenue exclusive of any potential rebate. This commercialized Kentucky-fried IVF franchising has become a cause of great distress and confusion for patients trying to figure out what to do. This is just a money making insurance plan, but most couples in a high prognostic category who would qualify do not care for it because it is likely to cost them more than if they just pay separately for each cycle.

Because many clinics make false claims of exaggerated pregnancy rates by selecting younger patients (with a short duration of infertility and large ovarian reserve), published rates are simply an unreliable measure. Therefore, the patients' only resource in deciding where to go for treatment is to understand fully how their reproductive system works, and to learn in a detailed way how IVF and ICSI work. You will need in-depth understanding in order to go through the many steps that are part of every IVF cycle. Furthermore, only with this detailed understanding will you be able to decide where to go for help. You need to learn how to pick the right place by interviewing the doctors and the nurses who are directly involved so you can evaluate their results in a sophisticated manner.

For the energy, the time, and the money that must be put into the effort to conceive, you need to make a good choice for yourself, based on your own understanding.

In summary, you can now monitor your own biological clock from your early twenties on so that you can decide when you ought to try to have a baby naturally and avoid the need for infertility treatment altogether. You may decide you need to freeze your eggs, or a piece of your ovary, just to stop your biological clock. Or, if infertility treatment does become necessary for you, we will explain what you should expect every step of the way. Understanding how this technology works will give you the best chances for a successful pregnancy.

Our Program Philosophy

We work individually with each couple to determine what is the best choice of treatment for their personal situation. No fees are charged for such evaluation. We keep your own personal doctors well informed, and once you are pregnant, you can go back to them for your care.

We are happy to take the most difficult cases, which have lower prognosis, that other programs may refuse to treat or even cancel in mid-cycle (for fear it would lower their reportable pregnancy rate and thereby hurt their "marketing" efforts). We will give you an honest appraisal of your chance for pregnancy in any given treatment cycle and will not artificially "inflate" statistics by "patient selection." We are happy to take patients over 35 with only small numbers of follicles, couples with previous IVF failure, and men with severely low sperm counts or no sperm at all in the ejaculate (requiring microsurgical testicular sperm extraction). Nonetheless, by maintaining the highest possible quality of care and always being on the cutting edge of new technology, we will give even these difficult, lower prognosis patients their best possible chance. We have very high pregnancy rates despite taking on some of the most unfavorable cases. We have been ranked as one of the top 5 infertility centers in the country and the number one center in the entire mid-west and south.

PREGNANCY RATES PER CYCLE **(FRESH AND FROZEN TRANSFERS)**

Procedure Performed

ICSI w/uterine embryo transfer (ICSI/IVF)
Frozen Embryo Transfer (FET)

Pregnancy Rates

51% (361/711)
49% (58/119)

PREGNANCY RATES PER CYCLE **(BY WIFE'S AGE AND OVARIAN RESERVE)**

<u>Age</u>	<u>Normal Ovarian Reserve</u>		<u>Low Ovarian Reserve</u>	
	<u>Pregnancy</u>	<u>Delivery</u>	<u>Pregnancy</u>	<u>Delivery</u>
< 30 years old	64% (108/170)	56% (96/170)	48% (13/27)	41% (11/27)
30-39 years old	57% (183/323)	47% (151/323)	35% (62/175)	27% (47/175)
40-42 years old	37% (10/27)	15% (4/27)	20% (5/25)	16% (4/25)

There are many treatment additives that are often enthusiastically endorsed by some programs, that we feel have no validity. This includes varicocele surgery for the husband, and aspirin, heparin, or immunoglobulin infusions, etc., for the wife. We do not recommend such additives. However, we do employ the most effective stimulation protocols, the most advance culture systems, and very refined micro-techniques in the lab (such as ICSI, assisted hatching, fragment removal, and even blastomere biopsy to maximize your chance for having a baby) with no add-on fees or gimmick payment plans.

We do specialize in the most difficult infertility problems, where there has been failure to fertilize or to achieve pregnancy in previous efforts, and our results are quite good even with such cases. Patients with difficult infertility problems fly to St. Louis regularly from all over the world. But we will also treat simpler cases as well. We always prefer to avoid needless and expensive conventional testing and treatment approaches that give low success rates and just add to the couple's mounting frustration. Our policy is to recommend the most effective treatment that is likely to get you pregnant the soonest.

Infertility treatment can be emotionally wrenching and can place a great deal of stress on the patient. We insist on providing personal care and attention as we guide you through this difficult period of your life. You should please feel comfortable to call my office at any time regarding any questions, problems or worries.



*I hope this information has been of use
to you. I look forward to meeting you
personally when we have our
consultation.*

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