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## IVF PRIMER

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### I. Introduction



In vitro fertilization (IVF) and related procedures are collectively known as assisted reproductive technologies (ART). Each ART treatment is complex and consists of many different steps.

Even though a high percentage of patients achieve pregnancy in their first attempt, more than one cycle may be required to conceive and deliver a healthy baby.

< Madison

In the course of your treatment you may meet other couples with similar problems. Infertility can be a very stressful and frustrating experience. It often helps to know that you are not alone and to share your feelings.

### II. Indications for IVF

Whereas IVF was originally developed for tubal factor infertility, it has since become a most versatile therapy applicable to all forms of infertility. One of the universal findings in reproductive medicine has been the profound adverse effect of woman's advanced age upon the likelihood of successful outcome ([What is Age Factor?](#)). For that reason, we generally do not recommend starting IVF with the woman's own eggs beyond their 43rd birthday.

Older women are usually excellent candidates for pregnancy initiation with donated eggs ([Donor Egg Program](#)).

The presence of a uterus and at least one functioning ovary is an absolute prerequisite for traditional IVF. In the presence of male factor, normal fertilization rate can be achieved through ICSI ([What is ICSI?](#)) or the use of donor semen.



The Tang Twins >

### III. Pre-Treatment Preparation

#### A. Initial Visit

At the time of the initial consultation, the physician elicits your history, reviews past records, performs a physical examination and formulates the treatment plan. A major goal of the evaluation is to define as precisely as possible what is your individual likelihood of success with different therapies. If you have undergone evaluation or treatment at another program, please bring detailed records including the results of screening tests, the stimulation and laboratory summaries so that we can review them with you in detail.

A form for release of medical information should be signed by you and your partner and sent to each doctor who tested or treated you for infertility in the past.

A trial embryo transfer is usually done by passing a thin catheter into the uterus (womb) in order to assess the ease of passage and direction of the cervical canal and to measure uterine depth. The trial transfer is usually painless and allows us to perform the actual embryo transfer with as little irritation as possible.



## B. Standard Screening Tests

The usual blood tests for the woman include Blood type and Rh Factor, Rubella and Varicella Antibodies, prolactin, TSH, Hepatitis BsAntigen, Hepatitis C Antibody, HIV Antibodies and RPR. FSH and estradiol are measured on cycle day 3 ([How Do We Test for Ovarian Reserve?](#)) and an ultrasound is done to check the number of antral follicles in the ovaries (AFC) and uterine anatomy. We try to avoid repeating previously completed tests.

< Vivian preparing for injection class

The male partner is required to have a 5-test STD panel (Hepatitis Bs Antigen, Hepatitis C Antibody, HIV Antibody, HTLV Antibody and RPR) required by Health and Safety Code. As with all tests, there are occasionally misleading results (false positive and false negatives) which may necessitate confirmatory testing. A semen analysis is scheduled unless a very recent one is available.

Additional evaluation includes an HSG (dye study of uterus) and a saline infusion sonohysterogram (SIS) for evaluation of the uterine cavity. If one or both tubes are closed at the end near the ovaries, forming a hydrosalpinx, removal or ligation of the damaged tubes is recommended before IVF, because such closed tubes lower pregnancy rates ([What Is a Hydrosalpinx?](#)).

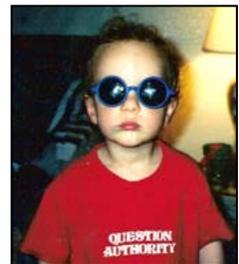
## C. Injection Training

Shortly before the first treatment the patient and her partner are instructed in the techniques of injections by one of the nurses in our office. At that time the medications you will use are reviewed and additional questions can be answered.

Please make sure that you have medications well in advance of starting the treatment cycle. We provide you with prescriptions and a list of participating pharmacies where the medications can be obtained. Comparative shopping can be worthwhile as prices do vary. Since many of these medicines are injectable, they are generally not stocked by neighborhood pharmacies and may need to be ordered from specialized pharmacies.

## IV. Controlled Ovarian Hyperstimulation

The single most important factor in improving the success rate of IVF in its early days was the transfer of more than one embryo (fertilized dividing egg). The reason is because a high percentage of early embryos do not implant. Furthermore, the maturity of each egg collected may not be ideal and only about 65% of eggs fertilize normally. While placing more than one embryo markedly increases the success rate, it also increases the chance of multiple pregnancy ([The Dilemma of Twins](#)). In our experience, one of every three pregnancies in women under the age of 40 years is multiple, with the majority being twins.



Max >

## A. Gonadotropins, or injectable “fertility drugs” (Follistim®, Gonal-F®, Bravelle®, Menopur®).

In order to stimulate development of multiple follicles, which are the fluid-filled sacs containing the oocytes (eggs), you receive gonadotropins the active ingredient of which is the FSH hormone. Menopur also contains the LH hormone or LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Luveris®, recombinant LH, can also be given as a separate injection in addition to FSH or alternatively, low-dose hCG can be used. These medications are given by subcutaneous injection. Proper dosage of these drugs and the timing of egg recovery require monitoring of the ovarian response, usually by way of frequent blood tests and ultrasound exams.

## B. Risks of Gonadotropins



As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to these drugs. Most women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Mild hyperstimulation usually responds to bedrest.

< Adrienne and Family

About 2% of women develop more severe Ovarian Hyperstimulation Syndrome ([How to Avoid OHSS](#)). Other risks and side effects of gonadotropins include fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

Some research suggested that the risk of ovarian tumors may increase in women who take any fertility drugs over a long period of time. These studies had significant flaws which limited the strength of the conclusions. More recent studies have not confirmed this risk. A major risk factor for ovarian cancer is infertility per se, suggesting that early reports may have falsely attributed the risk resulting from infertility to the use of medications to overcome it. In these studies, conception lowered the risk of ovarian tumors to that of fertile women.

**Human chorionic gonadotropin (hCG)** (Profasi®, Novarel®, Pregnyl®, Ovidrel®) is a natural hormone used in IVF to induce the final maturation of eggs. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to, breast tenderness, bloating, and pelvic discomfort.

Gonadotropins have been used for many years without any evidence of increase in birth defects or spontaneous miscarriage.

## C. GnRH Analogs: Agonists and Antagonists

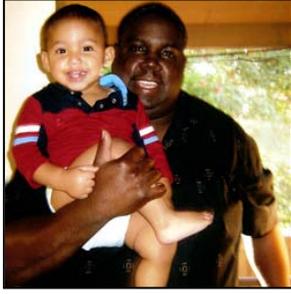
**Leuprolide acetate** (Lupron®) is a potent agonist of GnRH, the hormone which controls the release of FSH and LH by the pituitary gland. It is usually taken as a daily subcutaneous injection. Its primary role is to prevent a premature LH surge, which could result in the release of eggs before they are ready to be retrieved. Since GnRH-agonists initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation (see Flare Protocol).

Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way for more than 20 years. Potential side effects usually experienced primarily with use for over 6 weeks include but are not limited to hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. Few side effects are experienced with short-term use as is usually the case in IVF.

**Ganirelix and cetrorelix** (Antagon®, Cetrotide®) are antagonists of GnRH hormone and are also used to prevent premature ovulation. As they have a rapid onset of action, they tend to be started later during the stimulation and used for just a few days. They are given subcutaneously. The potential side effects include, but are not limited to, abdominal pain, headaches, skin reaction at the injection site, and nausea.



Consultant >



#### D. Treatment Plan

An individualized treatment plan will be discussed with you prior to starting and again at baseline ultrasound so you will know what to anticipate. It is of utmost importance that we have your current telephone numbers so that we can always reach you and/or your partner in case there is a change in the treatment plan.

< Happy Family

Currently there are 3 common protocols for the use of above medications: the Long Protocol, the Antagonist Protocol and the Flare Protocol.

#### E. Long Protocol

The long protocol is used in patients who have good ovarian reserve and are not at high risk of severe OHSS ([How To Avoid OHSS](#)). Leuprolide is usually started after ovulation has been confirmed by a progesterone blood test but before menses. Alternatively it can be started while the patient is on pre-treatment with oral contraceptives. It is given as once-a-day subcutaneous injection in the morning. This protocol was originally described by Dr. Chetkowski in 1989 ([Dr. Chetkowski's CV](#), Publication # 12) and popularized by Dr. David Meldrum. It is still considered the gold standard to which newer protocols are routinely compared.

When leuprolide is to be begun before the onset of menses, we recommend that a barrier method of contraception (condoms, diaphragm or spermicidal jelly) be used during that cycle. If your period is more than 2-3 days delayed, please call the office to schedule a sensitive blood pregnancy test. While there is no evidence that leuprolide would cause any congenital anomalies, it might interfere with implantation of the fertilized egg in the uterus.

#### F. Antagonist Protocol

The antagonist protocol is used in patients at high risk for developing severe OHSS ([How to Avoid OHSS](#)) and it may or may not follow a pre-treatment with oral contraceptives. The antagonist medication is added to FSH after 5-6 days and continued until the trigger injection. In patient with very prolific ovarian response leuprolide can be used for the trigger injection in place of the standard hCG bolus, thus reducing the risk of ovarian hyper-stimulation syndrome.

#### G. Flare Protocol

The flare protocol is used in patients with reduced ovarian reserve and in patients who have previously failed to respond to the long or antagonist protocols. It takes advantage of the initial stimulatory effect of leuprolide which results in release of FSH and LH from the pituitary gland before inducing suppression. This protocol usually follows a pretreatment with oral contraceptives. Micro-dose leuprolide injections are given twice per day starting 3 days after the last pill and two days later high-dose FSH injections are added. As in the long protocol, hCG must be used for the trigger injection.

#### H. Monitoring of Ovarian Response

Prior to beginning stimulation, a baseline ultrasound and blood test are done to detect any preexisting ovarian cysts or ovarian activity. A vaginal probe is used so a full bladder is not necessary. Simple ovarian cysts are common and they usually resolve on their own. However, if a large cyst is found, the treatment cycle may be delayed.

Waiting Area >

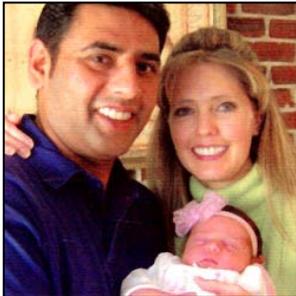


At the baseline ultrasound, the nurse will dispense your supplies -- syringes, extra needles, and alcohol wipes. After three to four days of gonadotropins, a blood test is usually done to assess your response by measuring hormone estradiol which is secreted by the growing follicles in your ovaries.

Once your estradiol reaches 200-300 pg/mL another vaginal ultrasound is scheduled to examine the size and number of the follicles. Most patients have 5-6 ultrasounds. Ultrasound is harmless to you and to the developing eggs. Depending on the growth of the follicles and estradiol levels, variable doses of gonadotropins are given for a total of 8-13 days. Unlike some other programs, we monitor your response closely and frequently adjust the dose of medications in the course of stimulation.

The HCG trigger injection is in the evening and needs to be taken no earlier than the appointed time. HCG provides for the final phase of egg development.

## V. Egg Retrieval



Oocyte retrieval, i.e., removal of the eggs from your ovaries, takes place about 36 hours after the injection of HCG just before ovulation would occur in response to the hCG trigger injection. A transvaginal ultrasound probe is used to visualize the ovarian follicles and a long needle, which can be seen on ultrasound, is inserted into each follicle to aspirate as many eggs as possible. It is usually performed with intravenous sedation because aspiration causes moderate discomfort.

< Jackie and Family

It is possible that the aspiration will fail to obtain any eggs or the eggs may be abnormal or of poor quality and otherwise fail to produce a viable pregnancy.

Following this procedure you may have a small amount of vaginal spotting.

The risks of egg retrieval include:

**Infection:** Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are used to reduce the risk of pelvic infection but there is no way to eliminate this risk completely.

**Bleeding:** The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels. In addition, there are other blood vessels nearby. Small amounts of blood loss are common during egg retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding would require transfusion or surgical repair and could result in loss of the ovary. Although very rare, review of the world experience with IVF indicates that unrecognized internal bleeding has led to death.

**Trauma:** Despite the use of ultrasound guidance, it is possible to damage other intra-abdominal organs such as the bowel, appendix, bladder, uterus, and ovary. Damage to internal organs may result in the need for additional treatment such as surgery for repair or removal of the damaged organ.

**Anesthesia:** The use of anesthesia during the egg retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting and in rare cases death.





## VI. Semen Collection

We suggest that prior to the retrieval, your partner refrain from ejaculation for two to three days. We will keep you informed as to the progress of follicular development to enable him to judge when abstinence should begin. The morning of the egg retrieval, your partner provides a semen specimen by masturbation in a private area in our office.

We understand that he may feel under stress but we have allowed ample time to avoid any problem in providing the specimen. If any difficulty is anticipated with the semen collection, we recommend that a specimen be frozen for back-up in advance of the treatment cycle.

< Men's Room

## VII. In Vitro Fertilization and Embryo Development

After eggs are retrieved, they are transferred to the embryology laboratory where they are kept in conditions that support their needs and growth. The embryos are placed in small dishes or tubes containing "culture medium," which is special fluid developed to support development of the embryos made to resemble that found in the fallopian tube or uterus. The dishes containing the embryos are then placed in incubators, which control the temperature and atmospheric gasses the embryos experience.

A few hours after eggs are retrieved, sperm are placed in the culture medium with the eggs, or individual sperm are injected into each mature egg in a technique called Intracytoplasmic Sperm Injection ([What is ICSI?](#)). We inseminate all the mature eggs so that there will be an optimal chance of obtaining several healthy-appearing embryos.



The day after the retrieval, the eggs are examined for presence of 2 circular structures within the eggs (pro-nuclei) which constitute evidence of normal fertilization (see picture below).

< Normally fertilized egg 1 day after retrieval



The eggs are examined for evidence of cell division (cleavage) at two and/or three days after retrieval. Two days after insemination or ICSI, normal embryos have divided into about 4 cells.

< Two-cell embryo 2 days after retrieval with sperm in zona



< Four-cell embryo 2 days after retrieval



Three days after insemination or ICSI, normally developing embryos contain about 8 cells.

< Eight-cell embryo 3 days after retrieval



Five days after insemination or ICSI, normally embryos have developed to the blastocyst stage, which is typified by an embryo that now has 80 or more cells, an inner fluid-filled cavity, and a small cluster of cells called the inner cell mass.

< Blastocyst 5 days after retrieval

It is important to note that since many eggs and embryos are abnormal, it is expected that not all eggs will fertilize and not all embryos will divide at a normal rate. The chance that a developing embryo will produce a pregnancy is related to whether its development in the lab is normal, but this correlation is not perfect.

This means that not all embryos developing at the normal rate are in fact also genetically normal, and not all poorly developing embryos are genetically abnormal. Nonetheless, their visual appearance is the most common and useful guide in the selection of the best embryo(s) for transfer.

### Untoward Events in the IVF Laboratory

In spite of reasonable precautions, any of the following may occur in the lab that would prevent the establishment of a pregnancy:

- Fertilization of the egg(s) may fail to occur.
- One or more eggs may be fertilized abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos will not be transferred.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Bacterial contamination or a laboratory accident may result in loss or damage to some or all of the eggs or embryos.
- Laboratory equipment may fail, and/or extended power losses can occur which could lead to the destruction of eggs, sperm and embryos.
- Other unforeseen circumstances may prevent any step of the procedure to be performed or prevent the establishment of a pregnancy.
- Hurricanes, floods, or other 'acts of God' (including bombings or other terrorist acts) could destroy the laboratory or its contents, including any sperm, eggs, or embryos being stored there.

### VIII. Embryo Transfer and Post-Transfer Care

While transfer of multiple embryos increases the chance of pregnancy, it also increases the risk of multiple pregnancy ([The Dilemma of Twins](#)). The decision regarding the number of embryos to transfer can be difficult.



Connor and Logan >

In making a recommendation we take into account the woman's age, the appearance of the embryos, the couple's prior history, the advisability of embryo freezing and the couple's concern about multiple pregnancy and the potential need for multi-fetal pregnancy reduction. In general, we transfer 2-3 embryos in women under the age of 35, 3-4 embryos in women aged 35-39, and 5-6 embryos in women over 40 years of age. Some couples may choose a lower number of embryos to have transferred because of concern about the risks of multiple pregnancy.

The embryo transfer is done in a room adjacent to the laboratory. The transfer requires no anesthesia. If at all possible, we would like your partner to be present. We use an abdominal ultrasound to confirm that the catheter is within the uterine cavity. Therefore it is best if you drink extra fluid 1-2 hours and stop voiding about 1 hour before the transfer. In the usual position for a pelvic examination, a tiny catheter containing minute amount of fluid with the embryos is gently inserted into the uterus and the fluid is deposited. You then rest for 5-10 minutes before discharge. Following transfer you might notice light spotting for a couple of days.



Transfer room is adjacent to the laboratory >

The embryos not transferred are either frozen for future use or discarded ([Embryo Freezing](#)). If you have embryos which will be discarded, you may either permit us to study them first for research or quality control or you may choose to discard them without any study.

If you do not plan to freeze additional embryos for future use, if you are healthy and under 30 years of age, you may consider donating some of the eggs before fertilization to an infertile woman who does not produce eggs of her own. If you are willing to do so, please inform Dr. Chetkowski well in advance of the treatment cycle so that appropriate screening and arrangements can be completed. Even if you agree to donate extra eggs, we will only do so if a large number of mature eggs are recovered so that your decision would in no way decrease your own chance of conception in that cycle. Donation of the extra eggs may reduce your total expenses significantly.

### Post-Transfer Care



Individualized luteal phase support schedule is provided to you in advance of the actual embryo transfer procedures. Currently we use micronized progesterone capsules or tablets (Endometrin) vaginally, progesterone vaginal gel (Crinone 8%), intramuscular injections of progesterone-in-oil 50 mg/mL and subcutaneous injections of hCG. Progesterone supplementation usually begins in the morning two days after egg retrieval.

< Patty

It is our recommendation that you refrain from vaginal intercourse and orgasm, which can be associated with strong uterine contractions, for five days after the transfer until embryo implantation (attachment of the embryo(s) to the womb) has been completed. While there is direct data to this effect, uterine contractions could in theory expel the free-floating embryos from the uterine cavity. Otherwise, we leave it up to your discretion to what extent you may want to modify your usual activities. Bedrest after transfer is not required for high pregnancy rate.

## IX. Pregnancy Tests



Two weeks after retrieval a sensitive blood pregnancy test (quantitative hCG) is performed to determine if implantation has taken place. It is important to have the test done even if you are spotting or bleeding. If the test is negative, luteal supplementation with progesterone is stopped and a period follows within a few days. If the test is positive, it is repeated in a couple of days to determine whether there is normal growth.

< The Keeley Family

In cases where hCG is used during the luteal phase, a low hCG level is detected from the residual of the injection and the test has to be done twice before implantation can be confirmed. In the presence of pregnancy, progesterone is often continued unless a blood test determines that your ovaries are producing sufficient quantity of this hormone.

In some instances the first HCG test is higher than the second even in the absence of hCG injections during the luteal phase. These cases are classified as "biochemical" pregnancies, which do not progress to the clinical state. Biochemical pregnancies are not included in the calculation of the success rate in our program. If your pregnancy progresses normally, you will be scheduled for an ultrasound examination about 4 weeks after the retrieval in order to visualize the pregnancy. About 4-5% have been ectopic, i.e., in the tube. This complication usually requires either a laparoscopy to remove the ectopic pregnancy or medical treatment with methotrexate.

With intrauterine pregnancies there is still the risk of miscarriage which increases with advanced age. We usually perform a second ultrasound examination at 9-10 weeks to confirm normal development of the fetus. In the unlikely event that a high-order multi-fetal pregnancy, i.e. more than twins, is found, we discuss with you the relative benefits and risks of the multi-fetal pregnancy reduction procedure ([The Dilemma of Twins](#)).

## X. ICSI

ICSI (intra-cytoplasmic sperm injection) was initially developed for severe male factor cases when the number and/or function of sperm is not sufficient for standard insemination ([Male Factors](#)). The first baby from ICSI at the Alta Bates IVF Program was born in April 1995. Recently the use of ICSI has been extended to couples with milder forms of male-factor as well as couples with unexplained or multi-factorial infertility. The reason for expanding the indications for ICSI is to avoid absent or low which occurs in some of these cases unexpectedly and which can severely reduce the chance of success.

The tests for functional capacity of the sperm (such as semen analysis, strict sperm morphology and the hamster egg penetration assay) do not always predict low or absent fertilization in the laboratory. While uncommon, this can happen even with sperm of men who had previously achieved pregnancy naturally and who have normal semen characteristics. For this reason, we recommend the use of ICSI on some of the eggs in first IVF cycles even in the absence of obvious male factor.

ICSI Procedure >



During ICSI, a single sperm cell is injected directly into the egg. The procedure is carried out under a microscope while the eggs are kept on a warm stage at 30°C. During the injection procedures, micromanipulators are used to reduce hand movements to microscopic movements. The sperm injection pipette is used to immobilize and then to inject the sperm into the egg which is kept in place with a larger holding pipette.

After egg retrieval, about 80 to 100% of the eggs are expected to be mature (MII) and ready for sperm injection. A small percentage of the eggs may be damaged by the ICSI procedure. Not all eggs will fertilize after ICSI and some fertilized eggs may not divide into a cleavage stage embryo. Overall, however, the live birth rates with ICSI are comparable to those achieved by conventional IVF. For most couples with severe male factor infertility, ICSI is the only option available to achieve parenthood with their own gametes.



Dr. Andras Szell at micromanipulation table >

## XI. MESA



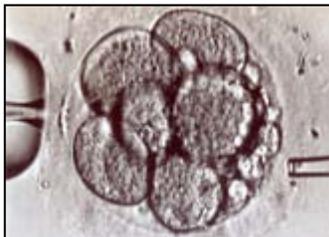
In cases where the ejaculate does not contain sperm, **MESA** (microsurgical epididymal sperm aspiration) is performed to obtain sperm by a urologist specializing in male infertility. Epididymal and testicular sperm require ICSI for fertilization. In our program MESA is typically done in advance of the ICSI-IVF cycle and the sperm are frozen. One MESA procedure often provides enough sperm for several ICSI-IVF cycles.

< Reception Area

The risk of genetic abnormalities in children born from ICSI has been of equal concern to patients and health professionals. Studies carried out world-wide showed that some forms of congenital abnormalities had a higher incidence in male babies born from ICSI but the most recent studies showed no difference between IVF with and without ICSI. Men with marked sperm abnormalities have a high chance of carrying mild genetic abnormalities which would then be transmitted to their offspring conceived through ICSI but would not be the result of the ICSI procedure itself. Specifically, men with very low sperm counts often have deletions or mutations in the long arm of the Y chromosome which would be passed on to their sons born from ICSI. Therefore, when the sons born from ICSI reach reproductive age, they may also find that they are sub-fertile or infertile due to the genes inherited from their fathers.

## XII. Assisted Hatching

Assisted hatching is a laboratory procedure designed to facilitate implantation or attachment of the dividing embryos to the wall of the uterus. In order for implantation and pregnancy to occur, the embryo must "hatch" out of the zona pellucida (the egg's outermost membrane). In some patients, failure to establish a pregnancy after IVF may be related to the inability of the embryos to get out of the zona. When transfer is done 3 days after retrieval, a small opening is created in the zona pellucida under microscopic control, thus aiding the hatching process. Assisted hatching is not done on day 2 and day 5 transfers. Patients whose embryos undergo hatching, receive extended antibiotic and steroid treatment for 5 days.



< Assisted Hatching 3 days after retrieval

Although assisted hatching has been around as long as ICSI, its clinical value remains highly controversial. Whereas in the past we utilized this technique widely, more recently we have restricted its application to select cases where poor implantation rate may occur.

## J. Reasons for Delay or Cancellation of a Treatment Cycle



Infection of the male reproductive tract (prostatitis) may be evident on semen analysis or semen culture, even though the man may be entirely without symptoms. Since infection can be associated with decreased fertilization rate and also introduce contamination into the laboratory, we attempt to first eradicate the infection with antibiotics before proceeding with ICSI-IVF. Sometimes prolonged treatment is required.

About 10% of women fail to respond to the ovulatory medications as expected. Some develop no or few follicles and others may develop only a single dominant follicle as in a spontaneous cycle. These stimulation cycles are usually canceled before egg retrieval. Individual patients are directly involved in the decision-making process about the retrieval cancellation. Ovarian reserve testing ([How Do We Test Ovarian Reserve?](#)) identifies many of the patients who are likely to respond poorly to ovarian stimulation.

A small percentage of patients ovulate prematurely before retrieval because their pituitary gland releases LH hormone surge before the hCG trigger. The use of GnRH analogs has markedly reduced the frequency of premature ovulation but it has not been eliminated entirely. Occasionally patients develop such a large number of follicles that they are at very high risk of ovarian hyperstimulation syndrome and the hCG trigger is withheld and retrieval cancelled or the hCG trigger is reduced and all the embryos are frozen for a future transfer ([How to Avoid OHSS](#)).

The maturity of oocytes varies considerably and not all fertilize. The average fertilization rate is about 65%. In rare cases no eggs fertilize. Sometimes the sperm prove incapable of fertilization despite a normal semen analysis. In such cases, ICSI can be done the day after retrieval ("rescue ICSI"). While fertilization can usually be established, the pregnancy rate with "rescue ICSI" is lower than in cycles with timely fertilization. At other times the eggs are not as ready to be fertilized as they appear to be by ultrasound and blood tests. Finally, cell division and embryo development may fail to occur despite apparently normal fertilization. In some cases embryo quality may not be optimal or the embryos may stop developing.

Obviously the embryo transfer would have to be canceled if one of these problems arose, but fortunately they are quite uncommon and over 90% of patients in our program either undergo transfer of fresh embryos or have embryos frozen for a future transfer.

Handling of the eggs, which are very minute, outside of the body is inherently hazardous and requires great skill and care. On occasion, an egg or an embryo, fresh or frozen, may get stuck to the side of a culture dish and cannot be found. These kinds of mishaps are rare but you need to be aware of their possibility.