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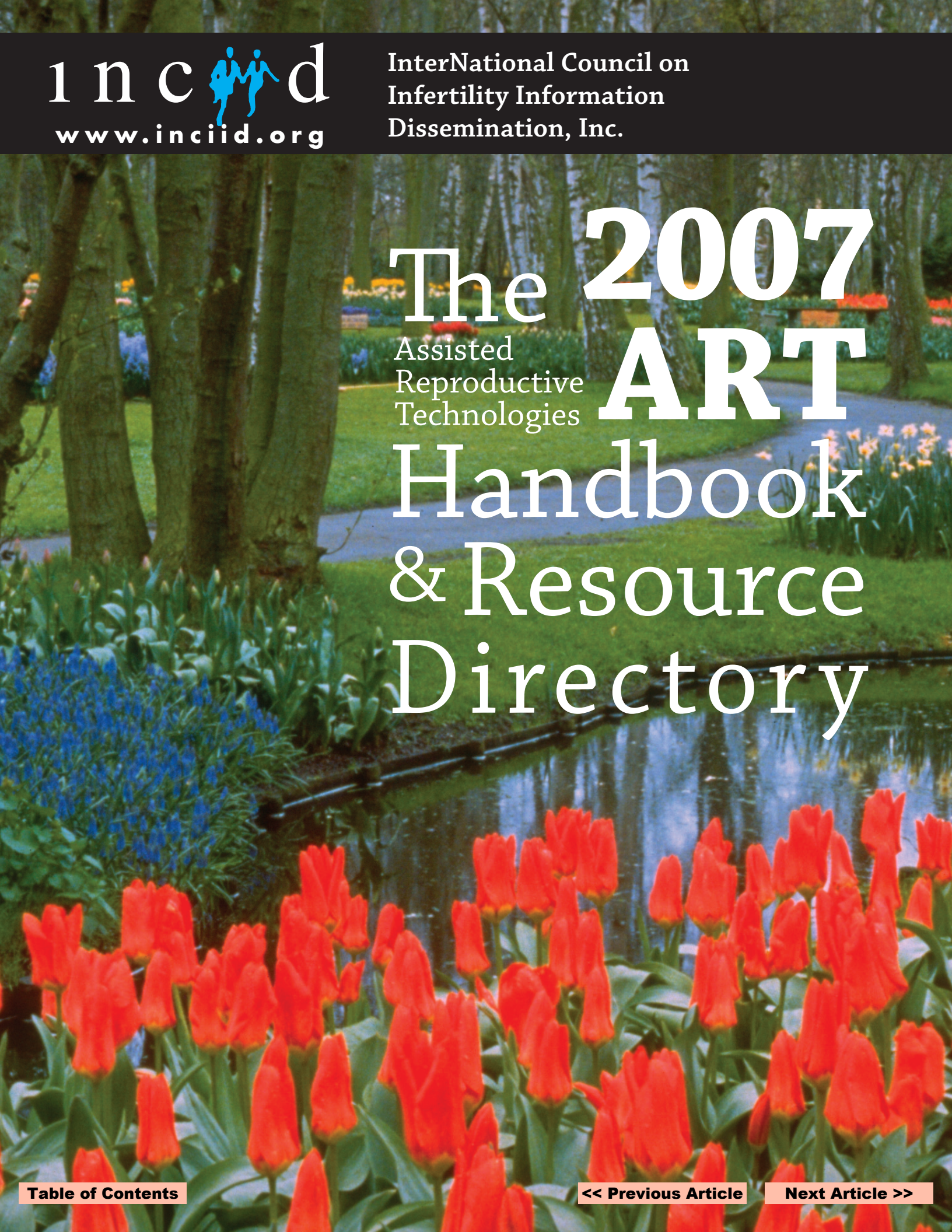

The 2007 ART Handbook & Resource Directory

Assisted Reproductive Technologies

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"For the First Time, We Had Hope..."

"None of the doctors we saw could seem to figure out why we couldn't get pregnant. We had pretty much given up on having our own baby, when we happened to meet a doctor from SIRM at an adoption conference. It was such an incredible experience - we asked him every question we'd always wanted to ask... questions that other doctors hadn't had the time or ability to answer. By the end of the day, my husband and I both knew that this was the place we needed to be.

I remember how excited I was at our consult with SIRM. I felt like we were finally getting down to the nitty gritty of what was happening and why things weren't working... The doctor told me that he suspected an egg quality issue and set up a protocol that was specifically tailored to my needs and my issues.

"We signed up for the Outcome Based Plan so we would have 3 tries and we could still get our money back if they didn't work. In our first cycle, they retrieved 40 eggs, of which 16 fertilized, and only 3 made it to transfer. This confirmed that my issue was definitely poor egg quality, which was a liberating feeling, since at least we knew why I had trouble getting pregnant.

After my first beta, the doctor called me with the results. His first words were "I have some good news for you..." The sonogram a few weeks later confirmed that we're having twins.

"I just couldn't believe that there were doctors out there like that..."

- Ellen Ford, SIRM Graduate and Expecting Mom

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The InterNational Council on Infertility Information Dissemination, Inc.

"INCIID is resilience, hope, friendship, support, and future breakthroughs.

"They say when one faces a challenge or problem in life, it is then that you discover who your true friends are. Nowhere is that more clear than on INCIID. The support of those that post on the boards, the staff, volunteers and moderators is phenomenal.

"Resilience, because even in the most trying times, INCIID helps me to keep going forward, to overcome the problems I may face, the fears I may experience, the heartbreak I have known, and celebrates with me the joy I know now.

"Hope, because even in my darkest moments when I would see a success from an INCIID sister and it gave me the hope to keep trying.

"Future breakthroughs, because of the commitment to reach for and create programs that research infertility or help women and men to achieve their dreams of being a parent. Together with tenacity, strength, and their desire to serve, there will be many future breakthroughs and INCIID will be at the heart of every one."

– INCIID Member

INCIID is a nonprofit organization and depends on your donations to provide support and programs like From INCIID the Heart.

Please donate generously today. Visit our secure online donation page at

www.inciid.org

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Our sponsors

Organon *Leaders in the Field of Fertility*

Organon is a company where health matters. Organon is a global leader in the creation of innovative prescription medicines for women's health and other products that contribute to the health of people and their quality of life. They are proud sponsors of the From INCIID the Heart Scholarship program. We urge you to explore their website. They are a company with "Heart".

BabyBeat

BabyBeat was the *very first* company to offer Dopplers for pregnant women to use at home and continues to be the market leader.

CSP Center for Surrogate Parenting

The Center for Surrogate Parenting, Inc. is a world renown surrogate parenting agency with offices in California and Maryland. CSP was established because of the strong belief that couples who are ready and willing to take on the responsibility of parenthood deserve that opportunity.

THE CENTER FOR RERPODUCTIVE MEDICINE AND INFERTILITY

HUNTINGTON Reproductive Center
MEDICAL GROUP
REPRODUCTIVE ENDOCRINOLOGY & INFERTILITY

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SCSA Diagnostics

From the Director

Dear Friends,

Every week, we receive phone calls, emails, faxes and other notes about personal feelings of isolation due to infertility struggles. Patients often tell us they feel very lonely and isolated from the rest of the world. INCIID is here to help you find a community where you can feel understood and accepted. *And* we are here to help you realize that infertility patients do have rights and should expect to be treated with dignity and respect.

The INCIID Infertility Bill of Rights

1. You have the right to have your reproductive history taken without shaking hands through your legs, and without wearing paper pajamas.
2. You have the right to be on equal footing with your doctor. If your physician calls you by your first name, you have the right to respond in kind.
3. You have the right to regular and individual time with the doctor—not a technician, not a nurse, but the physician managing your case—and you have the right to expect your phone calls to be returned.
4. You have the right to ask questions about the process and the program and receive direct answers to your questions from the physician and staff.
5. You have the right to be seen promptly—within half an hour of your scheduled appointment. To make you wait an hour or more clearly sends the message that your time is not as valuable as your physician's time.
6. You have the right to be heard and to play an important role in your own treatment. Physicians and patients should be on the same page and in the same boat. There should be a vested interest on the part of both patient and doctor in keeping that boat afloat.
7. You have the right to ask for and receive valid outcome-based reporting of IVF statistics. The current cost of producing a baby is around $85,000.00, and the over-reporting of success in the IVF arena is important to note. Until IVF is based on outcome, with an adequate reporting of "factual" statistics, insurance coverage will remain elusive.
8. You have the right to a universal insurance provision for infertility treatment, or at least equality of access.
9. You have the right to full disclosure about your treatment. You have the right to know if your protocol is research-based or if any experimental methods will be used.
10. You have the right to be treated fairly with dignity and sensitivity, regardless, of size, shape, color, sex or sexual orientation, marital status, national origin, race or creed.

INCIID is here for you: we offer a helping hand, a listening heart and a strong voice. We willingly share expertise, information, professional listings and access to others walking the same path. We provide the knowledge it takes to help you on your family-building journey. INCIID believes that with support, education, and knowledge come empowerment and success!

We hope this annual resource directory, as well as the INCIID website, will arm you with the information you need to guide you toward success whether that be family-building or a child free lifestyle.

With warm regards,

Nancy P. Hemenway

Nancy P. Hemenway
INCIID Executive Director
http://www.inciid.org
Email: inciidinfo@inciid.org
Phone: (703) 379-9178

Part 1

The Basics

The Contemporary Fertility Evaluation

Daniel Potter, M.D., F.A.C.O.G.

Infertility is a complex medical, emotional and social condition that afflicts more than four million reproductive-age couples in the United States. Successful fertility treatment includes not only achieving pregnancy, but also achieving it in the most efficient and cost effective manner possible. The frequently ignored psychological toll of repeated treatment failures must also be considered. To achieve success, it is imperative that a timely and complete evaluation of both partners be performed. As our knowledge of reproductive physiology has expanded, the fertility workup has evolved as well. In this article, the contemporary fertility workup will be discussed. Attention will also be given to organizing the evaluation to prevent unnecessary testing.

Evaluation of the male

It is natural for the attention of the gynecologist and family practitioner to turn initially toward the female in cases of infertility. Although infertility is generally viewed as a 'female problem,' fully 45% of infertile couples have male factor as a contributing cause. It makes sense then to begin the fertility evaluation with a basic evaluation of the male partner. Because significant male factor is generally treated with in vitro fertilization, needless hysterosalpingograms, laparoscopies and clomiphene cycles can be avoided by early detection of significant dysfunction in the male partner. The savings of time and money can be tremendous. In vitro fertilization with intracystoplasmic sperm injection (IVF/ICSI) has made it possible to successfully treat virtually all cases of male factor infertility, even with only a few moving sperm in the entire ejaculate.

The evaluation of the male partner starts with a competent semen analysis. Non-specialized laboratories, such as LabCorp and Unilab, perform a World Health Organization (WHO) semen analysis. This is a crude screening test and should be replaced by the strict semen analysis (Kruger) that is done by most fertility centers. The difference between the WHO and the Kruger test is that, with the Kruger test, sperm morphology is evaluated in a very stringent manner. The results of the Kruger test predict fertilization rates in vitro and presumably in vivo as well. The WHO does not predict outcome and will frequently miss subtle but clinically significant sperm abnormalities. The cost of the Kruger test is the same or less than a WHO analysis at our center.

When the male has abnormal semen parameters, the couple should be referred to a reproductive endocrinologist and/or urologist for further evaluation. Conditions warranting referral are: a sperm concentration of less than 20 million per mL, motility less than 35%, and morphology less than 5% (Kruger) or 30% (WHO).

A direct anti-sperm antibody test should be considered in cases where the male has a history of genital trauma, genital surgery or has never initiated a pregnancy. The direct antibody test is done on a semen sample and detects whether antibodies are attached to the sperm themselves. The cutoff for a positive test varies between labs but is usually considered positive when greater than 10%–20% of sperm are bound. Couples with anti-sperm antibodies should be referred to a reproductive endocrinologist for further evaluation and treatment.

Daniel Potter, M.D., is board certified in the subspecialty of Reproductive Endocrinology and Infertility.

Huntington Reproductive Center
270 Laguna Rd #220
Fullerton, CA 92835
Phone: 714-738-4200 Fax: 714-738-4496
Email: doctor06@havingbabies.com
URL: http://www.havingbabies.com

Genetic evaluation is indicated in males with a sperm concentration less that 5 million per milliliter. This evaluation should consist of a karyotype and a study to look for micro-deletions on the long arm of the Y chromosome (Yq deletion study). An assay for DNA fragmentation in the sperm cells (SCSA) may also be helpful in select patients. If azoospermia is present, carrier status for one of the cystic fibrosis mutations should be ruled out. Azoospermic men should be referred for a urological evaluation. In cases of obstructive azoospermia (congenital or post-vasectomy), percutaneous sperm epididymal sperm aspiration (PESA) can be done to harvest sperm for use with IVF without major surgery. Hormonal evaluation of the male is indicated when there is a history of sexual dysfunction, azoospermia or abnormal physical findings. This work-up, which consists of testosterone, FSH, LH and prolactin levels, should be accompanied by urological consultation.

Evaluation of the Female

The work-up of the female partner has undergone several changes over the years but the basics have remained the same. The well-orchestrated female work-up can be completed in a single menstrual cycle. At the end of this work-up, along with the male data, the clinician should be able to plot a definitive course of treatment. The work-up will be divided between female patients who are ovulatory by history and those that are not. Ovulation is presumed if the female has had regular menses every 26-32 days for the last six months. It is important to organize the work-up to prevent unnecessary testing.

The female work-up should start with an initial intake that includes a thorough history, physical examination and a transvaginal pelvic ultrasound. Important historical details include those that might indicate previous exposure to STDs (such as a history of abnormal pap smears), recurrent pregnancy loss and the duration of infertility. Physical examination and pelvic ultrasound will identify patients that have gross pathology requiring surgical treatment prior to further fertility evaluation. For example, a dermoid cyst requiring surgery would allow the surgeon to evaluate tubal patency at the time of surgery rather than ordering an HSG.

Ovarian Reserve Testing

After the initial intake, the next step in the evaluation of the ovulatory female is the evaluation of ovarian reserve. The level of ovarian reserve and the age of the female partner are the most important prognostic factors in the fertility work-up. Ovarian reserve is evaluated with a cycle day three FSH and estradiol level. On the third day of bleeding, a simple blood test yields a lot. An FSH level alone is never useful and should always be accompanied by an estradiol (E2) level. Normal ovarian function is indicated when the FSH is <10 mIU/mL and the estradiol is <65 pg/mL. If the FSH is >15 mIU/mL, the patient will probably need egg donation. If the FSH is 10-15 mIU/mL or the E2 is >65 pg/mL, the more sensitive clomiphene citrate challenge test (CCCT) should be performed to further define ovarian reserve. CCCT should also be routinely performed in all women aged 38 years and up regardless of how the cycle day 3 levels look. This will identify patients with incipient ovarian dysfunction. CCCT should also be considered in women of any age with otherwise unexplained infertility, as approximately 30% will show abnormalities that adversely impact their prognosis with fertility treatment. A CCCT is performed as follows: After drawing a cycle day 3 FSH/E2, the patient begins taking 100 mg of clomiphene per day on cycle days 5 through 9. On cycle day 10, the FSH only is repeated. The patient's prognosis is only as good as her worst FSH level. A level less than 10 mIU/mL is normal. A level from 10-12.5 mIU/mL predicts resistance to fertility medications and a diminished prognosis. At 12.5-15 mIU/mL, the prognosis is poor but pregnancies do occur with aggressive treatment. Levels greater than 15 mIU/mL indicate that fertility treatment with the patient's own eggs is not likely to succeed and that egg donation should be offered. Patients with any FSH level greater than 10 mIU/mL should be referred to a reproductive endocrinologist for further evaluation.

Tubal Patency

The next step in the ovulatory patient is to confirm tubal patency. This has been done traditionally with the hysterosalpingogram (HSG) and nothing has really improved on this. This test should be done in the

follicular phase of the cycle after bleeding has stopped and before possible ovulation. The ordering physician should personally review the films to confirm findings of the study. Loculation of spill and tubal phimosis indicate that laparoscopy may be helpful. If large hydrosalpinges are identified, they should be clipped or removed laparoscopically prior to in vitro fertilization. Several large studies as well as a recent metanalysis, have confirmed the pregnancy rates with IVF are reduced by half in the presence of hydrosalpinges and that the rates are normalized with salpingectomy. The exact etiology of the phenomenon is not known.

Confirmation of Ovulation

Confirmation of ovulation is unlikely to be helpful in women when a careful history is consistent with ovulation. If there is doubt, a cycle day 21 progesterone with a level greater than 4 ng/mL is indicative of ovulation with most conceptions cycles having levels greater than 10 ng/mL. Alternately, sonographic confirmation of follicle rupture with serial ultrasound can be performed.

Anovulatory Patients

The apparently oligomenorrheic patient should have the cause of their anovulation evaluated thoroughly prior to the initiation of treatment. The initial physical examination should note the presence or absence of goiter, acanthosis nigricans, striae, normal secondary sexual characteristics, Turner's stigmata, galactorrhea, hirsuitism and abnormalities of the reproductive tract. Ultrasound should note the thickness of the endometrial lining as well as whether the ovaries are polycystic in nature. An endometrial biopsy should be considered if the uterine lining measures greater than 15mm.

Endocrine Evaluation

In anovulatory patients, the initial laboratory evaluation should include random levels of FSH, LH, prolactin, TSH, DHEAS and testosterone. Insulin resistance should be considered in patients that have any of the following: obesity, hirsuitism or acanthosis nigricans on physical exam; polycystic ovaries on ultrasound; inverted FSH/LH ratio or androgen excess on laboratory examination. Evaluation for insulin resistance can be accomplished simply with a 2 hour glucose tolerance test with insulin levels. A glucose to insulin ratio of >4.5 being normal. Routine testing of patients that don't meet these criteria is not useful. Patients with abnormal insulin to glucose ratio should be referred to a reproductive endocrinologist for further evaluation.

Summary

In summary, the contemporary fertility evaluation should be both thorough and rapidly accomplished. All aspects of both the female and male reproductive systems should be considered. The work-up should be completed within a single menstrual cycle if at all possible. Referrals to sub-specialists should be made when appropriate. Some referral guidelines are listed below:

Factors Warranting Referral to REI (Reproductive Endocrinology & Infertility) Subspecialist

1. Female age greater than 37 years
2. Tubal occlusion
3. Abnormal semen parameters
4. Insulin resistance
5. Abnormal ovarian reserve testing
6. Clomid failure
7. Infertility for greater than 3 years

Factors Warranting Referral to a Urologist

1. Male sexual dysfunction
2. Abnormal male physical findings
3. Azoospermia

Misconceptions About Conception: Are You TTC (Trying to Conceive)?

The insiders guide to conception, including misconceptions, myths, legends and some practical advice.

Serena Chen, M.D.

It is estimated that of the millions of people attempting to conceive in the United States, only about 50% of those who feel that they are having trouble conceiving will seek help or advice. We know that the stresses of infertility are of a similar magnitude to the stress that people experience with the death of a family member. However, even in our modern, no-holds-barred society, infertility sometimes seems to carry a greater stigma than death. Rates of anxiety, depression and marital problems are significantly higher in the infertile population than they are in the fertile population. Even once a couple conceives, people who have experienced infertility will still have higher rates of anxiety, depression and less confidence in their parenting skills than parents who have not experienced infertility. In my experience as a reproductive endocrinologist who has treated thousands of infertile people, information and advice about the process of trying to conceive can go a long way towards relieving some of the stress and anxiety.

"TTC" in the title of this article comes from popular internet slang used on numerous forums and bulletin boards. The acronym TTC is the abbreviation for "Trying To Conceive." The fact that so many people today turn to the internet for advice, information and comfort about such an intimate and potentially devastating problem is a reflection of the simultaneous hunger for communication and a strong need for privacy. Although the internet is a powerful generator of information, it can also be a forceful perpetrator of misinformation. Care should be taken to evaluate the information on websites for both content and attribution. The INCIID organization is a prime example of a good information from a variety of attributed sources.

Despite the fact that people attempting to conceive today have access to more information than ever, many people still feel very much in the dark about how to make a baby. The problem with much of this information is that it generates needless anxiety and does not improve a person's chance to conceive. Misinformation, combined with lack of success leads to feelings of loss of control, increased anxiety and then depression. This article will attempt to address some of the more common misconceptions about conception, set the record straight and relieve a little bit of the anxiety while TTC.

Serena Chen, M.D., is director of the Institute for Reproductive Medicine and Science of St. Barnabas Medical Center
Old Short Hills Road East Wing, Suite 403
Livingston, NJ 07039
Phone: 973-322-8890 Fax: 973-322-8890
Web: http://www.sbivf.com
Email: serenac@sbivf.com

Boxers or Briefs?

While physicians who specialize in infertility frown upon soaking the testicles in hot water, this does not mean that everything that might generate some heat is a bad thing. This is typical of many myths – an exaggeration of truth. The testicles hang away from the body in the scrotum to allow them to remain at a temperature a couple of degrees below normal core body temperature. For some reason, this seems to be more optimal for sperm production. Submersion of the testicles in a hot Jacuzzi can rapidly increase their temperature and can have adverse effects upon sperm production, but does this mean that tight underwear is bad and loose underwear is good? In the *Journal of Urology* in 1988, two researchers, R. Munkelwitz and B.R. Gilbert, studied scrotal, core and skin temperatures of 97 males complaining of infertility. Males were divided into two groups – those who wore briefs and those who wore boxers – and semen analyses were performed on all. No differences were noted be-

tween the two groups in prevalence of abnormal semen analyses and no differences were noted between the two groups in scrotal temperature. So, gentlemen, you can wear what you want, but please stay out of the hot tub while you are trying to conceive.

"Really Trying"

"Trying to conceive" means that you stop using contraception. Stop the birth control pills, stop the condoms, stop the spermicidal gel, don't use the diaphragm, don't withdraw prior to ejaculation, have sex when you feel like it – not just when it is "safe." Trying to conceive should be easier than trying *not* to conceive, but for many couples, just the opposite is true: morning after morning taking the temperature; using the fertility monitor; peeing on a stick; having sex at times when you do not feel like it; more often than you feel like it and not having sex even if you do feel like it; using particular sexual positions because you were told they are associated with a higher chance of pregnancy; lying still with your hips in the air for prolonged periods of time after sex to keep the sperm in, checking your cervical mucus, worrying about your cervical mucus, etc. Trying to do the right thing, the best thing, the thing that helped your friend or your friend's friend conceive can drive you crazy.

People who are trying to conceive spend hours each week worrying about these details, and yet, all they are doing is driving themselves and their partner crazy. There is no data that any of this is helpful. The fertile period in a typical 28 day cycle is cycle day 10 to 16. If you have intercourse twice during that period of time, that will result in the same pregnancy rate as if you have intercourse 10 times during that period of time. When researchers looked at how often and when couples have intercourse, they found that couples have intercourse more often when they are more fertile and less often when they are less fertile. In other words, external signals about when and how often to have sex are no better than just having sex when you feel like it. Temperature charts and fertility monitors do not improve your chances of conception, are disruptive, time consuming and therefore increase stress. Twenty percent of normally ovulating women do not show a "normal" biphasic temperature chart. Throw out the thermometer.

Sex: Who's on Top?

The position of intercourse should not really matter as long as the male ejaculates into the vagina. The good sperm move very quickly into the cervix and the liquid that leaks out of the vagina after intercourse is mostly liquid, and some dead or immotile sperm. Holding onto this liquid for prolonged periods of time will not increase your chances of pregnancy. So if you feel like lying down after sex, then do it. If not, don't. You will not affect your chances of conception either way.

Cervical Mucus

Cervical mucus is often a source of stress for infertile couples. Is there enough? Is it the right time? What is the right way to check the mucus? Should I take cough syrup or do other things to make my cervical mucus better? The bottom line is that cervical mucus can be abnormal in fertile women and normal in infertile women. It is not a good predictor of fertility and is not a reliable method of timing intercourse for couples attempting to conceive. Again, have intercourse when you feel like it. If you never feel like having sex, seek help. But do not drive yourself crazy at home worrying about cervical mucus because this will not help you to conceive.

Food

There are no magic bullets when it comes to food. All women who are trying to conceive should make sure that they are getting 100% of the RDA (recommended daily allowance) for folic acid or folate. This B vitamin can lower the risk for some serious birth defects known as Neural Tube Defects, or Spina Bifida. A full 100% of the RDA is 400 micrograms of folic acid, or 0.4 milligrams. Most multivitamins contain this amount of folate. Do not take extra vitamins, because some common vitamin supplements, such as vitamin A and beta carotene, can actually cause birth defects if taken in amounts greater than the RDA. If you have questions, discuss the details with your gynecologist.

Aim for a Healthy Weight

Overweight and obesity are extremely common in this country. Unfortunately this can lead to significant-

ly higher rates of infertility, miscarriage and birth defects. Underweight is less common but can also have adverse effects upon fertility. Do not suffer in silence. Talk with your doctor. See a professional nutritionist. Get some help! Losing weight is not easy and being overweight is truly a medical problem. If you had cancer, you would not try to battle it on your own.

"Just Relax"?

You have probably heard these two words many, many times. There is no scientific evidence to support this advice. You cannot make yourself infertile by being stressed out and you cannot solve your problem by "just relaxing." While the people who tell you to "just relax" are trying to be helpful, this advice can often become destructive rather than constructive. People who are having trouble conceiving often blame themselves for their problem. By telling someone who is infertile to "just relax," you are, in some way, blaming them for their own problem.

On the other hand, while stress does not cause infertility, the opposite is true: infertility does cause stress. Stress management is often a good idea, especially for those having trouble conceiving. Studies have demonstrated that couples who undergo proactive stress management may have higher rates of conception than couples who only seek help on an emergent basis. What is meant by stress management? This has to be individualized. Formal individual, couples or group psychotherapy is one method. Acupuncture (no herbs), massage therapy, yoga, meditation, may all help one manage stress. Unloading your plate a little while you are trying to conceive can sometimes be beneficial. On the other hand, putting your life on hold while trying to conceive may lead to more stress. Each person must figure out what works for them. The important thing is to realize that infertility can cause enormous amounts of stress and to be proactive about attempting to reduce stress.

Preconception Health and Lifestyle: What To Do, What Not To Do

Just say no to cigarettes, drugs and alcohol. Cigarette smoke is so toxic to sperm and eggs that even regular exposure to second-hand smoke can lead to significantly higher rates of male and female infertility, miscarriages and birth defects. Drugs and alcohol can interfere with normal hormonal function and can increase the rates of serious birth defects.

In general, discuss the medications that you are on with your gynecologist and with the doctor who prescribed the drugs. People trying to conceive should still be able to take medication, if it is needed, but some alternatives may be better than others. In general, herbal remedies should be avoided. Many people take herbal remedies on a regular basis. Agents such as echinacea, ginkgo biloba, St John's wort, ginseng and DHA may have some beneficial health effects, but some studies have demonstrated negative effects upon sperm and eggs. In addition, since these types of agents are not regulated by the FDA, the consumer cannot be certain of the accuracy of the labeling.

Some agents used to enhance athletic performance contain anabolic or other types of steroids. These can have significant adverse effects upon the heart and liver and can cause the testicles to completely stop producing sperm. In theory, once the agents are stopped, sperm production should resume, but some men never recover normal function.

Aspirin and related compounds, such as Advil, Alleve, ibuprofen, and Motrin, can interfere with release of the egg if taken near the middle of the cycle. Tylenol, if taken as directed, does not have this effect and usually can be taken safely.

Women who are trying to conceive should limit caffeine intake to about 50 milligrams a day. This is about 6 ounces of brewed coffee or 2 cups of tea or 2 sodas. High levels of caffeine intake have been associated with infertility, miscarriage and pregnancy complications.

Men with high blood pressure should be aware that a particular group of anti-hypertensive medications – calcium channel blockers – can cause infertility. These agents block the calcium channels located in the head of the sperm and can prevent the sperm from fertilizing the egg. If your doctor feels that there is a reasonable alternative to calcium channel blockers, then it may be worthwhile to consider a change. For men who must use a calcium channel blocker, IVF with ICSI (in vitro fertilization with intracytoplasmic sperm injection) can be used with great success.

There may be other issues associated with other drugs. In general, anyone with a chronic health con-

dition may have to make adjustments in their medications once they decide to conceive. In addition, the condition may worsen with pregnancy or the pregnancy may be at risk due to the condition. Speak with your doctor and your gynecologist about planning for a healthy pregnancy in light of your condition or your partner's condition.

Infertility 9-1-1

How do you know when it is time to seek professional help? Timing is very important. The older a person is, the more likely they are to have a problem conceiving a healthy pregnancy. This is especially true for women. Generally, if a woman is 34 or under and has had unprotected intercourse for one year without pregnancy, she should have a full infertility evaluation by a fellowship-trained reproductive endocrinologist. If a woman is 35 or over, the evaluation should be performed after 6 months of unprotected intercourse. After age 40, infertility is extremely common and an evaluation with a specialist should be considered immediately.

Other people should consider evaluation sooner rather than later. Anyone, male or female, with a chronic medical condition should speak with their doctor before attempting to conceive. Women who do not have a period every month are probably not ovulating and will need medical help in order to conceive. If you have a family or personal history of endometriosis, you should seek evaluation early. Women who have had major abdominal or pelvic surgery in the past; men with a history of groin or reproductive tract surgery are at increased risk for infertility.

Do not be afraid to let your doctor know that you are trying to conceive. She or he may have some helpful advice and reassurance for you. If you have concerns that your doctor does not take seriously, it is not unreasonable to see advice from a specialist—a board-certified and/or fellowship-trained reproductive endocrinologist.

Bottom Line

Trying to conceive should not be an excessively stressful process. If it is, it may be time to seek some expert help and advice. Hopefully some of the myth-busting in this article will relieve some of the stress. If not, please do not suffer in silence. Seek some professional help. Call your doctor.

Visit the folks at INCIID www.inciid.org. INCIID provides a number of physician-moderated message boards and a community of tens of thousands who have been through or are going through fertility treatment successfully.

The forums at INCIID include both medical and emotional support by experts as well as other patients. The INCIID community also includes many who have become parents after treatment for infertility. There you will find a vast amount of solid information as well as peer support.

What does INCIID mean to me?

INCIID enabled me to have a second child. I don't know if I would have found the answers I needed to have a second successful pregnancy if it were not for the people here who are so giving of their knowledge and support. I still send people to the INCIID website every day because I know it is the best piece of information I can offer them as they struggle with infertility. Even though my conception journey is finished and my family complete, INCIID also means a community of women, some of whom have become my closest friends, who can share the parenting journey with me as I move forward.

—An INCIID Member

Nuts & Bolts of Insurance for Infertility

Brenda Messick

Insurance benefits for infertility-related medical services can be quite complex and confusing at best. But the good news is, if you have a basic understanding of infertility language and you're prepared with the right questions to ask of your health plan, you can receive an accurate explanation of your healthcare benefits and understand how you can best manage the benefits to suit your situation.

Explanation of Benefits

The first step to understanding your benefits is to obtain an accurate explanation of benefits from your health plan's Member Services department. Phrase the question specifically ("What are my infertility benefits?") and know that the benefits are often described in more than one section, i.e., "Infertility," "Family Planning," etc. If you sense that you aren't receiving the "whole picture," request that the analyst probe further into the plan description until you have all of your questions answered. Also, consider that some of the terminology within this benefit section isn't common and it's possible that the analyst isn't familiar him/herself with all of the terms. (Our practice staff has perfected the art of benefit verifications and knows exactly when they should call back to obtain a quote from a different analyst.)

Benefit limits are typically described as follows:

a) Gynecology only
b) Infertility Diagnosis only
c) Infertility Diagnosis and Partial Treatment
d) Infertility Diagnosis and Treatment

Brenda Messick is Practice Manager, Georgia Reproductive Specialists, Atlanta, Georgia.

5445 Meridian Mark Road, Suite 270
Atlanta, GA 30342
Phone: 404-843-2229 Fax: 404-843-0812
Web: http://www.ivf.com

Gynecology only benefits are the most restrictive and often provide little to no benefit for services performed at a Reproductive Endocrinology/Infertility (RE/I) practice. Health plans will request physician notes from the consultative visit and look for phrases such as "We are trying to get pregnant" or "I was referred for an infertility work-up" and assuredly deny the claim.

Infertility Diagnosis only benefits will typically cover the initial and follow-up consultative visits with the RE/I provider. Services provided at the consultative level usually include a history, exam, transvaginal ultrasound, bloodwork and follow-up visit about two weeks later to discuss test results and treatment options. Approximately 80% of the patients in our practice have diagnostic coverage only. However, within this coverage area it's very important that you determine if you have unlimited diagnostic coverage or if coverage is limited to an initial diagnosis. For example, a year ago you underwent diagnostic testing but didn't move forward with treatment. You're now ready to start a treatment cycle but must first update some of your diagnostic tests. Do you have continued diagnostic coverage? Another example is a patient who went to Practice A for a consult but would like a second opinion from Practice B. Do you have diagnostic coverage with Practice B even though Practice A has submitted a diagnosis to your health plan? A majority of our practice's patients who have diagnostic coverage only have unlimited coverage. It is important to know and understand this information.

Partial Treatment Coverage refers in this article to a couple of scenarios. One describes coverage for "surgical treatment of the underlying condition" that has caused the infertility. For example, coverage is available to surgically correct an anatomical cause of infertility, i.e., a blocked fallopian tube. The

second scenario is where we see partial treatment coverage. This is when a portion of, but not all of, a treatment cycle is covered. The most common example we see is coverage for ovulation induction as part of an intrauterine insemination (IUI) or in vitro fertilization (IVF) cycle but the actual IUI or IVF procedures themselves are not covered.

Treatment Coverage refers to insurance benefits for a portion or all of treatment cycles available in an infertility center. When there is insurance coverage for treatment, the analyst will be able to provide to you a very specific list of procedures and advanced reproductive techniques (ART) that are covered under your plan such as IUI, IVF, ICSI, Assisted Hatching, Donor Oocytes (eggs) and Embryo Cryopreservation. It's common to have infertility drug coverage for the treatment cycle for which you have coverage, but again, it is important to confirm the benefit. A word of caution, the higher levels of benefits often carry higher levels of restrictions and it's critical that this information is clearly understood. An example of restriction often seen in our practice is the requirement of a "documented two-year history of infertility" by a healthcare provider. Another example of restriction is the delay of infertility benefit payment until a pre-existing condition period is satisfied. It is critical that the health plan analyst communicates any and all restrictions affecting payment of infertility benefits.

Benefit Limitations

Once coverage for fertility services is determined and restrictions have been satisfied, a benefits level of the health plan can be determined. The benefit level for the health plan is amount they are obligated to pay. It is uncommon to see unlimited infertility benefits. Typically benefits are capped by:

a) dollar limit, or
b) number of attempts.

With dollar limits, you may have a maximum benefit in the range of $5,000 to $25,000. It's important to note that only payments made by the health plan for infertility services will go toward reducing your dollar maximum. Essentially, your healthcare provider's charges aren't a component of this calculation, only the health plan's payments. You can obtain a running total of your paid benefits from your health plan.

The second method of capping infertility benefits is based on number of attempts and relates to treatment cycles such as IUI and IVF. An example of coverage limits defined in this way is coverage for a maximum of six IUI cycles and three IVF cycles. In some cases a health plan may stipulate IUI cycles must be attempted before IVF coverage is available, but this is becoming a rarity as health plan are beginning to realize it would be an inefficient course of treatment in certain situations such as tubal factor, male factor, etc.

Note: An important consideration for capped benefits based on attempts:

Health plans typically define an IVF attempt as the transfer of embryo(s). Therefore, if you plan to undergo a frozen embryo transfer (FET), you should know that the FET will be counted as one of your attempts. Patients at our practice often choose to pay out-of-pocket for their FET (at 1/3 the price of an IVF cycle) and "save" that attempt for the higher cost IVF procedure that may need to be performed at a later date.

In conclusion, insurance benefits for infertility services range from restrictive to liberal and are most often determined by employers through group health plans. Human Resources representatives can also be a great resource for employee health benefit questions if you're comfortable sharing this personal information. Comparing benefit information received from both your employer and the health plan is an excellent way of securing accurate benefit information and putting you in control of your benefits.

Affordable Infertility Treatment . . . It's Not a Myth!

Brenda Messick and Nancy P. Hemenway

Infertility treatment is often expensive and most often not covered by health insurance policies. Finding out that you have limited or no insurance coverage does not have to mean the end of your journey to parenthood. As a patient, it is important to find a practice not only where you feel comfortable but also one that has your best interest at heart. A quality IVF center should do everything possible to ensure that the cost of treatment does not become a major factor in the decision to undergo treatment. There are a number of ways to make treatment more affordable. It's important to do your research before selecting an IVF center so you can find out which centers provide the best options for you to successfully build your family.

Refund Programs

Many centers offer a refund program, often under the name Shared Risk or Family Building. This type of program allows patients to pay an upfront, flat fee for a set number of IVF cycles over a certain time period. If the patient does not conceive after completing all of the cycles, they are given a refund minus, in most cases, a minimal enrollment fee. Third parties sometimes administer these programs while other programs may be run directly by the center staff itself. Before you select any refund program it is important to understand how statistics are collected and organized. INCIID suggests reading: "Reading Between the Lines in the CDC IVF Clinic Reports," by Sam Thatcher, M.D., Ph.D. (This article can be found at http://www.inciid.org/article.php?cat=ivf&id=333 on the INCIID website.)

Details and substance varies from one refund program to another. Always read the fine print before you sign on to any refund program. For example, some may count frozen embryo transfers as a separate cycle while others may count all fresh and frozen embryos transfered from one retrieval as a single cycle. It is important to understand all the details of the program and the way statistics are utilized before committing to it because, as the name implies, there is a "risk" involved. Couples who become pregnant during the first cycle will pay more by participating in these programs than they would with traditional fee-for-service; however, couples who achieve pregnancy in future cycles will save money.

There are advantages and disadvantages to this type of program. The most obvious advantage is the promise of a refund if there is not a successful pregnancy by the completion of all cycles. Another advantage is the effect that participation in the program can have on a patient's anxiety level. Patients may feel less anxious during treatment because they knew all of their hopes for a family are not riding on just one cycle. If things didn't go as planned in a refund program couples would get money back with which they could continue treatment or pursue other family-building options, such as adoption.

The following is an example of the parameters of a Shared Risk program:

The IVF Shared Risk Program is offered to women age 37 or younger who have normal ovarian reserve, no evidence of uterine abnormalities and have had no more than two prior IVF cycles. The one-time fee for Shared Risk is $22,660, covering the cost of up to three IVF treatment cycles in two years. One cycle is defined as the transfers of all fresh and frozen embry-

Brenda Messick is the Practice Administrator for Georgia Reproductive Specialists LLC, Atlanta, Georgia, and **Nancy P. Hemenway** is the Executive Director for INCIID, Inc.

Web: www.inciid.org
mail: http://www.inciid.org/contact.php
Phone: (703) 379-9178

os from a single retrieval. If all three attempts fail, the couple will receive a refund minus the non-refundable enrollment fee, which ranges from $2,500 to $6,500 depending on the age of the female patient and number of prior IVF cycles.

As mentioned, each center offers a variation of the program so it is important to look at a variety of programs and read the fine print. Find out which program best fits your needs. Ask a lot of questions. A success for one clinic may mean something else entirely for another. Any patient will tell you an IVF success should be a live birth. Be sure to ask what happens if you miscarry? Do you get your money back? Being an educated and informed patient consumer is your best option.

Pre-Paid Treatment Plans

A common complaint about infertility treatment is that it is not only high, but also often hard to predict expenses. Pre-paid treatment plans were developed to allow patients to know, in advance, exactly how much their treatment will cost. As with the refund plan, each center that offers a pre-paid treatment plan has different requirements. For instance, in some centers all couples participating in the pre-pay plan pay the same flat amount regardless of their treatment plan and are then reimbursed at the end of the cycle for any unused monies. In other centers, there is a different fee structure for each possible treatment plan, so each patient's pre-paid amount is customized. The advantage to this plan is that there are no surprises. All money is paid before treatment begins rather than an ongoing fee-for-service arrangement. Before you pay for services, be sure you understand what the parameters of those services include and how much each services costs.

Financial Loans

There are many options available for patients interested in securing a loan to cover the cost of infertility treatment. There are banks that provide loans for couples going through treatment. There are loan services available directly through some clinics and also through third-party lending institutions. Various programs offer various rates. It would be important to find low fixed rates and/or low monthly payments for patients who are ready to commit to treatment but do not have the funds readily available. Home equity loans may also be an option for treatment.

Flexible Spending Accounts

Some patients work for companies that offer flexible spending accounts for non-covered medical procedures. Flexible spending accounts are offered by some companies to their employees as part of their benefits package. These accounts allow fixed amounts of pre-tax wages to be set aside for qualified expenses. Qualified expenses usually include uncovered medical expenses which are predetermined by the employer. The amount set aside must be determined in advance and employees lose any unused dollars in the account at year-end. Check with your employer to see if your benefits include a Flexible Spending Account.

Do Your Homework

For most patients, every dime and nickel count when it comes to paying for fertility treatment. It is important to make sure everything is being done to make sure you receive the best care possible, but also at the lowest cost. Understanding your insurance benefits is very important. Often there are some benefits covered by insurance, even if IVF is not fully covered. If you've called your insurance company and been told that you do not have any benefits, it would be wise to provide insurance information anyway. Clinics often have specialists on staff working to verify insurance benefits and they can oftentimes find coverage for diagnosis or medications when the patient thought there was nothing available. Patients should keep copies of all medical records, treatments, diagnostic tests, etc. in a notebook. They should also keep all insurance claims, EOBs (evaluation of benefits), and denials in a separate notebook. We suggest you read the insurance section on the INCIID website for basic understanding of insurance, denials and appeals, online at http://www.inciid.org/index.php?page=insurance101

Another way to reduce the overall cost of treatment is to do price comparisons before purchasing your medications. In addition to the local pharmacies that supply infertility medications, there are also a number of mail-order pharmacies offering fertility medi-

cations in one to two days. A few phone calls and online searches to compare prices could end up saving you a significant amount of money!

It is important to gather all relevant medical records before your first appointment with a fertility specialist. In order to give you the most effective treatment possible, your physician needs to have your complete medical history and access to past test results, physician notes and treatment plans. We suggest patients keep medical records in one notebook, insurance communications, EOBs, etc., in a second notebook, and have a third notebook for articles, pamphlets and fact sheets pertaining to your particular situation. In many cases, the physician is able to get significant information from your records and can then bypass certain costly diagnostic tests and procedures.

Infertility treatment often causes a great amount stress and anxiety for a those who struggle with it. By doing research and reviewing all financial options, it is possible to eliminate some of the financial stress. Talk to the financial coordinator at the center where you are undergoing treatment and find out exactly what your options are and then do some investigating on your own. Don't be afraid to ask questions during any part of your treatment, whether it is during a meeting with the financial counselor or an appointment with the physician.

Additional information of interest:

State insurance mandates:
http://www.inciid.org/article.php?cat=statemandates&id=275

From INCIID the Heart Scholarship Program:
http://www.inciid.org/article.php?cat=&id=239

The New York State Grant Program:
http://www.inciid.org/article.php?cat=statemandates&id=273

Companies who may provide infertility benefits:
http://www.inciid.org/article.php?cat=statemandates&id=243

Health Insurance Basics:
http://www.inciid.org/index.php?page=insurance101

What you need to know about insurance coverage for IVF:
http://www.inciid.org/article.php?cat=benefits&id=16

Male Infertility

Samuel S. Thatcher M.D., Ph.D.

Infertility is a relative term and indicates a desired pregnancy *has not* been achieved, which is often very different from *cannot* be achieved. This is especially true in male infertility where our new technologies have greatly expanded male reproductive potential. If *any* sperm are present, even if they need to be surgically extracted, a pregnancy may be possible. This translates into a simple fact that the vast majority of male infertility is eminently treatable. This treatment can be as simple as lifestyle changes, or may require assisted reproduction (ART) including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or surgical extraction of sperm. But with our new advances it truly now may take only one sperm.

For the male, chances of conception are dependent on the length of time attempting a pregnancy, frequency of intercourse, level of female fertility, and sperm quality. If given enough time and a fertile partner, pregnancy can be achieved by men with very low sperm counts, although time and a high level of female fertility are luxuries not afforded for many. Some degree of male factor infertility is present in about 40% of couples attempting a pregnancy and one third of couples have combined male and female causes of their inability to conceive. Therapeutic intervention may speed conception in some cases and in others bypass a block that otherwise would have made pregnancy impossible.

Various tests may be more or less predictive of male fertility and can help direct therapy, but in very few cases can they absolutely predict fertility as long as sperm are present. In the general population there are probably many cases of larger families fathered by men with semen samples judged to be in the infertile range. Most often there are no outward signs to suggest lowered sperm count and in as many as 50% of men with abnormal sperm quality no specific cause can be found (idiopathic) based on their history and examination. While male factor can never be completely excluded, it is reassuring if there is a negative medical history and a normal *semen analysis* (SA), especially if the male partner has also previously fathered children.

Samuel S. Thatcher M.D., Ph.D., is the founder and director of Center for Applied Reproductive Science.

408 North State of Franklin Road
Johnson City, Tennessee, 37604
Phone 423-461-8880 Fax 423-461-8887
E-mail thatcher@ivf-et.com
Web: http://www.ivf-et.com

"Mantality"

There is always considerable performance anxiety before the first semen sample is produced and great pride when it is discovered to be normal. For a man to be told of an abnormal semen analysis is equivalent to a woman being told that she cannot carry a child. Men equate sperm counts with potency, potency with virility and virility with manliness. Most infertile men are both virile and potent. Men may not awake each morning and go to bed at night thinking about infertility, but they certainly carry the burden with them. Infertility is just as much of an insult to the male self image as it is in the female. A goal for both partners is to remove the stigma of infertility from male and female identity and treat it as the disease that it is.

Initial assessment

The goals of the male evaluation[1] are to identify

1) potentially correctable conditions,
2) irreversible conditions amenable to assisted reproductive techniques using the sperm of the male partner,

3) irreversible conditions that are not amenable to therapy and for which donor insemination or adoption are possible options,
4) life or health threatening conditions that may underlie the infertility and require medical attention,
5) genetic abnormalities that may affect the health of offspring if assisted reproductive techniques are to be employed.

As a part of the initial fertility assessment, a complete *personal and family history* of the male partner should be taken to include specific questions regarding previous and present illnesses, medication use, tobacco, alcohol and illicit drug use, surgery, pelvic injury, infectious diseases (childhood, respiratory, sexually transmitted), and potentially hazardous environmental exposure. Family history should include number of siblings, their spacing, history of infertility, birth defects and summary of hereditary diseases.

A *physical examination* of the male is no less important than that of the female and can be performed as a part of the initial evaluation, or after routine SA.

Male Reproductive Biology

Production of mature sperm begins at puberty and continues until very advanced ages. There is now evidence that sperm quality decreases somewhat as men grow older, but the aging effect is considerably later and is much less important for fertility than in the female. In part, the lack of an aging effect is due to the continuous production of sperm in contrast to the fixed number of eggs present at birth in the female.

The testis of the male is under the same control of pituitary gland hormones as the ovary of the female. Through a precise integration of the *gonadotropins*, *luteinizing hormone* (LH) and f*ollicle stimulating hormone* (FSH) the testis performs its hormonal function of making testosterone and its procreative function of sperm production (*spermatogenesis*). The process of spermatogenesis lasts approximately 64 days at which point the testis has sperm in various stages of continual maturation. This is important because it implies that any intervention to improve sperm, or insult that would decrease sperm, may take as long as three months to be manifested.

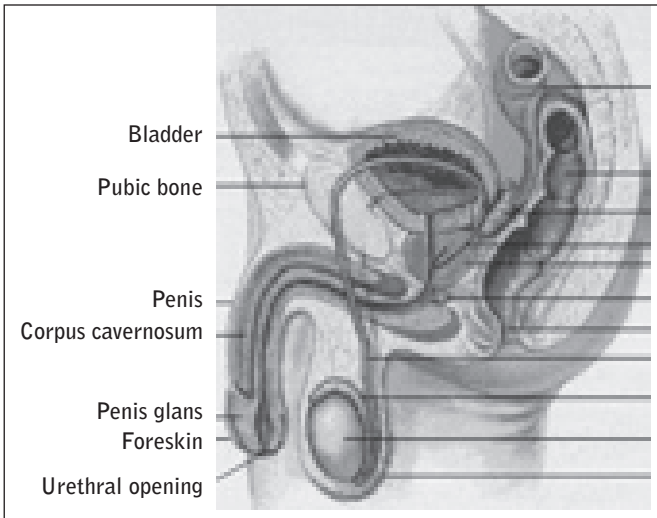
Male Infertility Inventory (The Twelve "I"s)

Inheritance (genetics)
Infancy (undescended testis, congenital anomaly)
Infection (mumps, sexually transmitted, prostatitis)
(I)ndocrine* (thyroid, diabetes)
Illness (recent and chronic)
Incision (surgery)
Injury (trauma)
Impotence (erectile dysfunction)
[I]nvironment* (occupational exposure, stress)
Intoxicants (smoking, alcohol, illicit drugs)
Ingestants (medications, diet)
Idiopathic (unknown causes)
(*Okay, but "E" sounds like an "I"!)

Spermatogenesis is better at a temperature lower than what would occur if the testis were located inside the body. Any change, whether it be a temporary fever from an infection, a reversible condition such as occupational exposure, or a longstanding abnormality such as a varicose vein around the testis (*varicocele*) can increase testicular temperature and potentially reduce sperm counts. Interventions to reduce testicular temperature are marginally effective at best. While reasonable to avoid long hot baths and saunas, no evidence exists that changing from briefs to boxer shorts will make a difference.[2]

Immature sperm detach from their support cells in the testis (*sertoli cells*), leave the testis and enter the *epididymis*, a tube about 15 feet long coiled into about an inch structure and lying very close to the testes. Usually the epididymis can be felt as a small, slightly softer ridge adjacent to and attached to the testes. During their stay in the epididymis, sperm become progressively more motile and mature. Clearly, sperm surgically extracted from the testis can be used to initiate a pregnancy by directly injecting the sperm into eggs obtained for IVF, but these sperm do not have the capacity to fertilize eggs without this mechanical assistance.

With ejaculation, the epididymis contracts, forcing sperm into the *vas deferens*. About 5% of an *ejaculation* is from sperm and epididymal fluid while the remainder is about equally from the prostate and *seminal vesicles* (*accessory glands*). The seminal vesicles do not store sperm, but produce a buffering fluid rich in the sugar,



The male reproductive sysem

fructose, which serves as an energy source for sperm and its absence in a semen sample can indicate absence of blockage of the seminal vesicles. The amount of seminal fluid is dependent on the period of abstinence and accessory gland function. Small amounts of semen can contain normal amounts of sperm, but low semen volume can also indicate obstruction, or *retrograde ejaculation* into the bladder rather than through the *urethra*.

The urethra as it exits the bladder is joined by the paired seminal vesicles and surrounded by the *prostate gland*. The prostate may enlarge with age (*hypertrophy*), causing more frequent or more difficult urination. Prostate cancer is the second most common cancer of males, but is relatively uncommon before age 50. Difficult or painful ejaculation may be a symptom. Painful urinating or ejaculation can also indicate prostatitis, which has a clear association with infertility. While mild occasional aching may accompany ejaculation recurrent painful ejaculation or erections should be evaluated.

After ejaculation, semen undergoes *liquefaction,* whereby the consistency of semen becomes more watery. During liquefaction a small amount of semen may drain from the vagina. For the infertile couple there is often a concern that sperm is being lost from the vagina, but fears should be allayed that this is a normal part of the liquefaction process. The initial part of the ejaculation has the highest number and portion of sperm most capable of fertilization. This portion is also most likely to be inserted into the deepest portion of the vagina. No scientific evidence exists that one intercourse position is better than another for fertility.

The erect penis is about 5.5 to 6 inches in length and there is no evidence penile size affects fertility nor is there evidence that circumcision has an effect. While there can be congenital abnormalities such as an abnormal opening (*hypospadias*), *erectile dysfunction* (ED) with the help of the pharmaceutical industry has lost some of its stigma. Erection is caused by dilation of the blood vessels of the penis under the influence of nitric oxide. The stimulus for erection can either be mechanical by touching of the penis and/or psychogenic by erotic stimuli.

The causes of ED are many and varied. ED may arise from endocrine abnormalities of testosterone deficiency, or *hyperprolactinemia*, medical diseases such as diabetes and hypertension as well as a variety of pharamcologic agents, notably antidepressants and anti-hypertensives. While it is generally known that alcohol can alter erection, few realize the profound effect that nicotine can have. ED is 1.5 times more common in smokers,[3] with the effect increased by the amount and length of smoking history. Capacity for erection tends to improve on cessation of nicotine intake. ED should be investigated to exclude modifiable causes. Male performance stress may lead to erectile dysfunction that may be improved with sildenafil (Viagra®) without compromise of sperm parameters.[4] Longer acting drugs, vardenafil (Levitra®) and tadalafil (Cialis®) should be similar in effectiveness and safety.

There is clear evidence that couples who are more sexually active are more fertile. To a point, the more intercourse, the more sperm available for fertilization. The highest chance of conception is related to intercourse within 2 days before ovulation. Ovulation occurs toward the *end* of a 5–7 day time span called the *fertile period*.[5, 6] In an idealized 28-day cycle, ovulation occurs on days 13–15. If the cycles are within the optimal 26–32 day range, the fertile period is from days 11–16. If intercourse occurs 3 times during the fertile period there is adequate exposure. Intercourse every day may reduce sperm counts, while intervals of over 3 days may decrease the number of viable sperm.

Parts of a sperm cell

Once released from the ovary, the life span of an egg is short, probably 12–24 hours, but sperm may remain viable in the female genital tract up to 7 days.[7] More precise planning may increase stress without increasing chance of pregnancy. The goal is for capacitated sperm to be at the site of fertilization in the distal Fallopian tube awaiting ovulation.

It should be realized that, once ejaculated, sperm take a very short time to reach the site of fertilization, but it may take as long as six hours for the process of capacitation, a series of processes necessary for the sperm to develop the capacity for fertilization. *Capacitation* takes place in the female genital tract, or can be artificially effected during sperm preparation for artificial insemination, or IVF. Well timed artificial insemination can increase chances of pregnancy by bypassing various barriers and increasing the number of sperm in the Fallopian tubes, but may also decrease sperm longevity and bypass the usual natural slow release of sperm over several days from a reservoir in the cervical mucus.

Not only are sperm numbers (concentration) and movement (motility) important, but also sperm quality. The *acrosome*, a small cap on the head of the sperm, contains enzymes that disperse or dissolve the several layers of barriers around the eggs. During capacitation, sperm also develop the capacity to *bind* to receptors, or dock, with the egg surface. Just before fertilization sperm undergo a burst of energy known as *activation*. It is known that caffeine activates sperm but this may also abnormally decrease their lifespan.

Preconception counseling

Preconception counseling is no less important for men than women. Often modifiable risks can be identified that may make the difference between fertility and infertility. Most recommendations or the question "should I or shouldn't I?" rest on common sense. If you think you shouldn't, don't.

Vitamins and supplements Sperm are very sensitive to oxidative stress. Antioxidants theoretically could have a stabilization effect and improve semen quality. Placebo controlled trials with sufficient statistical power to make meaningful statements are lacking. Vitamins C and E and folic acid, along with glutathione and the minerals zinc and selenium, each have been proposed in observational studies to improve fertility, but each has also been subject of studies with negative findings. While there is little basis to recommend them universally, their high safety profile and relatively low cost make their use hard to dissuade. High doses are discouraged.

Substance abuse An unequivocal association exists with *smoking* and infertility, both male and female.[8, 9] Although not specifically reported, it seems likely that smokeless tobacco and nicotine replacement also may have adverse effects. Chronic alcohol consumption has a detrimental effect on male reproductive hormones and on semen quality.[10, 11] Studies on caffeine use are more inconsistent than either smoking or alcohol and range from a significant reduction in fertility, especially at higher amounts,[12] to no evident effect.[13] Use of marijuana alters hormone secretion and reduces fertility,[14] while cocaine reduces spermatogenesis.[15]

Weight and exercise As in women, either high or low body weight is associated with reduced fertility.[16] Observational data suggests that metabolic syndrome, a potentially modifiable condition, is strongly associated with hypogonadism in men.[17] Regular physical activity should be encouraged. Little doubt exists that strenuous activity alters endocrine function in men[18] and it seems likely that this can be translated into decreased fertility. While studies on aggressive exercise are limited, moderation in activity with emphasis on flexibility and mobility rather than endurance and strength seems justified.

Occupational exposure Over 100, 000 chemical and physical agents have been identified in the workplace, some of which may lower fertility.[19] While shift work and long working hours do not seem to decrease fertility[20, 21] job stress does.[22]) Prolonged sedentary positions, or increased occupational heat exposure may reduce sperm quality.[23]

Medications Very few drugs can be pronounced unequivocally as safe. To compound the problem, it is difficult to separate the cause and effect between the disease process itself and the drugs used to treat it. A careful history of prescription and non-prescription drugs as well as seemingly innocuous supplements often uncovers potential harmful agents for which there may be safer alternatives. An excellent example of the complexity of drug use is high blood pressure (*hypertension*) which can affect spermatogenesis directly through altered blood supply to the testis, increase oxidative stress and have a toxic effect on sperm, and/or alter libido and sexual performance. Virtually all antihypertensive agents influence one or more of the above mechanisms.[24] While calcium channel blockers have minimal effect on sexual function, they have been implicated to block fertilization[25] in an unsubstantiated observational study.[26]

The commonly used antacid, cimetidine, has been shown to adversely alter the hormonal balance.[27] Drugs used for gout, specifically colchicine, inhibit mitosis, and methotrexate used to treat psoriasis or arthritis is a folic acid antagonist. Each of these drugs could have negative effects on spermatogenesis. Virtually every class of antibiotic has been shown to have some effect on sperm function.

Stress Despite intensive research, it has been impossible to establish a causal relationship between stress and infertility.[28] Some couples embrace, others rebuke attempts at psychological and emotional intervention. Regardless, couples should be made aware of support groups and counseling. Psychological services are becoming increasingly and specifically available for infertile couples. Support groups, whether local or Internet based, are judged by patients to be helpful. Any stress reduction can easily be translated into less emotional suffering and therefore, should be a therapeutic goal.

Semen Analysis (SA)

Why, what, when, where and by whom

If there is a single test that is most important in determining origin of infertility, it is a SA. SA represents a highly predictive, integrative test of both hormonal and anatomic factors. It very much matters how and when the sample is produced and who performs the analysis.

Semen samples should be analyzed after 3–4 days of abstinence for optimal results. In reality, it may be more appropriate to produce a sample at natural intercourse intervals. Regardless, it is most important that the days of abstinence be recorded. Withdrawal sex should not be used for producing a sample for analysis because higher quality and concentration of sperm may be present in the first portion of the ejaculate. Artificial lubricants may lower motility or viability and should be avoided. If successful masturbation is not possible, condoms especially designed for this purpose are commercially available; however, standard condoms may be spermicidal.

Samples should be kept at room or body temperature and should be analyzed within one hour of production. Time produced and time of analysis, any febrile illness within the previous 3 months, and medication use should be recorded. Be aware of the laboratory that is performing the SA. Hospital labs are notorious for letting the sample sit too long before analysis, or using individuals inexperienced in semenology. The quality of the semen may be better than reported, but often more detailed evaluation shows less good quality.

Semen quality among men of proven fertility can vary considerably between samples. It has been recommended that two samples be analyzed. Often an efficient approach is to evaluate semen parameters as a part of a midcycle timed insemination if ovulatory cycles are suspected.

Components of the semen analysis

Semen volume, sperm count (concentration), motility, and morphology are independent markers of fertility. The chances of pregnancy fall as the number of abnormal factors increases from one to two and from 2 to 3.[29] Considerable overlap exists between fertile and subfertile males.[30]

Volume Less semen may be seen when there was recent intercourse. Low or absent volume could indicate obstruction or retrograde ejaculation. Lack of ejaculate is an indication for evaluation of a post-ejaculation urinalysis to exclude retrograde ejaculation. Men with *retrograde ejaculation* often complain of ejaculation pain and mucus in urine after ejaculations. History of medication use, surgery with retro-

peritoneal dissection and peripheral neuropathy each can be an etiology of retrograde ejaculation.

Concentration is expressed as the number of sperm in each milliliter of ejaculate. *Azoospermia*, complete absence of sperm in the ejaculate, should be confirmed by a centrifuged specimen and microscopic evaluation of the "pellet." Azoospermia can have a genetic, obstructive, and/or hormonal origin. Unless the cause is immediately obvious, genetic evaluation is indicated. Counts under 20 x 10^6/ml, are considered *oligospermia*, which is really not a diagnosis, but a finding indicating likelihood of pregnancy, not its etiology.

Motility (movement of the sperm) is very seldom above about 80%. Samples under 10% should be scrutinized for lab or collection errors. Labs differ in what they consider normal motility. Normal ranges are probably about 40–70%. Be aware of the sample that looks too good on paper. Very rarely do samples have over 80% motility. Total absence of motility in association with relatively normal count, *sick cilia syndrome*, is associated with abnormalities of the contractile proteins within the cilia throughout the body. When accompanied by *dextrocardia* (heart on the right instead of left side of the chest) and chronic respiratory infections, it is known as *Kartagener syndrome*.

Often an SA is read as abnormal because the sperm concentration per milliliter rather than the total count is considered. The most useful parameter in evaluation of a semen sample is total motile sperm.

Total motile = (volume of sample) x
(concentration of sperm) x (motility).

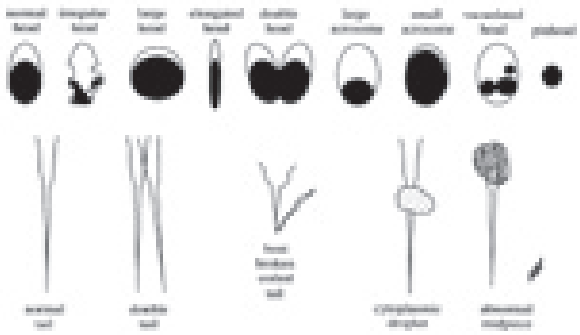
A total motile count of above 20 x 10^6 is considered normal.

Morphology refers to the shape of the sperm. There are two different classification systems in use. According to the traditional World Health Organization (WHO) classification, normal forms should be over 30%.[31]

Round cells/white blood cells If over 1 x 10^6 per ml "*round*" cells are seen, special staining is required to distinguish between white blood cells (WBCs) and immature sperm cells. This distinction cannot be made by conventional microscopic analysis. Often WBCs are reported, when they are actually immature sperm cells and antibiotics unnecessarily prescribed.

Agglutination Prior genital surgery, trauma, or infections are risk factors for breech of the blood testis barrier and sperm antibody formation. Antibodies are commonly present after reversal of vasectomy. Antibodies are often detected on SA by obvious clumping (*agglutination*). While specific tests are available, all vary in their reliability and prognostic value. Testing has been largely abandoned due to lack of specific corrective therapy and normal course of therapy is not usually altered.[32]

Sperm Morphology



Special semen studies

The most common derivative of semen testing is use of a more refined classification of morphology, or "strict" (Kruger, Tygerberg) criteria. Using these criteria, fertilization after IVF was 37–47% with <14% normal forms and 85–88% with >14% normal forms.[33] This system has not been universally adopted in ART centers because results are blurred when ICSI is employed.

Some laboratories utilize *computer assisted sperm analysis* (CASA) for routine SA and more precise quantification of sperm velocity. There has been no proven value of CASA over conventional SA, especially with a trained semenologists.[34]

In the past a number of specialized assays were developed in an attempt to predict fertilizability of eggs. In theory, a test that could predict outcome with assisted reproduction would help counsel patients before the financial commitment of IVF. Examples of these are *sperm penetration assay* using zona free hamster eggs, or binding of sperm to harvested sections of human zona pellucida, *hemizona assay*. Each of these tests correlates with IVF success, but has been largely

General guidelines for interpretation of semen

Measurement	Normal	Low
Volume	2–5 ml (cc)	
Concentration (count)	> 20 million per ml (cc)	oligospermia
Motility (movement)	> 60%	asthenospermia
Morphology (appearance)	> 30% WHO criteria > 14% strict criteria	teratospermia

outdated with the widespread use of *intracytoplasmic sperm injection* (ICSI), which bypasses the blocks tested in these assays. Other tests that may have diagnostic capacity and correlate with sperm quality include *donor mucus penetration* test, *hyperosmotic swelling test*, and tests of the *acrosome reaction*.[35]

Post-coital testing

In the past, the *post-coital test* (PCT) has been used to evaluate the quality of the cervical mucus, the presence and motility of sperm. Although the PCT has predictive value about fertility status, its usefulness in a clinical evaluation is highly questionable and its use largely abandoned.[36]

Endocrine testing

If a repeat SA is also low, the next step is endocrine testing and physical exam. If there have not been laboratory studies, a *comprehensive metabolic panel* (CMP) that evaluates liver and kidney function, *lipid profile* to evaluate risks of cardiovascular disease and complete blood count (CBC) may be useful as part of a general health evaluation. Together with hormone levels, these tests may uncover unsuspected, possibly serious medical problems. Infertility may be the presenting complaint of diseases such as diabetes, hypothyroidism, and hemochromatosis. Potentially life-threatening prostate and testicular cancer are sometimes found.[37, 38] Low testosterone levels may be a marker of metabolic syndrome.[39] The most basic endocrine evaluation includes blood tests for *follicle stimulating hormone* (FSH) and testosterone. If specifically indicated, an endocrine evaluation may be expanded to include TSH, prolactin, luteinizing hormone (LH) and estradiol.

A markedly elevated FSH level indicates gonadal failure, while more modest elevations are often associated with compromised spermatogenesis. Usually infertility characterized by elevated FSH is not amenable to endocrine therapy.

Mildly decreased level of gonadotropins and/or testosterone usually indicates a "stress" pattern of HPG axis dysfunction and is generally not responsive to hormone therapy. Complete absence of gonadotropin secretion, the most severe form of *hypogonadotropic hypogonadism* is *Kalmann syndrome*, a relatively rare X-linked recessive genetic disorder usually associated with lack of ability to smell. Kalmann syndrome results from failure of nerve cells that produce GNRH, the hormone that stimulates gonadotropin production to organize properly during embryonic growth. While more likely to present with delayed puberty, occasionally Kalmann syndrome is first diagnosed by infertility.

Anatomic evaluation

Normal hormonal levels with an abnormal SA may indicate anatomic abnormality. A physical examination should include weight, blood pressure, thyroid gland, breast and genital exam. Scrotal exam is important to evaluate testicular volume, insure presence of the vasa and exclude varicocele. *Transrectal ultrasonography* can be helpful in cases of low or absent ejaculates and palpable vas deferens where dilation of the seminal vesicles and/or ejaculatory ducts can indicate obstruction.

Men with no sperm in the ejaculate, non-obstructive azoospermia, who have relatively normal testicular volume and FSH levels often have maturation arrest or *sertoli cell only syndrome*. While the diagnosis may be suspected, it can only be diagnosed by testis biopsy. If biopsy is elected, it is highly preferable that logistics are planned in advance so that if sperm are found, they can be cryopreserved for later use with IVF/ICSI and a second aspiration procedure avoided. Biopsy for diagnostic purposes has little benefit with elevated FSH or small testis.

A *varicocele*, tortuosity and dilation of the veins within the spermatic cord, occurs in about 15% of men in the general population and about twice that rate

present in the infertile population. Varicoceles, more commonly occurring on the left, are often very obvious on physical exam. Some *subclinical* varicoceles require scrotal *Doppler* studies for detection. Varicocele may adversely affect fertility by raising testicular temperature. Sperm DNA fragmentation is increased in adolescents with varicocele in advance of alteration in semen parameters.[39] Sperm counts may improve after surgery, but the hard evidence is lacking that fertility is increased. A meta-analysis has revealed that "treating varicocele in men from subfertile couples seems ill-advised,"[41] but this conclusion has been criticized by inclusion of men with subclinical varicocele, which is a dubious indication for surgery. An exception is probably the larger and symptomatic varicocele in younger men that has an independent indication for ligation due to pain. Treatment of varicocele may misdirect the course of the fertility evaluation with undo expense, inconvenience, and time lost. Symptoms and other factors found in the male evaluation together with female factors, especially age, should be taken into consideration before electing repair.

Genetics

Congenital absence of the vas deferens (CBAVD) is frequently associated with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *Cystic fibrosis* is the most common fatal autosomal recessive genetic disorder in the Caucasian population, with an incidence of 1/2500 live births and a carrier frequency of 1/25. Almost all men with cystic fibrosis have CBAVD, and over half with CBAVD have a CFTR mutation.[42] Testing of the female partner for carrier status should be performed before procedures when planning to use sperm from the male partner.

Prevalence of karyotype abnormalities is inversely proportional to sperm count.[43] *Klinefelter syndrome* (47,XXY) (1/600 male births) is the most common chromosomal anomaly associated with male infertility.[44] Sperm production is possible, but usually markedly reduced in 47,XXY mosaics. The findings of gynecomastia, tall stature, small testes, and azoospermia usually raises suspicion, but the typical appearance is not always found.[45] Sperm have been surgically extracted from azoospermic non-mosaic 47,XXY males resulting in genetically normal children after IVF/ICSI.[46]

Microdeletions of the Y chromosome are too small to be recognized by standard mapping of chromosomes, a karyotype, and require specific DNA analysis by PCR (polymerase chain reaction) to be detected. The deletions occur in the long arm of the Y chromosome in specific regions designated as *AZF* (azoospermic factor).[47] Microdeletions may be found in 10%–15% of men with azoospermia/severe oligospermia, and, while inheritable (passage to sons), they are not thought to be associated with health problems outside infertility.[48] IVF/ICSI is generally associated with good success rates.[49]

Sperm quality not only influences fertilization, but early embryonic development, especially in the first cell cycles.[50] Decreased sperm chromatin integrity has been implicated in poor embryo development after IVF. The *sperm chromatin structure assay* (SCSA)® is a commercially available technique using a special stain to separate normal and abnormal DNA, with results expressed as the *DNA fragmentation index* (DFI). DFI appears to be an independent predictor of IVF success, with specific thresholds suggested for predicting success.[51] Touted to be superior to routine semen analysis, the SCSA failed to identify a threshold for negative pregnancy outcome.[52] While theoretically attractive, the SCSA and other tests of DNA integrity, TUNNEL, COMET, Halosperm®, have yet to have their clinical usefulness established.

Picking the professional for male factor evaluation

Semen analysis is often ordered by the female partner's gynecologist as a part of a routine fertility investigation. If the semen sample is considered abnormal, referral to a urologist is common. Urologists, while very capable of a thorough exam, unfortunately are often not interested, or specifically trained, in complete evaluation and treatment of the infertile couple. Probably the best route is a relatively quick referral to a fertility center. The reproductive endocrinologist (RE) receives training in both male and female infertility and may be the best individual to explain options and coordinate efforts. When selecting a "fertility clin-

ic," inquiry should be made on whether their team includes an andrologist and reproductive urologist. The andrologist may be either a scientist or a clinician specifically skilled in male reproductive biology and infertility. Reproductive urologists, who are unfortunately sometimes difficult to locate, have a specific interest in andrology, as well as medical/surgical treatment of male infertility.

Hormonal therapy for male infertility

While spermatogenesis can be induced with gonadotropin therapy in cases of hypogonadotropic hypogonadism,[53] no hormonal therapy has been conclusively demonstrated in randomized controlled trials to be effective in increasing sperm number or quality when hormonal levels are normal. Antiestrogens (for example, clomiphene) appear to have a beneficial effect on endocrine parameters, but there is not enough evidence to recommend use for idiopathic oligo-asthenospermia.[54] Clomiphene therapy has been in and out of favor several times. Other than expense and inconvenience, there does not seem to be substantial negative effects of clomiphene and a several month empiric trial may be of benefit in select cases. An interesting concept has been advanced by improved semen parameters with non-obstructive azoospermia/severe oligospermia and elevated estrogen/testosterone ratio treated with aromatase inhibitors.[55]

It has been theorized that supplemental testosterone lowers endogenous testosterone levels and results in a rebound effect when it is discontinued. There is no evidence that this is effective, and androgen therapy can further suppress the HPG axis and worsen spermatogenesis.[56] It is surprising how many men presenting with lower sperm counts are using supplemental testosterone, sometimes illicitly for bodybuilding, but also prescribed for decreased libido treatment, or lower testosterone levels. Testosterone supplementation should be avoided in infertility therapy.

Intrauterine insemination

IUI has the potential to circumvent a number of blocks to fertility and has become a mainstay of fertility therapy. For a number of reasons, the procedure is attractive to both patient and physician. It is a reasonable, cost-effective alternative before proceeding to IVF. Success, while not impossible, is severely limited when total motile counts are $< 1 \times 10^6$, and significantly reduced with $< 10 \times 10^6$ sperm. IUI improves the chance of conception over timed intercourse in male subfertility[57] and is of benefit in unexplained infertility where the etiology may be equally divided between male and female. IUI provides additional evaluation of semen parameters, ovulation parameters including cervical mucus, and the cervical canal. Proper timing of IUI is imperative for it to be successful. During preparation, sperm are activated and capacitated which considerably limits their lifespan. IUI should be performed immediately prior to anticipated ovulation. Insemination is usually the next morning after an OPK change, or 32–40 hours after injection of hCG in stimulated cycles. There is no advantage of one versus two inseminations per cycle.[58] If the female partner is ovulatory, natural cycles are preferable to stimulated cycles due to cost and risk of multiple gestations. The greatest success with IUI is in the first three attempts.

The lower limits

Every fertility specialist has been surprised with a pregnancy achieved without therapy with sperm counts so low as to border on sterility. Generally, when there are more than 20 million total motile sperm in a semen sample, the chances of male fertility are good. With IVF, there is little difference in fertilization rates with samples above 5–10 million sperm. In the past prognosis for men with sperm counts under one million was very poor, but pregnancies are now relatively routine after *intracytoplasmic sperm injection* (ICSI). The confines of male infertility have been pushed even farther back with the technique of removal of sperm directly from epididymis (*percutaneous epididymal sperm aspiration*) or the testis (*TESE*, microsurgical extraction for the testes). Clearly, we are now in a new era of male infertility therapy in which the lower limit of male fertility cannot be absolutely predicted. Success may mean aggressive and expensive intervention, but most male factor infertility is now treatable with good success.

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Adoption Q&A

Hilary M. Neiman, LLC

Q. What is the difference between an intrastate adoption and an interstate adoption?

A. In an intrastate adoption, both the birth parents and adopting parents live in the same state. But in an interstate adoption, the birth parents and the adopting parents live in different states.

Q. What is the difference between a closed and open adoption?

A. In a closed adoption, the process is done anonymously. But in an open adoption, the birth parents and adoptive parents share identifying information about themselves and have contact with each other even after the baby is placed with the adoptive parents.

Q. What do adoption agencies do and what are the different types of agencies?

A. Agencies match adoptive parents with children. There are three different kinds of agencies; public, non-profit private, and for-profit private.

Hilary M. Neiman is an attorney at law in Rockville, Maryland, concentrating on adoption and surrogacy law.

30 Courthouse Square, Suite 106
Rockville, MD 20850
Phone: 301-340-7228
Email: neimanlaw@hilaryneiman.com
Web: www.hilaryneiman.com

For more information on Adoption, Surrogacy, and Third Party methods to build your family:

Visit the INCIID Third Party Legal Forum:
http://www.inciid.org/forums/legal/index.html

Visit the INCIID Third Party Medical Forum:
http://www.inciid.org/forums/third_party/index.html

Visit the Adoption Forums:

Exploring Adoption:
http://www.inciid.org/forums/adoption_exploring/index.html

Expecting through Adoption:
http://www.inciid.org/forums/adoption_waiting/index.html

Q. How long does it take to adopt?

A. That depends on what type of adoption you are pursuing. The wait time is generally anywhere from 4 months to several years.

Q. How much does it cost to adopt?

A. This also depends on what type of adoption you are undertaking and the agency that you use. Costs range from $0 if you are pursuing foster care adoption to $50,000 and above if you are pursuing an international adoption.

Q. What happens during the homestudy?

A. The homestudy involves several interviews with a social worker to make sure that adoption is the right decision for them. By law, the social worker must look into all areas of the adoptive family's life from their criminal and employment history to their health and family values and beliefs.

Q. I am older, can I still adopt?

A. Yes, you just need to find an agency that does not set age limits. Also, if you are pursuing international adoption, some countries have age limits.

Q. I am single, can I adopt?

A. Yes, adoption by single parents is legal in all states.

Q. I am gay, can I adopt?

A. Yes, but it depends what state you are in.

Q. What is embryo adoption?

A. Embryo adoption is the process in which embryos are donated from individuals who do not wish to use them. The adopting family can either transfer the embryos to the womb of the adoptive mother or have a surrogate mother carry.

Surrogacy Q&A

Hilary Neiman

Q. What is the difference between Traditional and Gestational Surrogacy?

A. Traditional surrogacy uses the ova of the surrogate and either the husband's sperm or donor sperm. Gestational surrogacy uses the ova and the sperm of either the Intended Parents or donor ova and sperm.

Q. What is the cost of surrogacy?

A. Surrogates are compensated between $15,000-$30,000, depending on if they have experience being a surrogate. Surrogates also receive additional fees for procedures like c-sections, amniocentesis, selective reductions, and carrying multiples. On top of that, you w ill also have to pay for the pre-testing of the surrogate, your fertility clinic's fees, legal fees, and if you are working with an agency, agency fees.

Q. How are surrogates screened?

A. Most fertility clinics require surrogates to have blood work, a sonogram, a psychological evaluation, and an MMPI test.

Q. Will working with a surrogacy-matching agency help us find a surrogate faster?

A. It depends on what you are looking for in a surrogate (age, location, experience, etc.). The more open you are, the quicker you will be able to get matched. However, it is important to feel comfortable with the surrogate that you are working with. This is not a process that should be rushed.

Q. Can I pursue surrogacy if I am a single male or female?

A. Yes, there are many surrogates who want to help single intended parents.

Q. Can I pursue surrogacy if I am gay?

A. Yes, there are many surrogates who want to help gay intended parents.

Q. Can I pursue surrogacy if I can't quite afford the process?

A. It depends. Your attorney can help you form a payment plan and some attorneys and agencies offer reduced fee arrangements. It's also possible to find surrogates who are willing to be compensated a lower amount.

Q. I am from a country where surrogacy is illegal, can I still pursue it?

Y. Yes, you just have to work with an American surrogate in a surrogacy friendly state.

Q. If I am the Intended Parent(s), will my name be on the birth certificate?

A. It depends on what state you are from.

Part 2

Beyond the Basics

Single Embryo Transfer: Something to Consider

Eric Flisser, MD

The frustration experienced by infertile patients can lead to a "pregnancy at any cost" attitude in which every effort is directed at achieving pregnancy no matter what the consequence. Although emotionally difficult, some patients may be well served by transferring only one embryo. While it may not seem logical to limit the number of embryos transferred after in vitro fertilization (IVF), particularly with patients who have experienced long periods of infertility, in select patients limiting the number of embryos to one-at-a-time may be a highly successful option that also minimizes risks to the mother and her pregnancy. At the moment, single embryo transfer is not for all patients, but something that all patients should consider.

A common side effect of infertility treatment is a twin pregnancy. Although twins and high-order multiple pregnancies, such as triplets and greater, are not uncommon, they are also carry increased risks. Patients often perceive twins as a benign benefit of infertility treatment and welcome them as a "two-for-one" deal because of the bonus baby for the same treatment cost and effort. However, patients are also often unaware of the increased risks to their unborn offspring.

With in vitro fertilization treatment, twin pregnancy generally results from the transfer of more than one embryo. Although frequently leading to a happy outcome, twin pregnancy has increased risks that are not uncommon and that can have lasting effects on the health of the mother and her babies. Preterm labor, premature delivery, gestational diabetes, pregnancy-induced hypertension, intrauterine growth restriction, placental abruption and preeclampsia are all more likely with twin pregnancy than with singleton pregnancies. Compared with singleton births, twins are 5 times more likely to suffer an intrauterine demise, 7 times more likely to die within the first 30 days after birth and 4 times more likely to have cerebral palsy. For this reason, the goal of successful infertility treatment is a healthy, singleton birth.

When multiple embryos are available for transfer, high quality "extra" embryos can be cryopreserved or "frozen" for future transfer. By having these supernumerary embryos "banked," a patient may undergo a second attempt at embryo transfer without having to take daily injections of gonadotropins (the stimulation medications) and undergoing surgical oocyte retrieval. These frozen-thaw embryo transfer cycles cost less than "fresh" cycles, are less physically taxing, and avoid the risks of anesthesia and a surgical procedure. Studies of cumulative transfers, such as a single "fresh" embryo transfer followed by a single or double "frozen" embryo transfer when the first transfer is not successful have shown no difference in the "take home baby" rate. However, a significant reduction in the twinning rate is seen with this approach. Because embryos can spontaneously divide, even a single embryo transfer can occasionally result in twins.

In some European countries, preventative health policy places a legal limit to the number of embryos transferred in order to maximize patient safety in select patient groups, such as young infertility patients, restricting these patients to single embryo transfers. No such law currently exists in the United States. However, because all infertility clinics in the United States are required by law to report IVF success rates to the Center for Disease Control and Prevention, which collects and makes available this data for public

Eric Flisser, M.D., is board certified in reproductive endocrinology and infertility.

Reproductive Medical Associates of New York (RMA NY)
635 Madison Ave, 10th Floor
New York, NY 10022
Telephone : (212) 756-5777 Fax : (212) 756-5770
Web: http://rmany.com/

scrutiny, emphasis is placed on achieving high pregnancy rates. This number, and not the average number of embryos transferred to achieve this rate, is often the focus of patients seeking treatment. Whereas national guidelines exist for the number of embryos that should be transferred, a single embryo transfer success rate is not yet its own distinct, reportable category, limiting patient awareness and interest in this type of treatment.

Past inefficiencies in infertility therapy led to the establishment of the idea that multiple embryos must be transferred during IVF cycles in order to achieve good results. However, since technology and medical understanding have improved, it is no longer necessary to transfer many embryos to achieve the same or even better results. For this reason, and because research has demonstrated that singleton pregnancies are the least risky, a singleton pregnancy is the goal of infertility treatment.

For patients who already have children at home from prior infertility treatment, single embryo transfer may offer the safest way to produce a sibling with minimal risks of twinning; for patients without children, single embryo transfer may offer a way of producing a healthy pregnancy while minimizing risks to the developing fetus. When properly chosen, patients choosing single embryo transfer can have comparable success to patients receiving multiple embryos; all patients should inquire of their physicians whether single embryo transfer is appropriate for them.

Assisted Hatching

Jeffrey Nelson, D.O., F.A.C.O.O.G.

There are a multitude of factors contributing to a couple's inability to conceive, including male factor, uterine factor, tubal factor, pelvic factor, and ovulatory dysfunction. The majority of these factors can be circumvented through the application of advanced reproductive treatments like in vitro fertilization (IVF).

The success of IVF depends on three primary components: good quality embryos, a technically uncomplicated embryo transfer, and a receptive intrauterine environment for embryo implantation. When we talk about "good quality embryos" the two most common criteria discussed are rate of embryo growth, and embryo grade. The rate of embryo growth is determined by the number of cells, or blastomeres, contained within the embryo on a specific day of development. For example, on the third day following egg collection and insemination, an appropriately developing embryo should consist of six to eight cells. It is believed that embryos growing at a slower rate have a less favorable chance of implantation. The grade of the embryo is determined by the appearance of the individual blastomeres. A high-grade embryo contains blastomeres that are symmetrical in size and shape, without evidence of intracellular fragmentation. Conversely, embryos made up of asymmetrical cells with a significant degree of fragmentation, are less likely to successfully initiate a pregnancy.

There is another critically important component of the embryo that does not get as much attention. This important structural component is the elastic outer shell, which surrounds the embryo, known as the *zona pellucida* (ZP). The ZP is formed from a matrix of various proteins that are secreted by the egg, and in photographs it appears as a translucent halo enveloping the embryo. The ZP has several important functions. During the process of fertilization, it serves to prevent the access of more than one sperm to the egg. Following fertilization, the ZP keeps the cells of the embryo together during early development, until the embryo reaches the blastocyst stage. At the blastocyst stage, the embryo has enough structural integrity that it no longer needs the protection of the ZP. In fact, it is mandatory that the blastocyst break free of the ZP, once it is in the uterine cavity, in order to successfully implant within the uterine wall. This eventual escape from the ZP by the expanding blastocyst is called embryo hatching.

Standard IVF protocols include culturing of embryos within the laboratory for three days, followed by transfer of cleavage stage embryos (6–8 cells), on day three, to the uterine cavity. Following transfer, the embryos must continue to progress to the blastocyst stage, shed the ZP, and embed into the uterine wall. In 1989, Cohen and his co-investigators observed a higher implantation rate in patients undergoing IVF who had the ZP of their embryos mechanically opened. They therefore hypothesized that artificially creating a gap in the ZP might serve to facilitate embryo hatching and implantation. Microscopic manipulation of the ZP, in order to augment hatching and implantation, subsequently became known as "assisted hatching." Prospective randomized clinical studies have been performed in order to evaluate the effectiveness of assisted hatching. Several studies report a significant increase in embryo implantation and clinical pregnancy rates in select groups of patients whose embryos have undergone this procedure. These select patient groups include women greater than 38 years of age, those with elevated day three FSH levels, couples with previous IVF failures, embryos with

Jeffrey Nelson, D.O., is an osteopath, board certified in obstetrics and gynecology and practicing at Huntington Reproductive Center.

Huntington Reproductive Center
333 S. Arroyo Parkway, 3rd Floor
Pasadena, CA 91105
Phone: 626-440-9161 FAX: 626-440-0138
URL: http://www.havingbabies.com

an abnormal-appearing zona pellucida, and when using previously cryopreserved embryos. Some IVF programs will globally perform assisted hatching on all embryos prior to transfer, but the data on this is less clear.

A variety of techniques have been employed to perform assisted hatching. These techniques are designed to assist the embryo in the timely shedding of the ZP, and they share a common endpoint of either thinning out or completely perforating a focal area of this surrounding membrane. Some embryologists will perform assisted hatching by mechanically piercing the ZP with a specifically designed sharp pipette. Currently, the most commonly practiced method of assisted hatching involves exposure of the embryo to an acidified media called acidified tyrode's solution. This acidic solution is microscopically applied to a focal area of the ZP to induce thinning. Complications and consequent diminished pregnancy rates can result from assisted hatching if the embryo is damaged, or if the size of the defect in the ZP is not precise. When the defect is too small, the embryo may get pinched and damaged. When the hole in the ZP is too large, the embryo may escape prematurely, which will compromise its development. The described techniques therefore require a highly skilled and experienced embryologist in order to be performed in a way that is beneficial and not detrimental to the health and viability of the embryo.

A new technique for assisted hatching has been introduced, which we now routinely use at Huntington Reproductive Center. This technique involves the creation of a precise gap in the ZP of selected embryos using a 1.48 micron infrared diode laser. This specifically designed laser system includes the laser, which serves as the energy source to create an opening in the ZP, and a computer which allows the operator to precisely control the laser energy output, laser pulse duration, and gap size. This system has many benefits when compared to the more standard mechanical and acidified tyrode's techniques. The computer-assisted laser method is more precise, resulting in a more consistent ZP opening. This technique is also more quickly mastered by the embryologist, with a quality outcome less dependent on the skill and experience of the technician. Laser assisted hatching takes less time and does not expose the embryos to potentially adverse chemicals, so embryos spend less time out of optimal culture conditions. It also requires significantly less physical manipulation of the embryos. The cumulative effect of these factors is to minimize the stress placed upon the embryo during the performance of assisted hatching. This in turn should then translate into improved implantation and pregnancy rates. We have completed a limited study at our center, which confirmed the laser is safe, and was associated with excellent implantation and pregnancy rates.

Assisted hatching has demonstrated the potential for improving embryo implantation rates, and clinical pregnancy rates in select patient groups undergoing IVF.

Infertile couples considering advanced assisted reproductive treatments should consult with their reproductive specialist regarding their candidacy for assisted hatching.

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Ovarian Aging and Infertility

Jane Frederick, M.D., F.A.C.O.G.

The decrease in female fecundity, beginning after the age of 30 and exaggerated after 40, is a well documented finding. This age-related decline in fertility is the result of several factors that contribute to overall reproductive failure. Women over 35 require a longer period to achieve conception than younger individuals, and a higher percentage of older than younger women will never achieve pregnancy. In addition, the rate of early pregnancy wastage increases substantially during the 30s, and is over 50% percent after age 40.

With the aging of the baby boom generation and social trends to delay childbearing, the treatment of women ≥ 40 years of age who desire fertility has become a major challenge of today's fertility specialists. For many women, the option to exercise other choices while deferring their reproduction, has resulted in the need to use new reproductive technologies while treating their infertility. These technologies include controlled ovarian hyperstimulation (COH), intrauterine insemination (IUI), and assisted reproductive techniques (ART).

Literature Review

Over the past 15 years, there has been a surge in the assisted reproductive technologies available to treat infertility. Given such a vast array of treatments, clinicians are faced with uncertainty about the optimal technique for an individual patient with functional Fallopian tubes. The optimal choice depends on the pregnancy rates per cycle (cycle fecundity) and costs, as well as the degree of invasiveness associated with each of these procedures. Recently, some authors have suggested superovulation with HMG, combined with IUI as an alternative treatment for couples with nontubal causes of infertility.

A review of the literature dealing with IUI by Allen et al. evaluated the results in 18 studies with a 28% mean pregnancy rate (range 3.4%–62%) in 714 patients. Confounding variables including specifics of sperm preparation, reason for IUI, insemination timing, and number of attempts per cycle, and few studies reported on the efficacy of IUI with respect to age of the patient. Further studies by Dodson et al. showed that the mean serum estradiol concentration per follicle is inversely proportional to age, and that the woman's age is inversely proportional to cycle fecundity with IUI. My results show there is a very poor live birth rate (1.4%) per cycle in infertile couples in which the female partner is ≥ 40 years of age and treated with COH/IUI. This study seriously questions the indication of COH and IUI in women ≥ 40 years old. (See Table 1).

Spontaneous Abortion Rate

Even when an older woman does conceive, the aging process affects the viability of her embryo. With increasing menstrual age there is an increased risk for spontaneous abortion, implantation failure, and cleavage failure. Spontaneous abortion rates increase from 10% in women who are under 30 to 34% in woman in their early 40s.

Cytogenetic studies have shown that in 40% of all first trimester miscarriages, there is evidence of chromosomal abnormalities, and the majority of these anomalies are autosomal trisomic defects. Among recognized conceptions there is an exponential rise

Jane Frederick, M.D., F.A.C.O.G. is board certified, in the subspecialty of reproductive endocrinology and infertility.

Huntington Reproductive Center
270 Laguna Road Suite 220
Fullerton, CA 92835
Phone: 714-738-4200 Fax: 714-738-4496
Email: doctor05@havingbabies.com
Web: http://www.havingbabies.com/

in the frequency of trisomies of almost every human chromosome with advancing maternal age.

In Vitro Fertilization

The early use of IVF in the treatment of women over 40 was influenced by the experience of Steptoe and Edwards, who reported a pregnancy rate less than half of that for women over 40, along with a spontaneous abortion rate that was almost 60%, yielding a live birth rate of only 3%.

The most recently published data from the U.S. IVF-ET registry mimics the early Bourne Hall experience. The result of 115,392 IVF cycles from 391 clinics in 2002 where a delivered pregnancy rate for women 40 or older was 10% compared with 35% for all age groups. The older women also suffered a 36% spontaneous abortion rate. Older women undergoing IVF have high cancellation rates, most often because of insufficient follicular development, but the pregnancy rate declines with increasing age regardless of the number of embryos transferred.

Leading Factors

Biological data suggests at least three factors undergo change at age 37: the uterus becomes increasingly unreceptive to maintaining pregnancy; oocyte abnormalities, most commonly expressed as chromosomal trisomies, finally become clinically dominant and compose half of all conceptions after 45; and altered patterns of gonadotropin release, marked by rising basal FSH levels, increase incidence of irregular menstrual function, which finally expresses itself as the inability to conceive.

It is biologic or ovarian age and not chronologic age that most likely determines the end-point of fertility. Women who conceive late in life generally have a late menopause – the number of years from the loss of fertility to menopause appears to be about ten years. As there is no accurate way to predict the onset a decade in advance, perhaps women have been right all along when they say they hear the ticking of their biologic clocks.

Assessing Ovarian Reserve

Of the few good tests for ovarian reserve, an abnormal result can predict poor reproductive performance, but normal results are less reliable. The most commonly used test are basal FSH with estradiol and the clomiphene citrate challenge test (CCCT). FSH and estradiol are drawn on day three of the menstrual cycle. Clomiphene citrate 100 mg is given on days five through nine of the cycle, and on day ten FSH is redrawn. An elevation of either FSH level (greater than 10 IU/l) and an estradiol over 80 pg/ml are considered abnormal, indicating a diminished ovarian reserve. Women older than 40 who have a normal FSH level are still less likely to conceive than younger women due to the reduced quality of their oocytes.

Impact of Oocyte Donation

Oocyte donation dramatically alters the fertility of women over 40. Success rates are independent of age. Most series reports now demonstrate live birth rates above 50% per embryo transfer in patients up to 55. Life table analysis indicates that more than half of perimenopausal women will be successful within three attempts of oocyte donation, and more than 85% by the fifth try. Furthermore, miscarriage rates reflect that of the donor, who is usually under 35. Thus, losses are experienced typically in fewer than 15% of conditions.

Maternal age decreases live born rates after assisted reproductive technology (ART). These data are from 115,392 fresh ART cycles with patients' own oocytes reported to the Society for Assisted Reproductive Technology and the Centers for Disease Control and Prevention for the year 2002. Advancing maternal age adversely affects live birth rates following ART. When fresh donor ART cycles are plotted, pregnancy rates do not decrease even into the 40s. (Figure 1).

Results of oocyte donation suggests that although the uterus is less receptive in women over 40, it is the ability of the aging oocyte that is the most important factor in the decreasing fertility of older women. Patients have indicated satisfaction after having made the decision to proceed with oocyte donation. Only time will tell if this trend becomes the accepted norm.

Oocyte Preservation (Egg Freezing)

Until recently, the ability to freeze an egg was an unrealistic dream due to the delicate structure of the unfertilized egg. Fortunately, a number of advances in our knowledge of oocyte physiology and laboratory techniques are changing this dream into a reality. Women concerned with their "biological clock" could store oocytes for use later in life. At Huntington Reproductive Center, we have started a number of studies that are helping oocyte preservation become a viable option for women to preserve their reproductive options.

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New Application for Follicular Reduction

Mark Perloe, M.D.

Ovulation Induction

Ovulation induction medications, often referred to as fertility drugs, are used to stimulate the follicles in a patient's ovaries resulting in the production of one or more eggs in one cycle. The use of medications can help pinpoint the time of ovulation, so sexual intercourse, intrauterine inseminations (IUIs) or in vitro fertilization (IVF) scheduling is optimized.

There are different levels of ovulation induction commonly used to treat infertility related to ovulation disorders, male factor or unknown causes. One method of treatment involves oral medication–clomiphene citrate (Clomid or Serophene) or letrozole (Femara)–taken in pill form for 5 days at the beginning of a cycle. For women whose only infertility problem is anovulation, up to 80% of patients will ovulate using this medication and 50% of those will conceive . Clomiphene may be combined with IUI to boost the success of the medication by placing the sperm and egg in closer proximity to each other.

The more aggressive level of ovulation induction is called superovulation. This treatment uses gonadotropins or a combination of clomiphene or letrozole and gonadotropins to stimulate the production of multiple eggs. Patients undergoing superovulation must be closely monitored with blood tests and ultrasounds. Monitoring ensures that the patient does not hyperstimulate and also helps the physician administer the correct dosage of medication so that only a few follicles develop. This is a critical step to keeping the multiple pregnancy rates low. At the end of the superovulation treatment process, a low dose HCG (human chorionic gonadotropin) may be prescribed to stimulate ovulation. Ovulation will occur between 42-48 hours after HCG. The patient is instructed to either have intercourse during this time or to come in for an IUI. Depending on the cause of infertility, the success rate per superovulation treatment cycle is approximately 6-20% based on the woman's age and medication protocol.

Ovulation Induction Risks

Two significant risks associated with ovulation induction treatment are ovarian hyperstimulation syndrome (OHSS) and multiple births. Mild OHSS is diagnosed when ovarian enlargement and discomfort are noted either after an HCG trigger shot or when pregnancy follows an ovulation induction treatment cycle. Luckily, severe OHSS exemplified by marked ovarian enlargement and accumulation of intra-abdominal fluid (ascites) is rare, occurring in less than 1% of ovulation treatment cycles. Multiple births can occur in 3-7% of those taking oral medications and in up to 25% of those using injectable gonadotropins (FSH, HMG). With the combination of both oral medications and injectables, triplets can occur in about 6% of cases.

Risk Prevention

As these conditions pose risks to both patients and the pregnancy, prevention is the best treatment. Identifying the patient at risk and modifying drug regimens are the best options. Previously, it was common to attempt ovulation treatment with clomiphene (Clomid) and if that was unsuccessful, injection treatment was

Mark Perloe, M.D., is the Medical Director of Georgia Reproductive Specialists, LLC. He is board certified in Reproductive Endocrinology and Infertility.

5445 Meridian Mark Road Suite 270
Atlanta, GA 30342
Phone: 404-843-2229 Fax: 404-843-0812
Web: http://www.ivf.com

recommended. Metformin therapy offers new options for patients with polycystic ovary syndrome (PCOS) to restore normal cycles when combined with diet and exercise regimens. If this treatment regimen fails, the addition of oral medications such as letrozole or clomiphene may restore normal cycles. The oral medications may be combined with injections of FSH (Bravelle, Follistim, Gonal-F) or hMG (Menopur) to improve development of the ovarian follicles and oocytes. Alternatively, low dose gonadotropins cycles starting at 50-75 units for up to three or more weeks may be successful when OHSS is a risk.

Factors considered when determining your medication regimen include patient age, response during prior cycles and weight, as well as the number of small antral follicles seen during a day 3 transvaginal ultrasound. While intuitively, it is reasonable to believe that more follicles is better, that may not always be the case. In fact, recent data suggests that despite finding a single follicle in up to 85% of letrozole treatment cycles, pregnancy rates appear to be higher than cycles using other protocols where more large follicles are recruited. Taking into account the above factors, your physician chooses your treatment protocol to recruit one to three follicles. Unfortunately, cycle design is not an absolute science and occasionally your individualized treatment plan will result in recruiting a larger number of follicles than expected.

Treatment Options

During the course of ovulation treatment, frequent transvaginal ultrasound examinations and blood testing will help your physician adjust the dose to limit your risk of complications. Coasting (withholding all medications) or the use of low dose hCG injections instead of FSH or hMG may also be beneficial. Despite these steps, the number of follicles and the estradiol rise may indicate that your risk of multiple births and OHSS are unacceptably high. Options such as conversion to in vitro fertilization (IVF), cycle cancellation or follicular reduction and IUI were the only options previously available.

Conversion to IVF is a proven safe and effective option as oocyte retrieval significantly reduces the risk of OHSS and blastocyst culture and limiting the number of embryos transferred reduces the risk of multiple births. However, IVF is costly and not financially available to all patients.

Canceling the treatment cycle and starting over with a lower medication dose or different protocol is an unfortunate outcome for anyone who has investment time and money for treatment.

Follicular Reduction

Follicular reduction (FR) involves oocyte retrieval as done with IVF. Yet with FR, a few oocytes are left behind and an IUI is carried out. While large studies evaluating follicular reduction are not available, our experience has been that pregnancy rates are similar to IUI cycles without FR.

Options for the "extra oocytes" removed during FR include disposal or IVF with cryopreservation of the embryos that result. Oocyte vitrification (cryopreservation) avoids disposing of valuable "extra oocytes", while avoiding the expense of IVF. As part of the follicular reduction-oocyte vitrification research protocol, the cost of oocyte vitrification and thawing is covered. IVF is provided at a significantly reduced cost if the IUI does not result in pregnancy and the oocytes are thawed for a second attempt at pregnancy.

The results from the first three patients enrolled in this study have been one ongoing pregnancy from IUI after FR, a healthy singleton delivered pregnancy following oocytes vitrification, oocyte thaw and IVF and one patient with no pregnancy resulting.

Follicular reduction, oocyte vitrification and IVF should not be seen as an alternative to low dose ovulation induction cycles or IVF. Rather, as further data become available, this technique may be one more tool available to avoid canceling stimulation cycles when an excessive follicular response occurs.

Superior IVF Pregnancy Rates May Be Achieved with a Disciplined Approach

John G. Wilcox, M.D., F.A.C.O.G.

The mean United States IVF pregnancy rates reported to the CDC are approximately 25%. Few programs are reporting significantly higher pregnancy rates in excess of 60% for selected groups of patients. Superior IVF pregnancy rates result from improvements in multiple factors involving IVF including: more efficient patient selection; improvements in the IVF laboratory; improved media with blastocyst transfer; development of recombinant FSH; improved luteal phase protocols for uterine preparation; and improved embryo transfer technique. Clearly, the pursuit of enhanced ART pregnancy rates is multifaceted.

However, patient selection is the most important factor predicting success with ART. Female age is inversely proportional to IVF success rates due to increased ovarian gonadotropin resistance and deteriorating egg quality.[1] Reduced egg quality presents at age 33 and accelerates after age 38. IVF pregnancy rates are 50% lower for women older than 39 compared to women younger than 35. Moreover, few women are successful with ART after 43.

Fortunately, there are techniques to identify poor candidates for IVF prior to cycle initiation. The most useful test to identify poor responders is a day 3 FSH and estradiol level.[2, 3] If the FSH and the estradiol level are less than 10 mIU/ml and 70 pg/ml, respectively, then the patient generally has an excellent prognosis. If either level is elevated the prognosis is guarded, and for those with an FSH level greater than 20 mIU/ml, success rates are less than 1%.[4]

For women with the intermediate test results, a more provocative test is appropriate, the clomiphene challenge test.[5] This evaluation requires treatment during cycle days 5 through 9 with 100 mg of clomiphene followed by an FSH level on cycle day 10. If the FSH level is greater than 15 mIU/ml, the couple have a poor prognosis and egg donation is recommended.[6]

HRC performed a prospective randomized study evaluating the impact of ovarian response to gonadotropin stimulation on pregnancy rates.[7] A pilot study of 61 women with fewer than 5 dominant follicles were determined to have a poor prognosis regardless of pre-cycle testing, 4/61. We subsequently randomized patients into two groups. In Group 1, IVF cycles were cancelled using more selective criteria of at least 5 dominant follicles greater than 16mm on the day of hCG compared to the more commonly used criteria of less than 3 dominant follicles. (See Table 1.) Group 1 demonstrated higher pregnancy rates in all three age groups, with the < 35 years and >40 years statistically significant (submitted to ASRM October, 2001).

Therefore, using pre-cycle evaluations and ovarian response criteria, superior pregnancy rates may be achieved. However, patient selection alone will not suffice.

To enable ART programs to achieve ideal pregnancy rates, it is important to have a state-of-the-art IVF laboratory with an embryologist well trained in techniques of intracytoplasmic transfer, assisted hatching, preimplantation genetic diagnosis, and defragmentation of the embryo. The laboratory requires state-of-the-art incubators maintaining near-physiologic conditions for the developing embryo, as well as laminar flow with selective filters to remove organic solvents. In addition, specialized lighting protocols may improve clinical outcomes. More recently in selected

John G. Wilcox, M.D., is board certified in reproductive endocrinology and infertility and practices at the Huntington Reproductive Center, Pasadena, California.

Huntington Reproductive Center
333 S. Arroyo Parkway 3rd Floor
Pasadena, CA 91105
Phone: 626-440-9161 Fax: 626-440-0138
Email: doctor07@havingbabies.com
Web: http://www.havingbabies.com/

patients, data has been presented suggesting delayed embryo transfer until day 5 following fertilization (versus day 3) may improve implantation rates from 20% to 50%. With an average of 2.2 blastocysts transferred, pregnancy rates approach 70%.[8] This technique may provide superior pregnancy rates with fewer embryos transferred, minimizing multiple gestation rates. This is especially important for women less than 35, the highest risk group for multiple gestation.

Other factors contributing to higher pregnancy rates include improved medications for ovarian stimulation. The FDA has recently approved recombinant FSH for use in women undergoing superovulation, a product created by infecting hamster ovary cells with the human FSH gene. This provides a continuous source for highly purified FSH. Since these products were never in vivo, there is no digestion of the glycoprotein. Recombinant FSH has minimal lot variation and contains 99.9% bioactive FSH. Studies treating women with recombinant FSH support improved pregnancy rates compared to urinary gonadotropins.[9, 10]

Recently, GnRH antagonists were approved to suppress ovulation during ovarian stimulation.[11] Antagonists will likely replace GnRH agonists, a product requiring up to ten days to suppress ovulation, improving ovarian stimulation efficiency. And finally, a vaginal progesterone gel (Crinone) has been developed for luteal phase support following IVF. The polycarbophil base maintains continuous absorption of progesterone, providing high progesterone concentrations within the uterine cavity. Crinone is undergoing investigation to determine the impact on IVF pregnancy rates.

HRC performed a prospective randomized study comparing two luteal phase protocols using Crinone for luteal phase support in frozen embryo transfers.[12] All patients received pre-cycle screening with sonohysterography and mock embryo transfers. Uterine cavity preparation was achieved with estradiol 2–4 mg intramuscularly every 3 days, starting cycle day 2, until the endometrium measured at least 8 mm. In Group 1, women were randomized to receive 50 mg of intramuscular progesterone in oil with Crinone 8% vaginally daily, versus Group 2, who received Crinone 8% vaginally twice daily. There were no significant differences in the mean ages of the women within the two groups.

Table 1

	Mother's Age		
	< 35 years	**35–39 years**	**> 40 years**
Group 1	37/55 (67.3%)	24/49 (48.9%)	11/30 (36.7%)
Group 2	23/73 (31.5%)	36/112 (32.1%)	3/32 (9.3%)
p value	p < .01	p = .063	p = .024

	Pregnancy Rates (%)
Group 1	20/43 (46.5%)
Group 2	16/54 (29.6%)
p value	p = .13

Group 1 had a higher success rate than Group 2, although not statistically significant. The combination provides a high local concentration of progesterone while maintaining physiologic concentrations of serum progesterone. This may provide more physiologic intrauterine and serum conditions resulting in higher implantation rates and pregnancy rates. Further investigation is required.

Finally, variations in embryo transfer technique among physicians has been demonstrated to have a profound impact on individual pregnancy rates in the same institution.[13] For quality control, women should receive measurements of the length and the direction of the uterine cavity prior to initiation of an in vitro cycle. HRC has been extremely successful performing cervical dilation prior to uterine preparation in patients with cervical stenosis, allowing atraumatic transfers. Pretreatment with vaginal cytotec 200 μgm facilitates dilation in difficult cases. Aseptic technique during embryo transfer and prophylactic antibiotics with doxycycline may improve pregnancy rates.[14] Uterine bleeding must be prevented during embryo transfer by avoiding contact with the uterine fundus, potentially increasing uterine contractility. In addition, ultrasound guidance during transfer may reduce transcervical embryo expulsion.[15]

In conclusion, maintaining superior pregnancy rates requires a multifaceted, disciplined approach. Previously mentioned factors may influence IVF pregnancy rates. Providing the highest possible pregnancy rates require continual evaluation of IVF laboratories,

stimulation protocols, patient selection, luteal phase protocols and embryo transfer techniques.

With multiple physicians, individual pregnancy rates must be determined, since variations may occur with stimulation protocols and embryo transfer techniques.

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Reproductive Surgery Techniques

Michael Doyle, M.D., and Shaun Williams, M.D.

An integral part of the fertility evaluation is an assessment of the anatomy of the reproductive tract, as abnormalities of the uterus, Fallopian tubes, ovaries, and lower pelvis are common causes of both infertility and recurrent pregnancy loss. Anatomic abnormalities can be identified through the medical interview process, the physical exam, or through specific imaging evaluations, such as the hysterosalpingogram and ultrasound. Surgical treatment of any conditions is an option which is often considered prior to any traditional fertility treatments. Reproductive specialists utilize numerous techniques to correct specific problems while minimally altering surrounding structures in efforts to increase the efficiency of the reproductive organs.

Reproductive surgical procedures within the abdomen are usually approached one of two ways, either by a larger incision on the lower abdomen (called a *laparotomy*), or through minimally invasive means utilizing small incisions and cameras (called *laparoscopy*). Most procedures can be performed utilizing laparoscopy, and reproductive specialists typically have greater expertise with this form of surgery than other general practitioners. Many uterine cavity abnormalities can be corrected without any incisions at all, through the use of *hysteroscopy*. This involves dilating the cervical opening of the uterus and passing an operating camera into the cavity. Both laparoscopy and hysteroscopy are usually outpatient procedures, allowing women the ability to go home the same day with minimal recovery necessary, while larger incisions require at least an overnight hospital stay.

During laparoscopy, different instruments are available to help surgeons perform the delicate surgeries often needed when correcting abnormalities. These are specially designed to be passed through small incisions in the abdomen allowing procedures to be performed while observing the monitor image from the laparoscopic camera. Typical surgical instruments, such as scissors and scalpels, can be modified for this use, but also other means to cut and dissect are often employed. Electrosurgical, laser, and ultrasonic instruments are available to help surgeons perform many procedures with ease. All methods are equally effective in experienced hands.

Many procedures can be performed laparoscopically. Laparoscopy is commonly performed in many women for the evaluation of pelvic pain which is often due to endometriosis. It is of particular benefit to be able to closely evaluate the surface lining of the pelvis with the camera in close proximity, to diagnose and treat endometriosis, a disease which can cause both pain and infertility. For many women, a laparoscopy following an initially normal evaluation can be of benefit to diagnose pelvic conditions such as endometriosis and pelvic scar tissue.

Laparascopy has also been used to repair tubes after a prior tubal ligation, allowing women who have had the tubes "tied" an opportunity to become pregnant. Uterine fibroids can be excised laparoscopically, although this procedure is most commonly performed through a larger incision. Other procedures which have traditionally been performed by laparotomy are

Michael Doyle, M.D., is the founder and medical director of the Connecticut Fertility Associates. His specific areas of expertise include microsurgery, advanced laser laparoscopy and hysteroscopy, treatment of severe endometriosis, management of male fertility, and in vitro fertilization. **Shaun Williams, M.D.,** is board certified in obstetrics, gynecology, and reproductive endocrinology. His interests include recurrent pregnancy loss, ovulation disorders including polycystic ovarian syndrome, and assisted reproductive technologies.

Connecticut Fertility Associates
4920 Main Street
Bridgeport, CT 06606
Phone: (203) 373-1200 Fax: 203-365-6516
Email: michael.doyle@ctfertility.com
http://www.connecticutfertility.com

now able to be performed through laparoscopy. These include removal of diseased ovaries or tubes, hysterectomy, bladder surgery, and lymph node surgery in cases of pelvic cancers.

Hysteroscopy involves the placement of an additional telescope (the hysteroscope) through the dilated cervix, directly into the uterine cavity. No incisions are required for this, and depending on what is found, hysteroscopy usually takes about 15–45 minutes to perform.

This procedure also can be performed as a diagnostic test to help identify abnormalities during an initial evaluation. Defects involving the uterine cavity, such as fibroids, polyps, scar tissue, and developmental abnormalities, can be corrected using hysteroscopy. Additionally, blockages of the Fallopian tubes can at times be corrected during this procedure.

Even though hysteroscopy involves no incisions, it is usually performed under anesthesia as dilation of the cervix can be uncomfortable. Small, flexible hysteroscopes are available and can be used in the physician's office using only minor or local anesthesia. This provides a convenient method to identify uterine abnormalities without requiring anesthesia, but if significant abnormalities are present, an outpatient surgery is usually necessary. The recovery from a hysteroscopy alone is generally only 24–48 hours, since no incision is required. Risks are minimal, and include very low chances of bleeding, infection, or uterine perforation.

Following laparoscopy, 3–4 days of recovery is the average time most patients need to feel basically back to normal. Some amount of abdominal pain often persists for a few days, so patients are advised to take prescribed narcotics to control this pain before it gets severe, rather than letting it get out of control. The anesthesia effect (feeling "washed out") can also last several days. Most people return to work after 3–4 days, though there is a wide range of variation.

Laparoscopy, hysteroscopy, and at times laparotomy are excellent tools to assist the reproductive endocrinologist in diagnosing and correcting physical conditions that can impact fertility. With the information provided from this surgery, the physician can also determine which additional non-surgical therapies may also be considered to assist patients in achieving a healthy pregnancy.

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Microsurgical Management of Male Infertility

Jonathan Schiff, M.D.

The surgical management of male infertility is one of the most exciting topics in all of medicine. Over the last 25 years, the application of advanced microsurgical techniques has made the treatment of the infertile male one of the great success stories in medicine. We can now offer successful treatment options to thousands of couples affected by male factor infertility whose only options in the past were donor sperm or adoption.

The most common correctable conditions that are associated with male infertility are varicoceles, vasal obstruction, or severe testicular sperm production defects. Microsurgical ligation of a varicocele and surgical reconstruction of the vas deferens can correct these two states. With severe sperm production problems, microsurgical testicular sperm extraction is the most successful means of retrieving sperm for IVF.

Varicoceles

Varicoceles are found in 35–40% of men with primary infertility (never had a pregnancy). The presence of a varicocele is even more likely among couples who have had a child in the past and now cannot (secondary infertility) and is found in 75–80% of these men. Ligation of a varicocele may prevent infertility and low testosterone levels after repair.

The microsurgical, subinguinal approach is the preferred technique to fix varicoceles. This approach with optical magnification produces the best results in terms of removing all of the veins that may contribute to the formation of a varicocele. Furthermore, the microsurgical approach minimizes the complications associated with fixing varicoceles. We can precisely identify the testicular artery and prevent damage to this important structure. We also preserve any cremasteric arteries and lymphatic channels to prevent the formation of hydroceles.

Vasal Obstruction

Obstruction to the vas and epididymis represents the most treatable causes of male infertility. In these states, the testis functions normally and the problem is strictly a transport problem. In the United States, the most common cause of obstruction of the vas deferens is vasectomy. Up to 500,000 vasectomies are done annually and up to 5% ultimately are reversed. Injury to the vas is another common cause of obstruction, most often the result of childhood hernia repair or testis surgery. Several conditions, including congenital bilateral absence of the vas deferens, also result in variable lengths of vasal or epididymal obstruction. Microsurgical techniques have vastly improved the success rate of surgery to repair vasal or epididymal obstruction. Vasovasostomy is successful in up to 99% of cases, while vasoepididymostomy has a success rate of up to 90%.

Vasectomy Reversal (Vasovasostomy)

Overall patency rates of 86% and pregnancy rate of 51.6% were reported with the results, for men with obstruction less than 3 years, of 97% patency with a 76% pregnancy rate. Others have reported similarly good results with a microsurgical approach to vasectomy reversal. Several recent innovations have improved vasovasostomy outcomes. The use of the microdot technique represents an important technical point in terms of planning for optimal suture placement. Using

Jonathan Schiff, M.D., is Assistant Clinical Professor of Urology at Mount Sinai School of Medicine, New York.

Mount Sinai School of Medicine
1120 Park Avenue, New York, NY, 10128
Phone: 212-996-6660
Email: dr.schiff@gmail.com

this technique allows the surgeon to precisely target where to place sutures to achieve a water-tight anastomosis and can result in up to a 99.5% rate of return of sperm to the ejaculate.

Vasectomy Reversal (Vasoepididymostomy)

Vasovasostomy is not always a feasible option to restore vasal patency. If epididymal obstruction is present, whether primary or secondary to chronic vasal obstruction, a vasoepididymostomy is required proximal to the obstruction in order to restore continuity for sperm transport. In the situation of epididymal obstruction, the decision to perform a vasovasostomy or vasoepididymostomy is made intraoperatively and is based on the microscopic examination of the vas fluid and the time of obstruction. To provide optimal outcomes, surgeons should be skilled at performing a microsurgical vasoepidymostomy if they perform vasectomy reversals.

Results comparing the four main techniques of vasoepididymostomy were recently published. The newer intussusception techniques, which provide a more water-tight anastomosis, have comparable patency rates with lower late failure rates than the older techniques. This very important finding suggests that men undergoing the intussusception techniques have a much lower failure rate after reconstruction and will remain potentially fertile longer.

Sperm Retrieval Techniques

Not infrequently, men will have severe impairments in sperm production, with or without female factors. In these cases, sperm retrieval for assisted reproductive techniques may be the most appropriate option. Most couples prefer natural conception, and we make every effort to enable couples to conceive on their own. However, we evaluate each couple's best reproductive options on a case by case basis, and when needed, microsurgical sperm retrieval is the surest path to success.

Several genetic and acquired problems cause men with obstructive azoospermia to be unreconstructable. Some patients with congenital bilateral absence of the vas deferens have defects in the sperm transport system. Many of these men are not candidates for reconstruction. Non-obstructive azoospermia occurs when men without obstruction have no sperm in their ejaculation. This is caused by either genetic or environmental problems, such as chemotherapy, that results in severe depression in spermatogenesis to the point that no sperm are present in the ejaculate. However, sperm retrieval is still possible in the majority of cases. Sperm production within the testicle is very variable. We believe that a technique that exposes the entire testis is critical to find sperm in these difficult cases.

Men with Klinefelter's syndrome have a very severe form of genetic infertility associated with an abnormal karyotype of 47 XXY. Prior to modern assisted reproductive techniques, men with this problem were sterile. Today, a technique of sperm retrieval with intracytoplasmic sperm injection (ICSI), is the preferred treatment modality in those desiring paternity. Even in this severely impacted group of men, sperm can be retrieved in over 70% of cases and pregnancies are now routinely reported.

The technique of microsurgical epididymal sperm aspiration is used to obtain sperm in men with an intact epididymis. In men with non-obstructive azoospermia, the microdissection testicular sperm extraction technique provides the highest yield in terms of sperm retrieval while preserving as much testicular parenchyma as possible. Even in men with severe genetic causes of infertility, such as Klinefelter's syndrome, successful retrieval of sperm is possible in up to 70% of men. After chemotherapy, sperm can be found in nearly half of retrieval attempts in men with azoospermia.

Microsurgical testicular sperm extraction is the most successful technique to retrieve sperm in men with nonobstructive azoospermia and it results in the least damage to the testis. Postoperative scarring is substantially lower with this technique, compared to open biopsy. The disadvantages of any microsurgical technique are the need for experience and the acquisition of microsurgical skills.

Conclusion

Most men with infertility are treatable using either medical therapy or surgical techniques. The advanc-

es of microsurgery in the past 20 years have enabled thousands of men who would otherwise have been unable to father their own genetic children to help create life. Some obstacles remain, but each day brings new advances that allow us to help couples conceive.

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Embryoscopy in the Evaluation of Clinical Miscarriages

Peter Ahlering, M.D.

Miscarriages occur frequently, perhaps as often as 20% of all pregnancies. Chromosomal abnormalities, specifically aneuploidy, are considered to cause at least 50% of all isolated miscarriages. Physicians that care for early pregnancies diagnose miscarriages often before the patients have clinical symptoms of vaginal bleeding. When a miscarriage is diagnosed by early ultrasound with the absence of fetal cardiac activity, often the patient undergoes dilatation and curettage. This procedure is done to remove the products of conception sparing the patient the unpleasant physical and emotional aspects of undergoing a miscarriage with spontaneous passage of the pregnancy. In addition the dilatation and curettage (D and C) represents the chance to make a diagnosis of the cause of the miscarriage by ruling out the purported most common cause of pregnancy losses: aneuploidy. However with the D and C, maternal cells often contaminate the miscarriage specimen, yielding the false results that the pregnancy loss was normal female karyotype. This is a very common problem. Perhaps 50–80% of the 46XX (normal female karyotype) results from D and C specimens are in reality due to maternal contamination thus the results are erroneous and the patient is then quite possibly falsely advised that the pregnancy loss was 'normal'.

The physician has one chance to evaluate the cause of a miscarriage and that opportunity comes at the time the D and C is done. If the results of a standard karyotype come back "normal 46 XX", as it does at least 50% of the time, then unfortunately one cannot confirm that these results are indeed true. The opportunity to make a diagnosis is lost then. If the karyotype comes back showing that there is a "Y" chromosome, then one knows that there is no contamination as the maternal cells of course have no "Y" chromosome. Likewise if the chromosome analysis after a D and C comes back showing an abnormal number of chromosomes (called aneuploidy) then one knows that this must indicate an embryo abnormality since the female cannot have such an aneuploidy, thus one knows that there was no contamination of the specimen. But the all too common result of 46XX from the D and C specimen remains a frustration for the patient and the physician.

Hysteroscopy is a procedure whereby a small telescopic instrument is placed into the uterus prior to the D and C. Thus 'embryoscopy' is simply using the small hysteroscope immediately prior to the D and C procedure to visualize the contents of the uterus (i.e., the embryo and the gestational sac). With this simple technique, the physician can directly sample the products of conception under visualization preventing the problem of maternal cell contamination. In addition one can assess the physical attributes of the embryo prior to D and C. This is helpful because 20% of the embryos that are chromosomally normal will have abnormal physical features, thus confirming a 'genetic' cause rather than chromosomal or other cause—like uterine defect, immune problem, etc.

If on the other hand the assessment with embryoscopy and chromosome analysis both look normal, then one should of course strongly consider further evaluation with immunology testing and hysteroscopy in the non pregnant state to rule out uterine anomalies and endometritis. In addition one may look at male factors that may contribute to early pregnancy loss such as DNA fragmentation and detailed morphologic assessment of sperm

Peter Ahlering M.D., is Medical Director of Sher Institutes for Reproductive Medicine, St. Louis and Central Illinois. He is a board certified OB/GYN with a focus in operative laparoscopy and advanced laparoscopic procedures.

Phone: 314-983-9000
Email: pahlering@sherinstitute.com
URL: www.haveababy.com

A lot of work has been done with embryoscopy by Phillip et al. They recently showed a series of cases where 272 patients were assessed. These patients had a sonographically visible pregnancy that was 7–8 weeks; 232 were able to be visualized prior to D and C; 85% showed abnormal development visually; 14% looked normal; 30% of the abnormal appearing embryos had normal chromosomes; 50% of the normal appearing embryos on embryoscopy had abnormal chromosomes. Thus one can see that embryoscopy definitely helps delineate the miscarriage cause.

Ferro et al. also conducted a study where they compared traditional D and C and karyotype versus that of embryoscopically directed sampling prior to D and C. Here is a summary of the results:

- 36/68 cases had karyotype results for both biopsy and curettage
- 8/36 (22%) would have been completely misdiagnosed as normal without direct biopsy via embryoscopy beforehand
- 1/3 curettage specimens, despite precautions of rinsing the specimen to attempt to cleanse the maternal cells away, were contaminated. Embryoscopy would of course help in these instances
- Thus the miscarriage specimens with karyotype 46XX was inaccurate often times

At SIRM St Louis, we have performed many such procedures with embryoscopy prior to D and C specifically in patients that have unfortunately miscarried after an IVF procedure. Typically I perform these procedures in the office setting with the patient under sedation for pain management. The 2.9mm hysteroscope is inserted into the uterine cavity, typically without the need for dilatation of the cervix. Using saline as a distention medium, the contents of the uterus can be visualized clearly. The gestational sac can be seen, incised with small scissors and directly biopsied for the chromosome analysis—not much tissue is needed. Then one can look into he gestational sac to view the embryo, the yolk sac, etc. One can also directly sample the embryo also for chromosme analysis. Then D and C can be performed to evacuate the uterine contents for pathological assessment. In addition, one can often the look again into the uterus to confirm that the products of conception have been completely re-

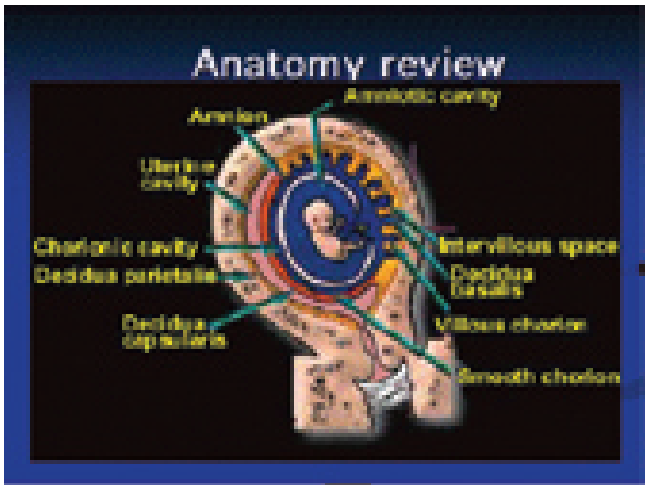

Diagram A. Normal early pregnancy anatomy. Embryoscopy is the process of making an incision in the Decidua Capsularis and the Amnion to enter the amnionic cavity. In very early losses (4th and 5th week), one would grasp the entire sac and remove it, as seen below in Fig. 4.

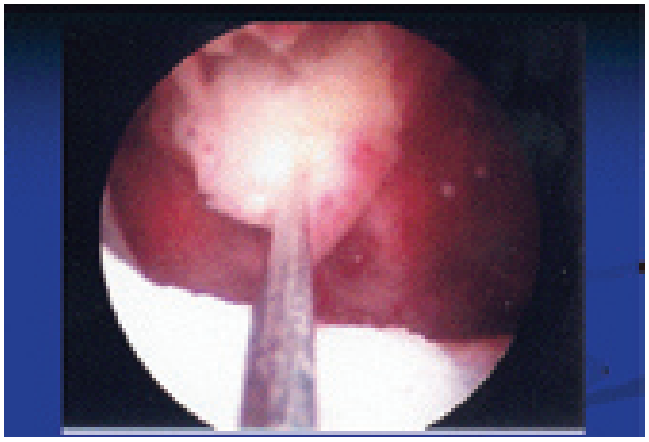

Fig 1. Hysteroscopic scissors making incision into the gestational sac (Decidua Capsularis) of a 6th week pregnancy loss.

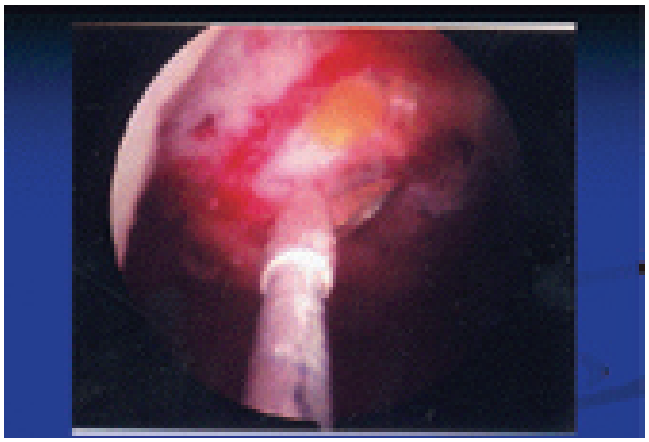

Fig 2. Hysteroscopic graspers sampling the gestation sac (Decidua Capsularis) of the same pregnancy loss. The chromosomes of this are the same as the embryo itself.

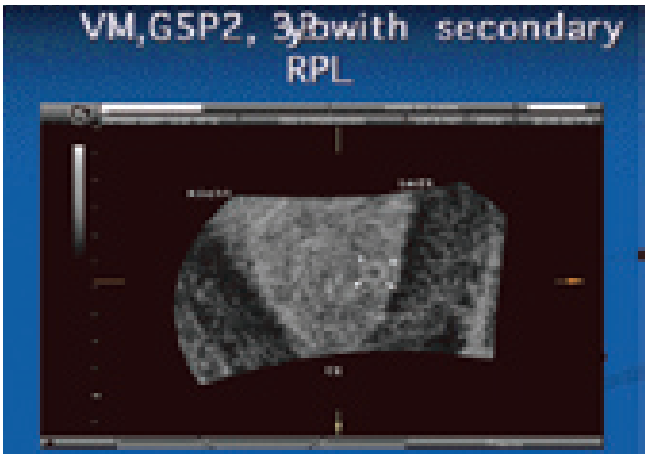

Fig 3. Ultrasound picture of early pregnancy. This was made in the late 5th week after natural conception in a patient with recurrent losses, previously unexplained. This US picture shows no change from the prior exam 5 days earlier (at 5 weeks 0 days). Thus miscarriage was diagnosed.

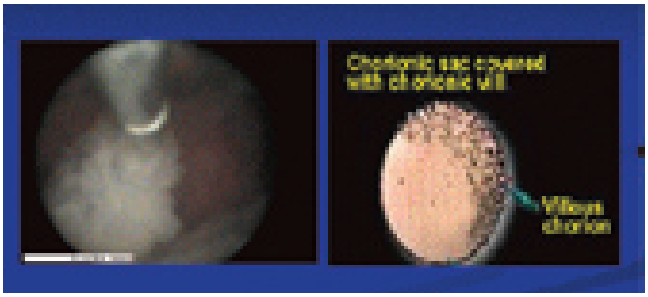

Fig 4. [left] Embryoscopic removal of the entire gestational sac. The chromosome analysis confirmed there was aneuploidy. **[Right] Gestational sac at 5 weeks** (for comparison to the left image).

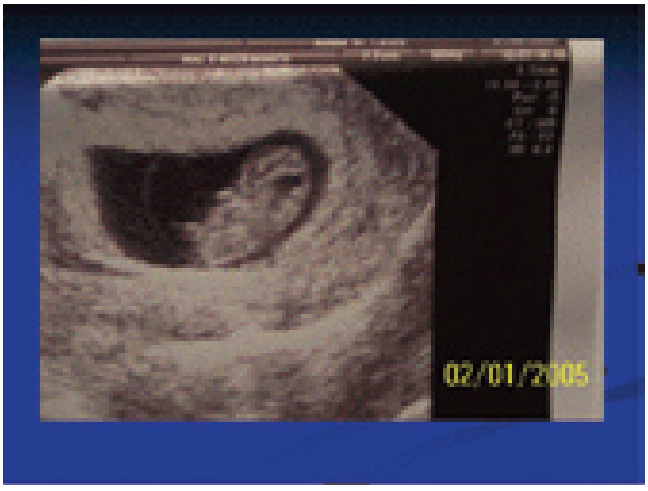

Fig 5. Ultrasound picture of a pregnancy loss at 9 weeks. The fetus appears normal, but there is no heart activity.

moved, preventing the problem of retained tissue.

I have also used the technique of embryoscopy to assess twin pregnancy losses, getting direct embryo samples from each sac, giving accurate analysis of the separate embryos. This is not possible to do accurately with basic D and C only.

We have found embryoscopy to be helpful in evaluation of all cases of pregnancy loss however; those conceived with natural conception, IUI or IVF/ICSI. The papers that have been published to date on this process have all dealt with pregnancy loss in cases in which there was an identifiable embryo on US, i.e. those after 6 weeks 0 days estimated gestational age from the last menses (4 weeks or so after ovulation/conception). However, we have utilized the basic technique of embryoscopy to extract the entire sac in pregnancies that have arrested in development as early as 5 weeks 0 days. We have been able to obtain accurate chromosome analysis on many such pregnancy losses, providing answers to the cause of the loss in many cases where, in the past, we could only speculate the cause. Being able to diagnose the cause of these very early pregnancy losses is extremely helpful in patient counseling, providing answers to the couple. Also, when one can rule in or out chromosome causes of pregnancy loss, one can focus further evaluation more directly. If the chromosome analysis confirms normality, one can embark on immune evaluation for example and direct treatment in a future early pregnancy to reduce the chance of loss there.

The key to being able to diagnose pregnancy loss this early involves of course recognizing pregnancy early with positive tests and then simply monitoring early growth of the embryo with ultrasound starting in the early 5th week of pregnancy. If appropriate growth and developmental milestones are not achieved then miscarriage can be diagnosed and evaluated as early as possible. These simple steps will allow intervention and an opportunity at accurate diagnosis of the loss.

Concluding remarks:

Current techniques of assessing the origins of miscarriage using simple D and C are insufficient. This is mainly due to the potential for inaccurate results related to contamination of the specimen by maternal endometrial tissue giving a falsely normal result.

However, there can also be truly normal karyotype results but abnormal embryonic growth, suggesting a non-chromosomal cause for the loss. Therefore visualization and direct tissue sampling of the embryo prior to D and C is very helpful in assessing growth patterns of the embryo and also obtaining an uncontaminated sample for chromosome analysis. Clearly embryoscopy is helpful in such instances. However it is also helpful if the results show normal appearance and normal karyotype, then one can focus attention of other issues like immunology, uterine factors, etc that may be treatable causes of miscarriage in a future pregnancy.

Embryoscopy using the current simple techniques for basic hysteroscopy pose no additional risk to the patient and do not require elaborate equipment. Nor does the procedure add significant time to the entire process. Application of this technique to the evaluation of pregnancy losses anytime there is a confirmed loss with ultrasound will advance our knowledge of early pregnancy and, of course, prove beneficial to patient counseling for future pregnancies. In addition, with this technique, one can find answers often to the cause of miscarriages—this is always helpful for patients to understand "why?" and cope with the loss.

Medical offices should evaluate pregnancies early after a positive pregnancy test. In this way, the patients can get early, serial ultrasound assessment and monitoring. Adopting this simple protocol will then lead to early diagnosis of miscarriages and hence we can evaluate them appropriately before the patient experiences bleeding and passage of the tissue. If this occurs, then the opportunity is gone for optimally assessing the pregnancy loss.

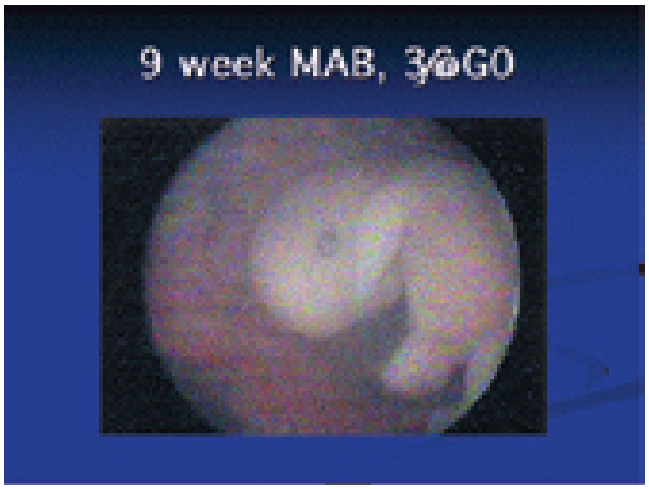

Fig 6. Embryoscopic picture of the pregnancy loss seen in Fig 5. There is normal development apparently of the embryo.

Modern Trends in the Management of Recurrent Pregnancy Loss

Vicken Sepilian, M.D., M.M.S.

Traditionally, recurrent pregnancy loss (RPL) is the miscarriage of three or more consecutive first- or early second-trimester pregnancies. It occurs in about 1–2% of women. However, the risk of having another miscarriage after having two consecutive miscarriages is similar to that of women who have had three consecutive miscarriages, approximately 30%. Hence, it is reasonable to initiate evaluation of couples who have had two previous miscarriages.

A number of diverse causes can lead to RPL. It is important for a couple who experience RPL to consult a physician with expertise with this condition. A thorough history, including history of medical conditions in either partner or first-degree family members and a full physical exam may help your physician to identify conditions that may predispose to RPL. Below is a brief discussion of the most common conditions that are associated with RPL. They are also the most common conditions that patients often are concerned with.

Genetic Causes

In approximately 5% of couples with RPL, chromosome analysis will reveal a balanced translocation, a condition in which part of one chromosome attaches to another, which could be present in either parent. Though the parent with the translocation is typically normal, he or she may pass on too much or too little genetic material to the embryo (early pregnancy). This often results in a miscarriage. Translocations can be diagnosed with a blood test of both parents that analyzes the chromosomes (karyotype). In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) is a well-established therapeutic option for couples who carry a translocation. IVF with PGD is a method in which a woman is given medications to produce multiple eggs which are then retrieved when they are mature. The eggs then are fertilized with the male partner's sperm. The embryo is then allowed to grow in a carefully controlled environment in the embryology lab until it is has grown to 8 cells. At this point, one cell is removed and tested for the suspected genetic abnormality. IVF with PGD allows the selection of chromosomally normal embryos to be placed in the uterus.

Uterine Anatomic Abnormalities

In approximately 10–15% of women with RPL, an anatomic factor is found. These anatomic abnormalities include congenital uterine malformation (birth defects of the uterus), uterine fibroids or polyps, and intrauterine adhesions (scar tissue inside the uterus). Typically, anatomic abnormalities cause pregnancy loss in the late first or second trimesters. Most common uterine malformation in women with RPL is a uterine septum. A hysterosalpingogram (X-ray test with dye), ultrasound with or without saline infusion, and hysteroscopy are often used to diagnose these disorders. A MRI may also help in differentiating between the types of congenital uterine anomalies. Most of these conditions are corrected surgically. A hysteroscopic approach is preferred to excise most uterine septa, uterine adhesions, polyps

Vicken Sepilian, M.D., is a fellowship-trained reproductive endocrinologist and infertility specialist at CHA Fertility Center in Los Angeles. His active interests include minimially invasive surgery, ectopic pregnancy, abnormalities of ovulation, ploycystic ovary syndrome, and infertility.

5455 Wilshire Blvd 1904
Los Angeles, CA 90036
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Also: http://www.inciid.org/forums/immune/index.html

For more information on tests and research into recurrent pregnancy loss, read this article: Immunology May be Key to Pregnancy Loss: http://www.inciid.org/article.php?cat=immunology&id=374

and most fibroids. Occasionally, a fibroid may be too large to be removed hysteroscopically and an incision in the low part of the abdomen may be necessary.

Hormonal Condition

Luteal phase deficiency is a controversial condition in which low progesterone production may contribute to RPL. Progesterone is a hormone made by the ovary after ovulation and is essential in preparing the lining of the uterus for pregnancy. Unfortunately, there is no good method to evaluate luteal phase deficiency. Historically, a biopsy of the uterine lining (endometrial biopsy) and blood progesterone levels were used to diagnose this condition, however, the accuracy of these tests has recently been challenged. Treatment for luteal phase deficiency includes ovulation induction, progesterone supplementation, or injection of human chorionic gonadotropin (hCG). There is limited evidence to support the effectiveness of these treatments. Any treatment for luteal phase deficiency should be individualized after careful discussion with your doctor.

Risk of pregnancy loss is increased in women with untreated overt or even mild conditions of the thyroid gland (a hormone producing organ located in the front of the neck). Women who experience RPL should be screened for thyroid disease by performing a blood test called TSH (thyroid stimulating hormone). Thyroid hormone replacement is simple and often will correct the problem.

Metabolic Conditions

Poorly controlled diabetes increases the risk of RPL. Women with RPL and diabetes should have an evaluation of their blood glucose (sugar) levels and hemoglobin A1C (a test that assesses how well the disease is under control). Women with poorly controlled diabetes can improve their pregnancy outcomes if they delay pregnancy until their test results have normalized. A consultation with a health care provider with expertise in diabetes is recommended as the guidelines of therapy are frequently updated.

Women who have insulin resistance as a result of polycystic ovary syndrome (PCOS, a condition of abnormal ovulation and high male hormone levels) or obesity have increased risk of miscarriage. Women suspected of having insulin resistance may be tested with an oral glucose tolerance test and measuring blood insulin levels. A balanced diet and moderate cardiovascular exercise may help improve insulin sensitivity. There is also increasing evidence to suggest that insulin sensitizing medications may reduce the risk of miscarriage in women with RPL.

Antiphospholipid Antibody Syndrome

This is a condition that increases the risk of RPL, blood clot formation in small vessels, second trimester pregnancy loss, and other pregnancy complications such as toxemia and intrauterine growth restriction. It is believed that blood clot formation in small vessels at the site where the early pregnancy attaches to the uterus may result in restriction of blood supply to the fetus and cause a miscarriage. The diagnosis is made based on the clinical factors mentioned above and specific blood tests. The blood tests include anticardiolipin antibody and lupus anticoagulant. Treatment of women with antiphospholipid syndrome and RPL includes heparin (blood thinner) with or without aspirin beginning in early pregnancy.

Inherited Thrombophilias

These are genetic conditions that increase the risk of blood clot formation and have been linked to RPL. The most common thrombophilias are factor V Leiden mutation, G 20210 prothrombin mutation, antithrombin III deficiency, methyltetrahydrofolate deficiency, protein C and protein S deficiency. Specific blood tests will help make the diagnosis. It should be stated, however that not all women with a thrombophilia experience adverse pregnancy outcomes. Many questions about the impact of these conditions on RPL remain unanswered. It is reasonable to consider screening for these conditions in women with personal or family history of blood clots and unexplained RPL. Treatments for thrombophilias include heparin (blood thinner) with or without aspirin.

Male Factors

There is increasing evidence that implicates defects in sperm DNA to be associated with RPL. Defective

sperm is capable of fertilizing an egg and producing an early pregnancy. This pregnancy, however is likely to be abnormal and eventually will result in a miscarriage. Our knowledge of sperm DNA abnormalities is at the very early stages and the best way to diagnose and treat such conditions is yet to be established.

Environmental Factors

Cigarette smoking, alcohol and heavy caffeine consumption have been implicated as environmental factors that could increase the risk of pregnancy loss. As little as 10 cigarettes, 2 alcoholic beverages, or three cups of coffee a day have been shown to increase the chance of miscarriage. If you are a smoker or a heavy consumer of caffeine or alcohol, it is best to reduce the intake as much as possible or to eliminate their use completely as no safe levels have been established.

Age

Over one-third of all pregnancies in women over the age of 40 result in a miscarriage. It is believed that genetic abnormalities arising in the oocyte (egg) with aging are transmitted to the embryo resulting in a miscarriage. Blood tests are available to examine the ovarian reserve (a rough estimation of the remaining normal eggs in the ovary). Your doctor may recommend one of these blood tests. Treatment is highly variable; however, women with diminished ovarian reserve may benefit from donor eggs (eggs obtained from a previously screened young woman with normal ovarian reserve who is selected by the patient).

Unexplained

Despite a thorough workup, more than half of women with RPL will have no apparent predisposing factor for their poor reproductive outcome. In such cases, the chance of having a successful pregnancy is very good and has been reported to range from 60%–75%.

Recurrent pregnancy loss is a potentially frustrating and devastating condition. Education and a thorough evaluation can provide important perspective. When a predisposing factor is identified, specific counseling and treatment can help improve the possibility of a normal future pregnancy. When no specific cause is identified, reassurance and encouragement are no less valuable as there is a strong likelihood of a future normal pregnancy.

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SAFETY INFORMATION

- **Follistim® AQ Cartridge administered with Follistim Pen® delivers on average an 18% higher amount of follitropin beta compared to lyophilized preparations administered using conventional syringes. A lower dose should be considered when using Follistim® AQ Cartridge.**
- **Follistim® AQ Cartridge, like all gonadotropins, is a potent substance capable of causing mild to severe side effects including Ovarian Hyperstimulation Syndrome (OHSS), with or without pulmonary or vascular complications.**
- **Follistim® AQ Cartridge should be prescribed only by physicians who are experienced in infertility treatment and should advise their patients of treatment risks, including OHSS and multiple births.**

* Based on total IU's sold from April 2005-March 2006

References: 1. Follistim® AQ (follitropin beta injection) Cartridge full Prescribing Information. Roseland, NJ: Organon USA Inc; 2005 **2.** Kettel LM, Scholl G, Bonaventura L, Pang S, Sacks P, Chantilis S. Evaluation of a pen device for self-administration of recombinant human FSH in clomiphene citrate-resistant Anovulatory women undergoing ovulation induction. RBM Online, 2004; Volume 9 no. 4 373-380. **3.** Pang S, Kaplan B, Karande V, et al. Administration of recombinant human FSH (solution in cartridge) with a pen device in women undergoing ovarian stimulation. RBM Online, 2003; Vol. 7 no. 3 319-326. **4.** Shoham Z, Insler V. Recombinant technique and gonadotropins production: new era in reproductive medicine. Fert. Steril: 1996;66:187-201. **5.** van de Weijer B, Mulders J WM, Bos E S, Verhaert P DEM, van den Hooven H. Compositional analysis of a human menopausal gonadotrophin preparation extracted from urine (menotropin): identification of some of its major impurities. RBM Online, 2003; Vol. 7 no. 5 547-557. **6.** Organon USA Inc. Data on file. IMS-National Sales Perspective, April 2005-March 2006.

 Printed in the USA **August 2006** **FER-1012**

Follistim® AQ Cartridge
(follitropin beta injection)

FOR SUBCUTANEOUS USE ONLY

BRIEF SUMMARY
Please see package insert for full prescribing information.

INDICATIONS AND USAGE
Follistim® AQ Cartridge (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Follistim® AQ Cartridge is also indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Selection of Patients
Before treatment with Follistim® AQ Cartridge (follitropin beta injection) is initiated:
1) A thorough gynecologic and endocrinologic evaluation of the patient must be performed. The evaluation should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of reviewing a patient's history, performing a physical examination, determining serum hormonal levels as indicated, and optionally performing an endometrial biopsy. Patients with tubal pathology should receive Follistim® AQ Cartridge only if enrolled in an ART program.
2) Primary ovarian failure should be excluded by the determination of circulating gonadotropin levels.
3) Careful examination should be made to rule out early pregnancy.
4) Evaluation of the partner's fertility potential should be included in the workup procedure.

CONTRAINDICATIONS
Follistim® AQ Cartridge (follitropin beta injection) is contraindicated in women who exhibit:
1) Prior hypersensitivity to recombinant hFSH products
2) A high circulating FSH level indicating primary ovarian failure
3) Uncontrolled thyroid or adrenal dysfunction
4) Tumor of the ovary, breast, uterus, hypothalamus, or pituitary gland
5) Pregnancy
6) Heavy or irregular vaginal bleeding of undetermined origin
7) Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS)
8) **Hypersensitivity reactions to streptomycin or neomycin. Follistim® AQ Cartridge may contain traces of these antibiotics and may cause hypersensitivity reactions in susceptible persons.**

WARNINGS
Follistim® AQ Cartridge (follitropin beta injection) should be used only by physicians who are experienced in infertility treatment. Changes in brand (manufacturer), type (recombinant, urinary, etc.), and/or method of administration (Follistim Pen®, conventional syringe, etc.) may result in the need to adjust the dose. Follistim® AQ Cartridge administered with the Follistim Pen® contains a potent gonadotropic substance and delivers on average an 18% higher amount of follitropin beta as compared to lyophilized preparations administered by conventional syringe. Accordingly, a lower starting dose for gonadotropin stimulation and dose adjustments during gonadotropin stimulation should be considered for each woman treated with Follistim® AQ Cartridge *(see DOSAGE AND ADMINISTRATION in the full prescribing information).*

Overstimulation of the Ovary During Treatment With Follistim® AQ Cartridge (follitropin beta injection)
In order to minimize the hazards associated with the occasional abnormal ovarian enlargement that may occur with Follistim® AQ Cartridge therapy, the lowest effective dose should be used *(see DOSAGE AND ADMINISTRATION in the full prescribing information).* Use of ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of treatment with Follistim® AQ Cartridge, hCG should not be administered in this course of treatment, to reduce the chances of developing Ovarian Hyperstimulation Syndrome (OHSS).

Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical entity distinct from uncomplicated ovarian enlargement and may progress rapidly to become a serious medical event. OHSS is characterized by a dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of OHSS developing are severe pelvic pain, nausea, vomiting, and weight gain. The following symptoms have been reported in cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events *(see WARNINGS-Pulmonary and Vascular Complications).* Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with Ovarian Hyperstimulation Syndrome (OHSS).

During clinical trials with Follistim® and Follistim® AQ Cartridge therapy, OHSS occurred in 60 (5.3%) of the 1132 women treated and of these 33 (2.9%) were hospitalized. Cases of OHSS are more common, more severe, and more protracted if pregnancy occurs; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and it can develop rapidly, reaching its maximum about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration *(see PRECAUTIONS-Laboratory Tests),* the hCG must be withheld.

If serious OHSS occurs, treatment should be stopped and the patient should be hospitalized. Treatment is primarily symptomatic and should consist of bed rest, fluid and electrolyte management, and analgesics (if needed). Hemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity, and the pericardial cavity may occur and should be thoroughly assessed in the following manner: 1) fluid intake and output; 2) weight; 3) hematocrit; 4) serum and urinary electrolytes; 5) urine specific gravity; 6) BUN and creatinine; 7) total proteins with albumin: globulin ratio; 8) coagulation studies; 9) electrocardiogram to monitor for hyperkalemia and 10) abdominal girth. These determinations should be performed daily or more often based on clinical need.

OHSS increases the risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should not be removed unless there is the necessity to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should, therefore, be avoided. If bleeding occurs and requires surgical intervention, the clinical objective should be to control the bleeding and retain as much ovarian tissue as possible. Intercourse should be prohibited in patients with significant ovarian enlargement after ovulation because of the danger of hemoperitoneum resulting from ruptured ovarian cysts.

The management of OHSS may be divided into three phases: an acute, a chronic, and a resolution phase. Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below.

Acute Phase: Management during the acute phase should be directed at preventing hemoconcentration due to loss of intravascular volume to the third space and minimizing the risk of thromboembolic phenomena and kidney damage. Treatment is intended to normalize electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation.

Management includes administration of limited intravenous fluids, electrolytes, human serum albumin, and strict monitoring of fluid intake and output. Monitoring for the development of hyperkalemia is recommended.

Chronic Phase: After stabilizing the patient during the acute phase, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.

Resolution Phase: A fall in hematocrit and an increasing urinary output without an increased intake are observed due to the return of the third space fluid to the intravascular compartment. Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space fluid as rapidly as it is mobilized. Diuretics may be indicated during the resolution phase, if necessary, to combat pulmonary edema.

Pulmonary and Vascular Complications
Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome) have been reported in women treated with gonadotropins. In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following gonadotropin therapy. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Births
Multiple births have been reported for all FSH treatments including Follistim® (follitropin beta for injection) treatment. The patient and her partner should be advised of the potential risk of multiple births before starting treatment.

PRECAUTIONS
General
Careful attention should be given to the diagnosis of infertility and in the selection of candidates for treatment with Follistim® AQ Cartridge (follitropin beta injection) *(see INDICATIONS AND USAGE-Selection of Patients).*

Information for Patients
Physicians must instruct patients on the correct usage and dosing of Follistim® AQ Cartridge (follitropin beta injection) in conjunction with the Follistim Pen®.

Patients should read and follow all instructions in the Follistim Pen® Instructions for Use Manual/Treatment Diary prior to administration of Follistim® AQ Cartridge.

Prior to treatment with Follistim® AQ Cartridge, patients should be informed of the duration of treatment and monitoring procedures that will be required. The risks of Ovarian Hyperstimulation Syndrome and multiple births *(see WARNINGS),* and other possible adverse reactions *(see ADVERSE REACTIONS)* should be discussed.

Laboratory Tests
In most instances, treatment with Follistim® AQ Cartridge (follitropin beta injection) will result only in follicular growth and maturation. In order to complete the final phase of follicular maturation and to induce ovulation, hCG must be given following the administration of Follistim® AQ Cartridge or when clinical assessment of the patient indicates that sufficient follicular maturation has occurred. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining and/or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of OHSS and multiple gestations.

The clinical evaluation of estrogenic activity (changes in vaginal cytology, changes in appearance and volume of cervical mucus, spinnbarkeit, and ferning of the cervical mucus) provides an indirect estimate of the estrogenic effect upon the target organs, and therefore, it should only be used adjunctively with more direct estimates of follicular development (e.g., ultrasonography and serum estradiol determinations).

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:
a) A rise in basal body temperature
b) Increase in serum progesterone
c) Menstruation following the shift in basal body temperature

When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:
a) Fluid in the cul-de-sac
b) Follicle showing marked decrease in size
c) Collapsed follicle

Drug Interactions
No drug-drug interaction studies have been performed.

Carcinogenesis and Mutagenesis, Impairment of Fertility
Long-term toxicity studies in animals have not been performed with Follistim® AQ Cartridge (follitropin beta injection) to evaluate the carcinogenic potential of the drug. Follistim® (follitropin beta for injection) was not mutagenic in the Ames test using *S. typhimurium* and *E. coli* tester strains and did not produce chromosomal aberrations in an *in vitro* assay using human lymphocytes.

Pregnancy
Pregnancy Category X: (See CONTRAINDICATIONS).

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from Follistim® AQ Cartridge (follitropin beta injection), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies did not include subjects aged 65 and over.

ADVERSE REACTIONS
Assisted Reproductive Technologies (ART)
Rates of adverse events from an open-label, non-controlled, multicenter study in 60 women undergoing COH for IVF or ICSI with Follistim® AQ Cartridge (follitropin beta injection) administered with the Follistim Pen® are summarized in Table 4.

TABLE 4: Incidence of Adverse Clinical Experiences (≥5%)

Adverse Event	Follistim® AQ Cartridge n=60	Adverse Event	Follistim® AQ Cartridge n=60
Abdominal pain	28%	Abdomen enlarged	8%
Flatulence	27%	Back pain	7%
Abdominal pain, gynecological	25%	Constipation	5%
Nausea	17%	Headache	5%
Breast pain, female	15%	Ovarian pain	5%
Injection site reaction	10%		

Ovulation Induction
Rates of adverse events from an open-label, non-controlled, multicenter study in 43 clomiphene-resistant women with chronic anovulation (WHO group II) undergoing Ovulation Induction with Follistim® AQ Cartridge (follitropin beta injection) administered with the Follistim Pen® are summarized in Table 5.

TABLE 5: Incidence of Adverse Clinical Experiences (≥5%)

Adverse Event	Follistim® AQ Cartridge n=43	Adverse Event	Follistim® AQ Cartridge n=43
Ovarian hyperstimulation syndrome	9%	Sinusitis	5%
Abdominal pain	5%	Upper respiratory tract infection	5%
Injection site reaction	5%		

The following adverse events have been reported in women treated with gonadotropins: pulmonary and vascular complications *(see WARNINGS),* hemoperitoneum, adnexal torsion (as a complication of ovarian enlargement), dizziness, tachycardia, dyspnea, tachypnea, febrile reactions, flu-like symptoms including fever, chills, musculoskeletal aches, joint pains, nausea, headache and malaise, breast tenderness, and dermatological symptoms (dry skin, erythema, body rash, hair loss and hives).

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

Congenital Anomalies
The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, sperm characteristics) and to the higher incidence of multiple gestations after ART. There are no indications that the use of gonadotropins during ART is associated with an increased risk of congenital malformations.

Storage
Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the Follistim® AQ Cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F). Protect from light. Do not freeze.

For more information, call 1-866-836-5633

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How Weight Affects Fertility and What You Can Do About It

Monica Callan, RD, CPT

Turn on the news today and chances are there will be some story about weight. Whether it's a story on the latest fad diet or a recent study linking obesity to disease, weight stories proliferate. But, before you stop reading, thinking you've had enough, keep reading; as this article just may surprise you.

It is estimated an astounding two-thirds of Americans are considered overweight, and, as we all know by now, weight can have numerous adverse effects on the body, including cancer, diabetes, and heart disease. It should be no surprise to anyone reading this that weight also affects the reproductive system and may be a contributing factor in up to 10 percent of 7.5 million infertility cases.

Why does weight play such a big role in your ability to become pregnant? The answer is really quite simple. The human body does not like extremes. So whether you are underweight or overweight, your chances of getting pregnant can be dramatically decreased if you are outside the "normal" weight range. In simple terms, the main reason for this influence is a connection between body fat and hormonal balance. In women, body fat can affect ovulation; in men, body fat can affect sperm count and concentration.

Let's get to specifics. A Body Mass Index (BMI) of 19–24 is ideal for health and fertility. If you are overweight, a weight loss of 5 to 10 percent can dramatically improve pregnancy rates. On the other hand, if you are underweight, a weight gain of as little as three to five pounds can increase the odds of conception.

Tips for a healthy fertility nutrition plan

Diet: Don't shock your system with crash diets; this will not support a reproductive balance. Weight loss of 1 to 2 pounds a week is considered healthy. It is best that you begin a good nutritional eating plan 3 to 12 months before conception, but it is really never too early to start.

Nutritional Plan: Eating for fertility is similar to eating for peak health. Focus on a whole food diet, where food is closest to nature. Choose organic foods when possible, especially with dairy and meat products. Eat five to nine servings of brightly colored fruits and vegetables per day.

Replace white bread with whole grains and look for carbohydrate foods with at least 3 grams of fiber per serving. Get your fat from healthy fats like olive oil, canola oil, nuts and avocados. Also try to include omega-3 fats in your diet by eating foods like wild salmon, flax, walnuts, or taking an omega-3 supplement.

Avoid: Excess alcohol, caffeine, refined carbohydrates, saturated and trans fats, and processed meats.

Get a Buddy: Studies show that when you embark on a healthy eating plan with someone else, the likelihood of success increases. So, get your husband involved, or a friend. The outcome will be better health before, during and after pregnancy . . . for the whole family! You might find a buddy at the INCIID Diet and Fitness forum at http://www.inciid.org/forums/dietfitness/index.html

In closing, it's important to remember that knowledge does not equal a change in behavior. Changing your diet is really about making a lifestyle change, so you may want to develop a more individualized plan with the help of a dietician or nutritionist. There are also numerous weight loss groups that can offer you support, coaching and accountability. Taking the step to develop a healthy lifestyle will not only help you get pregnant, but ensure that you're an active part of your child's life for many years to come.

Monica Callan, R.D., C.P.T., is the Director of Nutrition for Reproductive Wellness, which is the only clinic offering fully integrative Mind/Body fertility treatments in San Diego.

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Email info@reproductivewellness.com.
Web: http://www.reproductivewellness.com

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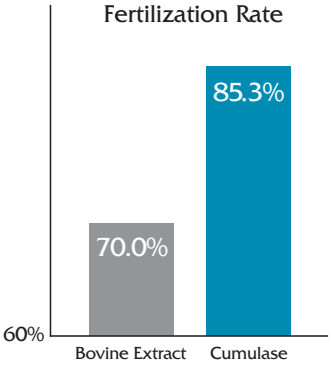

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Nutrition and Infertility Treatment

Carolyn R. Kaplan, MD

It is well known that women who are under or overweight have difficulty with reproduction. Obese women are at increased risk for miscarriage, gestational diabetes, hypertension, preterm delivery, low birth weight, stillbirth, and complicated delivery. Underweight women are also at risk for miscarriage, low birth weight, preterm delivery, and stillbirth. Therefore, pre-conceptual counseling about weight and lifestyle management may go a long way to reducing risks of pregnancy complications.

Underweight women should be evaluated for eating disorders and thyroid dysfunction. Working with a nutritionist and a psychologist may be necessary to resolve eating disorders. Limited weight gain (3 to 5 kg) is usually sufficient to restore ovulation and improve the outcome of subsequent pregnancy. Thyroid may be evaluated with simple blood tests.

Overweight women need a thorough endocrinologic evaluation to test for Polycystic Ovarian Syndrome (PCOS), diabetes, and thyroid disorders. High blood pressure may also be an issue. Nutritional counseling is important, as even limited weight loss (5 to 10 % of body weight) has also been shown to reduce the risks of pregnancy complications and may restore a more normal ovulation.

Polycystic Ovaries Syndrome

Many overweight women, especially those with irregular menses, are found to have insulin resistance and polycystic ovaries. PCOS is a metabolic disorder that is one of the leading causes of infertility in women. Insulin resistance means that the process of getting sugar (glucose) out of the blood stream into the cells is defective—the cells are "resistant" to insulin. The pancreas must secrete more and more insulin to get sugar out of the blood and into the cells. This high insulin level affects numerous organs, causes weight gain, increases the risk of heart disease (because of high LDL cholesterol and triglycerides and decreased HDL), and increases blood clotting factors. Insulin acts as a growth stimulator in the ovaries, but it stimulates the connective tissue cells. These cells secrete higher levels of weak male hormones, which can interfere with normal ovulation and cause symptoms such as increased facial hair, acne, balding or hair loss, and weight gain. Even more, if left untreated, the condition may lead to an increased risk of endometrial cancer, diabetes, and heart disease.

Why don't typical "low-fat" weight loss diets work?

Approximately 60% of women with PCOS are obese. It has been shown that losing even 5% of their body weight can lead to an improvement in skin, regularity of menstrual cycles, and decreased insulin levels. However, many women with PCOS have trouble losing weight, possibly due to high insulin levels promoting fat storage. Recent research has shown that the standard low-fat, high-carbohydrate diet may not be beneficial for women with insulin resistance. Refined carbohydrates (sweets, white bread, white rice, pasta, etc.) are quickly broken down into sugar, which causes elevations in insulin levels. Foods with a low glycemic index (less processed foods, foods with

Carolyn R. Kaplan, M.D., is the Director of In Vitro Fertilization at Georgia Reproductive Specialists, LLC.

5445 Meridian Mark Road Suite 270
Atlanta, GA 30342
Phone: 404-843-2229 Fax: 404-843-0812
Web: http://www.ivf.com

For additional help and information, visit the INCIID Diet and Fitness Forum:
http://www.inciid.org/forums/dietfitness/index.html

more fiber, protein, and complex carbohydrates) are broken down into glucose much more slowly, so insulin levels stay lower.

How many carbohydrates should you eat in a day?

There are a number of popular diets that limit carbohydrates. The Food Pyramid diet consists of 55% of calories from carbohydrates, but eating whole grains helps to reduce the glycemic load of foods (how quickly food is broken down into glucose or sugar). The "Zone" or South Beach diets includes 35–40% of calories from carbohydrates and encourages vegetables, whole fruits, and whole grains.

Atkins or Protein Power restricts carbohydrates to 20% of the diet but contains too much saturated fat. This increases risks of heart disease and does not contain sufficient fiber, vitamins, minerals, and disease-fighting phytochemicals.

Remember that this is not a temporary diet but one that needs to be maintained long-term. The goal is to make it as healthy as possible. Choose carbohydrates with fiber, which slows digestion of carbohydrates into the blood stream. Examples include 100% whole-wheat bread, crackers, pasta, cereal, brown rice, vegetables, whole fruits, and sweet potatoes. Look for foods with at least 3 grams of fiber per serving, with the goal of 20–35 grams of fiber per day. Legumes such as beans, chick-peas, and lentils are good choices and have sufficient protein to substitute for meat. Breakfast cereals should have 5 grams of fiber or more per serving and 3 grams of fat or less per serving. Remember to increase fluid intake when you increase fiber intake.

Regular Exercise and Physical Activity

Regular physical activity is essential for long-term weight management. Regular exercise increases energy expenditures while accelerating metabolism. This makes it easier to lose weight and maintain weight loss. A moderate intensity, moderate duration program should include resistance (weight lifting) as well as aerobic (cardiovascular) exercise training. This helps build lean muscle mass and helps to improve insulin sensitivity. Even if weight loss is minimal, regular exercise improves cardiovascular function and overall health which lowers the risks of pregnancy complications.

A minimum of 30 minutes of moderate intensity exercise at least 3 days per week is recommended. Multiple exercise sessions (e.g., three 10-minute sessions per day) are as beneficial as longer single exercise sessions and may make increasing physical activity less intimidating. Gradually increasing the exercise time to 1 hour daily may enhance weight loss and maintenance.

Weight and Assisted Reproduction

Weight control is very important for women about to enter an assisted reproductive technology (ART) program. Treatment outcome is clearly worse among obese patients. Pregnancy rates are lower and miscarriage rates and pregnancy complications are higher. Obesity can also limit the accuracy of ultrasound monitoring. Obese patients are at higher risk during egg retrieval, especially if anesthesia is provided.

Toxic Habits

Cigarette smoking has been associated with lower sperm number and motility. In woman, cigarette smoking has toxic effects on the ovary. Menopause occurs at an earlier age in women who smoke. Illegal drug use may also affect ovarian function by altering the stimulatory pathways of the central nervous system. Heavy alcohol consumption affects fertility in men and women. Caffeine intake is controversial during fertility therapy and is generally avoided in pregnancy.

Stress and Infertility

Whether or not stress can cause infertility is a question commonly asked during the infertility evaluation. Although one study has shown no effect of stress on pregnancy rates in women going through their first cycle of in vitro fertilization, many experts believe that stress can affect the outcome of infertility treatment. Implantation may be affected by stress.

Infertility treatment can have a major impact on a patient's psychological well-being. Taking extra-good care of your self prior and during infertility therapy can improve stress levels, and possibly outcomes of therapy.

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[1]Corson S. Conquering Infertility. Vancouver, BC:EMIS-Canada;1999.

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Integrative Medicine: Unlocking the Key to Infertility

Marc Sklar LAc (CA), DA (RI),

If you've been struggling with infertility, odds are you've heard the new "buzz word" in fertility—and for that matter, general healthcare treatment–integrative medicine. But, what does it really mean and how does it impact you? In this article, we'll explore this topic and help you understand how integrative medicine can help you not only conceive, but return to optimum health.

Defined by the U.S. National Center for Complementary and Alternative Medicine (NCCAM), Integrative Medicine combines conventional (allopathic) medical treatments and traditional alternative treatments for which there is some high-quality scientific evidence of their safety and effectiveness.

How Integrative Medicine Works

By integrating two or more styles of medicine into one practice, Integrative Medicine takes advantage of the strengths of each system to offset their weaknesses. The strengths of conventional medicine are that they allow us to treat extremely severe cases of disease and illness, quickly and effectively. The beauty of using complementary medicine is that it enables us to see the whole person, treat for prevention instead of disease and tend to the root problem of an illness instead of symptomatic relief.

Marc Sklar, LAc (CA), DA (RI), MSTOM, is a clinical director and founder of Reproductive Wellness, which offers fully integrated body and mind fertility treatments, including specialized acupuncture, botanical medicines, nutritional regimens, exercise programs and group support programs.

3944 Murphy Canyon Rd. C200
San Diego, CA 92123
Phone: (877) 843-7100 Fax: (619) 583-2695
Email: msklar@reproductivewellness.com
Web: http://www.reproductivewellness.com

For more information on acupuncture, visit the INCIID acupuncture forum at http://www.inciid.org/forums/acupuncture/index.html

Integrative Medicine is also unique, because it encourages patients to be active participants in their health care. To achieve maximum benefits, Integrative healing is based on a practitioner-client partnerships in which both conventional and complimentary modalities are used to stimulate the body's natural healing potential. By working together, the patient and providers develop a diagnostic and therapeutic program that draws on a variety of traditions, expertise and modalities to address an individual's specific needs.

What Exactly Are Conventional and Alternative Treatments?

Whether treating infertility or another health problem, a comprehensive approach that combines both conventional and alternative medicine is the wave of the future. So, what exactly are conventional and alternative treatments?

Conventional treatments are those provided by your medical physician, such as pharmaceutical medication, surgery, and scientifically developed diagnostic tools to help return a patient to health. In the case of infertility these may include:

- Prescription drugs, such as Clomid
- Lab work
- Insemination procedures, such as intrauterine

Some of the most common forms of alternative treatments include:

Acupuncture Acupuncture has been effectively used for the treatment of infertility and other health problems for more than 3,000 years. Benefits include:

- Restoring blood, nutrients and air flow
- Restoring visceral (organ) and immune function
- Promoting physiological and autonomic balance–Homeostasis

- Relieving pain
- Promoting the healing of tissue

Natural Botanical Medicines Natural botanical medicines have been used and prescribed in traditional medicine long before the development of synthetic pharmaceuticals. Botanical Medicines differ from synthetic pharmaceuticals in that they have exceptionally low to no toxicity, leave no residual negative accumulations in the body and have minimal to no side-effects.

Nutrition Correct foods are natural medicine, able to support and heal, so it's no surprise that a proper diet increases your chances of not only getting pregnant, but maintaining a healthy pregnancy and life.

Fertility Yoga Yoga is said to help promote relaxation and reduce anxiety, stress and depression. Research suggests that yoga may also help to promote conception on a physiological level. The regular practice of yoga has the potential to enhance the self-regulation of hormonal imbalances, increase circulation and stimulation to the reproductive organs, and assist couples in managing their emotions with conscious awareness.

The Arvigo Technique for Maya Abdominal Massage™ Maya Abdominal Massage™ is an ancient Mayan technique of abdominal massage designed to return the uterus to its proper position and restore one's body's natural healthy balance. The technique uses noninvasive uterine massage techniques to reposition internal organs that have shifted making conception more difficult. The massage works by using massage techniques to open up the pelvis, so that a woman's body is aligned properly, and therefore ready for conception.

Conclusion

Integrative Medicine emphasizes healing techniques that value mind, body and soul. While this new movement was first driven by consumer demand, it is now getting the attention of many academic health centers. If you're struggling with infertility, utilizing an integrative treatment plan can help you ensure that you're taking full advantage of the strengths of both conventional and alternative treatments, thereby helping you reach your goal of starting a family more quickly and effectively.

I could not have weathered my four losses without INCIID! INCIID is made up of a wonderfully supportive group of people who know how difficult it is to face infertility and pregnancy loss. I first found INCIID 5 years ago after I lost my first pregnancy, and I am still an active member of the community -- 4 losses and 3 children later. The women of INCIID got me through some of my darkest hours; they were there for me day and night with exactly what I needed at the time — new ideas, information, or just sincere empathy and support. I'm certain I could not have weathered my four miscarriages without the support I found here.

—An INCIID Member

Yoga and Infertility

Leslie Daly, MS ADTR LCAT RYT

Yoga is a practice about connecting with oneself. It is about clearing the space—physically and mentally—to experience the *prana*, or life force, already present within you. Yogis believe that illness and suffering (*douka*) is in part caused by obstructions in our bodies and minds. Happiness (*souka*), on the other hand, is literally translated as "unobstructed space."

Hatha yoga practice, with the intention of increasing fertility, focuses on clearing space in the reproductive environment so that more prana and breath (and oxygenated blood) can move into the system.

Hatha yoga is the physical path of yoga and includes postures (*asana*), breathing (*pranayama*), meditation (*dhyana*), cleansing (*kriyas*) and relaxation (*yoga nidra*). Fertility yoga sessions highlight all of these areas, with the exception of the cleansing practices. The following describes how they each address infertility.

Asanas Highlighted postures include ones that strengthen and stimulate the endocrine and reproductive systems. Poses that open the hips and soften the low belly help to create a receptive and open environment. The practice of the postures with dynamic alignment and muscle engagement help to bring awareness to tension held throughout the body and allow for more efficient use of energy.

Pranayama Breath work and control is the one of the most powerful aspects of a yoga practice. By simply bringing awareness to breathing, we become more focused in the present. By deepening the breath, we bring more prana to the system, we increase blood flow, we support our movement and postures and we feel our emotions–our experience–more fully.

Meditation Addressing infertility is a very stressful and emotional process. So much time is spent thinking about treatments and costs, feelings of disappointment, failure, loss and anger are at the forefront. It is all too easy to get wrapped up in these negative thoughts, feelings, worries about appointments, procedures, and difficult and emotional conversations. Often there is a loss of perspective and you are completely immersed in being "infertile." The practice of meditation helps to refocus the busy mind, to practice presence in the moment, to experience the fluctuations of our thoughts and feelings. Most importantly, meditation can help you to feel more in control. Yoga and meditation remind you that you are so much more than your thoughts and pathology.

Relaxation When we feel stress the body goes into "flight or fight" mode. The sympathetic nervous system is in full gear, preparing out bodies for danger. Other systems of the body slow down or shut down altogether, which is why constant and unrelieved stress is largely believed to be a huge factor in illness. The good news is our bodies have a natural mechanism to counteract the stress response. We have a relaxation response, the parasympathetic nervous system, and we have the ability to "hook" into it by breathing and relaxing the body. Every fertility yoga session ends with time to relax, release, to allow the body time to go into its natural restorative state where it can heal.

In addition, a fertility yoga session includes chanting and energy configurations (*mudras*), which are used to highlight and stimulate the second *chakra*, or energy center, that correlates with reproduction, emotion, sexuality and creation.

What is the best part of practicing yoga for fertility? Having a positive experience in your amazing body and spending time honoring your body for what it can do and for the wisdom it contains within!

Leslie Daly received her yoga certification from Integral Yoga Institute and is registered with the Yoga Alliance. She has a BS from New York University in Dance and Education and an MS from Pratt Institute in Dance/Movement Therapy. Leslie is a member of the Academy of Registered Dance/Movement Therapists through the American Dance Therapy Association (ADTA).

Acupuncture and IVF

Brian Acacio, M.D.

An old Chinese proverb states, "A flower cannot blossom without sunshine." The same holds true with fertility. Chinese medicine emphasizes the proper conditions for a successful and healthy pregnancy. This is where Traditional Chinese Medicine (TCM) can play a very important role in improving IVF outcomes.

TCM has been practiced for hundreds of years. While Western medicine has been slow to embrace the benefits of TCM, we are beginning to see the benefits of the combined efforts. There are many studies that reveal TCM, and specifically acupuncture, can improve blood flow, enhance the immune system, and increase pain tolerance. While there are many other wild claims of the benefits of TCM, we believe that these therapies are best served when used in combination with Advanced Reproductive Technologies (ART), such as IVF.

In our acupuncture clinic, the first thing we do with a new patient is an extensive intake and physical examination. Using a specialized system of pulse taking and palpation, we can evaluate the overall status of the systems of the body that affect fertility. While some conditions can be treated fairly quickly, others may take months to address and may involve a combination of modalities. For example, if a patient wants to improve ovarian quality, it generally takes a minimum of three to six months of treatment using acupuncture, herbs and nutrition, whereas a simple case of thin uterine lining may only take one month on average for improvement.

Brian Acacio, M.D., is Medical Director of Sher Institute of Reproductive Medicine–Los Angeles.

1520 Chevy Chase Dr. Suite 101
Glendale, CA 91206
Phone: 818-291-1985 Fax: 818-291-1986
Email: briana@lnovamgmt.com
Website: http://www.haveababy.com
INCIID: http://www.inciid.org/members/member.php?cust_id=10049

Therefore, in preparation for an IVF cycle, the number of treatments can vary substantially. It is best to consult with an acupuncturist as far in advance of your IVF cycle as possible to determine your individual needs.

During the actual IVF cycle we use several base protocols. These protocols are then modified depending on a patient's particular needs. Typically, a patient will receive four to ten treatments. Modifications are done if the patient has a history of poor response to a prior cycle, thin uterine lining, elevated FSH, etc. Modifications may be recommended if progress is not as expected. For example, if the endometrial thickness is below a certain level at various times during stimulation, another set of acupuncture treatments is added to help increase the lining to optimal thickness.

Most treatments are done in our office except on the day of the embryo transfer or in certain circumstances during retrieval. On the day of the embryo transfer, we administer two treatments. These are usually done at the IVF clinic: one immediately before and one immediately after the embryo transfer. Studies have shown differences in ongoing pregnancy rates with acupuncture. One factor impacting the pregnancy rate may be the timing of the embryo transfer protocol. In one acupuncture study the protocol was applied immediately before and immediately after embryo transfer, pregnancy rates increased by more than 60%. In another study, the protocol was applied on the day of the transfer, but not immediately before and after. They had a 40% increase in ongoing pregnancy rates.

It is also important to consider not only what protocols are being used, but how they are being applied. If improperly administered, acupuncture can potentially hinder a cycle. In fact, one study demonstrated that the improper administration of a protocol could reduce blood flow to the reproductive system.

However, when done correctly, studies have shown that acupuncture can increase implantation rates, improve uterine and ovarian blood flow, increase live birth rates, increase sperm counts, morphology and motility and reduce miscarriages and ectopic pregnancies.

While acupuncture can do many things to improve IVF outcomes, there are also things it cannot do. Acupuncture can increase blood flow, but it cannot give you the nutrients that your body needs to prepare for and support a healthy pregnancy. Because of this, proper nutrition is indispensable; not just for getting pregnant, but to have a healthy and lasting pregnancy.

Nutritional issues are one of the most important and often neglected contributory factors to infertility. Almost everyone takes a prenatal vitamin without concern for their actual nutritional requirements. This can result in too much of one nutrient and too little of another. So, just as nutrient deficiencies may cause problems, too much of many nutrients can bio-accumulate and become toxic. For example, too little iron can cause infertility, but so can too much.

Also, taking a certain amount of a nutrient doesn't mean your body is absorbing it. For example, most people know how important folic acid is for proper neural tube development. However, it will not work unless you are absorbing it. Symptoms like heartburn, bloating, bad breath and belching could indicate a reduced ability to absorb folic acid. Also, there can be genetic problems with metabolizing folic acid that require much higher doses to be taken. If you take too much folic acid, it can mask a vitamin B12 deficiency which could result in permanent neurological problems both for the mother and the fetus. So it is a very good idea to find out what your individual body needs and how much.

Finally, Herbal Medicine is another very useful adjunct to IVF. However, while herbs can be very useful to improve ovarian quality and quantity, endometrial thickness, progesterone levels, estrogen levels and many other aspects of a woman's cycle, they can also be detrimental if taken at the wrong time during a cycle. This is especially so during an IVF cycle, where certain herbs or combinations thereof can block the IVF medications and potentially cause problems.

A final consideration is to work with a reproductive endocrinologist who not only is open to acupuncture, but who is proactive in their treatments. For example, in our clinic, Dr. Mory Nouriani and I encourage acupuncture for our patients as a general policy. Management of our patients includes referring them for proper TCM (herbal and acupuncture) evaluation before or even during a cycle.

Incorporating Traditional Chinese Medicine into your IVF cycle can not only substantially increase your chances of a successful IVF pregnancy, but a healthier IVF pregnancy. If you are contemplating IVF and would like to incorporate Traditional Chinese Medicine, we recommend you find a practitioner who is well versed in IVF acupuncture (and herbal medicine) and a reproductive endocrinologist who is open to incorporating Eastern therapies while allowing acupuncture on-site during an embryo transfer.

Anger and Infertility

Helen Adrienne, LCSW, BCD

You always knew that some day you would have a family. Life went mostly as you planned it. Depending upon what aspect of the American culture you hearken from, you would have had certain expectations as to when the time would be right. The confluence of variables such as education, career path and meeting the right mate became settled and you were good to go. So you thought. Nature had another idea, and now your plan has exploded in your face.

Show me someone in this situation of infertility or questionable fertility and I'll show you someone who is either 1) openly angry, 2) coping with the very natural feeling of anger by denying it, or 3) using significant mental muscle to manage feelings such as impatience, disappointment and lack of control that are components of anger.

Especially in this age where women have been led to believe that they can have it all, to arrive at the brink of the next planned phase of life only to be met by what feels like a cruel joke is unbearable and enraging. And to make matters worse, it is typical in these times to buy into the myth that things should be easy.

What makes the anger response to the infertility news so intense and yet so poignant is its attachment to an existential reality: the injustice of it all. Your thoughts travel to how unfair it is. You can name a list of people who have children that they can only complain about. Then there is so-and-so who has children she didn't plan. You may find yourself thinking about someone from work who regrets having had a child. You feel sorry for the babies and damn it, you and your spouse know that you would make wonderful parents and you're so ready! How could this be happening?

On good days, you feel your determination will get you through this nightmare. You and your spouse might even feel closer to each other because of this struggle. On other days, you could care less about rational thinking and derive a perverse pleasure from marinating in your anger.

Anger does have its rationale. To feel angry at your body for failing you, or angry at your spouse's body for failing him/her, makes sense. So does anger at the insensitive comments of well-meaning family members, friends or co-workers. Insensitivity of any kind makes your blood boil. Your medical team may be highly skilled as technicians, but why hasn't someone trained this doctor or that nurse or secretary to be more delicate with the presentation of facts or news? And let's not even talk about insurance companies. In fact there's hardly an aspect of life that is untouched by this predicament. Decision-making about career, housing, vacations and money, when so much is up in the air, is enough to make anyone feel in a real frenzy.

But anger can be sneaky and present with the violence of a tsunami without the recognition that it was the earthquake out a sea that caused the tidal wave in the first place. Likewise within us, sadness, disappointment, jealousy and other emotions happen (like the earthquake), and sometimes without conscious awareness convert into anger (the tsunami). Anger can always be justified and is therefore an easier emotion to experience. Anger's energy legitimizes making its discharge feel like a relief; sadness, disappointment or jealousy demand self-reflection, which feels like a job for which you are in no mood.

Helen Adrienne, LCSW, BCD, psychotherapist, clinical hypnotherapist, practitioner of mind/body medicine in New York City. Her practice offers psychotherapy for people who struggle with infertility or gynecological and reproductive issues.

420 East 64th Street–1D(East)
New York, NY 10021
212-758-0125 212-888-2558 (fax)
helen@helenadrienne.com
www.helenadrienne.com

Though anger may seem easier, it is not without its cost. If we think about the energy it takes to be angry, we will realize that anger is a big emotion. Perhaps you want to scream, punch or stomp. If you have a habit of internalizing anger, it costs even more. Unless anger is attended to in one way or another, it simmers like a pot au feu. And like a pot au feu, is always hot. Both the pot on the stove and the anger within us drain energy.

Whether you are aware of feeling angry or not, if anger is part of the gestalt of infertility for you, then given the mind/body connection, the value in dealing with our anger has the enormous benefit of giving ourselves a respite from the physiology of stress. It is stressful to be angry.

Although the anger is legitimate and may seem impossible to tame (unless a baby resulting from a full-term pregnancy could materialize in your arms NOW!), taming anger is not impossible at all.

I have been working with infertility patients for over 27 years. I have the results of a currently unpublished study that I did with 39 respondents from 7 mind/body support groups that I ran between the spring of 2002 and the fall of 2005. For this study, the women were asked to fill out a questionnaire (which included 3 self-rating scales) before and after the 10-week group experience. My hypothesis was that by learning and practicing stress reduction techniques, participants could reverse the physiology of stress. These techniques are designed to intervene in the vicious cycle of stress from both mind and body perspectives. I predicted that changes would be measurable on the self-rating scales as improved mood and outlook and lowered subjective experience of bodily stress.

To my delight, the data from all 3 assessment instruments demonstrated a trend toward improvement in mood and outlook and a lessening of physical tension. To my surprise, as a by-product of the mind/body interventions, there was a statistically significant decrease in levels of anger.

What does this tell us?

For one thing, a mind/body support group for infertility patients, which includes instruction in a whole array of stress-reduction techniques, can be a real boon. These techniques must be practiced and if they are, we give ourselves a respite by returning our physiology to neutral as a balance for all of the demands on us at a difficult time. This alone, can make an enormous difference. (These techniques can be learned in private sessions as well.)

In addition, attending to our anger may mean teaming up with a therapist who can help acknowledge and examine, understand and discharge aspects of your anger which may be an emotional heirloom. An emotional heirloom is the inheritance of a family style of dealing with distress by imitating family elders. The process of imitation is largely unconscious and is so strong that it may as well be genetic. (But unlike the genetics of blue or brown eyes, emotional inheritance can be changed.) By becoming mindful of your anger, it is possible to transform the energy of it and thus dissipate it. This stops the leak of energy and allows for connection to feelings of well-being and emotional growth. This process ultimately enhances your sense of self rather than drains you—even under these painful circumstances.

You always knew that some day you would have a family. You want to reclaim the confidence of this feeling and keep the space open for hope. Embrace the unwanted symptom of anger and learn from it.

HELEN ADRIENNE, LCSW, BCD

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420 East 64th Street—1D (East)
New York, NY 10021
Office: 212.758.0125 Fax: 212.888.2558

Email: HAMSW@aol.com www.helenadrienne.com

Human Oocyte Cryopreservation

John G. Wilcox, M.D., F.A.C.O.G.

Introduction

Human oocyte cryopreservation, or "egg freezing," has long been an elusive goal of cryobiologists. Although sperm and embryos (fertilized eggs) have been successfully frozen and subsequently thawed to create healthy children for decades, egg freezing has only recently become a successful reality. The cryopreservation of human oocytes is highly beneficial for several reasons, most importantly to preserve a woman's fertility. Oocyte storage allows: (i) women at risk of becoming sterile due to cancer to preserve their oocytes prior to radio- or chemotherapy or ovariectomy; (ii) the salvage of an in vitro fertilization (IVF) cycle when no sperm is available; (iii) the alleviation of religious and ethical concerns of embryo storage; (iv) the elimination of donor-recipient synchronization problems; (v) a "quarantine period" on donated oocytes similar to that of donated semen; and (vi) women to delay reproduction until later in life, providing them with more reproductive choices.

Background Information

The theoretical basis for cryopreservation of cells was first proposed in 1965 (Mazur, 1965). These theories were not tested, however, until 1972, resulting in the first births of mice from cryopreserved embryos (Whittingham et al., 1972). In 1976, the first successful birth of mice from frozen-thawed oocytes was reported (Parkening et al., 1976). More recently, a review of the literature reported embryos from at least 22 other mammalian species have now been successfully cryopreserved (Rall, 2001; Leibo et al., 2002). In the early eighties, the first human pregnancy (Trounson et al., 1983) and births (Zeilmaker et al., 1984) were reported from cryopreserved human embryos. The freezing and storage of human embryos is now standard practice in clinical in vitro fertilization laboratories around the world (Shaw et al., 1993). According to the CDC website, 5,047 children were born in the year 2001 alone from the transfer of frozen-thawed human embryos (Wright et al., 2004).

Oocyte Cryopreservation

The first report of a pregnancy from a frozen-thawed human oocyte was in 1986 (Chen, 1986). Until recently, progress with frozen oocytes was slow, with few births reported (Al-Hasani et al., 1987; Van Uem et al., 1987; Chen, 1988). This was due mainly to two factors: concerns of a higher incidence of chromosomal abnormalities in the cryopreserved oocyte as compared to fresh oocytes (Johnson et al., 1987; Pickering et al., 1987; Sathananthan et al., 1988), and poor fertilization due to "zona hardening" (Vincent et al., 1990; Wood et al., 1992; George et al., 1993).

Following the development of intracytoplasmic sperm injection (ICSI) to assist fertilization following cryopreservation of oocytes in the 1990's, significant progress has been reported in cryopreservation of oocytes (Gook et al., 1995; Kazem et al.,1995). Subsequent research demonstrated cryopreservation of oocytes was not as detrimental as previously believed (Gook et al., 1993,1994). By 2000, there were over 20 normal children born from frozen-thawed oocytes (Tucker et al.,1996, 1998; Porcu et al.,1997, 1998, 1999a,b; Antinori et al.,1998; Borini et al., 1998; Nawroth et al.,1998; Polk de Fried et al.,1998; Vidali et al.,1998;Yang et al.,1998,1999;Young et al.,1998;

John G. Wilcox, M.D., is board certified in reproductive endocrinology and infertility and practices at the Huntington Reproductive Center, Pasadena, California.

333 S. Arroyo Parkway 3rd Floor
Pasadena, CA 91105
Phone: 626-440-9161 Fax: 626-440-0138
Email: doctor07@havingbabies.com
Web: http://www.havingbabies.com/

Porcu,1999). Currently, there are approximately 100 children reported following oocyte freezing (Leibo, 2003; Stachecki et al., 2004).

Current Methodologies

Slow Freezing

Slow freezing is the most reported method for cryopreservation of oocytes, resulting in the vast majority of babies born worldwide. Slow freezing methods, with only slight modifications, are based on the procedure first described by Willadsen (1977) for the freezing of ovine and bovine embryos. The equilibration time and amount of permeating cryoprotective additive (CPA) as well as the concentration of sucrose are among most common changes between various protocols (Fabbri et al., 2001). Recent alterations include the use of low or sodium free freezing solutions (Azambuja et al., 2002; Quintans et al., 2002; Boldt et al., 2003). However, the basic principles, remains the same. Oocytes are suspended in a solution containing CPAs, cooled and then seeded to induce ice formation promoting dehydration of the oocyte as the solution is cooled slowly at 0.3° C/min to -30° C or below. Finally, the oocyte is plunged into liquid nitrogen solution for storage.

Ultra Rapid Freezing (Vitrification)

Vitrification, or achieving a glass-like state, represents a potential alternative to slow freezing (first described in 1985 (Rall et al., 1985)). Since chilling injury to oocytes is time-dependent, the rationale is to prevent ice formation and injury by freezing at a rate fast enough to solidify the intracellular water before it can crystallize (Martino et al., 1996). This is accomplished by exposing the cell to high concentrations of CPAs for a very short equilibration, followed by very rapid cooling by plunging into liquid nitrogen. The high osmolarity of the vitrification solution rapidly dehydrates the cell and the submersion into liquid nitrogen quickly solidifies the cell before the remaining intracellular water has time to form damaging ice crystals. Two important concerns with this technique are the increased toxicity of high levels of CPAs at room temperature (Shaw et al., 1992) and the ability to freeze and thaw fast enough to avoid crystal formation and devitrification (Vajta et al., 1998). Several recent reports describe their ability to overcome these issues resulting in healthy children from vitrified oocytes (Kuleshova et al., 1999; Kuwayama et al., 2000; Yoon et al., 2000, 2003; Katayama et al., 2003).

Validation Studies

Over the past 9 years, the cryopreservation of more than 5000 human oocytes have been described in over 20 articles and abstracts resulting in over100 births (summarized in reviews: Leibo, 2004; Stachecki et al., 2004). However, these numbers are conservative and anecdotal evidence points to over 200 healthy live births to date. Extrapolating from reports, estimations of the average oocyte survival rates, fertilization rates, and clinical pregnancy rates are 54%, 61%, and 35% respectively (Kazem et al., 1995; Gook et al., 1995; Tucker et al., 1996, 1998; Porcu et al., 1997, 1999, 2000; Polak de Fried et al., 1998; Young et al., 1998; Kulehova et al., 1999; Hong et al., 1999; Yoon et al., 2000, 2003; Fabbri et al., 2001; Winslow et al., 2001; Yang et al., 2002; Boldt et al., 2003; Katayama et al., 2003; Fosas et al., 2003; Borini et al., 2004).

In May 2005, an abstract presented by the Huntington Reproductive Center at the annual Pacific Coast Reproductive Society demonstrated human oocyte survival and fertilization rates as high as 79% and 81% respectively. Also, in June 2005, Porcu presented his experience with over 500 cycles at the European Society for Human Reproduction and Embryology (ESHRE). His results supported pregnancy success rates with cryopreserved oocytes that were comparable to cryopreserved embryos.

Huntington Reproductve Center and Extend Fertility, Inc.

Extend Fertility is a company committed to furthering the advancement of oocyte cryopreservation research and providing services to women in need of preserving their fertility due to cancer, age, or other medical conditions.

Experience and Innovation

Extend Fertility has partnered with six premier medical centers across the U.S., including Stanford University's Reproductive Endocrinology and Infertility program (Northern CA), Huntington Reproductive Center (Southern CA), Reproductive Medicine Associates of New York (NY), IVF New Jersey (NJ), Reproductive Science Center (MA) and Texas Fertility Center (TX), to further research of oocyte cryopreservation through multi-center clinical trials.

Together, Huntington Reproductive Center and Extend Fertility provide state of the art technology for women interested in cyropreservation of oocytes. An IRB protocol has been established to continue researching new techniques for cryopreserving oocytes. Any woman under the age of 38 can be screened to determine whether she is a candidate to cryopreserve oocytes for future reproduction. Currently, a pharmaceutically sponsored multicenter study made possible through extend is available for women meeting inclusion and exclusion criteria (publication expected in 2006).

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Testing terms to know...

CCCT = Clomiphene Citrate Challenge Test (Clomid Challenge)

CASA = Computer-Assisted Semen Analysis

CVS = Chorionic Villae Sampling

IVC = Intra-Vaginal Culture

SPA = Sperm Penetration Assay

TORCH = Toxoplasmosis, Other, Rubella, Cytomegalovirus and Herpes test

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Genetic Counseling

Michael Doyle, M.D.

While the vast majority of babies are born healthy, approximately 2-3% of all babies are born with some type of birth defect or genetic condition. Genetic counseling is the process of providing individuals and families with information and support on the nature, inheritance and implications of genetic and related conditions. Genetic counseling offers tests to assess the risks for passing on various genetic diseases.

Those benefiting from genetic counseling would be women who are age 35 or older, couples with recurrent miscarriages, individuals with family histories of birth defects and/or genetic conditions, patients planning fertility treatments such as intrauterine inseminations (IUI), in vitro fertilization

(IVF) and pre-implantation genetic diagnosis (PGD). Couples with male factor infertility, patients with questions regarding genetic screening or gender selection, prospective egg donors and directed semen donors, as well as newly pregnant patients who are over age 35 or who have questions regarding prenatal testing options, would also benefit.

Using PGD, healthy, chromosomally normal embryos can now be distinguished from nonviable and diseased ones. This is particularly helpful for women over 35, since chromosomal problems account for a large percentage of miscarriages and infertility in these women. This is chiefly due to the fact that as a woman ages, her eggs decrease in both number and quality. Consequently, over time, a couple's chances of becoming pregnant with a healthy baby decrease, and the rate of miscarriage climbs. In fact, if a healthy 40 year-old woman in excellent health does conceive, her chances of having a chromosomally abnormal embryo are over 50% without PGD, resulting in infertility, inevitable miscarriage, or fetal abnormality. Traditionally, the overall appearance of embryos conceived by IVF have been assessed microscopically to predict their chances of implanting. Pre-implantation genetic diagnosis (PGD) takes fertility treatment to a new level. By screening the genetic

information contained within the embryo prior to deciding which embryos to transfer, genetically normal embryos can be selected and transferred back to the patient. These pre-screened embryos are much more likely to implant and when they do, the chance of a problem is much lower.

The optimal time to perform genetic testing is before a couple begins trying to conceive. Genetic Counselors, with a specialized graduate degree in the areas of medical genetics and counseling, meet with patients to determines which genetic conditions are the most appropriate to screen for based on family history and ethnicity.

Most of the genetic screening tests are for conditions which are inherited in an autosomal recessive manner, which means that both parents would need to be carriers in order to have an affected child. It is common for the female partner to be tested initially, and if she is found to be a carrier for a particular genetic condition, it is recommended that the male partner consider testing. If both members of the couple are carriers for the same genetic condition, a genetic counselor will review the implications of these results, and discuss appropriate testing options.

Some of these options include preimplantation genetic diagnosis (PGD) and prenatal diagnosis. Testing during pregnancy may involve chorionic villus sampling (CVS), usually done between 10 and 12 weeks of

Michael Doyle, M.D., is the medical director for Connecticut Fertility Associates.

4920 Main Street
Bridgeport, CT 06606
Phone: (203) 373-1200 Fax: 203-365-6516
Email: michael.doyle@ctfertility.com
Web: http://www.connecticutfertility.com

pregnancy, or amniocentesis which is typically performed between 16 and 18 weeks of pregnancy.

Screening for the following genetic disorders are available: Cystic Fibrosis, Sickle Cell Disease, Alpha Thalassemia, Beta Thalassemia Fragile X Syndrome, and for conditions with increased frequency in the Ashkenazi Jewish population: Tay-Sachs disease, Canavan disease, Familial Dysautonomia, Fanconi Anemia group C, Bloom syndrome, Gaucher disease, Niemann-Pick disease type A, Glycogen storage disease type 1A , Maple syrup urine disease, and Mucolipidosis type IV.

Genetic counseling can provide individuals and families with the information and support on the nature, inheritance and implications of genetic and related conditions. Genetic counselors can offers tests to assess the risks for passing on various genetic diseases to assist patients in achieving the goal of having a healthy baby.

Preimplantation Genetic Diagnosis (PGD)

Barry Behr, Ph.D., H.C.L.D. & Victor Ivakhnenko, H.C.L.D.

Genetic errors arise from deletions or insertions of genetic material, abnormal numbers of whole chromosomes or genes, and even from misplacement of a single base in the DNA sequence. Genetic abnormalities can range from relatively harmless to severe: from vitamin deficiencies and food allergies to cancer, birth defects and infant mortality.

In recent years, significant advances in technology have enabled researchers to trace many disorders and diseases to their roots in the genetic code. Chromosome stretches, or even isolated genes, can now be used as markers to identify individuals at risk for certain illnesses. Additionally, the Human Genome Project, which aims to identify the chromosome location and DNA sequence of every human gene, is providing an ever-expanding catalogue of potential genetic markers. The ability to recognize these genetic warning signs is rapidly becoming most effective tool for prevention, diagnosis and treatment of genetically based disorders.

An estimated 60 percent of all naturally occurring reproductive losses in pregnancies are associated with chromosomal abnormalities in the embryo.

A normal embryo has 22 pairs of chromosomes called autosomes and 1 pair of sex chromosomes (XX or XY). Embryos that do not carry the normal pair of each chromosome are called aneuploids. Those that contain three copies of a particular chromosome (Trisomy) are the cause of some genetic disorders such as Down syndrome (Trisomy 21). Other less common are trisomies of chromosomes 13, 16, 18, and 22. Embryos that contain only one copy of a chromosome (Monosomy) are, by and large, nonviable.

Abnormal aneuploid embryos, either with monosomy (one missing) or trisomy (an extra one), are usually normal in appearance. It is not possible to distinguish these morphologically from other embryos. It is only through genetic analysis that they can be differentiated. Without such an analysis, many of these embryos are unknowingly transferred to patients. Depending on the specific abnormality, in IVF pregnancies, research has shown that chromosomal abnormalities such as aneuploidies (extra or missing chromosomes per cell) of the embryo increase either the risk of spontaneous miscarriage, the development of a genetically abnormal child, or no pregnancy at all.

Preimplantation genetic diagnosis (PGD) refers to the procedure involved in obtaining genetic diagnosis prior to embryo implantation (or embryo transfer). PGD is based on the ability of the human preimplantation eggs and embryos to continue their development into normal pregnancy after microsurgery (embryo or polar body biopsy), since cleavage stage cells of the embryo are pluripotent and removal of one or two cells at this time does not appear to affect further development of the embryo.

PGD involves several obligatory steps: genetic counseling; reproductive counseling and treatment; in vitro fertilization and genetic laboratory with DNA technologies, such as fluorescence in situ hybridization (FISH) for sex determination; and screening for chromosomal abnormalities and polymerase chain reaction (PCR) for single-gene diseases.

Barry Behr, Ph.D., H.C.L.D., is Consulting Scientific & Laboratory Director at the Huntington Reproductive Center in Pasadena, California. He is a Board Certified Laboratory Director (HCLD). **Victor Ivakhnenko, H.C.L.D.,** is a reproductive embryologist at Huntington Reproductive Center. Dr. Ivakhnenko has been certified by the American Board of Bioanalysts as a decision-making embryologist and presently is conducting Preimplantation Genetic Diagnosis procedures at HRC.

300 Pasteur Drive HH333
Stanford, California 94305-5317
Phone: (650) 723-0951
Fax: (650) 723-7737
Email: behr@stanford.edu
Web: http://www.havingbabies.com

The technique entails in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), microsurgical removal of one or two blastomeres at the six- to eight-cell stage (usually three days after fertilization), either molecular analysis (by PCR, in case of single-gene diseases) or molecular cytogenetic analysis (e.g., fluorescence in situ hybridization [FISH], in case of chromosome abnormalities), studies of the biopsied cells, and uterine transfer of unaffected embryos. In cases of X-linked recessive diseases, sexing and selective transfer of female embryos can be performed.

An alternative source of material that has been used for PGD, when the disorder tested for is of maternal origin, is the polar body. A polar body is a small section of an egg and contains the complementary set of chromosomes present in the oocyte. Therefore, the genotype of the oocyte can be deduced by examining that in the polar body.

The first polar body of an egg has been extruded prior to the egg retrieval and thus before fertilization. This polar body is not necessary for complete embryonic development and is available for analysis. A second polar body is extruded at the time of oocyte fertilization by a sperm. These polar bodies, removed using micromanipulation, can be a valuable source of genetic information. By using fluorescent-tagged genetic probes (i.e., FISH), we can examine them, thus allowing the chromosomal make-up of the oocyte to be inferred.

Studies have shown that the majority of embryo aneuploids (85%) are due to the female oocyte. The remainder is of sperm origin. Large chromosomal abnormalities, such as extra or missing chromosomes (aneuploidies), gender determination and unbalanced chromosomal translocations resulting from a parental balanced translocation, can be detected by a laboratory procedure called fluorescence in situ hybridization (FISH). For this technique, DNA probes are labeled with colored fluorescent tags that light up so one can see specific chromosomes or genes under a microscope. The reagents are optimized for use with imaging software for probe-signal enumeration. This software allows the simultaneous analysis of up to 12 different target-specific fluorophores in a single cell. However, up until now only 9 chromosomes can be accurately assessed during one analysis using FISH, with up to a 10% error rate.

In cases involving more subtle abnormalities, on the scale of single genes or even DNA bases or single gene diseases, highly specialized techniques such as PCR are required. Such methods rely on the fundamental principles of the genetic code, and specifically on the ability to generate a matching, or complementary, segment of DNA. Structurally, DNA is composed of two single strands attached to each other to form a double helix. The bases of one strand always bind to the bases (A,T,G and C) of the other in a specific fashion: A pairs with T, and G with C. If one knows the sequence of the bases in one strand, one can deduce the complementary sequence of bases in the other strand. Based on a known sequence of DNA, a synthetic copy of the matching strand called a DNA probe is created; it will then bind, or hybridize, to that specific gene within a chromosome. The mutation in the carrier parent(s) needs to be characterized before PGD is applied.

Both FISH and PCR procedures typically take 24–48 hours to complete. However, since diagnostic tests are performed on a single cell, the possibility of misdiagnosis has to be considered. There are limitations of the test procedures, e.g., allele dropout in PCR, either non-specific or inefficient hybridization in FISH. New techniques, like comparative genomic hybridization (CGH), offer the possibility to analyze all 23 pairs of chromosomes simultaneously for aneuploidy, translocations and single-gene defects. Unfortunately, this technology is not clinically useful due to the time it takes to generate the results. It currently takes 4–5 days for the results to be obtained using CGH. This requires the biopsied embryos to be cryopreserved after biopsy to allow time for the analysis. There is a single report in the literature that has accomplished this approach successfully.

Another technique that is also emerging and that may have application to PGD is Gene Chip technology, where literally thousands of DNA sequences may be analyzed simultaneously. This technique is a little further off, on the horizon.

PGD was first employed in 1989 with subsequent birth of normal females to couples at risk of various X-linked recessive diseases. The number of genetic diseases potentially diagnosable by PGD is vast. Examples of such disorders that have been reported include:

- Chromosomal translocations,
- Down Syndrome,
- Turner Syndrome,
- DiGeorge Syndrome,
- Alfa-1-Antitrypsin Deficiency,
- Beta-Thalassemia,
- Charcot-Marie Tooth Disease,
- Cystic Fibrosis,
- Fancony Anemia,
- Fragile X Syndrome,
- Hemophilia A,
- Huntington Disease,
- Lesch-Nyhan Disease,
- Marfan Syndrome,
- Myotonic Dystrophy,
- Sickle Cell Anemia, and
- Tay-Sachs Disease.

To date, a few hundred normal births have been achieved. The overall pregnancy rate per embryo transfer is 25% and birth rate is 15%. Selective implantation of embryos with normal chromosome compliments have also been shown to result in high pregnancy rates with decreased spontaneous miscarriage rates. At present, there are approximately 50 PGD centers worldwide.

The PGD procedure is considered experimental by the U.S. Food and Drug Administration. Huntington Reproductive Center remains committed to keeping pace with the rapid advances in the fields of genetics and human reproduction and making them available to couples as soon as is practically possible. Physicians and staff of are committed to maintaining the highest standard of care in reproductive medicine in terms of moral and ethical practices. Significant experience in infertility treatment and embryo culture, highly skilled medical and laboratory personnel make it possible to offer PGD technology to couples at risk of having a genetically abnormal fetus which can help them avoid the birth of an affected child or having to face the painful decision of a pregnancy termination.

"INCIID is the place to seek support, information, and personal experiences on the lonely and frustrating road of infertility. A place to rejoice in successes together and know just how precious life is. An invaluable resource to anyone who is suffering from infertility or going through the journey of adoption. A place to share your feelings and 'listen' to others share theirs. A community all working toward the same thing . . . family." **— An INCIID Member**

Preimplantation Genetic Diagnosis Can Save Time and Money

Carolyn R. Kaplan, MD

Preimplantation genetic diagnosis (PGD) is a technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) before transferring them into the uterus. PGD may be recommended for both fertile and infertile patients.

There are two types of PGD testing. The first type looks specifically for a known genetic problem such as a single gene defect or a translocation (see below). The second type looks at the overall number and balance of chromosomes (aneuploidy screening). PGD is offered to patients who are found to be carriers of certain common genetic conditions such as cystic fibrosis, sickle cell disease, or any of several rare genetic disorders often diagnosed because an affected child was born into either parent's family.

The three major categories of chromosomal disorders that PGD may screen for include Aneuploidy, Translocations, and Single Gene Defects.

Aneuploidy Screening

Aneuploidy (abnormal chromosome number) screening has primarily been offered to older women or women who have had multiple pregnancy losses or multiple failed IVF attempts. The IVF team uses PGD to select embryos with a normal number of chromosomes in order to increase the chances of a normal pregnancy. Testing is not 100% accurate and currently only 11 chromosomes can be tested (23 sets of chromosomes are normally present in every embryo). However, these 11 chromosomes do cause a large percentage of miscarriages. By transferring only normal embryos into the mother's uterus, we can reduce the risk of adverse outcomes, such as miscarriages or birth defects (physical and/or mental). PGD also provides an alternative to current post-conception diagnostic procedures, e.g., amniocentesis or chorionic villus sampling. These procedures test chromosomes of the fetus. If results are abnormal, the options for the pregnant woman include delivering an abnormal child or undergoing pregnancy termination, which is unacceptable to many patients.

Some parents may have never achieved a viable pregnancy without using PGD, because previous conceptions resulted in aneuploid embryos or chromosomally unbalanced embryos often leading to spontaneous miscarriage. "When we test the embryos on the third day, roughly 80% are abnormal," says Dr. Carolyn Kaplan. "When we transfer on the fifth day, the 'best looking' embryos are not always the ones PGD identifies as the best ones for transfer. If we judged on 'looks' alone, we would select the wrong embryos 50% to 60% of the time."

Translocations

Chromosomes are string-like structures found in the center of the cell, the nucleus. Chromosomes contain genes that are made of DNA. Therefore, our inherited information is housed on the chromosomes. A translocation is a change in chromosome struc-

Carolyn R. Kaplan, M.D., is the Director of In Vitro Fertilization at Georgia Reproductive Specialists, LLC

5445 Meridian Mark Road Suite 270
Atlanta, GA 30342
Phone: 404-843-2229 Fax: 404-843-0812
Web: http://www.ivf.com

For more information about PGD, visit the INCIID Genetics forum at http://www.inciid.org/forums/genetic/index.html

For more information about IVF, visit one of these INCIID IVF forums:

General IVF Questions answered by Dr. John Gordon at http://www.inciid.org/forums/ivf_high_tech/index.html

Tough Cases of IVF answered by Sher Institute for Reproductive Medicine Group at http://www.inciid.org/forums/Advanced_IVF/index.html

ture in which chromosomes are attached to each other or pieces of different chromosomes have been interchanged.

Individuals with balanced translocations typically have no disease process, though some do have fertility problems. The concern of having a balanced translocation is that the egg or sperm of that individual can have an unbalanced chromosome make-up that leads to the resultant embryo or pregnancy being unbalanced.

The presence of an unbalanced translocation can lead to an embryo not implanting, a pregnancy being lost, or a child being born with mental and physical problems. As such, individuals with a translocation may experience multiple pregnancy losses or have a child affected with physical and mental disabilities.

Single Gene Defects

PGD can be applied to cases where couples are at risk of passing on an inherited genetic disease because of a Single Gene Disorder (SGD).

PGD for SGD can alert the couple to serious genetic conditions that they may want to avoid for their offspring. In this case, PGD allows the IVF team to identify affected embryos and transfer only embryos unaffected by the gene, thus, reducing the risk of an affected child. The most common SGDs are:

- Cystic Fibrosis
- Fragile X
- Myotonic Dystrophy
- Thalassemia
- Tay-Sachs Disease
- Sickle Cell Disease

According to Dr. Kaplan, "While there is an added expense in doing PGD, in the long run, couples may save time and money by transferring only normal embryos. Also, since abnormal embryos can look totally normal, we can avoid cryopreservation of blastocysts that would not generate a successful pregnancy."

You can view a video clip of Dr. Mark Perloe discussing PGD at http: .

Third Party Parenting

Michael Feinman, M.D., F.A.C.O.G.

Since the very first IVF procedure, the theoretical ability to perform egg donation or gestational surrogacy has existed. It took doctors and society a few years to realize this fact and get comfortable with the concept. Considering the wide variation in the legal status of egg donation and surrogacy throughout the world, it is also clear that not all societies have gotten comfortable with these procedures. In the U.S., especially in California, these procedures are helping many couples have children when they may not have been able to in the past. In addition, their high success rates demonstrate the true potential of assisted reproduction when all factors have been optimized.

This article will review the medical indications for both egg donation and surrogacy. We will briefly consider how egg donors and surrogate mothers are chosen and screened. Since the process for egg donation and gestational surrogacy are actually similar, we will discuss them together. Finally, a few thoughts about the legal and ethical aspects of third party parenting will be considered.

Egg Donation

The first egg donor cycles reported were actually donor embryo cycles, where frozen embryos from one couple were transferred to the uterus of another woman. These early reports proved that women could carry a pregnancy, even if they had no ovarian function. From these humble beginnings, there are now an estimated 2,500 ovum donor cycles performed annually in the U.S. In 2003, Huntington Reproductive Center performed approximately 200 egg donor cycles. In the early years, each center devised rather casual arrangements to provide egg donors. With the increasing demand for donors, and increased public scrutiny, more formal procedures are used to find and screen donors.

Indications for Egg Donation

Women who benefit from egg donation can be divided into two groups: non-menstruating and menstruating females. Non-menstruating candidates are women with premature ovarian failure or physiologically menopausal women. The medical necessity and benefits of egg donation to these women is clear. Society is still struggling with the question with establishing an upper age limit for the latter group.

Menstruating women who may benefit from ovum donation include:

1. Women with waning ovarian function. These women may have high baseline FSH levels or respond poorly to ovarian stimulation when they try IVF.
2. "Older" women. As women mature, a higher percentage of the eggs they ovulate contain abnormal chromosome numbers. Women over age 43 almost never conceive with their own eggs through IVF, and eventually need to consider egg donation.
3. Women with poor egg quality. Some women who experience multiple IVF failures may produce poor quality embryos, regardless of their age and FSH levels. These women often conceive with donor eggs.

Michael Feinman, M.D., is board certified in the subspecialty of Reproductive Endocrinology and Infertility.

Huntington Reproductive Center
1220 La Venta Avenue, Suite 103
West Lake Village, CA 91361
Phone: (866) 472-4483 FAX: (805) 374-1736
Email: doctor02@havingbabies.com
URL: http://www.havingbabies.com

4. Women who carry genetic or chromosomal abnormalities. Examples of these conditions are recessive traits like cystic fibrosis, dominant traits such as Huntington's Disease, and balanced translocations. In many cases women with these conditions can now use their own eggs with the help of pre-implantation genetic diagnosis (PGD). If, for any reason, PGD is unacceptable, egg donation becomes an option for some.

"I need an egg donor. Now what?"

The recipient and egg donor both require screening. An often understated issue is the enormous psychological struggles and pain that a couple will endure as they grapple with the reality of abdicating the woman's genetic ties to their child. Most of these couples should have a session with a psychologist to discuss these issues. When these issues are resolved appropriately, couples can better focus on their primary objective, which is to start or enlarge their family. Both partners must undergo an infectious disease screen that includes, but is not limited to, HIV, HTLV, hepatitis B and C, syphilis, gonorrhea, and chlamydia. We encourage the male partner to undergo genetic screening for conditions that may be more common in his ethnic group. Examples include cystic fibrosis, Tay-Sachs disease and sickle-cell disease. Uterine pathology, such as fibroids and polyps, should be ruled out through hysterosalpingogram, sonohysterogram, or hysteroscopy.

Finding a suitable donor may be difficult for many couples. Occasionally, younger friends, sisters, or relatives may be interested in helping. Most couples do not have these people available, and we work with agencies that recruit donors and provide legal contracts and short-term health insurance policies for the donors. Experienced agencies recruit donors from college campuses, professional or acting trade journals, etc. Most of these agencies maintain internet sites that allow couples to view the donors in the privacy of their own homes. Couples focus on physical characteristics, IQ information, age, overall health history, and whether or not the woman has been a donor before.

Some ethicists and physicians have criticized the agency system for commercializing the process. While agencies provide a useful service, they have also created egg donor "fee inflation." As agencies compete for the same pool of potential donors, they begin raising the donor fees to attract women to their agency. This plays right into the hands of the critics. Currently, donors receive an average of $5,000 per cycle. This fee was supposed to compensate them for time, effort, and discomfort. As the fees go higher, they clearly go beyond this goal. The news media has reported stories of some women receiving as much as $50,000 because they claim supermodel/genius status. At Huntington Reproductive Center, we strongly discourage such practices and encourage our patients to seek appropriately-compensated donors, rather than being held hostage to these situations. A brilliant, gorgeous, athletic woman does not necessarily produce similar children!

Once a donor is selected, she will undergo a medical evaluation. She and her partner, like the recipients, are screened for infectious diseases. She also takes a drug screen. A thorough genetic/family history is taken to look for any possible genetic traits that the donor may not be aware of. Obviously, this feature requires the donor to understand her family history and be honest about it.

Results

In general, results with egg donation in appropriately selected couples are excellent. When discussing results, it is important to distinguish pregnancy rates per egg retrieval and per embryo transfer. Most donors produce 10 or more eggs. Our results show that success rates do not improve greatly by transferring more than 2 embryos to the recipient's uterus, in most cases. Thus, most donor cycles produce several extra embryos for freezing. At HRC, our success rates with fresh donor egg cycles average around 50% per embryo transfer. Our results with frozen embryos is not much lower, so the added success rate of the fresh plus frozen transfers exceeds 75%. This cumulative success rate is the same as the pregnancy rate per egg retrieval procedure. When a couple fails to achieve a pregnancy with egg donation, the situation can be quite overwhelming due to the high expectation of success and the substantial drain on financial resources. Our group is always cognizant of these realities

and every attempt is made to work with couples in the event of failure to help them continue in the donor program, unless it appears that the failures are due to an underlying medical problem in the recipient, which obviously needs to be addressed and resolved.

Surrogacy

In general, surrogacy has not gained widespread acceptance in most of the world. Almost all European countries, Japan, and Australia forbid the practice. Some of these countries allow "altruistic" surrogacy if no financial compensation is involved. "Traditional surrogacy" refers to artificial insemination of a surrogate mother with the semen of the intended father. In contrast, gestational surrogacy involves the production of embryos through IVF, using the eggs and sperm of the intended parents, and transferring the embryos to the uterus of the surrogate. Most surrogacy performed these days is the latter type, so we will focus on gestational surrogacy here.

In general, gestational surrogacy is indicated when a woman can produce viable embryos but cannot carry a pregnancy. Examples include:

1. Previous hysterectomy
2. Congenital absence of the uterus
3. Congenital malformations of the uterus
4. DES uterus
5. Uterine pathology, such as fibroids or scarring of the cavity
6. Maternal disease that makes pregnancy dangerous, such as severe diabetes, renal failure, lupus, or rheumatoid arthritis
7. Rh isoimmunization
8. Some breast cancers (there are differences of opinion here)
9. Multiple IVF failures with good embryo quality

Since there are potentially significant legal, financial, ethical, and psychological issues with surrogacy, we encourage couples to work with agencies that have experience in selecting surrogate mothers and provide the infrastructure to deal with these issues. Surrogate mothers should have at least one biological child that they have raised. Compared to egg donors, surrogate mothers undergo a much more intensive psychological assessment. Most applicants are rejected following this initial evaluation.

After completing the psychological evaluation, the candidate undergoes a medical evaluation, similar to the one performed on egg donor recipients.

A good contract between the gestational surrogate and her couple is critical. Examples of covered issues are: How many embryos can be transferred? What happens if there is a multiple pregnancy? Will the surrogate permit a termination if an abnormal fetus is discovered? Health insurance, life insurance, clothing allowances are discussed. Agreements regarding nutrition, smoking, travel, and other behaviors may be covered. The couple and the surrogate remain in contact throughout the pregnancy. Surrogacy is about relationships, and this aspect can be very rewarding to all parties involved.

Results

In general, results with gestational surrogacy are excellent, but vary according to the age of the egg provider. In a given age group, results with surrogacy tend to be higher than with routine IVF. This is largely due to patient selection. Proper selection of candidates implies that these women could have children on their own, if it were not for the medical problem that lead them to surrogacy. Good embryos placed into a well-prepared, proven uterus theoretically optimizes the IVF process.

How the Process Works

In reality, egg donation and gestational surrogacy are similar techniques. The only difference is who goes home with the baby! In general terms there is an egg provider and a recipient. The cycles of the two women are synchronized using a combination of birth control pills and Lupron. Upon stopping the pills, the egg provider begins using one of the brands of injectable gonadotropins to stimulate multiple egg production. The use of these drugs requires several office visits for blood and ultrasound monitoring to determine how many eggs are being produced and when they are likely to be mature. When the follicles seem large enough, a single injection of hCG is given. The transvaginal ultrasound guided egg retrieval is timed

to this injection. Most centers perform this procedure with conscious sedation, especially with egg donors.

While the egg provider is taking her injections, the recipient begins twice weekly injections of estrogen. Around the time of the retrieval, the recipient adds some combination of vaginal and injectable progesterone, thus creating an artificial cycle timed to the egg provider's cycle. The eggs are combined with the sperm from the intended father, and three days later a small number of embryos is transferred to the recipient's uterus. Since success rates are rather high, we discourage transferring large numbers of embryos, and in many of our egg donor cycles, or surrogacy cycles with young eggs, we often transfer two embryos, with excellent results. Extra embryos can be frozen for future use.

As with any medical procedure, there is a small potential for risk. For the egg provider, the retrieval procedure can cause internal bleeding or infection. We give prophylactic antibiotics to greatly reduce the risk of infection. Occasionally, the egg provider experiences the complication of hyperstimulation syndrome. This results from an overabundant response to the stimulation drugs. When this occurs, women experience significant abdominal distension and pain. Since these women will not be pregnant, the symptoms quickly recede with the menses, and most of these women can be managed successfully on an outpatient basis.

In contrast, egg donor recipients and surrogates face few risks from their procedures. The main risks are associated with pregnancy itself, and multiple births is an important issue. That is why it is important to use caution when deciding how many embryos to transfer in these often optimal situations.

Conclusion

While many ethical questions are still being debated in society, third-party parenting, when applied appropriately, can help many couples have a family that they otherwise could not achieve. The high success rates seen in our third-party parenting program demonstrates the true potential of assisted reproductive procedures, when all elements of the reproductive process are optimized.

As I look at the precious faces of my twin girls, I know that I owe their lives to the support of INCIID. Without the information I received from this organization, I know my girls wouldn't be here. INCIID kept me going until I achieved my dream. It didn't happen without loss and grief, it didn't happen the"old-fashioned" way, but it happened and I am forever thankful. **— An INCIID Member**

Selecting Your Egg Donor

Vicki L. Schnell, M.D., and Terry Nichtberger, R.N., M.S.N., C.F.N.P.

Egg donation is an excellent option for those couples who cannot conceive using their own oocytes. This process has an excellent success rate.

Selecting your egg donor can sometimes seem difficult, overwhelming, stressful, and exhausting. There are many things to consider while you go through the journey of finding the best egg donor for you. It is important to address these issues one at a time, taking time with this process, addressing any concerns but most importantly talking with each other. Your goal is to have a child but to also reach this goal together as a couple. Open communication is very important during a stressful experience. You should feel good and generally at peace with this decision.

An egg donor should be young, generally between the ages of 20 and 30. She should have an appropriate baseline FSH level, which indicates the degree of ovarian aging. The donor should have an ultrasound to assess the basal antral follicle count (or amount of follicles less than 10mm in size), pass a physical exam, and complete the FDA screening guidelines. These tests include screening for infectious diseases, along with asking the potential donor pertinent questions regarding her sexual lifestyle, tattoos and body piercings. Screening will also look for any close contacts or exposure to infectious diseases, SARS, West Nile Virus, and any neurological disorders (e.g., Crutchfield Jacobs Disease) of unknown etiology. Donors are screened for medical and genetic disorders as well as psychological well being.

Your egg donor may be anonymous or known to you, such as a friend or a family member. However, most couples do not utilize a friend or family member because they are not available and therefore choose an egg donor who is anonymous. You may choose an egg donor from a physician's office that has an egg donor program or from an agency that recruits egg donors.

Both egg donor programs in physician offices and egg donor agencies utilize similar recruitment techniques. Egg donors may be recruited through community newspapers, college newspapers, the Internet, and word of mouth.

It is very important for the agency or physician's office to guide you through the donation process. The process will be comprehensive, and should be much more than reading profiles or looking at pictures. The most important objective to be reached is to find an egg donor whom you connect with or whom you feel positive about using in the process for the ultimate goal of achieving a pregnancy.

The first thing to do when selecting your egg donor is to understand what are the most important attributes you require as a couple. These may include physical characteristics, such as height, eye color or hair color, ethnicity, overall personal and family health history, education, special interests and personality. Some programs or agencies also offer audio interviews with the donor, which may be helpful in the selection process. You should ask if you can view donors online or the available list online, which can help you be prepared before your initial consultation.

Before you schedule your appointment with an agency or with an egg donor program, you and your

Terry Nichtberger, R.N., M.S.N., C.F.N.P., is a Family Nurse Practitioner and has been actively involved in the Third Party Program with Dr. Schnell at the Center of Reproductive Medicine.
Vicki Schnell, M.D., has been Medical Director of the Center of Reproductive Medicine, in Webster, Texas since 1993. Dr. Schnell is board certified in both Obstetrics/Gynecology and in Reproductive Endocrinology/Infertility.

Center of Reproductive Medicine
450 Medical Center Blvd., Suite 202
Webster, Texas 77598
Phone:281-332-0073 Fax:281-332-1860
Email: TNichtberger@infertilitytexas.com
Website:www.infertilitytexas.com

partner should write down what is important to you separately. Once you've done this, discuss and compare the lists together before your appointment. Do you want to have a child who looks physically similar to you or has the same ethnicity? Or is the family health history more important to you? Whatever it is, it is very important for both you and your partner to feel good about this decision.

You and your partner may want to schedule an appointment with a therapist or psychologist to discuss the process, which can at times feel overwhelming. The psychologist or therapist can help you focus on what is the primary goal with this process (which is to have a family). You may want to attend a seminar offered by a physician regarding egg donation, or attend a support group meeting, such as Resolve, which involves many couples going through the same process, having the same feelings, etc. You can also ask your physician for the name of another patient who has gone through this process previously and is willing to talk with both you and your partner about any concerns you may have.

Ask opinions or recommendations from your physician, nurses or the agency about donors that they may consider for you. Also ask about the availability of the donor, for example, when will you be able to start the process? This will help them guide you in your selection. The program or agency should have spent a lot of time with these donors, reviewing their medical and social history and getting to know them as individuals and potential egg donors. They can offer you insight into the donors in ways that you may not see on paper. If there are any questions that you have for the donor that are not in her profile, ask your doctor's office or agency to ask her your specific questions. You may also want to ask if the donor has done an egg donor IVF cycle before and, if so, what were the results?

Now is the time for you to get all the information about your donor that you can. Photographs from your donor's childhood or adulthood may be important to you. Ask if you may keep a photo and or the profile of the donor to take home so that you can review it in the privacy of your home.

Other things to consider during this process are the nature-vs.-nurture debate. Is it more important for you to want someone who has a Ph.D. or someone who worked hard but never had the opportunity or financial means to go to college? Remember that this child is yours and with that will come a great deal of your nurturing, your goals, your values, your personality, your idiosyncrasies, and your interests.

The most important thing to consider when choosing your egg donor is what is going to make you feel good and make your family complete. This is a time consuming process but one that needs to have a shared discussion with both you and your partner to meet your goal of having a family.

Did you know . . .

Consumer membership is free and available to anyone who registers to participate on the INCIID site. INCIID provides a mechanism for community members to support the organization with tax-deductible sustaining memberships, but no one is ever denied services because of an inability to contribute. To learn about membership, visit **www.inciid.org**.

Appendixes

INCIID Directory of Professionals

Appendix A
INCIID Directory of Professionals, by state

ALABAMA

Mobile

George Koulianos, M.D.
Center for Reproductive Medicine

3 Mobile Infirmary Circle
Suite 312
Mobile, AL 36607
334-438-4200
334-438-4211

Fellowships in Reproductive Endocrinology and Infertility at Tulane Medical School and at the University of South Alabama.
crmal@bellsouth.net
http://www.infertilityalabama.com/

ARIZONA

Scottsdale

Ketan S. Patel, M.D.
Arizona Associates for Reproductive Health

8573 E. Princess Dr.
Suite 101
Scottsdale, AZ 85255
(480) 946-9900
(480) 946-9914

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
kpatel@AzARH.com
http://www.AzARH.com

Jay Nemiro, M.D.
Medical Director, Arizona Center for Fertility Studies

8997 E. Desert Cove Avenue
2nd Floor
Scottsdale, AZ 85260
480-860-4792
480-860-6819

Residency in OB/GYN at George Washington University Hospital and is board certified. Fellowship in Reproductive Endocrinology at Georgetown University.
drjsn@acfs2000.com
http://www.acfs2000.com/index.html

Tucson

Timothy J. Gelety, M.D.
Director, Division of Reproductive Endocrinolgy & Infertility, University of Arizona College of Medicine, Department of Obstetrics and Gynecology, Arizona Center for Reproductive Endocrinology and Infertility

5190 E Farness #114
Tucson, AZ 85712
520-326-0001
520-326-7451

Board Certified Reproductive Endocrinology & Infertility, Board Certified OB/GYN
t.gelety@gci-net.com
http://www.infertility-azctr.com/

Scot Hutchison, M.D.
Director, Division of Reproductive Endocrinolgy & Infertility, University of Arizona College of Medicine, Reproductive Health Center

4518 E. Camp Lowell Drive
Tucson, AZ 85712
520-733-0083
520-733-0771

Board Certified: OB/GYN and Reproductive endocrinology & infertility
http://www.ivftucson.com/

CALIFORNIA

Agoura Hills

Anita Singh, M.D.
LifeStart Fertility Center

29525 Canwood Street
Suite 220
Agoura Hills, CA 91301
818-889-4532
818-889-4536

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
drsingh@lifestartfertility.com
http://lifestartfertility.com

Beverly Hills

Michael M. Kamrava, M.D.
West Coast Infertility Medical Clinic, Inc.

250 N. Robertson Blvd.
Suite 403
Beverly Hills, CA 90211
310-285-0333
310-285-0334

info@westcoastinfertility.com
http://www.westcoastinfertility.com

Sam Najmabadi, M.D.
Center for Reproductive Health & Gynecology

99 N. La Cienega Blvd.
Suite 109
Beverly Hills, CA 90211
(310) 360-7584
(310) 360-9827

Reproductive Endocrinology and Infertility
najmabadi@reproductive.org
http://www.reproductive.org

Brea

Terence C. Lee, M.D.
Fertility Care of Orange County

203 N. Brea Blvd
Suite 100
Brea, CA 92821
714-256-0777

Reproductive Endocrinology and Infertility
terencelee@fcare.com
http://www.fcare.org

Chula Vista

Diana Van
President, Surrogate Alternatives, Inc.

363 Calle La Quinta
Chula Vista, CA 91914
619-397-0757
619-397-0736

SurroInc@aol.com
http://www.Surro.com

Dale City

Christo Zouves, M.D.
Zouves Fertility Center
901 Campus Drive
Suite 214
Dale City, CA 94015
650-301-4933
650-301-4939
zouves@goivf.com
http://www.goivf.com

Encino

Jeffrey M. Steinberg, M.D.
Fertility Institutes
16030 Ventura Blvd.
Suite 404
Encino, CA 91436
800-222-2802
(818) 728-4616
Embryology, Fellowship - Reproductive Endocrinology & Infertility, Laboratory, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Residency Obstetrics & Gynecology
TZFertility@aol.com
http://www.fertility-docs.com

Fremont

Jane L. Frederick, M.D., F.A.C.O.G.
Huntington Reproductive Center
270 Laguna Road
Suite 220
Fullerton, CA 92835
714-738-4200
714-738-4496
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
doctor05@havingbabies.com
http://www.havingbabies.com/

Mary Hinckley, M.D.
Reproductive Science Center of the San Francisco Bay Area
1999 Mowry Ave.
Suite 1
Fremont, CA 94538
888-377-4483
510-494-2000
Obstetrics & Gynecology
valerie.arno@integramed.com
http://rscbayarea.com

Rinku Mehta, M.D.
Reproductive Science Center
1999 Mowry Ave.
Suite 1
Fremont, CA 94538
888-377-4483
925-901-1480
Fellowship - Reproductive Endocrinology & Infertility
joanne.brian@integramed.com
http://rscbayarea.com Fullerton

Daniel A. Potter, M.D., F.A.C.O.G.
Huntington Reproductive Center
270 Laguna Rd
Suite 220
Fullerton, CA 92835
714-738-4200
714-738-4496
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
doctor06@havingbabies.com
http://www.havingbabies.com

Glendale

Brian Acacio, M.D.
Sher Institute for Reproductive Medicine – Orange County
1520 Chevy Chase Dr.
Suite 101
Glendale, CA 91206
(818) 291-1985
(818) 291-1985
INCIID the Heart IVF Scholarship Program Donor,Reproductive Endocrinology and Infertility
briana@Inovamgmt.com
http://www.haveababy.com

Mory Nouriani, M.D.
Sher Institute for Reproductive Medicine – Los Angeles
1520 East Chevy Chase Drive
Suite 101
Glendale, CA 91206
(818) 291-1985
(818) 291-1985
INCIID the Heart IVF Scholarship Program Donor, Obstetrics & Gynecology
moryn@sherinstitute.com
http://www.haveababy.com

Rodolfo Quintero
Associate Medical Director, Sher Institute for Reproductive Medicine – Los Angeles
1520 E. Chevy Chase Dr.
Suite 101
Glendale, CA 91206
866-415-4953
818-291-1986
Reproductive Endocrinology and Infertility
losangeles@haveababy.com
http://haveababy.com

Irvine

Lawrence B Werlin, M.D.
Coastal Fertility Medical Center
4900 Barranca Parkway
Suite 103
Irvine, CA 92604
949-726-0600
949-726-0601
Reproductive Endocrinology and Infertility,Embryology,Genetics,Surgery
info@coastalfertility.com
http://www.coastalfertility.com

Lafayette

Diane Michelsen, J.D., M.S.W.
Law Offices of Diane Michelsen
3190 Old Tunnel Road
Lafayette, CA 94549
(925) 945-1880
(925) 933-6807
Attorney, Adoption Services
diane@lodm.com
http://www.FamilyFormation.com

Laguna Hills

Aaron Spitz, M.D.
South Orange County Urology
24301 Paseo de Valencia
Suite A
Laguna Hills, CA 92653
949-855-1101
949-855-8710
Urology
aaronspitz@cox.net

Los Angeles

Sheri E. Cohen
Adoption & Family Formation Law Offices
2658 Griffith Park Blvd.
#338
Los Angeles, CA 90039
(800) 669-3614
(800) 669-3714
Attorney, Authors
sheri@giftofsmiles.com
http://www.giftofsmiles.com

Thomas J. Kim, M.D.
CHA Fertility Center

5455 Wilshire Boulevard
Suite 1904
Los Angelos, CA 90036
323-525-3377
323-525-3376

Reproductive Endocrinology and Infertility
margie@chaivf.com

Vicken Sahakian, M.D.
Medical Director, Pacific Fertility Center – Los Angeles

10921 Wilshire Blvd.
Suite 700
Los Angeles, CA 90024
310-209-7700
310-209-7799

Reproductive Endocrinology
prc@pfcla.com
http://www.pfcla.com/

Vicken Sepilian, M.D
CHA Fertility Center

5455 Wilshire Blvd
Site 1904
Los Angeles, CA 90036
(323) 525-3377
(323) 525-3376

Embryology,Fellowship - Reproductive Endocrinology & Infertility,Reproductive Endocrinology and Infertility
margie@chaivf.com
http://chaivf.com

Orinda

Susan Willman, M.D.
Medical Director, Reproductive Science Center of the San Francisco Bay Area

89 Davis Rd.
Suite 280
Orinda, CA 94563
888-377-4483
925-254-7810

Obstetrics & Gynecology
valerie.arno@integramed.com
http://rscbayarea.com

Newport Beach

Robert E. Anderson, M.D.
Southern Californina Center for Reproductive Medicine

361 Hospital Road
Suite 333
Newport Beach, CA 92663
949-642-8727
949-642-5413

Reproductive Endocrinology and Infertility
rea@socalfertility.com
http://www.socalfertility.com

Beth Ary, M.D.
Reproductive Specialty Center

1441 Avocado Ave,
Suite 203
Newport Beach, CA 92660
(949) 640 -720
(949) 720-0203

Fellowship Trained in Reproductive Endocrinology and Infertility
drary@drary.com
http://www.drary.com/

Orange

Tisha Lene Harman
Attorney, A Center for Children & Family Law

One City Blvd., West
Suite 1115
Orange, CA 92868
(714) 937-1234
(714) 937-1211

B.S. from California State University at Long Beach, J.D. (with honors) from Western State University
tisha@centerforchildren.com
http://www.centerforchildren.com

Palo Alto

Francis Polansky, M.D.
Nova In Vitro Fertilization

1681 El Camino Real
Palto Alto, CA 94306
(650) 322-0500
(650) 322-5404

Board Eligible Reproductive Endocrinology and Infertility
Info@novaivf.com
http://novaivf.com/index.php3?page=in_vitro_fertilization

Pasadena

Michele L. Evans, M.D., F.A.C.O.G.
Huntington Reproductive Center

333 S. Arroyo Parkway
3rd Floor
Pasadena, CA 91105
(626) 440-9161
(626) 440-0138

Obstetrics & Gynecology
jackiesharpe@havingbabies.com
http://www.havingbabies.com

Bradford A. Kolb, M.D., F.A.C.O.G.
Huntington Reproductive Center

333 S. Arroyo Parkway
3rd Floor
Pasadena, CA 91105
626-440-9161
626-440-0138

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility,Residency Obstetrics & Gynecology
doctor04@havingbabies.com
http://www.havingbabies.com/

Jeffrey R. Nelson, D.O., F.A.C.O.G.
Huntington Reproductive Center

333 S. Arroyo Parkway
3rd Floor
Pasadena, CA 91105
626-440-9161
626-440-0138

Obstetrics & Gynecology,Osteopath
doctor05@havingbabies.com
http://www.havingbabies.com/

John G. Wilcox, M.D., F.A.C.O.G.
Huntington Reproductive Center

333 S. Arroyo Parkway
3rd Floor
Pasadena, CA 91105
626-440-9161
626-440-0138

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
doctor07@havingbabies.com
http://www.havingbabies.com/

Poway

Theresa Marie Erickson
Law Offices of Theresa Erickson

12780 Danielson Ct.
Suite B
Poway, CA 92064
866-864-4133
858-748-4244

Attorney
terickson@ericksonlaw.net
http://www.ericksonlaw.net

Mary Ann Lathus
Conceptual Options, LLC

12780 Danielson Court
Suite B
Poway, CA 92064
858-748-4222
858-748-4244

Author
MaryAnn@ConceptualOptions.com
http://www.ConceptualOptions.com

Roseville

Janice Andreyko
Northern California Fertility Center

1130 Conroy Lane
Suite 100
Roseville, CA 95661
(916) 773-2229
(916) 773-8391

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
dkoenes@ncfmc.com
http://www.ncfmc.com

John L. Gililland, M.D.
Northern California Fertility Medical Center

1130 Conroy Lane
Suite 100
Roseville, CA 95661
916-773-2229
916-773-8391

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
doctorg@ncfmc.com
http://www.ncfmc.com/

Carlos E Soto-Albors, M.D.
Northern California Fertility Medical Center

406 1/2 Sunrise Avenue
Suite 3A
Roseville, CA 95661
916-773-2229
916-773-8391

Reproductive Endocrinology and Infertility
csoto@ncfmc.com
http://www.ncfmc.com

Sacramento

Ellen Snowden, M.D.
Medical Director, Sher Institute for Reproductive Medicine – Sacramento

2288 Auburn Ave.
Ste. 204
Sacramento, CA 95821
(916) 568-2125
(916) 567-1360

Reproductive Endocrinology and Infertility
sacramento@haveababy.com
http://www.haveababy.com

Salinas

Edward Joseph Ramirez, M.D.
The Fertility and Gynecology Center/ Monterey Bay IVF

212 San Jose Street
Suite 201
Salinas, CA 93901
831-769-0161
831-759-0939

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
ejrM.D.@montereybayivf.com
http://montereybayivf.com

San Diego

Andrew Kim
Halozyme Therapeutics, Inc.

11588 Sorrento Valley Road
Suite 17
San Diego, CA 92121
858-794-8889
858-259-2539

akim@halozyme.com
http://www.cumulase.com

Marc Sklar, Doctor of Acupuncture
Reproductive Wellness

3944 Murphy Canyon Rd.
C200
San Diego, CA 92123
(877) 843-7100
(619) 583-2695

Alternative Medicine, Complementary Medicine, Mental Health Professional, Acupuncture
msklar@reproductivewellness.com
http://www.reproductivewellness.com

San Francisco

Philip Chenette, M.D.
Pacific Fertility Center

55 Francisco Street
Suite 500
San Francisco, CA 94133
888-834-3000
415-834-3099

Author, Fellowship - Reproductive Endocrinology & Infertility, Reproductive Endocrinology and Infertility
chenette@pacificfertility.com
http://www.infertilitydoctor.com/

Carolyn R. Givens, M.D.
Pacific Fertility Center

55 Francisco Street
Suite 500
San Francisco, CA 94163
415-834-3000
415-834-3099

Reproductive Endocrinology and Infertility
givens@pacificfertility.com
http://www.infertilitydoctor.com

Carl Herbert, M.D.
Pacific Fertility Center

55 Francisco Street, Suite 500
San Francisco, CA 94133
888-834-3095
415-834-3080

herbert@pacificfertility.com
http://www.infertilitydoctor.com

Elissa R Levin, M.S., C.G.C.
Clinical Director, DNA Direct

Pier 9
Suite 105
San Francisco, CA 94111
415 646-0222
415 646-0224

Genetic Counselor
expert@dnadirect.com
http://www.dnadirect.com

Isabelle Patricia Ryan, M.D.
Pacific Fertility Center

55 Francisco Street
Suite 500
San Francisco, CA 94133
415-834-3000
415-834-3099

Reproductive Endocrinology and Infertility
ryan@pacificfertility.com
http://www.infertilitydoctor.com

Eldon Schriock, M.D.
Pacific Fertility Center

55 Francisco Street
Suite 500
San Francisco, CA 94163
415-834-3000
415-834-3099

Reproductive Endocrinology
eschriock@pacificfertility.com
http://www.infertilitydoctor.com/

Collin B Smikle, M.D.
Fertility Associates of the Bay Area

1700 California Street
Suite 570
San Francisco, CA 94109
(415) 673-9199
(415) 673-8796

Reproductive Endocrinology and Infertility
drsmikle@laurelivf.com
http://www.laurelivf.com

San Jose

Carmelo Sgarlata
Reproductive Science Center of the San Francisco Bay Area

2505 Samaritan Dr.
Suite 408
San Jose, CA 95124
888-377-4483
408-358-9287

Obstetrics & Gynecology
valerie.arno@integramed.com

San Rafael

Anca Sira, L.Ac.

1299 Fourth Street, Suite 208
San Rafael, CA 94901
415-456-7808
661-457-4337

Acupuncture
ancasira@ancasira.com
http://ancasira.com

San Ramon

Donald J. Galen, M.D.
Reproductive Science Center of the San Francisco Bay Area

3160 Crow Canyon Road
Suite 150
San Ramon, CA 94583
925-867-1800
925-275-0933

American College of Ob/Gyn (FACOG)
Reproductive Endocrinology/IVF/ Microsurgery/ Minimally-Invasive Gyn Surgery
rscbayarea@lucy.integramed.com
http://www.rscbayarea.com/
http://www.drgalen.com/

Louis Weckstein
Reproductive Science Center of the San Francisco Bay Area

3160 Crow Canyon Rd.
Suite 150
San Ramon, CA 94583
888-377-4483
925-275-0933

Obstetrics & Gynecology
valerie.arno@integramed.com
http://rscbayarea.com
http://rscbayarea.com

Tarzana

Robert Boostanfar, M.D., F.A.C.O.G.
Huntington Reproductive Center

5525 Etiwanda Avenue
Suite 311
Tarzana, CA 91356
818-996-2188
818-996-2111

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
doctor01@havingbabies.com
http://www.havingbabies.com

Michael Vermesh, M.D.
Center for Fertility & Gynecology

18370 Burbank Blvd.
3Suite 01
Tarzana, CA 91356
818-881-9800
818-881-1857

Reproductive Endocrinology and Infertility
paulaclare96@vermesh.com
http://www.vermesh.com

Tustin

Tamara McNulty
Law Offices of Tamara McNulty

17621 Irvine Blvd., Ste. 210
Tustin, CA 92780
(714) 730-4744
(714) 730-1225

Attorney
Tamara@buildafamily.com
http://www.buildafamily.com

West Lake Village

Michael Feinman, M.D., F.A.C.O.G.
Huntington Reproductive Center

1220 La Venta Avenue,
Suite 103
West Lake Village, CA 91361
(866) 472-4483
(805) 374-1736

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
doctor02@havingbabies.com
http://www.havingbabies.com

West Los Angeles

David E. Tourgeman, M.D., F.A.C.O.G.
Huntington Reproductive Center

11500 W. Olympic Blvd.
Suite 504
West Los Angeles, CA 90064
(310) 481-0881
(310) 481-9017

Obstetrics & Gynecology
jackiesharpe@havingbabies.com
http://www.havingbabies.com

COLORADO

Fort Collins

Kevin E. Bachus, M.D.
Rocky Mountain Center for Reproductive Medicine

1080 E. Elizabeth Street
Fort Collins, CO 80524
970-493-6353
970-493-6366

Dr. Kevin Bachus is fellowship trained in reproductive endocrinology with OB/GYN and Reproductive Endocrinology board certifications.
rmcrm@uswest.net
http://www.drbachus.com/

Lafayette

Mark Bush, M.D.
Conceptions Reproductive Associates

300 Exempla Circle
Suite 370
Lafayette, CO 80026
303-449-1084
303-449-1039

Board Certified OB/GYN, board Certified Reproductive Endocrinology and Infertility
info@conceptionsrepro.com
http://www.conceptionsrepro.com

Littleton

Michael Swanson, M.D.
Conceptions Reproductive Associates

271 W. County Line Road
Littleton, CO 80129
303-794-0045
303-794-2054

Obstetrics & Gynecology
info@conceptionsrepro.com
http://www.conceptionsrepro.com

CONNECTICUT

Bridgeport

Michael Doyle, M.D.
Connecticut Fertility Associates
4920 Main Street
Bridgeport, CT 06606
203-373-1200
203-365-6516
Fellowship - Reproductive Endocrinology & Infertility, Reproductive Endocrinology and Infertility
michael.doyle@ctfertility.com.
http://www.connecticutfertility.com

Greenwich

Yaron Seidman, L.Ac., M.He.
Hunyuan Fertility
9 Benedict Place
Greenwich, CT 06830
203-325-2000
203-629-6290
Acupuncture,Alternative Medicine,Complementary Medicine
info@Hunyuan.org
http://www.Hunyuan.org

Norwalk

Mark P. Leondires, M.D.
Reproductive Medicine Associates of Connecticut
10 Glover Avenue
Norwalk, CT 06850
203-750-7400
203-846-9579
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
inquiries@rmact.com
http://www.rmact.com

Nora Rachele Miller, M.D.
Connecticut Fertility Associates
148 East Ave.
Suite 2C
Norwalk, CT 06851
203-855-1200
(203) 866-3668
Fellowship - Reproductive Endocrinology & Infertility
Nora.Miller@ctfertility.com
http://www.ctfertility.com

Spencer S. Richlin, M.D.
Reproductive Medicine Associates of Connecticut
10 Glover Avenue
Norwalk, CT 06850
203-750-7400
203-846-9579
Obstetrics & Gynecology
inquiries@rmact.com
http://www.rmact.com

Stamford

Gad Lavy, M.D., F.A.C.O.G
New England Fertility Institute
1275 Summer Street
Suite 201
Stamford, CT 06905
203-325-3200
203-323-3130
Reproductive Endocrinology and Infertility
mwelch@nefertility.com
http://www.nefertility.com

Trumbull

Andrew Levi, M.D.
Park Avenue Fertility and Reproductive Medicine
5520 Park Avenue, Suite 103
Trumbull, CT 06611
203-372-6700
203-372-6706
Reproductive Endocrinology and Infertility
andrewleviM.D.@yahoo.com
http://www.andrewleviM.D..com

Westport

Diane Johnston, N.P., M.S.
Director, Mind/Body Infertiltiy Program
181 Post Road West
Westport, CT 06880
203-226-6688
Mental Health Professional
dianejohnston@optonline.net
http://www.mind-body-fertility.com/

Yaron Seidman, L.Ac., M.He.
Hunyuan Fertility
15 Treadwell Ct
Westport, CT 06880
203-325-2000
203-629-6290
Acupuncture, Alternative Medicine, Complementary Medicine
info@Hunyuan.org
http://www.Hunyuan.org

DELAWARE

Newark

Ronald F. Feinberg, M.D., Ph.D.
Medical Director
Reproductive Associates of Delaware
4735 Ogletown-Stanton Rd.
Suite 3217
Newark, DE 19713
(302) 623-4242
(302) 623-4241
Board Certified in Reproductive Endocrinology and Infertility, Board Certified in Obstetrics and Gynecology,
miracles@ivf-de.org
http://www.ivf-de.org

FLORIDA

Boca Raton

Mark S. Denker
Palm Beach Fertility Center
9970 Central Park Blvd
Suite 300
Boca Raton, FL 33428
561-477-7728
561-477-7035
Obstetrics & Gynecology
info@palmbeachfertility.com
http://www.palmbeachfertility.com

Gainesville

Larry Wurn, L.M.T.
Clear Passage Therapies
3600 NW 43rd St.
Suite A-1
Gainesville, FL 32606
352 336-1433
352 336-9980
Alternative Medicine, Author, Complementary Medicine, Other
cptherapy@aol.com
http://www.clearpassage.com

Jacksonville

Samuel E. Brown, M.D.
Florida Institute for Reproductive Medicine
Baptist Medical Center Pavilion
836 Prudential Dr. #902
Jacksonville, FL 32207, FL 32207
904-399-5620
904-399-5645
Reproductive Endocrinology and Infertility
sambrown99@yahoo.com
http://www.firmjax.com

Margate

Marcelo J Barrionuevo, M.D.
IVF Florida Reproductive Associates
2960 N. State Road 7
Suite 300
Margate, FL 33063
954-247-6200
954-247-6262
Reproductive Endocrinology and Infertility
drbarrionuevo@ivfflorida.com
http://www.ivfflorida.com

David I. Hoffman, M.D.
IVF Florida Reproductive Associates

2960 N. State Road 7
Suite 300
Margate, FL 33063
954-247-6200
954-247-6262

Reproductive Endocrinology and Infertility
drhoffman@ivfflorida.com
http://www.ivfflorida.com

Edward Illions, M.D.
IVF Florida Reproductive Associates

2960 N. State Road 7
Suite 300
Margate, FL 33063
954-247-6200
954-247-6262

Reproductive Endocrinology and Infertility
drillions@ivfflorida.com
http://www.ivfflorida.com

Wayne S. Maxson, M.D.
IVF Florida Reproductive Associates

2960 N. State Road 7
Suite 300
Margate, FL 33063
954-247-6200
954-247-6262

Reproductive Endocrinology and Infertility
kimberleylogan@yahoo.com
http://www.ivfflorida.com

Steven J. Ory, M.D.
IVF Florida Reproductive Associates

2960 N. State Road 7
Suite 300
Margate, FL 33063
954-247-6200
954-247-6262

Reproductive Endocrinology and Infertility
drory@ivfflorida.com
http://www.ivfflorida.com

Miami

Fernando M. Akerman, M.D.
IVF Center of Miami

8950 N Kendall Drive,
Suite 103
Miami, FL 33176
305-596-4013
305-596-4557

Reproductive Endocrinology & Infertility
meamado@miami-ivf.com
http://www.miami-ivf.com/

Michael D. Graubert, M.D.
Medical Director, Palmetto Fertility Center of South Florida

7100 W. 20th Avenue
Suite 205
Miami, FL 33016
305-558-0808
305-558-0806

Board Eligible in Reproductive Endocrinology & Infertility
palmettoivf@aol.com
http://www.palmettoivf.com/

Michael H. Jacobs, M.D.
Medical Director, IVF Center of Miami

8950 N Kendall Drive,
Suite 103
Miami, FL 33176
305-596-4013
305-596-4557

Reproductive Endocrinology & Infertility
fivf@msn.com
http://www.miami-ivf.com/

Wellington

Scott Roseff, M.D., F.A.C.O.G.

10115 West Forest Hill Boulevard
Suite 401A
Wellington, FL 33414
561-333-8232
973-736-5201

Fellowship - Reproductive Endocrinology & Infertility, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
doc@reproendo.com
http://www.reproendo.com

GEORGIA

Atlanta

Susan C. Conway, M.D.
Georgia Reproductive Specialists

5445 Meridian Mark Road
Suite 270
Atlanta, GA 30342
404-843-2229
404-843-0812

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
sconway@ivf.com

Carlene W. Elsner, M.D.
Reproductive Biology Associates

1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404-256-6999

Reproductive Endocrinology and Infertility
Carlene.Elsner@rba-online.com
http://www.rba-online.com

Carolyn R. Kaplan, M.D.
Georgia Reproductive Specialists

5445 Meridian Mark Road
Suite 270
Atlanta, GA 30342
404-843-2229
404-843-0812

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
kaplan@ivf.com
http://www.ivf.com

Daniel B. Shapiro, M.D.
Reproductive Biology Associates

1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404)256-6999

Board certified in obstetrics and gynecology and reproductive endocrinology by the American Board of Obstetrics and Gynecology.
Daniel.Shapiro@rba-online.com
http://www.rba-online.com

David L. Keenan, M.D.
Reproductive Biology Associates

1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404)256-6999

Reproductive Endocrinology & Infertility
David.Keenan@rba-online.com
http://www.rba-online.com

Hilton I. Kort, M.D.
Reproductive Biology Associates

1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404)256-6999

Obstetrics & Gynecology
Hilton.Kort@rba-online.com
http://www.rba-online.com

Joe B. Massey, M.D.
Reproductive Biology Associates

1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404)256-6999

Joe.Massey@rba-online.com
http://www.rba-online.com

Dorothy Mitchell-Leef, M.D.
Reproductive Biology Associates
1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
404-843-3064
404)256-6999
rba-online@rba-online.com
http://www.rba-online.com

Mark Perloe, M.D.
Georgia Reproductive Specialists
5445 Meridian Mark Road
Suite 270
Atlanta, GA 30342
404-843-2229
404-843-0812
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
Mperloe@ivf.com
http://www.ivf.com

Scott M. Slayden, M.D.
Reproductive Biology Associates
1150 Lake Hearn Dr.
Suite 400
Atlanta, GA 30342
770-277-3361
404-256-6999
Reproductive Endocrinology and Infertility
Scott.Slayden@rba-online.com
http://www.rba-online.com

Andrew A. Toledo, M.D.
Institute for Endocrinology and Reproductive Medicine
1150 Lake Hearn Drive
Suite 400
Atlanta, GA 30342
404-257-1900
404-355-5667
Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
Fertman790@aol.com

ILLINOIS

Buffalo Grove

John J. Rapisarda, M.D.
Fertility Centers of Illinois
135 N. Arlington Heights Rd
Suite 195
Buffalo Grove, IL 60089
(877) FCI-4IVF
(847) 215-8996
Fellowship - Reproductive Endocrinology & Infertility, Obstetrics & Gynecology, Residency Obstetrics & Gynecology
editor@inciid.org
http://www.fcionline.com/

Chicago

Carolyn B. Coulam, M.D.
Rinehart Center for Reproductive Medicine
233 East Erie Street
Suite 500
Chicago, IL 60610
(312) 944-2600
(312) 944-0100
Reproductive Endocrinology and Infertility
cbcoulam@aol.com
http://www.illinoisivf.com/

Jan Friberg, M.D.
Friberg Medical Associates
845 N Michigan Ave
935 E Water Tower Plaza
Chicago, IL 60022
(312) 642-6777
(312) 642-8383
Obstetrics & Gynecology
Info@FribergMedical.com
http://www.fribergmedical.com

Brian R. Kaplan, M.D.
Fertility Centers of Illinois
900 N. Kingsbury
River North: Suite RW6
Chicago, IL 60610
(877) FCI-4IVF
(847) 433-6145
Acupuncture,Embryology,Fellowship - Reproductive Endocrinology & Infertility,Reproductive Endocrinology and Infertility
editor@inciid.org
http://www.fcionline.com/

Crystal Lake

Laurence A. Jacobs, M.D.
Fertility Centers of Illinois
5911 Northwest Highway
Suite 205
Crystal Lake, IL 60014
(877) FCI-4IVF
(847) 215-8996
Fellowship - Reproductive Endocrinology & Infertility,Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Residency Obstetrics & Gynecology
editor@inciid.org
http://www.fcionline.com/

Glenview

Aaron S. Lifchez, M.D.
Fertility Centers of Illinois
3703 W. Lake Ave.
Suite 106
Glenview, IL 60026
(877) FCI-4IVF
(847) 998-6880
Author, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Residency Obstetrics & Gynecology
editor@inciid.org
http://www.fcionline.com/

Highland Park

Edward L. Marut, M.D.
Fertility Centers of Illinois
Highland Park Hospital Medical Office Building
767 Park Avenue West, Sui
Highland Park, IL 60035
(877) FCI-4IVF
(847) 433-6145
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
editor@inciid.org
http://www.fcionline.com/

Hoffman Estates

Marie Davidson, Ph.D.
Fertility Centers of Illinois
1535 N. Barrington Road
Suite 305
Hoffman Estates, IL 60169
847 843 1510
847 843 1582

Vishvanath Karande
Karande & Associates S.C.
1585 N Barrington Road
Suite 406
Hoffman Estates, IL 60169
847-884-8884
847-884-8093
Reproductive Endocrinology and Infertility,Embryology
info@karandeivf.com
http://www.karandeivf.com

Jane M. Nani, M.D.
Fertility Centers of Illinois
1585 N. Barrington Road
Suite 305
Hoffman Estates, IL 60169
(877) FCI-4IVF
847 843 1582
Reproductive Endocrinology and Infertility
editor@inciid.org
http://www.fcionline.com

Ramaa P Rao, M.D.
Fertility Centers of Illinois

1585 N. Barrington Rd.
Professional Bldg II, Sui
Hoffman Estates, IL 60194
(847) 843-1510
(847) 843-1582

Fellowship trained in reproductive endocrinology and infertility
http://www.fcionline.com/

Joliet

Marek W. Piekos, M.D.
Reproductive Health Specialists, LTD

744 Essington Road
Joliet, IL 60435
815-730-1100
815-730-1066

info@reproductivespecialist.com
http://www.reproductivespecialist.com/

Lindenhurst

Angeline N. Beltsos, M.D.
Fertility Centers of Illinois

2592 Grand Avenue
Emerald Square - Suite 20
Lindenhurst, IL 60046
877 FCI 4IVF
(847) 215-8996

Alternative Medicine, Fellowship - Reproductive Endocrinology & Infertility, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Residency Obstetrics & Gynecology
editor@inciid.org
http://www.fcionline.com/

Naperville

Meike L. Uhler, M.D.
Fertility Centers of Illinois

2056 Westings Ave
Suite 130
Naperville, IL 60563
(877) FCI-4IVF
630-305-7990

Reproductive Endocrinology and Infertility
editor@inciid.org
http://www.fcionline.com

Orland Park

Kevin J. Lederer, M.D.
Fertility Centers of Illinois

8651 W. 159th Street
Suite 5
Orland Park, IL 60462
(877) FCI-4IVF
(773) 472-4404

Fellowship - Reproductive Endocrinology & Infertility,Reproductive Endocrinology and Infertility
editor@inciid.org
http://www.fcionline.com/

Peoria

Kathy Trumbull, M.D.
Sher Institute for Reproductive Medicine -- Central Illinois

5401 N. Knoxville
Suite 110
Peoria, IL 61614
309-689-0411
309-689-0784

Reproductive Endocrinology and Infertility
centralil@haveababy.com
http://www.haveababy.com

INDIANA

Indianapolis

John C. Jarrett, M.D.
Midwest Reproductive Medicine

8081 Township Line Road
Indianapolis, IN 46260
317-875-5978

Board certified in Reproductive Endocrinology & Infertility
http://www.FertilityMRM.com

KANSAS

Overland Park

Rodney Lyles, M.D.
Reproductive Resource Center of Greater Kansas City

12200 W 106th St.
Suite 120
Overland Park, KS 66215
913-894-2323
913-894-0841

Reproductive Endocrinology and Infertility
tclark@rrc.com
http://www.rrc.com

KENTUCKY

Louisville

Henry Bohler
Associate Professor, Louisville Women's Healthcare

Norton Health Care Pavillion, Dept. of OB/Gyn – REI
315 East Broadway, M-18
Louisville, KY 40202
502-629-2448
502-629-2444

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
hcbohl01@gwise.louisville.edu
http://www.kyinfertility.com

Steven Nakajima
Associate Professor, Louisville Women's Healthcare

Norton Health Care Pavillion, Dept. of OB/Gyn – REI
315 East Broadway, M-18
Louisville, KY 40202
502-629-2448
502-629-2444

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
steven.nakajima@louisville.edu
http://www.kyinfertility.com

LOUISIANA

Lafayette

John Storment
Fertility & Women

4630 Ambassador Caffery
Suite 206
Lafayette, LA 70508
337-989-8795
337 989 9728

Reproductive Endocrinology and Infertility
storment@fwhcla.com
http://www.FertilityAnswers.com

MARYLAND

Annapolis

Sherrie F. Smith
Center for Surrogate Parenting

9 State Circle, Suite 302
Annapolis, MD 21401
(410) 990-9860
(301) 879-5614

centersp@aol.com
http://www.creatingfamilies.com/

Rockville

Hilary Neiman
The Law Firm of Hilary M. Neiman
30 Courthouse Square
Suite 106
Rockville, MD 20850
301-340-7228
301-493-8481
Attorney
NeimanLaw@HilaryNeiman.com
http://www.hilaryneiman.com

Silver Spring

Barbara Blitzer, M.S.W., L.C.S.W.-C.
8 Park Valley Road
Sliver Spring, MD 20910
301-588-6461
301-588-6461
Mental Health Professional
barbarablitzer@comast.net
http://www.barbarablitzer.com

MICHIGAN

Highland

Kathleen M. Nelson,
Psychologist
1641 S. Milford
Suite A-102
Highland, MI 48357
(248) 889-5767
(248) 889-5767
kknPh.D.@msn.com

MINNESOTA

Eagan

Jennifer R. Bloome, M.S. O.T.R., H.W.C.
President and Founder, Anji, Inc.
4108 Havenhill Circle
Eagan, MN 55123
651-686-4763
651-452-8912
Occupational Therapy
Jennifer@AnjiOnline.com
http://www.AnjiOnline.com

Maple Grove

Steven H. Snyder, Esq.
Synder Law Firm
14788 77th Place North
Maple Grove, MN 55311
763-420-6700
763-420-9588
Attorney,Author
steve@snyderlawfirm.com
http://www.snyderlawfirm.com

MISSOURI

Creve Coeur

Peter Ahlering, M.D.
Medical Director, Sher Institute for Reproductive Medicine – St. Louis
456 N. New Ballas Rd.
Suite 101
Creve Coeur, MO 63141
(314) 983-9000
(314) 983-9023
Board certified obstetrician/gynecologist (OB/GYN) with a focus in operative laparoscopy and advanced laparoscopic procedures
petera@Inovamgmt.com
http://www.haveababy.com/

Elan Simckes
Attending Physician, Sher Institute for Reproductive Medicine – St. Louis
456 N. New Ballas Rd.
Suite 101
Creve Coeur, MO 63141
(314) 983-9000
(314) 983-9023
Obstetrics & Gynecology
stlouis@haveababy.com
http://www.haveababy.com

Barry Witten
Attending Physician, Sher Institute for Reproductive Medicine – St. Louis
456 N. New Ballas Rd.
Suite 101
Creve Coeur, MO 63141
(314) 983-9000
(314) 983-9023
Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
stlouis@haveababy.com
http://www.haveababy.com

NEVADA

Las Vegas

Jeffrey Fisch, M.D.
Medical Director
Sher Institute for Reproductive Medicine – Las Vegas
3121 S. Maryland Parkway
Suite 300
Las Vegas, NV 89109
702-892-9696
702-892-9666
Reproductive Endocrinology & Infertility
lasvegas@haveababy.com

Geoffrey Sher, M.D.
Medical Director - Mosiac
Sher Institute for Reproductive Medicine – Manhattan and Las Vegas
3121 S. Maryland Pkwy,
Ste 300
Las Vegas, NV 89109
(702) 892-9696
(702) 892-9666
gsher@sherinstitute.com
http://www.haveababy.com

NEW HAMPSHIRE

Durham

Kate Collopy
Center for the Evaluative Clinical Sciences at Dartmouth
8 Frost Drive
Durham, NH 03824
603-969-1078
kate.collopy@dartmouth.edu

NEW JERSEY

Bedminster

Alexander Dlugi, M.D.
Medical Director
Sher Institute for Reproductive Medicine – New Jersey
One Robertson Drive
Bedminster, NJ 07921
908-781-0666
908-781-6377
Reproductive Endocrinology and Infertility
dlugia@sherinstitute.com
http://www.haveababy.com

Edison

Gregory H. Corsan, M.D.
Center for Advanced Reproductive Medicine & Fertility

4 Ethel Road
Suite, 405A
Edison, NJ 08817
732-339-9300
732-339-9400

Board certified in Reproductive Endocrinology and Infertility.
http://www.infertilitydocs.com/

Suna M. Qasim, M.D.
Center for Advanced Reproductive Medicine & Fertility

4 Ethel Road
Suite, 405A
Edison, NJ 08817
732-339-9300
732-339-9400

Board certified in Reproductive Endocrinology and Infertility. Member. American Society for Reproductive Medicine and Society for Reproductive Endocrinology and Infertility
http://www.infertilitydocs.com/

Engelwood

Michael K Bohrer, M.D.
Reproductive Medical Associates of New Jersey

100 Franklin Square Drive
Suite 200
Englewood, NJ 07631
732-537-0631
732-537-0134

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
cimplicito@rmanj.com
http://www.rmanj.com

Doreen L Hock, M.D.
Reproductive Medical Associates of New Jersey

25 Rockwood Place
Englewood, NJ 07631
732-537-0631
732-537-0134

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
cimplicito@rmanj.com
http://www.rmanj.com

Philip R. Lesorgen, M.D.
New Jersey IVF Associates

106 Grand Avenue
Englewood, NJ 07631
201-569-6979
201-569-0269

Reproductive Endocrinology and Infertility
DrLesorgen@njfertility.com
http://www.njfertility.com

Bradley T Miller, M.D.
Reproductive Medical Associates of New Jersey

25 Rockwood Place
Englewood, NJ 07631
732-537-0631
732-537-0134

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
cimplicito@rmanj.com
http://www.rmanj.com

Michael J Slowey, M.D.
Reproductive Medical Associates of New Jersey

25 Rockwood Place
Englewood, NJ 07631
201-569-7773
201-569-8143

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
cimplicito@rmanj.com
http://www.rmanj.com

Hackensack

Patricia L. Hughes, M.D.
Patricia Hughes, M.D.

140 Prospect Avenue
Suite 10
Hackensack, NJ 07601
201-342-3428
201-342-3904

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
office@phughesM.D..com
http://www.phughesM.D..com

Hossein Sadeghi-Nejad, M.D.
Director, Center for Male Reproductive Medicine and Microsurgery

20 Prospect Ave.
Hackensack, NJ 07601
(201)342-7977
(973) 395 7197

Dr. Sadeghi-Nejad is certified by the American Board of Urology and is a member of the American Society of Reproduc
hossein@ix.netcom.com
http://www.hsadeghi.com/

Highland Park

Yakov M Epstein, Ph.D.
Acting Director, Rutgers Center for Math, Science & Computers

325 Lincoln Avenue
Highland Park, NJ 08904
732-246-1566
508-519-0514

Author, Mental Health Professional
yepstein@rci.rutgers.edu
http://www.gettingpregnantbook.com/

Livingston

Natalie Cekleniak, M.D.
Practice Director, IRMS - The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center

Old Short Hills Road
East Wing, Suite 403
Livingston, NJ 07039
973-322-8890
973-322-8890

Reproductive Endocrinology and Infertility
NatalieC@sbivf.com
http://www.sbivf.com

Serena Chen, M.D.
Director, IRMS – The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center

Old Short Hills Road
East Wing, Suite 403
Livingston, NJ 07039
973-322-8890
973-322-8890

Reproductive Endocrinology and Infertility
SerenaC@sbivf.com
http://www.sbivf.com

Margaret Garrisi, M.D.
IRMS - The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center

Old Short Hills Road
East Wing, Suite 403
Livingston, NJ 07039
973-322-8890
973-322-8890

Reproductive Endocrinology and Infertility
Bad Email MargaretG@sbivf.com
http://www.sbivf.com

Marlton

Jerome H. Check, M.D.
Cooper Center for IVF

8002E Greentree Commons
Suite # 409
Marlton, NJ 08053
856-751-5575
856-751-7289

Reproductive Endocrinology & Infertility
dcheck@ccivf.com
http://www.ccivf.com/

Morganville

Sandra Watson
Intended Parents, Inc

PO Box 57
Morganville, NJ 07751
732 526 7013
866 206 1925

info@intendedparents.com
http://www.intendedparents.com

Morristown

Paul Bergh, M.D.
Reproductive Medical Associates of New Jersey
111 Madison Ave.
Suite 100
Morristown, NJ 07960
973-971-4600
973-290-8370
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
askus@rmanj.com
http://www.rmanj.com

Michael Drews, M.D.
Reproductive Medical Associates of New Jersey
111 Madison Ave.
Suite 100
Morristown, NJ 07960
973-971-4600
973-290-8370
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
http://www.rmanj.com

Richard Scott, M.D.
Reproductive Medical Associates of New Jersey
111 Madison Ave.
Suite 100
Morristown, NJ 07960
973-971-4600
973-290-8370
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
http://www.rmanj.com

Paramus

Dehan Chen, M.D.
Reproductive Endocrinologist
The Valley Hospital Fertility Center
1 Valley Health Plaza
Paramus, NJ 07652
201-634-5400
201-634-5506
Obstetrics & Gynecology
www.valleyivf@valleyhealth.com
http://www.valleyivf.com

Eric Daiter, M.D.
34-36 Progress Street
Suite B-4
Edison, NJ 08820
908-226-0250
908-226 0830
Reproductive Endocrinology and Infertility
info@drdaiter.com
http://www.drdaiter.com/

Ali Nasseri, M.D., Ph.D.
Reproductive Endocrinologist
The Valley Hospital Fertility Center
1 Valley Health Plaza
Paramus, NJ 07652
201-634-5400
201-634-5506
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
www.valleyivf@valleyhealth.com
http://www.valleyivf.com

Phillipsburg

Al Peters
Medical Director
Sher Institute for Reproductive Medicine – Greater Lehigh Valley
201 Strykers Rd.
Phillipsburg, NJ 08865
888-591-2229
908-781-6377
Reproductive Endocrinology and Infertility
lehighvalley@haveababy.com
http://haveababy.com

Somerset

Michael Darder, M.D.
IVF New Jersey
81 Veronica Avenue
Somerset, NJ 08873
800-483-6544
732-545-1164
Reproductive Endocrinology and Infertility
info@ivfnj.com
http://www.IVFNJ.com

Summit

Jennifer Cina
6 Van Dyke Pl
Summit, NJ 07901
917-443-3440
908-277-3809
Mental Health Professional
jennycina@verizon.net

West Orange

Rita Gulati, M.D.
Reproductive Medical Associates of New Jersey
769 Northfield Ave.
Suite 228
West Orange, NJ 07960
973-325-2229
973-325-5645
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
http://www.rmanj.com

Victoria Jorda
Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052
973-325-4500
(973)325-4500
lindad@inciid.org
http://www.organonusa.com

Annette Lee, M.D., F.A.C.O.G.
Reproductive Medicine Associates of New Jersey
769 Northfield Avenue
Suite 228
West Orange, NJ 07052
973-325-2229
973-325-5645
Reproductive Endocrinology & Infertility
aleeoc@rocketmail.com
http://www.rmaofnj.com/

Jamie L Morris, M.D.
Reproductive Medical Associates of New Jersey
769 Northfield Ave.
Suite 228
West Orange, NJ 07960
973-325-2229
973-325-5645
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
http://www.rmanj.com

Eric Seaman, M.D.
Associates in Urology
741 Northfield Ave
Suite 206
West Orange, NJ 07052
973-325-6100
973-325-1616
info@AssociatesInUrology.com
http://www.njurology.com/home/index.php

NEW YORK

Albany

Peter M. Horvath, M.D.
Director, Albany IVF, Fertility & Gynecology
349 Northern Boulevard
Albany, NY 12204-1030
518-434-9759
518-436-9822
Board Certified Reproductive
mail@albanyivf.com
http://www.albanyivf.com

Brooklyn

Richard V. Grazi, M.D.
Director, Genesis Fertility and Reproductive Medicine

1355 84th Street
Brooklyn, NY 11228
718-283-8600
718-283-6580
Reproductive Endocrinology and Infertility
DrGrazi@genesisfertility.com
http://www.genesisfertility.com

David B. Seifer, M.D.
Scientific Director, Genesis Fertility and Reproductive Medicine

1355 84th Street
Brooklyn, NY 11228
718-283-8600
718-283-6580
Reproductive Endocrinology and Infertility
info@genesisfertility.com
http://www.genesisfertility.com

Garden City

Jeffrey Braverman
Medical Director, Sher Institute for Reproductive Medicine – Long Island

700 Stewart Ave
2nd Floor
Garden City, NY 11530
516-227-3333
516-227-0871
Obstetrics & Gynecology
newyork@haveababy.com
http://haveababy.com

Manhasset

Micheline Chu, M.D.
Center for Human Reproduction – North Shore University Hospital

300 Community Drive
Manhasset, NY 11030
516-562-2229
516-562-1710
Reproductive Endocrinology and Infertility
jtibaldi@nshs.edu
http://www.562baby.org

Matthew A. Cohen, M.D.
Center for Human Reproduction – North Shore University Hospital

300 Community Dr.
Manhasset, NY 11030
(516) 562-2229
(516) 562-1710
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
jtibaldi@nshs.edu
http://www.562baby.org

Avner M. Hershlag, M.D.
Center for Human Reproduction – North Shore University Hospital

300 Community Dr.
Manhasset, NY 11030
(516) 562-2229
(516) 562-1710
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
jtibaldi@nshs.edu
http://www.562baby.org

David L. Rosenfeld, M.D.
Chief, Center for Human Reproduction – North Shore University Hospital

300 Community Dr.
Manhasset, NY 11030
(516) 562-2229
(516) 562-1710
Reproductive Endocrinology and Infertility
jtibaldi@nshs.edu
http://www.562baby.org

Gerald M. Scholl, M.D.
Center for Human Reproduction – North Shore University Hospital

300 Community Dr.
Manhasset, NY 11030
(516) 562-2229
(516) 562-1710
Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
jtibaldi@nshs.edu
http://www.562baby.org

Mount Kisco

Katherine Dragisic Schoyer
Center for Reproductive Medicine and Infertility, Weill Cornell Medical College

400 East Main St.
3 North
Mount Kisco, NY 10549
814-242-8144
914-242-8167
Reproductive Endocrinology and Infertility
kgd2002@med.cornell.edu

New York City

Helen Adrienne, L.C.S.W., B.C.D.
Psychotherapist, Clinical Hypnotherapist, Practitioner of Body/Mind medicine

420 E 64th Street
1D-East
New York, NY 10021
212-758-0125
212-888-2558
Author, Social Work
HAMSW@aol.com
http://www.helenadrienne.com/

Joel Batzofin, M.D.
Medical Directo, Sher Institute for Reproductive Medicine – Manhattan

425 Fifth Ave
3rd Floor
New York City, NY 10016
646-792-7476
646-274-0600
Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
Jbatzofin@sherinstitute.com
http://www.haveababy.com

Natan Bar-Chama, M.D.
Reproductive Medicine Associates of New York, LLP

635 Madison Avenue, 10th floor
New York, NY 10022
212-756-5777
212-756-5770
Urology
NBarChama@RMAofNY.com

Aykut B Bayrak, M.D.
Sher Institute for Reproductive Medicine – New York

425 Fifth Ave. at 38th Street
Third Floor
New York, NY 10016
(866) 747-6692
(646) 274-0060
Obstetrics & Gynecology
abayrak@sherinstitute.com
http://www.haveababy.com

Mike Berkley, L.Ac., D.A. (R.I.)
Berkley Center for Reproductive Wellness & Women

16 East 40th Street
2nd Floor
New York, NY 10016
212-685-0985
212-684-1780
Acupuncture
mikeberkley@berkleycenter.com
http://www.berkleycenter.com

Alan S. Berkeley, M.D.
NYU Fertility Center

660 First Avenue at 38th St.
5th Floor
New York, NY 10016
212-263-7629
212-263-7853
Obstetrics & Gynecology
ivfprogram@med.nyu.edu
http://nyuivf.med.nyu.edu/

Ina N. Cholst, M.D.
Coordinator, Donor Egg Program, Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center
505 East 70th Street
Suite 340
New York, NY 10021
(888) 703-3456
(212) 746-8208
Reproductive Endocrinology and Infertility
ICholst@med.cornell.edu
http://www.ivf.org

Pak H. Chung, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center
505 East 70th Street
Suite 340
New York, NY 10021
(888) 703-3456
(212) 746-8208
Reproductive Endocrinology and Infertility
ivf@nyp.org
http://www.ivf.org

Alan Copperman, M.D.
Director, Reproductive Medicine Associates of New York, LLP
635 Madison Avenue, 10th floor
New York, NY 10022
212-756-5777
212-756-5770
Reproductive Endocrinology & Infertility
Acopperman@RMAofNY.com
http://www.rmaofny.com/

Owen K. Davis, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center
505 East 70th Street
Suite 340
New York, NY 10021
888-703-3456
212-746-8208
Reproductive Endocrinology and Infertility
okdavis@med.cornell.edu
http://www.ivf.org/

Dan Goldschlag, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center
505 East 70th Street
Suite 340
New York, NY 10021
(888) 703-3456
(212) 746-8208
Reproductive Endocrinology and Infertility
ivf@nyp.org
http://www.ivf.org

Marc Goldstein, M.D.
Surgeon-in-Chief, Male Reproductive Medicine Center for Male Reproductive Medicine & Microsurgery The New York Hospital–Cornell Medical Center
525 East 68th Street
Box 580
New York, NY 10021
212-746-5470
212-746-0977
Urology
mgoldst.med.cornell.edu
http://www.cornellurology.com/uro/cornell/faculty/goldstein.html

James A. Grifo, M.D., Ph.D.
NYU Fertility Center
660 First Avenue at 38th St.
5th Floor
New York, NY 10016
212-263-8990
212-263-7853
http://www.nyuivf.com/

Lawrence Grunfeld, M.D.
Reproductive Medicine Associates of New York, LLP
635 Madison Avenue, 10th floor
New York, NY 10022
212-756-5777
212-756-5770
Reproductive Endocrinology and Infertility
Lgrunfeld@RMANY.com
http://www.rmaofny.com/
http://www.rmaofny.com/

Nabil Husami, M.D.
American Fertility Services
115 East 57th St
Suite 500
New York, NY 10022
212-750-3330
212-750-3334
Reproductive Endocrinology, Obstetrics and Gynecology
Nhusami@aol.com
http://www.americanfertility.com

Hanna Jesionowska, M.D.
Medical Director, Manhattan Reproductive Medicine
159 E 74 Street
New York City, NY 10021
212-794-0080
212-794-0080
Reproductive Endocrinology and Infertility, Embryology
medyana@aol.com

Jeffrey Klein, M.D.
Reproductive Medicine Associates of New York, LLP
635 Madison Ave., 10th Floor
New York, NY 10022
(212) 756-5777
(212) 756-5770
Obstetrics & Gynecology, Reproductive Endocrinology and Infertility,Surgery
info@rmany.com
http://www.rmany.com

Isaac Kligman, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center
505 East 70th Street
Suite 340
New York, NY 10021
(888) 703-3456
(212) 746-8208
Reproductive Endocrinology and Infertility
ivf@nyp.org
http://www.ivf.org

Lisa M. Kump-Checchio, M.D.
NYU Fertility Center
660 First Avenue at 38th St.
5th Floor
New York, NY 10016
212-263-0040
212-263-7853
Obstetrics & Gynecology
ivfprogram@med.nyu.edu
http://www.nyuivf.com/

Frederick L. Licciardi, M.D.
NYU Fertility Center
660 First Avenue at 38th St
5th Floor
New York, NY 10016
212-263-7754
212-263-7853
Fellowship - Reproductive Endocrinology & Infertility,Obstetrics & Gynecology
ivfprogram@med.nyu.edu
http://www.nyuivf.com/

Hugh D. Melnick, M.D.
Advanced Fertility Services
1625 Third Avenue
New York, NY 10128
212-369-8700
212-722-5587
Andrology, Embryology, Genetics, Laboratory, Reproductive Endocrinology and Infertility
Hdm46@aol.com
http://www.advancedfertilityservices.com

Tanmoy Mukherjee, M.D.
Reproductive Medicine Associates of New York, LLP

635 Madison Avenue, 10th floor
New York, NY 10022
212-756-5777
212-756-5770

T.Mukherjee@mssm.edu
http://www.rmany.com/

Nicole Noyes, M.D.
NYU Fertility Center

660 First Avenue at 38th St.
5th Floor
New York, NY 10016
212-263-7981
212-263-7853

Reproductive Endocrinology and Infertility
ivfprogram@med.nyu.edu
http://www.nyuivf.com/

Kutluk Oktay, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center

505 East 70th Street
3rd Floor
New York, NY 10021
(212) 746-1762
(212) 746-8208

Reproductive Endocrinology and Infertility

kuo9001@med.cornell.edu
http://www.ivf.org/

Zev Rosenwaks, M.D.
Director & Professor, Obstetrics & Gynecology Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center

505 East 70th Street
New York, NY 10021
212-746-1743
212-746-1861

Reproductive Endocrinology

ivf@nyp.org
http://www.ivf.org

Benjamin Sandler, M.D.
Reproductive Medicine Associates of New York, LLP

635 Madison Avenue, 10th floor
New York, NY 10022
212-756-5777
212-756-5770

http://www.rmaofny.com/

Glenn Schattman, M.D.
Center for Reproductive Medicine & Infertility, The New York Hospital–Cornell Medical Center

505 East 70th Street
Suite 340
New York, NY 10021
(888) 703-3456
(212) 746-8208

Reproductive Endocrinology and Infertility
ivf@nyp.org
http://www.ivf.org

Peter N. Schlegel, M.D.
Co-director, Center for Male Reproductive Medicine and Microsurgery, The New York Hospital–Cornell Medical Center

525 E. 68th Street
Room F907-A
New York, NY 10021
212-746-5491
212-746-8425

Urology
http://www.maleinfertility.org/

Yaron Seidman, L.Ac., M.He.
Hunyuan Fertility

9 Benedict Place
New York City, NY 10021
203-325-2000
203-629-6290

Acupuncture, Alternative Medicine, Complementary Medicine

info@Hunyuan.org
http://www.Hunyuan.org

Steven D. Spandorfer, M.D.
Center for Reproductive Medicine & Infertility The New York Hospital–Cornell Medical Center

505 East 70th Street
Suite 340
New York, NY 10021
212.746.1762
212.746.8208

sdspando@mail.med.cornell.edu
http://www.ivf.org/welcome.html

Daniel Evan Stein, M.D.
Continuum Reproductive Center

425 West 59 Street
Suite 5A
New York, NY 10019
212-523-7751
212-523-8348

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
destein1963@yahoo.com
http://www.nywomenshealth.com/infertility/index.html

Erica A. Tennenbaum

11 West 89th Street 2B
New York, NY 10024
646-756-3968
845-647-8348

Author, Mental Health Professional
tennenbaum@fordham.edu

Andrea Vidali, M.D.
American Fertility Services

115 E. 57th Street
Suite 500
New York, NY 10022
212.750.3330
212.750.3334

Fellowship - Reproductive Endocrinology & Infertility, Obstetrics & Gynecology
andrea@vidali.net
http://www.americanfertility.com

Plainview

David Kreiner, M.D.
East Coast Fertility.

1074 Old Country Rd.
Plainview, NY 11803
(516)939-2229
(516)939-2252

Reproductive Endocrinology and Infertility
info@eastcoastfertility.com
http://www.eastcoastfertility.com

Purchase

Daniel Warren Levine
Medical Director, Sher Institute for Reproductive Medicine – Westchester

3020 Westchester Ave
Suite 304
Purchase, NY 10577
914-696-7476
(646) 274-0600

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
levined@sherinstitute.com
http://www.haveababy.com

Stony Brook

Richard Adam Bronson, M.D.
Director, Reproductive Endocrinology, Division of Reproductive Endocrinology Department of Obstetrics, Gynecology & Reproductive Medicine

Health Sciences Center
T9-080
Stony Brook, NY 11794
631-444-4686
631-444-5175

Andrology, Author, Embryology, Genetic Counselor, Genetics, Immunology, Laboratory, Maternal-fetal Medicine, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Residency Obstetrics & Gynecology,Urology
www.fertilityresults.org
http://www.stonybrookhospital.com/fertilityresults/

White Plains

Rachel Bennett, M.D.
American Fertility Services

811 North Broadway
White Plains, NY 10603
914-682-3330
914-682-3334

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
rbennett@americanfertiliy.com
http://www.americanfertility.com

NORTH CAROLINA

Arden

Randine Lewis, Ph.D.
Advisory Board Member
Fertility Retreats

P.O. Box 896
Arden, NC 28704
704-639-8086
828-687-7858

Acupuncture,Alternative Medicine,Complementary Medicine
coordinator@fertilityretreats.com
http://fertilityretreats.com

Asheville

James F Holman, M.D.
Center for Applied Reproductive Science

520 Biltmore Avenue
Asheville, NC 28801
(828) 285-8881
828-258-8887

Reproductive Endocrinology and Infertility
luann@ivf-et.com
http://www.ivf-et.com/

Chapel Hill

Gary S. Berger, M.D.
Medical Director
Chapel Hill Tubal Reversal Center

109 Conner Drive, Suite 2200
Chapel Hill, NC 27514
919-968-4656
919-967-8637

Surgery
gsberger@mindspring.com
http://www.tubal-reversal.net

Charlotte

Gordon B. Kuttner, M.D., F.A.C.O.G.
Medical Director, Center for Advanced Reproduction, Endocrinology & Surgery, PA

3325 Springbank Lane
Suite 300
Charlotte, NC 28226
704-542-6006
704- 542-0340

gkuttner@caresmed.com
http://www.caresmed.com

Raleigh

Jouko Halme, M.D., Ph.D.
Reproductive Consultants, P.A.

2500 Blue Ridge Road
Suite 300
Raleigh, NC 27607
919-881-7795
919-881-7796

Board Certified in Reproductive Endocrinology and Infertility
reprocon@mindspring.com
http://www.reproductiveconsultants.com

OHIO

Cincinnati

Glen Hofmann, M.D., Ph.D.
Bethesda Center for Reproductive Health and Fertility

10506 Montgomery Road, Suite 303
Cincinnati, OH 45242
800-634-1222
513-745-1676

Reproductive Endocrinology & Infertility
OB/GYN
bethesda_center@trihealth.com
http://www.ohioinfertility.com

Westlake

Elizabeth O'Donnell, P.C.C., P.T., N.C.
Minding Matters

P.O. Box 451174
Westlake, OH 44145
440.835.0664
419.621.7335

Therapist
liz@mindingmatters.com
http://www.mindingmatters.com/

OKLAHOMA

Edmond

Carol A. Mathison

212 East 2nd
Edmond, OK 73034
(405)820-6231
(405) 341-0207

Mental Health Professional
carolannmathison@sbcglobal.net

PENNSYLVANIA

Bethlehem

H. Christina Lee, M.D., J.D., H.C.
Family Fertility Center

95 Highland Avenue
Suite 100
Bethlehem, PA 18017
610-868-8600
610-868-8700

Andrology, Embryology, Genetic Counselor, Laboratory, Obstetrics & Gynecology, Reproductive Endocrinology and Infertility, Surgery
andes@early.com
http://www.familyfertility.com

Chester

Albert El-Roeiy, M.D.
Medical Director, Fertility Center of Crozer-Chester Medical Center

1 Medical Center Boulevard
Chester, PA 19013
610-447-2727
610-447-6549

Obstetrics & Gynecology,Reproductive Endocrinology and Infertility
kathy@crozerfertility.com
http://www.crozerfertility.com

Philadelphia

Frances Batzer, M.D.
Women's Institute for Fertility, Endocrinology & Menopause

815 Locust Street
Philadelphia, PA 19107-551
215-922-2206
215-922-3777

Board certified in reproductive endocrinology and infertility
info@womensinstitute.org
http://www.womensinstitute.org/

Ben Gocial, M.D.
Women's Institute for Fertility, Endocrinology & Menopause

815 Locust Street
Philadelphia, PA 19107-5507
215-922-2206
215-922-3777

info@womensinstitute.org
http://www.womensinstitute.org/

Jacqueline N. Gutmann, M.D.
Women's Institute for Fertility, Endocrinology & Menopause

815 Locust Street
Philadelphia, PA 19107-550
215-922-2206
215-922-3777

Residency in Obstetrics and Gynecology; fellowship trained in Reproductive Endocrinology and Menopausal Healthcare, at the Yale-New Haven Hospital
JacquelineG@womensinstitute.org
http://www.womensinstitute.org/

Maureen Kelly, M.D.
Women's Institute for Fertility, Endocrinology & Menopause

815 Locust Street
Philadelphia, PA 19107-550
215-922-2206
215-922-3777

Fellowship Trained and Board Certified in Reproductive Endocrinology
info@womensinstitute.org
http://www.womensinstitute.org/

Shahab S. Minassian, M.D.
MCP Hahnemann Fertility – Bala Cynwyd

Suite 418, Rowland Hall
4190 City Avenue
Philadelphia, PA 19131
215-477-4960
215-477-6107

minassian@drexel.edu
http://www.drexelfertility.medem.com

Spring House

Gayle D Crespy, Psy. D.
The Mind Body Center at The Carriage House

606 Spring House Village Center
Spring House, PA 19477
(215) 692-4224
(215) 692-4224

Mental Health Professional
drcrespy@infertilityblues.com
http://www.infertilityblues.com

SOUTH CAROLINA

West Columbia

Gail Whitman-Elia
Advanced Fertility & Reproductive Endocrinology Institute, LLC

2728 Sunset Blvd
Suite 305
W. Columbia, SC 29169
803-939-1515
803-939-0977

Acupuncture, Andrology, Embryology, Fellowship - Reproductive Endocrinology & Infertility,Genetic Counselor, Genetics, Immunology, Laboratory, Pathology
gwhitman@ivfwecare.com
http://www.ivfwecare.com

SOUTH DAKOTA

Brookings

Donald Evenson, Ph.D.
SCSA Diagnostics Corporation

Multiplex Research & Technology Center
807 32nd Aveue
Brookings, SD 57006
(605) 692-5938
(605) 692-9730

Corporation or Agency - See specialties
scsadon@brookings.net
http://www.scsadiagnostics.com

TENNESSEE

Johnson City

Joseph L. Kennedy, III, M.D.
Center for Applied Reproductive Science

408 N. State of Franklin Rd.
Johnson City, TN 37604
(423) 461-8880
(423) 461-8887

Reproductive Endocrinology and Infertility
luann@ivf-et.com
http://www.ivf-et.com/

Sam S. Thatcher, M.D., Ph.D.
Center for Applied Reproductive Science

408 N. State of Franklin Road
Johnson City, TN 37604
423-461-8880
423-461-8887

Reproductive Endocrinology and Infertility
thatcher@ivf-et.com
http://www.ivf-et.com/

Knoxville

Gayla Harris, M.D.
East Tennessee IVF and Andrology Center

1928 Alcoa Hwy
Suite 304, Bldg B
Knoxville, TN 37920
865 544 6756
865 544 6757

Board Certified in both Obstetrics/Gynecology and Reproductive Endocrinology
etnivfdoc@aol.com
http://www.utfertilitycenter.salu.net/

Jeffrey A. Keenan, M.D.
Southeastern Center for Fertility and Reproductive Surgery

10810 Parkside Drive
Suite 304
Knoxville, TN 37922
865-218-6600
865-218-6666

Embryology, Fellowship - Reproductive Endocrinology & Infertility, Reproductive Endocrinology and Infertility
jkeenan@bhset.org
http://www.baby4me.net

TEXAS

Dallas

Samuel J. Chantilis, M.D.
Dallas Fertility Center

8160 Walnut Hill Ln., Ste. 320
Dallas, TX 75231
(214) 363-5965
(214) 373-0217

Reproductive Endocrinology and Infertility
staff@dallasfertility.com
http://www.dallasfertility.com

Noel Peng, M.D., F.A.C.O.G.
Sher Institute for Reproductive Medicine – Dallas

7777 Forest Lane
Suite C-638
Dallas, TX 75230
972-566-6686
972-566-6670

Fellowship - Reproductive Endocrinology & Infertility, Obstetrics & Gynecology
dallas@haveababy.com
http://www.haveababy.com

Walid A. Saleh, M.D.
Medical Director, Sher Institute for Reproductive Medicine – Dallas

7777 Forest Lane
Suite C-638
Dallas, TX 75230
972-566-6686
972-566-6670

Board certified Ob/Gyn and board eligible in Reproductive Endocrinology and Infertility.
salehw@sherinstitute.com
http://www.haveababy.com

Houston

C. James Chuong, M.D., M.P.H.
Medical Director, Cooper Institute for Advanced Reproductive Medicine

7500 Beechnut Street,
Suite 308
Houston, TX 77030
713-771-9771
713-771-9773

Board Certified in Reproductive Endocrinology & Infertility
chuong@cooperinstitutearm.com
http://www.cooperinstitutearm.com/

Sonja B. Kristiansen, M.D.
Medical Director, Sonja Kristiansen Infertility Center of Houston

9055 Katy Freeway
Suite 450
Houston, TX 77024
(715) 862-6181
(713) 464-2810

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
SKapocsiich@aol.com
http://www.drkristiansen.com

Lewisville

Barry Jacobs, M.D.
North Texas Reproductive Medicine

751 Hebron Parkway
Suite 310
Lewisville, TX 75057
(972) 315-9245
(972) 315-9249

Fellowship trained in Reproductive Endocrinology & Infertility
jacobsM.D.@direcway.com
http://www.texasfertility.com/

Plano

Jeffrey P. Buch, M.D.
Male Fertility Specialists

1600 Coit Road
Suite 408
Plano, TX 75075
972-612-7131
972-612-7161

Urology, Other
info@vasectomyandreversal.com
http://www.vasectomyandreversal.com

Webster

Vicki L. Schnell, M.D.
Center of Reproductive Medicine

450 Medical Center Blvd
Suite 202
Webster, TX 77598
281-332-0073
281-332-1860

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
vschnell@infertilitytexas.com
http://www.infertilitytexas.com/

UTAH

Salt Lake City

Keith L. Blauer, M.D.
Reproductive Care Center

1220 E. 3900 S
Suite 4G
Salt Lake City, UT 84124
801-268-0306
801-268-6234

Obstetrics & Gynecology, Reproductive Endocrinology and Infertility
Info@Hope4Baby.com
http://www.fertilitydr.com/

VIRGINIA

Arlington

John David Gordon
Co-Director, Dominion Fertility and Endocrinology

46 South Glebe Road, Suite 301
Arlington, VA 22204
703-920-3890
703-892-6037

Reproductive Endocrinology and Infertility
info@dominionfertility.com
www.dominionfertility.com

WASHINGTON

Bellevue

Kevin M. Johnson, M.D.
Overlake Reproductive Health

1135 116th Avenue NE
Suite 640
Bellevue, WA 98004
425-646-4700
425-646-1076

Board certified in Obstetrics and Gynecology and is one of six board certified Reproductive Endocrinology and Infertility
info@fertileweb.com
http://www.fertileweb.com/

Kirkland

Michael S. Opsahl, M.D.
Northwest Center for Reproductive Sciences

12333 NE 130th Lane
Suite 220
Kirkland, WA 98038
(425) 284-4400
(425) 899-9803

Reproductive Endocrinology
info@nwreprosci.com

WEST VIRGINIA

Morgantown

Tamer Yalcinkaya, M.D.
Center for Reproductive Medicine

1322 Pineview Drive, Suite 2
Morgantown, WV 26506
304-598-3100
304-598-8301

Reproductive Endocrinology and Infertility
tyalcinkaya@hsc.wvu.edu\

Appendix B
INCIID Directory of Professionals, by name

Professional member	State	Agency or organization
Acacio, Brian, M.D.	CA	Sher Institute for Reproductive Medicine – Orange County
Adrienne, Helen, LCSW, BCD	NY	
Ahlering, Peter, M.D.	MO	Sher Institute for Reproductive Medicine – St. Louis
Akerman, Fernando M., M.D.	FL	IVF Center of Miami
Anderson, Robert E., M.D.	CA	Southern Californina Center for Reproductive Medicine
Andreyko, Janice	CA	Northern California Fertility Center
Ary, Beth, M.D.	CA	Reproductive Specialty Center
Bachus, Kevin E., M.D.	CO	Rocky Mountain Center for Reproductive Medicine
Bar-Chama, Natan, M.D.	NY	Reproductive Medicine Associates of New York, LLP
Barrionuevo, Marcelo J, M.D.	FL	IVF Florida Reproductive Associates
Batzer, Frances, M.D.	PA	Women's Institute for Fertility, Endocrinology & Menopause
Batzofin, Joel, M.D.	NY	Sher Institute for Reproductive Medicine – Manhattan
Bayrak, Aykut B, M.D.	NY	Sher Institute for Reproductive Medicine – New York
Beltsos, Angeline N., M.D.	IL	Fertility Centers of Illinois
Bennett, Rachel, M.D.	NY	American Fertility Services
Berger, Gary S., M.D.	NC	Chapel Hill Tubal Reversal Center
Bergh, Paul, M.D.	NJ	Reproductive Medical Associates of New Jersey
Berkeley, Alan S., M.D.	NY	NYU Fertility Center
Berkley, Mike, L.Ac., DA (RI)	NY	Berkley Center for Reproductive Wellness & Women
Blauer, Keith L., M.D.	UT	Reproductive Care Center
Blitzer, Barbara	MD	Barbara Blitzer, LCSW-C
Bloome, Jennifer R., MS OTR, HWC	MN	Anji, Inc.
Bohler, Henry	KY	Louisville Women's Healthcare
Bohrer, Michael K, M.D.	NJ	Reproductive Medical Associates of New Jersey
Boostanfar, Robert, M.D., FACOG	CA	Huntington Reproductive Center
Braverman, Jeffrey	NY	Sher Institute for Reproductive Medicine – Long Island
Bronson, Richard Adam, M.D.	NY	Division of Reproductive Endocrinology Department of Obstetrics, Gynecology & Reproductive Medicine
Brown, Samuel E., M.D.	FL	Florida Institute for Reproductive Medicine
Buch, Jeffrey P., M.D.	TX	Male Fertility Specialists
Bush, Mark, M.D.	CO	Conceptions Reproductive Associates
Cekleniak, Natalie, M.D.	NJ	IRMS - The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center
Chantilis, Samuel J., M.D.	TX	Dallas Fertility Center, The
Check, Jerome H., M.D.	NJ	Cooper Center for IVF
Chen, Serena, M.D.	NJ	IRMS - The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center
Chen, Dehan, M.D.	NJ	The Valley Hospital Fertility Center
Chenette, Philip, M.D.	CA	Pacific Fertility Center®
Cholst, Ina N., M.D.	NY	Center for Reproductive Medicine & Infertility: The New York Hospital-Cornell Medical Center
Chu, Micheline, M.D.	NY	Center for Human Reproduction - North Shore University Hospital
Chung, Pak H., M.D.	NY	Center for Reproductive Medicine & Infertility: The New York Hospital-Cornell Medical Center
Chuong, C. James, M.D., M.P.H.	TX	Cooper Institute for Advanced Reproductive Medicine
Cina, Jennifer	NJ	Jennifer Cina
Cohen, Matthew A, M.D.	NY	Center for Human Reproduction - North Shore University Hospital

Professional member	State	Agency or organization
Cohen, Sheri E.	CA	Sheri E. Cohen, Adoption & Family Formation Law Offices
Collopy, Kate	NH	Center for the Evaluative Clinical Sciences at Dartmouth
Conway, Susan C., M.D.	GA	Georgia Reproductive Specialists
Copperman, Alan, M.D.	NY	Reproductive Medicine Associates of New York, LLP
Corsan, Gregory H., M.D.	NJ	Center for Advanced Reproductive Medicine & Fertility
Coulam, Carolyn B., M.D.	IL	Rinehart Center For Reproductive Medicine
Crespy, Gayle D, Psy. D.	PA	The Mind Body Center at The Carriage House
Daiter, Eric, M.D.	NJ	Eric Daiter, M.D
Darder, Michael, M.D.	NJ	IVF New Jersey
Davidson, Marie, Ph.D.	IL	Fertility Centers of Illinois
Davis, Owen K., M.D.	NY	Center for Reproductive Medicine & Infertility: The New York Hospital-Cornell Medical Center
Denker, Mark S.	FL	Palm Beach Fertility Center
Dlugi, Alexander, M.D.	NJ	Sher Institute for Reproductive Medicine – New Jersey
Doyle, Michael, M.D.	CT	Connecticut Fertility Associates
Drews, Michael, M.D.	NJ	Reproductive Medical Associates of New Jersey
El-Roeiy, Albert, M.D.	PA	Fertility Center of Crozer-Chester Medical Center
Elsner, Carlene W., M.D.	GA	Reproductive Biology Associates
Epstein, Yakov M, Ph.D.	NJ	Acting Director, Rutgers Center for Math, Science & Computers
Erickson, Theresa Marie	CA	Law Offices of Theresa M. Erickson
Evans, Michele L	CA	Huntington Reproductive Center
Evenson, Donald, Ph.D.	SD	SCSA Diagnostics Corporation
Feinberg, Ronald F., M.D., Ph.D.	DE	Reproductive Associates of Delaware
Feinman, Michael, M.D., FACOG	CA	Huntington Reproductive Center
Fisch, Jeffrey, M.D.	NV	Sher Institute for Reproductive Medicine – Las Vegas
Frederick, Jane L., M.D., FACOG	CA	Huntington Reproductive Center
Friberg, Jan, M.D.	IL	Friberg Medical Associates
Galen, Donald J., M.D.	CA	Reproductive Science Center of the San Francisco Bay Area
Garrisi, Margaret, M.D.	NJ	IRMS - The Institute for Reproductive Medicine and Science of St. Barnabas Medical Center
Gelety, Timothy J., M.D.	AZ	Arizona Center for Reproductive Endocrinology and Infertility
Gililland, John L., M.D.	CA	Northern California Fertility Medical Center
Givens, Carolyn R., M.D.	CA	Pacific Fertility Center®
Gocial, Ben, M.D.	PA	Women's Institute for Fertility, Endocrinology & Menopause
Goldschlag, Dan, M.D.	NY	Center for Reproductive Medicine & Infertility: The New York Hospital-Cornell Medical Center
Goldstein, Marc, M.D.	NY	Center for Male Reproductive Medicine & Microsurgery, The New York Hospital–Cornell Medical Center
Gordon, John David	VA	Dominion Fertility and Endocrinology
Graubert, Michael D., M.D.	FL	Palmetto Fertility Center of South Florida
Grazi, Richard V, M.D.	NY	Genesis Fertility and Reproductive Medicine
Grifo, James A., M.D., Ph.D.	NY	NYU Fertility Center
Grunfeld, Lawrence, M.D.	NY	Reproductive Medicine Associates of New York, LLP
Gulati, Rita, M.D.	NJ	Reproductive Medical Associates of New Jersey
Gutmann, Jacqueline N., M.D.	PA	Women's Institute for Fertility, Endocrinology & Menopause
Halme, Jouko, M.D., Ph.D.	NC	Reproductive Consultants, P.A.
Harman, Tisha Lene	CA	A Center for Children & Family Law
Harris, Gayla, M.D.	TN	East Tennessee IVF and Andrology Center
Herbert, Carl, M.D.	CA	Pacific Fertility Center®
Hershlag, Avner M, M.D.	NY	Center for Human Reproduction - North Shore University Hospital
Hinckley, Mary, M.D.	CA	Reproductive Science Center of the San Francisco Bay Area
Hock, Doreen L, M.D.	NJ	Reproductive Medical Associates of New Jersey
Hoffman, David I., M.D.	FL	IVF Florida Reproductive Associates
Hofmann, Glen, M.D., Ph.D.	OH	Bethesda Center for Reproductive Health and Fertility
Holman, James F, M.D.	NC	Center for Applied Reproductive Science

Professional member	State	Agency or organization
Horvath, Peter M., M.D.	NY	Albany IVF, Fertility & Gynecology
Hughes, Patricia L., M.D.	NJ	Patricia Hughes, M.D.
Husami, Nabil, M.D.	NY	American Fertility Services
Hutchison, Scot, M.D.	AZ	Reproductive Health Center,The
Illions, Edward, M.D.	FL	IVF Florida Reproductive Associates
Jacobs, Michael H., M.D.	FL	IVF Center of Miami
Jacobs, Laurence A, M.D.	IL	Fertility Centers of Illinois
Jacobs, Barry, M.D.	TX	North Texas Reproductive Medicine
Jarrett, John C., M.D.	IN	Midwest Reproductive Medicine
Jesionowska, Hanna, M.D.	NY	Manhattan Reproductive Medicine
Johnson, Kevin M., M.D.	WA	Overlake Reproductive Health
Johnston, Diane, N.P., M.S.	CT	Mind/Body Infertiltiy Program
Jorda, Victoria	NJ	Organon, Inc.
Kamrava, Michael M., M.D.	CA	West Coast Infertility Medical Clinic, Inc.
Kaplan, Carolyn R., M.D.	GA	Georgia Reproductive Specialists
Kaplan, Brian R., M.D.	IL	Fertility Centers of Illinois
Karande, Vishvanath	IL	Karande & Associates S.C.
Keenan, David L., M.D.	GA	Reproductive Biology Associates
Keenan, Jeffrey A., M.D.	TN	Southeastern Center for Fertility and Reproductive Surgery
Kelly, Maureen, M.D.	PA	Women's Institute for Fertility, Endocrinology & Menopause
Kennedy, Joseph L, III, M.D.	TN	Center for Applied Reproductive Science
Kim, Thomas J., M.D.	CA	CHA Fertility Center, Thomas J. Kim, M.D.
Kim, Andrew	CA	Halozyme Therapeutics, Inc.
Klein, Jeffrey, M.D.	NY	Reproductive Medicine Associates of New York, LLP
Kligman, Isaac, M.D.	NY	Center for Reproductive Medicine & Infertility: The New York Hospital-Cornell Medical Center
Kolb, Bradford A., M.D., FACOG	CA	Huntington Reproductive Center
Kort, Hilton I., M.D.	GA	Reproductive Biology Associates
Koulianos, George, M.D.	AL	Center for Reproductive Medicine
Kreiner, David, M.D.	NY	East Coast Fertility.
Kristiansen, Sonja B, M.D.	TX	Sonja Kristiansen Infertility Center of Houston
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