History and State of the ART in Korea

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I. 서 론

지난 2003년 7월 28일은 25년전 영국의 시골마을인 Oldham의 병원에서 세계최초의 시험관아기인 Louise Brown이 출생한 기념비적인 날이었다. 영국의 과학자인 Patrick Steptoe와 Robert Edwards에 의해 세계처음로 시험관아기의 출생이 보고된 이래 지난 25년 동안 시험관아기 시술을 비롯한 다양한 생식보조술 (assisted reproductive technologies; ART)의 발전은 생명공학의 발전 중에서도 가장 놀라운 속도로 발전된 학문분야라고 할 수 있다. 지금까지 전세계적으로 생식보조술로 출생한 시험관아기만 해도 30만명이 넘고 있으며 한해동안 수십만건 이상의 시험관아기 시술이 이루어지고 있다. 한국도 1985년 서울대학교병원에서 장윤석 교수연구팀에 의해 최초의 시험관아기의 출생이 성공된 이래 현재는 매년 15,000건 이상의 시험관아기 시술이 이루어지고 있는 이 분야의 시술의 선도적 국가로 발전하였다. 이제 생식보조술은 불임증을 치료하는 가장 확실한 방법으로 인정받고 있으며 이 기술은 단순한 불임치료를 떠나 최근에는 배아줄기세포의 생산과 난치병치료라는 새로운 학분분야를 선도하는 단계에 이르고 있다.

저자는 시험관아기의 출생을 국내에서 최초로 성공한 연구팀의 일원중 하나로서 그동안 한국에서의 불임치료술로서의 생식보조술의 발전역사와 함께 향후의 발전방향에 대해 논하고자 한다.

II. 한국 생식보조술의 현황

한국 뿐만아니라 세계 불임치료 기술의 발전은 복강경을 통한 자연주기의 난자채취와 체외수정을 이용하던 고전적 시험관아기 시술법으로 부터 시작되었다. 이후 난소내의 원시난포를 자극하여 난포성장을 유도할 수 있는 다양한 배란유도제의 개발은 현재와 같이 환자의 특성에 맞는 다양한 배란유도 방법의 발전을 가져오게 되었고 또한 질식초음파의 도입은 난자채취의 효율을 극대화 시킴과 동시에 보다 안전한 난자채취를 가능하게 되어 본격적인 생식보조술의 발전을 이루게 하는 원동력이 되었다. 초기의 자궁내 배아이식에서 1984년과 1986년에 개발된 배우자 나팔관내이식술 (gamete intrafollopian tube transfer; GIFT)와 접합자 자궁내이식술 (zygote intrafollopian transfer: ZIFT)의 발전은 다양한 배아이식법을 제공함으로서 임신율 향상을 유도하였고, 1983년 Trounson 등에 의해 개발된 배아 동결보존법은 채취되는 난자의 이용효율을 극대화시킴과 동시에 환자에게는 최소 1회 이상의 배아이식을 더할 수 있는 기회를 제공하게 되어 시술당 임신율을 높이는 기술로 정착되었다. 한국의 시험관아기 시술은 이미 언급한 바와 같이 1985년 서울대 연구팀에 의해 최초의 출산이 보고된 이래 이후 부터

는 각 대학병원과 산부인과 전문병원을 중심으로 하여 경쟁적인 성공사례의 보고가 이루어져 왔고 이러한 환경은 국내 불임치료기술의 발전을 획기적으로 발전시키는 계기가 되었다. 선진외국에서 개발되는 다양한 신 기술이 속속 한국에 도입되었고 이를 정착화 시키는 연구보고가 1980년대 후반부터 1990년대 초반에 이르는 동안 활발히 진행되었고 일부 불임 치료센터에서는 외국기관과의 협력관계가 구축되기도 하였다. 이러한 환경적 변화는 국내 불임치료 연구의 발전에 밑바탕이 되었고 일부 기관에서는 세계 최초의 신 기술의 개발도 일부 이루어져 한국의 생식의학이 단순히 외국의 기술을 도입하고 수용하는 단계를 벗어나 새로운 기술을 개발하고 보급하는 단계로 발전되었다. 1989년 Handyside 등에 의해 개발된 착상전 배아의 유전진단 (preimplantation genetic diagnosis: PGD)은 미세조작기술의 발전과 분자유전학적 진단법의 발전으로 그동안 융모막검사나 양수검사에 의존하던 유전질환의 검사를 착상전단계에서 선별할 수 있는 기술로서 국내에 도입되어 현재까지 다양한 유전질환 환자에게 적용되고 있다. 1992년 Palermo 등에 의해 개발된 난자세포질내 정자주입법 (intracytoplasmic sperm injection: ICSI)의 개발은 그동안 불임치료 분야에서 소외될 수 밖에 없었던 남성불임환자 치료에 획기적 수단으로 이용되어 현재는 다양한 외과적 정자채취술 및 미성숙 정자를 이용한 방법까지도 국내에 적용되고 있다. 이와 같이 생식보조술은 초기만하더라도 외국에서 도입된 기술이 한국에 정착하는데 5년 이상의 격차를 갖고 있었으나 이후에는 1년 내에 그 기술이 도입되어 정착하는 등 세계 어느 국가보다 신속하게 선진기술을 도입하고 발전시키는 국가로 발전하였다. 이외에도 미성숙난자를 이용한 시험관아기 시술법 (IVM/IVF/ET program), 유리화난자동결법 (oocyte vitrification) 및 난소조직동결 및 이식 (ovarian tissue freezing) 등은 세계를 선도하는 시술법으로 발전되었다. 학술적으로는 미국생식의학학회 (American society for reproductive medicine: ASRM), 유럽생식의학학회 (European society for human reproduction and embryology: ESHRE) 및 세계불임학회 (International federation of fertility and sterility) 등과 같은 유수의 학회에 한국의 불임치료연구 성과가 발표되면서 각종 수상을 하는 등 국제적 연구업적을 인정받는 단계까지 발전하고 있다. 아울러 1998년 이후에는 한국의 불임치료기술이 외국에 진출하는 사례가 보고되면서 본격적인 의료기술의 수출시대가 열리게 되어 현재는 미국과 중국에 실제 불임치료센터를 운영하는 단계로 발전하였다. 최근에 들어서는 냉동보관중인 잉여배아를 이용한 줄기세포 개발을 시작하면서 국내 불임치료기관 3곳이 미국 국립보건원 (NIH)의 stem cell registry에 등록하고 NIH stem cell infrastructure aaward를 받는 등 이 분야에도 세계적인 수준의 연구가 진행되고 있다. 저자를 비롯한 국내 유수의 불임치료센터를 중심으로 하는 과학기술부 21세기 프론티어사업 세포응용연구사업단은 국내 줄기세포연구의 중심축으로서 그동안 발전한 생식보조술을 경험을 바탕으로 불임치료를 포함한 다양한 난치성 질환 치료법을 개발하는 연구단계로 발전하게 되어 그 활동영역을 넓히고 있다.

III. 결 론

한국의 생식보조술 연구분야는 그 역사가 20년이 채 되지 않는 짧은 역사에도 불구하고 그동안 놀랄만한 발전을 거듭하여 왔으며 초기의 외국 의존적 형태에서 현재는 세계 생식보조술 연구를 선도하는 단계까지 발전되어 오고 있다. 현재 의학협회 인공수태윤리소위원회에 등록되어 있는 불임치료기관은 90여개에 달하고 있는 것으로 알려져 있으나 미국과 같이 미국전역의 95% 이상의 불임치료기관이 생식보조학회 (Society for Assisted Reproductive Technology: SART)에 가입되어 각 기관의 생식

보조술 현황을 매년 보고함과 동시에 다양한 시술경험과 새로운 생식보조술을 보급하는 제도적 장치가 마련되지 못하고 있는 실정이다. 이제 우리나라도 미국의 SART와 같은 제도적 장치를 도입할 시기가 되었다고 생각되며 이러한 제도하에서 국내의 생식보조술의 발전을 더욱 가속화시켜야 할 것으로 생각되며 이러한 역할을 대한불임학회에서 주도적 역할을 수행하기를 희망한다. 마지막으로 미국 SART에서 제공하는 "A patient guide to assisted reproductive technologies"를 첨부하고자 한다. 생식보조술을 시행하는 환자들을 위한 가이드북이기는 하지만 국내 생식보조술에 참여하는 의료진과 연구진에 매우 유익한 정보가 들어있는 자료로서 참고하기를 기대한다.

A PATIENT'S GUIDE TO ASSISTED REPRODUCTIVE TECHNOLOGIES
SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY (SART)

Dear Patient:

Welcome! We hope that this handbook will answer many of your questions concerning assisted reproductive technology. The information presented is adapted from the ART Manuals of the University of Texas Health Science Center at San Antonio (Robert G. Brzyski, M.D., Ph.D., Editor) and NCIRE/IVF Florida and is reproduced with their permission. This booklet is in no way intended to replace, dictate or fully define evaluation and treatment by a qualified physician. It is intended solely as an aid for patients seeking general information on issues in assisted reproductive technology.

We strongly advise couples to review the material together. Fertility therapy generates a wide range of emotions. Waiting, uncertainty, and the demands of treatment can lead to feelings of frustration, confusion, and resentment. We believe that the more you know about the tests and treatments, the less anxiety and concern you will feel about your condition.

Most centers utilize a multi-disciplinary professional team. During your treatment cycle, many team members, in addition to your individual physician, will participate in your care. Advanced infertility procedures require time and energy, as well as an emotional and financial commitment. The entire staff should make every effort to provide you with personal and compassionate care in order to make this difficult time as comfortable and manageable as possible.

What is an infertility specialist?

A medical specialist who treats patients with infertility is known professionally as a Reproductive Endocrinologist. Training in Reproductive Endocrinology requires four years of college followed by four years of medical school. The physician must then complete a four-year residency in Obstetrics and Gynecology (OB/GYN), during which the physician receives broad training in general Obstetrics and Gynecology. The final course of training is a two or three-year Fellowship in Reproductive Endocrinology. Fellowship training focuses on the diagnosis and treatment of infertility and related disorders. This training includes experience in microsurgery, laparoscopic and hysteroscopic surgery, in vitro fertilization-embryo transfer, sonography, and ovulation induction. In addition, the physician spends a significant amount of time performing clinical or laboratory research.

Upon completion of a Fellowship in Reproductive Endocrinology, a specialist seeks Board certification, a multi-step process. To become Board certified in Reproductive Endocrinology, the physician must first obtain Board certification in Obstetrics and Gynecology. This requires successful completion of both a written and an oral examination. Board certification in Reproductive Endocrinology requires successful completion of additional

written and oral examinations. The entire certification process takes several years to complete. Only a physician who has successfully completed a Fellowship in Reproductive Endocrinology and passed the examinations can become Board certified as an infertility specialist.

It is often quite difficult for a patient to determine whether or not their physician is an infertility specialist. Some physicians have gained skills through experience outside fellowship training, and some physicians successfully complete fellowship training and do not obtain Board certification. However, Board certification is the only objective criterion by which patients can measure a physician's qualifications.

Advanced reproductive technologies

Advanced Reproductive Technology (ART) includes in vitro fertilization-embryo transfer (IVF-ET), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), tubal embryo transfer (TET), and frozen embryo transfer (FET). These are relatively new procedures for couples who are unable to conceive by other methods. Although ART has helped many people overcome their infertility, they are not the answer for every infertile couple. Most of the time we use ART only when less complex and less expensive methods of treatment have failed. However, in certain circumstances (such as advanced age or severe male factor) we may recommend ART as first-line therapy.

IVF, GIFT, ZIFT, and TET are very similar procedures although there are a few significant differences. During IVF-ET, ZIFT, and TET, the oocytes and sperm are combined in a culture dish in the laboratory. Fertilization and very early embryo development occur outside the body, rather than in the fallopian tube. Once early embryo development is recognized, the embryos are transferred either into the uterus (IVF-ET) or the fallopian tube (ZIFT, TET). Since most programs have seen no significant difference in success rates, they usually perform IVF-ET because it is less expensive and doesn't require laparoscopy and general anesthesia. In addition, IVF-ET is the only procedure available for women with damaged fallopian tubes.

GIFT differs from the other procedures in that sperm and oocytes are transferred into the fallopian tubes immediately after oocyte retrieval. Fertilization thus occurs in the body, rather than in the laboratory. GIFT originally was thought to represent a breakthrough in infertility therapy. National ART statistics suggest that success rates are higher with GIFT than IVF-ET. However, many investigators have concluded that GIFT does not increase the likelihood of conception compared to other ART procedures, and that the statistics may reflect differences in laboratory expertise or in the kinds of patients treated with GIFT versus IVF-ET. In addition, GIFT does not allow for confirmation of successful fertilization if the procedure does not produce a pregnancy. Your physician will discuss each of these procedures with you so that the most appropriate procedure for your individual situation will be used.

Couples who are considering ART should realize that it is an intensely emotional, physically arduous, and expensive procedure. Most couples find it difficult to consider the chances for success realistically without dampening the drive that allows them to undertake these procedures. Above all, couples should explore plans for the future, whether or not their attempts at ART are successful.

ART Candidates

Every patient should have completed a basic infertility evaluation. Because of the physical, emotional, and financial demands of ART, these advanced procedures generally are used in patients who have tried all less complex and less expensive methods of correcting their infertility. The majority of patients in ART programs suffer from tubal factor, male factor, or unexplained infertility. ART candidates who will be using their own eggs should be under 44 years of age and should have:

- No evidence of premature menopause
- At least one accessible ovary, and
- A normal uterus

Menopause and ovarian function are irrelevant for candidates using donor eggs. Donor egg recipients should be under 50 years of age and have a normal uterus. All ART candidates should be in good health and have no medical conditions that would pose a serious health risk to themselves or the child they would carry.

Success Rates

One of the first questions that most people ask is "what is the chance for success?" The initial hope of achieving a pregnancy by ART is often deflated by the answer to this question. The best estimate, based on our experience to date, is that the birth of a live baby occurs in approximately 15~25% of women in whom embryos are transferred into the uterus. The 1998 nationwide live birth rate as reported in the IVF-ET Registry, was 24.9%. The corresponding rate for 1989 was 14%. We believe that the delivery rate or "take home baby rate" is the only real measure of success. Patients should be aware, however, that some clinics define "success" as any positive pregnancy test or any pregnancy, even if miscarried or ectopic. These "successes" are irrelevant to patients desiring a baby.

Success varies with many factors, including the number of embryos that are transferred. If one embryo is transferred, there is approximately a 7% chance of successful implantation; with two embryos, the success rate increases to 18%. The rate peaks with the transfer of three to four embryos. Presently, the collection of oocytes, fertilization, and early embryo growth are accomplished with a high degree of efficiency. The major hurdles to success are implantation after embryo transfer and early pregnancy loss. The rate of early pregnancy loss is slightly, but not significantly, higher with ART compared to spontaneous conception. The risk of early pregnancy loss increases with age of the female partner. Over age 40, ART success rates decline dramatically. There is, however, no evidence that the risk of birth defects or chromosome abnormalities (such as Down's syndrome) is any different with ART than with natural conception. Pregnancy complications tend to be higher with ART pregnancies, primarily because of the much higher rate of multiple pregnancy. Twins occur in about 25% of ART pregnancies versus 1~2% of spontaneous pregnancies. The risk of more than a twin pregnancy is less than 5%.

To put these figures into perspective, studies have shown that the rate of pregnancy in couples with proven fertility in the past is approximately 20% per cycle. Therefore, although a figure of 15~25% may sound low, it is equal to or greater than the chance that a fertile couple will conceive in any given cycle.

We advise that patients plan at the outset to make several ART attempts. Programs that have the highest pregnancy rates average between three and four attempts per patient. There is no absolute restriction on the number of times that a couple can attempt ART. Although cumulative pregnancy rates increase through a total of six attempts, the success rate for any given cycle remains constant. A rest period between attempts is recommended, usually an interval of at least one normal menstrual cycle. Couples who have achieved an ART pregnancy and delivery in the past have an increased likelihood of ART -related conception in the future.

Patient Evaluation

General

Before starting ART therapy, certain tests should be performed to ensure that conditions for successful pregnancy are optimal. You should have a complete physical exam, including breast exam and Pap smear, within one year. You should also start taking prenatal vitamins, which may reduce the risk of spine abnormalities (neural tube defects) in the baby. Women 40 and older should have a mammogram prior to ART therapy.

Blood Tests

We confirm the woman's blood type and screen for antibodies that could affect

the health of a fetus. Documentation of immunity to rubella (German measles) and varicella (chickenpox) may also require a blood test. Rubella during pregnancy can cause serious harm to the fetus. We require blood tests for hepatitis and HIV (AIDS) for both the patient and her partner. We also require that patients be tested for syphilis (RPR). We may recommend a blood test for estradiol and FSH (a hormone that regulates ovarian function). This must be performed on the second or third day of the menstrual cycle. This test can reveal abnormalities in ovarian function, which may affect the success of ART therapy, especially in women over 35 years of age. In some cases a clomiphene challenge test may be recommended to further test ovarian reserve.

Semen

A complex semen analysis should be performed within one year of ART. Changes in sperm quality may occur over time that could affect ART therapy. The complex semen analysis checks for sperm number, shape, swimming ability, survival, significant infection, and antisperm antibodies. In some cases, additional semen testing may be recommended.

Uterus

We evaluate the anatomy of the uterus prior to ART. We may suggest an x-ray procedure (hysterosalpingogram or HSG) ultrasound procedure (sonohysterogram or SIS), or hysteroscopy. An HSG is performed by injecting a special liquid through the cervix into the uterus. The liquid is visible on x-ray films and outlines the anatomy of

the uterus and tubes. This is performed in a radiology suite and requires no anesthesia. An SIS is performed by injecting fluid into the uterus during transvaginal sonography. This procedure is performed in the office without anesthesia. Hysteroscopy involves insertion of a small telescope and light source through the cervix into the uterus to look for abnormalities. We may perform this procedure in the office using local anesthesia or in the operating room.

Prior to IVF/ET we also perform a uterine measurement called a trial transfer. The purpose of this procedure is to determine the length and direction of the uterine cavity. This enables us to guide the embryo transfer catheter into the proper position for the actual embryo transfer. Uterine measurement is similar to a pelvic exam or intrauterine insemination. Your physician will place a speculum in the vaginal and insert a thin, flexible plastic catheter through the cervix into the uterus. You may experience a small amount of cramping when the catheter goes through the cervix and again when the tip of the catheter touches the top of the uterine cavity. This cramping, which is similar to a mild menstrual cramp, should resolve within 30~60 seconds.

Pre-requisite testing

Certain tests must be performed prior to initiating a cycle of IVF. Some are required by law and others by national standards of care. Other tests are important to rule out problems that could reduce your chance of conception or increase the risk to mother or baby.

Mandatory prior to ivf

Female

Male

HIV, Hepatitis B antigen, Hepatitis C antibody, RPR, Pap smear, Cervical cultures for GC and Chlamydia, Blood group, RH, and antibody screen HIV, Hepatitis B antigen, Hepatitis C antibody, RPR, Complex semen analysis including 24-hour, motility, antisperm antibodies, and strict morphology.

STRONGLY Recommended Prenatal Tests

Female

Male

Rubella titer, Varicella titer, Cystic fibrosis carrier screen, Cystic fibrosis carrier screen,

Patients of Jewish Eastern European Origin

Tay Sachs, Canavan's, Gaucher's, Bloom's, Niemann-Pick, Fanconi's anemia

These tests are performed on the male if his partner has a positive test result.

Patients of French Canadian and Cajun Origin

Tay Sachs (enzymatic)

Patients of Mediterranean Origin

Hemoglobin electrophoresis

Patients of African or African American Origin
Hemoglobin electrophoresis

Patients of Asian Origin
Hemoglobin electrophoresis

Patients with Family history of Mental Retardation
Fragile X

If you are an oocyte donor, several additional tests are required. These include blood testing for evidence of previous or current cytomegalovirus (CMV infection), a genetic consultation to evaluate your family medical history, and a psychological screening interview.

Strongly recommended

§ Suggested

ART: A STEP-BY-STEP GUIDE

Every cycle of ART involves multiple steps, and each occurs at a specific time during a six-week period. The procedure begins around the time of ovulation in the month proceeding the ART cycle. Each patient will require a personal calendar for her individual schedule. The following is provided only as a general guide. Remember that you will be following an individual protocol designed specifically for you. This may differ from the protocol recommended to your friends or other women.

Cycle Preceding ART Cycle

1. Initiation of oral contraceptives or documentation of ovulation (mid-luteal)
2. Initiation of Lupron or other GnRH analog therapy

ART Cycle

1. Baseline pelvic ultrasound on cycle day 2
2. Ovarian stimulation with gonadotropins (e.g. Bravelle, Pergonal, Metrodin, Repronex, Follistim, Gonal-F, and/or Fertinex)
3. Monitoring follicle development with ultrasound and serum hormone levels
4. hCG administration (Profasi, Pregnyl, Novarel and Ovidrel)
5. Transvaginal oocyte retrieval

6. Embryo transfer
7. Progesterone supplementation
8. Hormonal studies and pregnancy test
9. Follow-up consultation

Step 1 - Initiation of Oral Contraceptives

Some of you will receive oral contraceptives in the cycle prior to the ART cycle. This ensures that GnRH analog therapy will start at the proper time if you have irregular cycles. There is also evidence that oral contraceptive can help prevent ovarian cysts, which sometime develop during GnRH analog therapy. You will usually begin a pack of oral contraceptives on the Sunday after your normal period begins. Alternatively, we may prescribe Provera or progesterone for patients who ovulate irregularly or not at all.

Step 2 - GnRH Analog Administration

You will begin treatment with a GnRH analog on the sixteenth day of oral contraceptive pills or the sixth day of Provera progesterone, although this may vary. You do not need a pregnancy test before you start the GnRH analog.

We will instruct you to reduce the dosage of GnRH analog by one-half on the day you begin ovarian stimulation. You will use the GnRH analog until the day of hCG (human chorionic gonadotropin) administration.

We sometimes treat patients with a different dosage or schedule of GnRH analog. For example, the GnRH analog is begun during the cycle preceding stimulation in the "mid-luteal" protocol, after the start of menses in the "flare" or "micro-flare" protocol, or after six or so days of stimulation in the "GnRH antagonist" protocol. Your physician will advise you if these variations apply to you.

Step 3 - Baseline Pelvic Ultrasound

Around the time of your expected period, we will perform an ultrasound scan to examine the ovaries. If we detect a cyst, we may withhold therapy until the cysts resolve spontaneously (usually in about a week). Occasionally, we recommend cyst aspiration (drainage). This is a procedure in which your doctor inserts a fine needle connected to a syringe, guided by ultrasound, into the cyst. We may also perform a serum estradiol measurement to confirm ovarian suppression.

Step 4 - Ovarian Stimulation

In general, we start ovarian stimulation after menstrual bleeding begins if the baseline ultrasound shows no significant cysts. We use several similar medications to stimulate follicle (egg) development. Bravelle, Pergonal, and Repronex are injected intramuscularly (into a large muscle under the skin). Lupron and the GnRH antagonists (Antagon and Cetrotide), Gonal-F, Repronex and Follistim may be injected just under the skin using a smaller needle.

Step 5 - Monitoring of Follicle Development

We monitor follicle development with a combination of vaginal ultrasound and hormone measurements (blood tests). We must perform these tests frequently during the ART cycle to ensure that you take the proper dosage of medication. We usually see patients every one to three days for an ultrasound and an estradiol level. This allows us to adjust the dose of medication in an effort to improve follicular development. When the largest follicle reaches 18 mm, we usually schedule daily visits for ultrasound exams and serum estradiol tests. The amount of medication we prescribe each afternoon depends upon the results of the blood tests and ultrasound exams. Typically, the lab results from the blood samples are not available until after 2:00 p.m. Patients must be available in the afternoon so that we can confirm the dosage of medication for that day.

Step 6 - Final Oocyte Maturation and hCG Administration

Human chorionic gonadotropin (hCG) is a hormonal drug that stimulates the final maturation of the oocytes. Determining the proper day for hCG administration is critical. If it is administered too early, few, if any, oocytes will be mature. If it is administered too late, the eggs within the follicles may be postmature (atretic) and will not fertilize. Optimal oocyte maturity occurs when we administer the hCG at the time when more than two follicles measure at least 20 mm and serum estradiol is greater than 500 pg/mL. The drug is given as a single intramuscular injection. The time of the injection is based on the time at which we schedule the egg retrieval.

Step 7 - Transvaginal Oocyte Retrieval

Oocyte retrieval is performed about 35 hours after hCG has been administered. An anesthesiologist usually administers intravenous medications (sedatives and pain relievers) in order to minimize the discomfort that may occur during the procedure. Side effects from these medications are much less common than with general anesthesia. Most patients sleep through the procedure but breath without assistance. A team member will discuss anesthetic options with you prior to your retrieval.

Once you are comfortable and relaxed, your physician will place the ultrasound transducer into the vagina. A guide attached to the transducer leads the needle through the wall of the vagina and into each follicle in the ovaries. Your physician will collect the oocytes and follicular fluid into a test tube for transport to the Embryology lab. The laboratory staff will examine the oocytes microscopically.

After the retrieval, you will be taken to a recovery room where you will be observed for 1~2 hours while the intravenous medications wear off. When you are fully awake, your vital signs are stable, and you have urinated, you will be released to go home. You may have some vaginal spotting and lower abdominal discomfort for several days following this procedure. Generally, patients feel completely recovered within 1~2 days. You should notify your physician immediately if you develop severe pain, heavy bleeding, or fever after the retrieval.

The number of oocytes retrieved is related to the number of ovaries present, their accessibility, and the number of follicles that develop in response to stimulation. Ultrasound provides only an approximation of the number of oocytes that one can expect to recover. On the average, 8~15 oocytes are retrieved per patient. More than 95% of retrievals result in the recovery of at least one oocyte.

Step 8 - Insemination of Oocytes

The Embryology laboratory staff examines the fluid aspirated from follicles for the presence of oocytes. We routinely aspirate all mature follicles in order to obtain as many oocytes as possible. Not every follicle contains an oocyte, and rarely, a follicle may contain more than one.

It is important to determine the maturity of the oocytes in order to time the insemination properly. The oocyte can only be fertilized during a short interval of about 12~24 hours. If the oocyte is either immature or postmature (too old), it may not be capable of fertilization or normal development. If immature oocytes are obtained at retrieval, they can sometimes be matured in the laboratory prior to insemination. Normal pregnancies have occurred with such oocytes.

Semen is usually collected by masturbation the morning of the retrieval. The staff will instruct you regarding time of collection and transportation to the office. On rare occasions, the laboratory staff may request a second semen sample. You must notify the staff beforehand if you are planning to leave town or will otherwise be unavailable after the first collection. We recognize the pressure that semen collection may generate under these circumstances. In many cases, some flexibility in the timing and even in the method of collection is possible. We also recommend semen cryopreservation (freezing) before oocyte retrieval as a backup or sometimes as the primary sperm source.

The laboratory staff prepares the semen specimen for insemination using techniques designed to separate the sperm from other material present in the ejaculate. As a result of this process, we select the most active sperm to inseminate the oocyte. We usually place about 10,000 sperm in a culture dish with each oocyte. The dish is placed into an incubator which maintains a specific temperature, pH, level of humidity, and concentration of carbon dioxide. After 12~20 hours, the laboratory staff may detect evidence of fertilization under the microscope. In our laboratory, approximately 70% of oocytes fertilize. This figure may be much lower for patients with severe male factor. It is extremely uncommon for couples without male factor infertility to experience complete lack of fertilization in IVF-ET.

Step 9 - Embryo Transfer

The embryo transfer procedure is usually performed three days after the oocyte retrieval. This procedure is nearly identical to the uterine measurement. Your physician will pass the same type of catheter gently through the cervix into the uterus and deposit the embryos into the uterine cavity along with an extremely small amount of fluid. You will require no anesthesia for the embryo transfer. You will be discharged after resting for two hours.

Several studies have indicated that maximal IVF-ET pregnancy rates occur in most cases with the transfer of two to four embryos. This depends on your age. Therefore, we usually transfer a maximum of four embryos. The transfer of five or more embryos may increase the likelihood of a multiple pregnancy, which increases the pregnancy risks for the woman and the fetuses. For those cases in which more than four embryos develop, programs should offer embryo cryopreservation. This allows them to store excess embryos for transfer at a later date.

Step 10 - Progesterone Supplements

You will administer progesterone daily beginning on the day of oocyte retrieval. Ordinarily, the granulosa cells in the follicle will produce progesterone following ovulation. During oocyte retrieval, some of these cells may be removed along with the oocyte. Supplemental progesterone helps prepare the uterine lining for implantation.

This daily medication will continue until your pregnancy test. If the test is positive, you may be advised to continue to take progesterone for several more weeks. This medication historically has been administered as an intramuscular injection, but vaginal and oral administration is also becoming an acceptable form of treatment.

Step 11 - Hormonal Studies and Pregnancy Test

We will usually perform a serum pregnancy test and a progesterone determination 10 days after the embryo transfer. On occasion, we may repeat tests every two to four days. If the test is negative, we will instruct you to stop the progesterone.

Step 12 - Early Pregnancy Follow-up

We will follow your early pregnancy for approximately two months. This close scrutiny is necessary to try to identify miscarriages or ectopic pregnancies and to counsel you regarding the status and treatment of multiple gestations. We generally will release you to your obstetrician at 8 to 10 weeks gestation, if all is going well. If you do not have an obstetrician already, we will help you select one.

Step 13 - Post IVF Consultation

If you are unsuccessful and do not achieve an ongoing pregnancy with your in vitro fertilization cycle, you should schedule a consultation with your physician to review the cycle and discuss future treatment options.

ART Medications

GnRH Analogs

Gonadotropin releasing hormone (GnRH) is a hormone produced in the brain that indirectly stimulates ovarian function. Analogs of GnRH are synthetic forms of this hormone which do not directly induce follicle development or ovulation but which have become very important in ART therapy. There are several advantages to using GnRH analogs. First, they make ovarian stimulation easier to regulate, since the patient's own hormone production is suppressed. Second, patients who are treated with GnRH analogs tend to produce a greater proportion of mature oocytes than patients who do not receive them. Third, GnRH analogs markedly decrease the risk of cycle cancellation for most patients. Prior to their use, 20~50% of IVF-ET cycles were canceled because patients would have a premature LH surge with spontaneous ovulation. Using GnRH analogs, the risk of cycle cancellation is less than 5%. Fourth, ovarian function can be suspended with GnRH analogs for variable periods of time if necessary, which allows for flexibility in cycle scheduling.

The major disadvantage of GnRH analogs is that most patients require more medication for ovarian stimulation.

This increases the cost of an ART cycle. For most patients, this disadvantage is far outweighed by the advantages. Occasionally, patients require adjustments in dosage of GnRH analogs or may respond better to treatment without analogs. Your doctor can discuss these issues with you.

Mechanism Of Action

Agonists of GnRH (such as Lupron) initially stimulate the pituitary gland to release all the stored gonadotropins (LH and FSH -the hormones that normally stimulate ovarian function). Over the course of a week to ten days, GnRH analogs suppress the production of any new LH and FSH. This effect appears to prevent the ovaries from receiving mixed signals from the patient's own LH and FSH and from the medications that we administer to stimulate follicle development. The result for many patients is a more synchronized development of mature oocytes.

New antagonists of GnRH are also available. These are started later in the cycle than Lupron and inhibit FSH and LH production.

Dosage and Monitoring

The GnRH analog we use most commonly is leuprolide acetate (Lupron). Lupron must be injected to be active. In ART therapy, we use a formulation of Lupron which can be injected just under the skin, in a manner similar to insulin injections for diabetes therapy.

The usual dosage of Lupron is 0.1 or 0.2 cc daily as a single injection. Menstruation usually occurs four to ten days later. During the time of actual ovarian stimulation, the dosage of Lupron is halved (e.g., 0.1 cc to 0.05 cc daily). Lupron is usually administered until the day of hCG administration. Some patients, because of their history or condition, are treated with a different dosage or schedule of Lupron. Your physician will advise you if these changes apply to you.

Another GnRH analog used in ART therapy is nafarelin acetate (Synarel). Synarel is administered as a nasal spray. The usual starting dose is two sprays twice a day. The timing of administration is identical to Lupron. The dosage of Synarel is usually halved (e.g., from two sprays twice a day to one spray twice a day) when ovarian stimulation is begun.

Adverse Effects

Adverse effects from GnRH analogs are uncommon. Occasionally, ovarian cysts may form during therapy. These usually resolve spontaneously. Rarely, cysts may grow so large as to cause abdominal bloating and pain. Even less common is ovarian torsion, in which the ovary twists and cuts off its own blood supply. Surgical removal of the ovary may be necessary in these very rare circumstances. Other adverse effects of GnRH analogs include headaches, mood changes, and altered sleep. Hot flashes may occur during prolonged therapy. Allergic reactions are rare. A slight redness and discomfort may occur at the Lupron injection site, and patients using Synarel may experience nasal stuffiness.

Over 300 inadvertent pregnancies have been reported in women who were taking GnRH analogs. Miscarriage and birth defect rates do not seem to increase. Some neurological problems have been observed in the children

born from pregnancies conceived while the mother was on GnRH analogs.

Gonadotropins

To increase likelihood of pregnancy through ART, multiple oocytes must be produced. This is accomplished through the administration of gonadotropins-hormonal medications that stimulate the ovaries. Stimulation can be achieved with a variety of drug regimens. Gonadotropin medications come in several forms, Repronex, Pergonal, Bravelle are combinations of FSH and LH. They replace a woman's own LH and FSH which are normally produced by the pituitary gland. Gonal-F and Follistim are preparations that contain only FSH. Gonal-F and Follistim are recombinant products which are made by genetically engineered cells. This process ensures uniform purity and potency. Because the dose of hormones we use in ART is greater than what the body normally produces, the ovaries typically develop more than one oocyte as occurs in a natural cycle.

Gonadotropins act directly on the ovary to stimulate the growth of follicles (the structures in ovaries which contain eggs). Granulosa cells within the follicles grow and develop which cause the follicles to enlarge and fill with follicular fluid. These developing follicles can be counted and measured using transvaginal ultrasound. As the follicles grow, they produce increasing amounts of estrogen, which can be measured with a laboratory blood test. Some physicians prefer one formulation or another. Your doctor can discuss this with you in more detail.

Dosage and Monitoring

Gonadotropins are packaged in vials containing 37.5, 75 or 150 International Units (IU). In the first cycle of IVF-ET we routinely administer 300 IU of gonadotropins daily for three days. This dosage may vary depending on the patient's history. We then see patients in the office for regularly scheduled transvaginal ultrasound examinations and serum estradiol tests. The dose of gonadotropins is then determined by the result of the ultrasound and estradiol tests. Most women require between seven to ten days of gonadotropin therapy.

Bravelle, Pergonal, and Repronex require intramuscular injection, usually into the muscles of the buttocks. Gonal-F and Follistim are administered subcutaneously, like an insulin or allergy shot.

Adverse Effects

Gonadotropin preparations are strong medications. Although rare, a potentially serious adverse effect of gonadotropins is ovarian hyperstimulation. Even after oocyte retrieval, the ovarian tissue may continue to grow in response to the prior gonadotropin stimulation. As the ovaries enlarge, discomfort and bloating may occur. Occasionally, an enlarged ovary may become twisted. This condition is referred to as ovarian torsion. When this occurs, surgery may be required to either remove the ovary or untwist it.

In addition to discomfort, women suffering from severe ovarian hyperstimulation may develop ascites (a collection of fluid in the abdomen or pelvis). This fluid enters the pelvis by leaking through blood vessels. Although rare, this condition can be severe enough to produce swelling of the abdomen and shortness of breath. Hospitalization is required in cases of severe ovarian hyperstimulation. Treatment for ovarian hyperstimulation usually consists of bed rest and intravenous fluids. On rare occasions it is necessary to drain fluid from a patient's abdomen. Hyperstimulation is more severe when pregnancy occurs, as the developing pregnancy produces the

hormone hCG, which stimulates the ovaries to continue to grow. Hyperstimulation can remain a potential problem for to 2~3 months during the pregnancy.

There does not appear to be any increased risk of birth defects in offspring of women who take gonadotropins compared to conceptions in the general population. However, there is a greater risk of early miscarriage in patients taking gonadotropins. Approximately 20~25% of gonadotropin-induced conceptions miscarry within the first trimester. Multiple pregnancies are another adverse effect of gonadotropin therapy. Approximately 25% of IVF-ET pregnancies are multiple. The risk of more than twins is about 5%.

Although not truly an "adverse effect," the cost of gonadotropins must be taken seriously. One ampule (amp) of 75 IU typically costs between $35 and $70. As these medications are commonly administered for seven to ten days, it is not unusual for the medication cost for a single cycle to cost $1,500 to $3,000. Some women have obtained gonadotropins in other countries. According to the FDA, it is illegal to import drugs from other countries for use in the United States. Some patients with poor response to stimulation have admitted to using imported gonadotropins.

In summary, gonadotropins are strong, effective medications for inducing follicle development. Their use must be monitored carefully, preferably with a combination of regular transvaginal ultrasound examinations and estradiol determinations. When administered and monitored carefully, the risk of adverse effects is acceptably low.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is an injectable medication that is administered to complete oocyte maturation. The brand names for hCG are Profasi, Ovidrel.

Novarel and Pregnyl. These medications come in 5,000 and 10,000 unit ampules. Typically a 10,000 unit ampule costs $40~$70.

Mechanism of Action

Human chorionic gonadotropin is structurally similar to the LH that is produced by a woman's pituitary gland. It acts on the ovary in a manner similar to a woman's own LH. Human chorionic gonadotropin, like LH, stimulates the final maturation of the oocytes in the follicle. It also stimulates progesterone production from the ovary after egg retrieval. This progesterone is important to prepare the uterus for implantation of the embryo.

Dosage and Administration

Human chorionic gonadotropin can be administered several different ways. We commonly administer a single injection of 10,000 units. Once hCG is administered, ovulation usually occurs in approximately 36 to 40 hours. We therefore routinely schedule oocyte retrieval at 35 hours after hCG. This helps ensure maximal egg maturity, which is important for fertilization and embryo development. Occasionally, several doses of 2,500 units (usually every three days) are administered after egg retrieval to stimulate progesterone production. If your response to stimulation is particularly exuberant, we may recommend decreasing the dose of hCG to 5000 units in an attempt to reduce the risk of ovarian hyperstimulation syndrome.

It typically takes 8~10 days for single injection of 10,000 units of hCG to be cleared from the blood stream. As hCG is the same hormone that is produced by a developing pregnancy, patients should not have a blood or urine pregnancy test sooner than ten days following the hCG injection. If a pregnancy test is performed earlier, it may measure the hCG that was given by injection rather than measure hCG produced by a pregnancy.

Adverse Effects

When given by itself, there are few, if any adverse effects to hCG. However, when given in conjunction with gonadotropins, ovarian hyperstimulation can occur. In fact, hyperstimulation is extremely rare if hCG is not administered.

Clomiphene Citrate

Clomiphene citrate (Clomid and Serophene) is an oral medication that is commonly administered to induce ovulation in women who do not ovulate regularly. We also use clomiphene citrate for minimal stimulation IVF-ET. Typically, each 50-mg pill costs approximately $5.00 to $8.00.

Mechanism of Action

Clomiphene acts within the brain to promote the production of the hormone, GnRH. As a result, the pituitary gland makes more FSH and LH, the hormones that stimulate ovarian function. In particular, the increased FSH stimulates more follicles in the ovaries to grow.

Dosage and Monitoring

For minimal stimulation IVF-ET, the usual dosage of clomiphene is 100 mg daily for five days, beginning on day three of the menstrual period. Follicle development in response to clomiphene is most accurately determined by ultrasound. Typically, you may take a cycle (pack) of oral contraceptive pills to regulate the start of your period before stimulation. We perform an ultrasound to examine the ovaries around the time you finish the oral contraceptives. The next ultrasound will be performed the day after the last clomiphene citrate dose. Additional ultrasounds will be performed (usually every other day or daily) until the day the largest follicle measures 20 mm or more in diameter. On that day hCG, 10,000 units will be injected intramuscularly in the evening. Oocyte retrieval will be performed 35 hours after the hCG injection. A urine ovulation predictor kit may be used in addition to ultrasound monitoring. These kits detect large amounts of LH in the urine. Once a follicle is mature, the pituitary releases a large amount of LH, called an LH surge. Most women will ovulate within 24 hours of detecting a urinary LH surge. When a spontaneous LH surge is detected in a minimal stimulation cycle, the cycle may be canceled as it is difficult to time the egg retrieval to obtain a mature egg prior to ovulation.

Adverse Effects

Severe adverse effects are uncommon with clomiphene citrate. First, as multiple follicles can sometimes develop, multiple pregnancies may occur. This complication is uncommon in minimal stimulation IVF-ET. Another complication is ovarian cyst formation. While these cysts usually resolve spontaneously, they may cause bloating

and abdominal discomfort. On rare occasions, these cysts may rupture causing abdominal pain. Approximately 10% of women who take clomiphene citrate experience hot flashes, which may disrupt sleep. A small percentage of patients (less than 5%) report some visual changes during clomiphene citrate therapy. Some patients describe blurred vision, while other patients describe seeing spots or flashes of light or after images. You should report any of these adverse effects to your physician.

There does not appear to be any increased risk of birth defects in offspring of women who take clomiphene citrate. In large studies, the risk of birth defects does not appear to be greater than that noted in the general population. Likewise, the risk of miscarriage in women taking clomiphene does not appear to be increased over that noted in the general population.

There has been recent concern about an association of the use of clomiphene with the subsequent development of ovarian cancer. At this time, information about this subject is very limited. While several studies have suggested an increased risk of ovarian cancer in women who have taken clomiphene citrate, these studies have been widely criticized for many reasons. If the risk of ovarian cancer in women taking clomiphene is increased at all, this increase appears small. The lifetime risk of ovarian cancer in all women is approximately 1 in 70. If the preliminary evidence turns out to be true, the increased rate of ovarian cancer in patients taking clomiphene may be as high as 3 to 4%. This increased risk of ovarian cancer in patients taking clomiphene seems to occur only in women who have taken clomiphene for greater than one year (12 cycles). The risk has not been observed in women who have a successful pregnancy from clomiphene therapy.

Infertility also is a risk factor for ovarian cancer and it is not clear whether there is increased probability is any worse with clomiphene.

Minimal Stimulation IVF-ET

The first IVF-ET baby, Louise Brown, was born in 1978 and was conceived without the benefit of any fertility drugs. In the years that followed her birth, the experience of most clinics was that the success of IVF-ET was improved by administering injectable fertility drugs to the woman. Thus, the use of injectable fertility drugs became the routine in IVF-ET. One disadvantage of injectable drugs is that they substantially increase the cost of IVF-ET. Not only are the injectable drugs themselves expensive; but their use necessitates more office visits and testing in the days preceding oocyte retrieval and more work for the IVF-ET laboratory personnel after retrieval to care for the resultant increased number of oocytes. In order to give some chance of pregnancy to infertile couples who simply cannot afford conventional IVF-ET with injectable drugs, some clinics have continued to offer IVF-ET without injectable drugs, which significantly decreases the total costs of the procedure, as well as the success rate.

There are several slightly different ways in which IVF-ET can be performed without the use of injectable gonadotropins. One is "minimal stimulation IVF-ET" in which the woman takes the relatively inexpensive oral fertility drug clomiphene citrate (Serophene or Clomid) early in her cycle. The other way is to take no fertility stimulants whatsoever, and simply aim to retrieve the oocyte produced in the woman's natural cycle. The maximum "take home baby" rate (chance of having an actual living child) of minimal stimulation IVF-ET is generally believed to be 10~15%. In the U.S.A. in 1998, the most recent year for which figures are available, the "take

home baby" rate of natural cycle IVF-ET in women less than 40 years old was 8.5% per cycle started, and 13% per oocyte retrieval procedure. The particularly low success rate of natural cycle IVF-ET may reflect a selection bias. That is, physicians may recommend natural cycle IVF-ET to patients who have previously demonstrated poor responsiveness to fertility drugs (thinking the fertility drugs will be of no benefit to them), thereby effectively selecting patients for natural cycle (IVF-ET) who have a particularly poor chance of becoming pregnant. Even if this is the case, it is unreasonable to expect any more than a 10~15% take home baby rate from minimal stimulation IVF-ET with current technology and methods.

A modest amount of preliminary testing is necessary prior to proceeding with minimal stimulation or natural cycle IVF-ET. Most of the time, much of this testing will already have been performed as part of the evaluation which led to the physician's recommendation that the patient have IVF-ET. Necessary preliminary blood testing would include blood type, Rh and antibody screen, a test for syphilis and a test for immunity to rubella (German measles). We also require blood tests for hepatitis and HIV (AIDS) for both the patient and her partner. The patient should have had a hysterosalpingogram, hysteroscopy, or saline infusion sonogram (SIS), as well as a vaginal ultrasound, to evaluate the normality of the uterine cavity. A semen analysis (sperm count) is essential. Either a postcoital test or sperm antibody testing (done on husband's semen and wife's blood) may be needed. Finally, a practice embryo transfer, also referred to as a "uterine measurement" (see previous discussion) will be performed. In this procedure, the physician passes the flexible plastic embryo transfer catheter through the cervix and into the uterus, thereby determining the depth and direction of catheter passage which will be ideal for the actual embryo transfer. Most women find that the practice embryo transfer is no more uncomfortable than a routine pelvic exam and Pap smear.

The patient undergoing minimal stimulation IVF-ET will take birth control pills in the cycle before stimulation. We will perform a baseline ultrasound around the time of your expected period after the pills. If that ultrasound is normal, the patient will take clomiphene (50 mg), two tablets by mouth daily, cycle days three through seven. The next ultrasound will be performed on cycle day eight. Several more ultrasounds will be performed in subsequent days, the exact number and frequency depending on the rate of growth of the oocyte-containing structures (follicles). Usually, no blood work is needed for monitoring for couples undergoing minimal stimulation IVF-ET. On the date that the ultrasound indicates that the largest follicle has an average diameter of 18~20 mm, human chorionic gonadotropin (hCG) 10,000 units intramuscularly will be injected in the evening. Oocyte retrieval will be performed 35 hours after the hCG injection. A GnRH antagonist and/or gonadotropins may be administered late in the cycle to suppress an unwanted spontaneous LH surge.

The basic techniques of oocyte retrieval, insemination, embryo culture, embryo transfer, progesterone supplementation after embryo transfer, and pregnancy testing after embryo transfer are very similar or identical to those used in conventional IVF-ET and are discussed elsewhere. Because patients undergoing minimal stimulation or natural cycle IVF-ET have only very few or one follicle(s), it may be possible to perform the oocyte retrieval procedure without the services of the anesthesiologist. Your physician can provide some medications for pain relief during the procedure, and most patients do well with this approach. You should discuss this matter with your physician before making a final decision.

INSTRUCTIONS FOR COLLECTION OF SEMEN

In order to obtain sperm of optimal quality it is important that you follow these instructions carefully.

1. Do not have any sexual activity (ejaculation) for at least two days before obtaining the semen sample.
2. We will give you a sterile, nontoxic plastic jar for the semen specimen. Other containers are not acceptable.
3. The sample should be obtained in the office. A private collection room is available.
4. If you have a problem with sample collection by masturbation, let us know and we will provide a special nontoxic condom for collection by sexual intercourse. Commercial condoms cannot be used because they kill the sperm.
5. Do not use lubricants (saliva, soap, lotion, oil, etc.) to collect the specimen. These can kill the sperm.
6. We will give you a label to fill out and attach to the container. It is critical that this label be filled out completely. Please keep the jar closed tightly to prevent leakage. Let us know if any of the specimen was lost or spilled.

Masturbation is the most frequent method used to produce a sperm sample on the day of oocyte retrieval. Occasionally, intercourse using a special condom or electroejaculation are required for successful collection. Some men are unable to ejaculate or have no sperm in their semen. In these special cases, urologists can often obtain usable sperm from the testicle or the epididymis utilizing a minor surgical procedure.

We strongly recommend that all men who are able to ejaculate and produce sperm preserve a semen sample by cryopreservation (freezing) several days prior to the day of egg retrieval. This frozen sample can be an important insurance policy if problems arise in the production or quality of the sample on the day of egg retrieval. These back-up sperm will be discarded if not needed on the day of retrieval unless otherwise specified.

Oocyte retrieval and embryo transfer

Day of hCG Administration

1. Lupron is discontinued when hCG is given.
2. hCG is given when three or more follicle are 20 mm or greater in diameter.
3. 5,000 or 10,000 units hCG are given intramuscularly at the time indicated by the nurse, depending on the time of retrieval.
4. The morning after hCG an estradiol level is drawn.

Day Before Retrieval

1. Nothing to eat or drink after midnight.
2. Husband will receive instructions regarding collection of a semen specimen, usually one hour prior to or following the retrieval. Most specimens are collected in the fertility office. Please review the information sheet for semen collection.

Day of Retrieval

1. Wear loose clothing.

2. Avoid jewelry, makeup, perfume and cologne.

3. Report as instructed at the appointed time.

4. Someone should accompany you to the IVF Center. This person will keep your belongings during the procedure and must escort you home after you are discharged.

5. An IV will be started and the procedure will be performed on site at the IVF center.

6. All good oocytes will be fertilized in the laboratory.

Following Retrieval

1. Following oocyte retrieval, you will be discharged home within approximately 1~2 hours.

2. You may not be fully alert for several hours after discharge. Do not drive after being discharged on the day of retrieval.

3. Limit your activity for 24 hours after the procedure.

4. Medications

A. Medrol 16 mg once a day for four days will be started on the night of retrieval.

B. Tetracycline 250 mg four times a day for four days will be started on the night of retrieval.

5. Call the office if you experience any of the following problems:

A. Difficulty breathing

B. Excessive bleeding

C. Severe pain

D. Fever

E. Any other disturbing problems

Day After Retrieval

1. A report concerning fertilization of the oocytes will be given by telephone 24 hours after the insemination has occurred.

Embryo Transfer

1. Embryo transfer is performed at the IVF Center 3 days or 5 days (blastocyst) after oocyte retrieval.

2. Valium 10 mg should be taken approximately one hour prior to transfer.

3. Avoid jewelry, makeup, perfume and cologne.

4. Following embryo transfer you will be discharged home within approximately 1~2 hours.

Progesterone Supplementation

1. Progesterone may be administered intramuscularly, orally, and/or vaginally depending upon your physician's instructions.

2. Progesterone 25 mg intramuscularly (IM) is given on the day of oocyte retrieval and the next day 25 mg or 50 mg, depending on the estrogen level.

3. Progesterone increases to 50 mg IM on the day before transfer and is maintained until a negative beta hCG

or until 10 weeks with a viable pregnancy.

4. The dosage of progesterone may vary in some instances based on the patient's history.

Pregnancy Follow-up

1. An initial pregnancy test is obtained 10 days after the embryo transfer and is repeated as necessary.

2. If pregnant, an ultrasound scan is recommended approximately 3½ weeks after embryo transfer to assess the pregnancy.

3. Patient will return to her obstetrician after ultrasound confirmation of a viable pregnancy to continue prenatal care. Non-local patients should report pregnancy results from their local obstetrician.

MICROMANIPULATION

Advances in microscopic equipment and knowledge about oocytes, sperm and embryos have lead to the development of new techniques in ART. Micromanipulation refers to the microscopic treatment of individual oocytes, sperm, or embryos in an effort to improve fertilization and/or pregnancy rates. These techniques require specialized equipment and personnel. Currently the most common micromanipulation techniques used are intra-cytoplasmic sperm injection (ICSI), which is used to assist fertilization in cases of severe male factor infertility, and assisted hatching which is used in an effort to facilitate implantation of the embryos.

Intracytoplasmic Sperm Injection

The ICSI technique has been developed over the past 10 years to treat cases of severe male factor infertility. Candidates for ICSI may include patients with severe reductions in sperm number or motility, regardless of cause, and patients with a history of failure of fertilization in conventional in vitro fertilization-embryo transfer (IVF-ET). The ICSI technique may also be used to achieve fertilization using surgically extracted sperm from patients with anatomic or surgical conditions (such as vasectomy) that prevent sperm from entering the ejaculate. In all these cases, donor sperm or ICSI may provide the only options for conception.

The ICSI technique attempts to achieve fertilization by the direct injection of a single sperm into the cytoplasm (interior) of the egg. This is accomplished in the following manner. Mature eggs are freed of surrounding cells by a combination of enzyme treatment and microdissection. Using special micromanipulation equipment, the eggs are individually injected with a single sperm. Injected eggs are returned to the laboratory incubator and are treated thereafter as in conventional IVF-ET.

The mechanical placement of a sperm into the egg bypasses all the normal processes of sperm-egg interaction that occur. These processes normally lead to the selection of the single fertilizing sperm based on its ability to pass through the many layers of cells surrounding the egg, to contact and bind to the egg coating (zona), to penetrate this coating, to contact and merge with the egg cell membrane and ultimately to be drawn into the egg where the genetic material in the sperm joins that of the egg. These interactions help assure that a viable sperm is selected by the egg for fertilization. Even when conventional IVF-ET is performed, the egg is exposed to tens of thousands of sperm. In sperm injection, it is the laboratory that chooses the best appearing sperm. We rely on the

size, shape, and motility of sperm to choose the ones for injection. While these characteristics are useful, they do not guarantee that the sperm selected for injection is normal.

The potential consequences of injecting a normal appearing sperm, which is in fact abnormal, include the development of a genetically abnormal embryo. Previous experience suggests that most abnormal conceptions do not implant or develop in the uterus. The incidence of congenital abnormalities (birth defects) following ICSI appears to be no higher than that of the general population. This observation is based on the experience of several thousand babies born worldwide following ICSI. Despite this reassurance, it is prudent to regard ICSI as an experimental technique not without risk since long term follow-up of offspring (regarding, for example their fertility, is unavailable). Recent evidence suggests that some forms of severe male factor infertility are genetic and may be passed on to male offspring through the ICSI procedure. In addition, you must realize that within the normal human population a certain percentage (approximately 4%) of children are born with physical or mental defects (congenital abnormalities), and that the occurrence of such defects is beyond the control of physicians.

Apart from the possible genetic consequences of selecting an abnormal sperm for injection, the physical trauma to the egg resulting from sperm injection can lead to degeneration of the egg, decreased fertilization rate, poor or arrested embryo development following fertilization, and reduced chance of a successful pregnancy outcome.

The benefit of ICSI is that it provides a way to treat extreme cases of male factor infertility which otherwise would remain untreatable. Experience shows that fertilization in vitro requires a minimum number of motile, normal shaped sperm. The chance for fertilization in vitro becomes very low when this minimum number of sperm is not available. Theoretically, only a few sperm are necessary to undertake ICSI. To date, however, the successful outcome of sperm injection is neither predictable nor consistent for all patients. The alternatives to ICSI for treatment of severe male factor infertility are limited. Sometimes all the eggs can be placed in one culture dish with all the available sperm. This is known as "clutch insemination", which differs from conventional IVF-ET in which each egg is inseminated with a separate batch of sperm. A minimum number of actively moving, normal shaped sperm is still required for fertilization to occur with clutch insemination. Another option is donor sperm. Use of donor sperm normalizes the success of conventional IVF-ET in couples with severe male factor infertility. In cases where male factor is the only diagnosis, pregnancies with donor sperm can be achieved through timed insemination, a treatment far less expensive and complicated than IVF-ET.

There is no guarantee that these inseminations will result in fertilization or a pregnancy. Coexisting female fertility problems can decrease the likelihood of conception. In general, the results of intracytoplasmic sperm injection decline with increasing age of the female partner. This probably reflects the progressive decline in oocyte quality with age of the patient and the older egg's decreased ability to survive the invasiveness of sperm injection. A separate consent form and additional charge are required for ICSI.

Assisted Hatching

Normally, embryos are transferred to the uterus three days after retrieval. Usually the embryos consist of six to eight cells at this stage. After transfer, the embryo must continue to develop to the blastocyst stage (a hollow ball of about 100 cells) before implantation can occur. This development takes several days. Immediately before implantation, the blastocyst must "hatch" from the zona coating which originally enveloped the oocyte. To assist

the hatching process, we micromanipulate the embryos immediately before embryo transfer. This involves dissolving part of the zona coating with an acid solution. Trained personnel using specialized micromanipulation tools must perform this under the microscope. There is a small risk of damage to the embryos from the procedure. It is not clear which patients are the best candidates for assisted hatching, and we therefore use the assisted hatching procedure on all embryos to be transferred.

CRYOPRESERVATION OF EMBRYOS

Embryo cryopreservation is another important part of successful ART programs. Cryopreservation affords patients several advantages. Couples can cryopreserve embryos in excess of the ones that are usually transferred during an ART cycle. These embryos provide a second or even third opportunity for pregnancy without undergoing another ovarian stimulation and retrieval.

Those embryos that meet developmental criteria for appearance and rate of growth can be frozen at any of several stages in their development. The freezing process is computer controlled and employs special solutions to protect the fertilized eggs from damage. Frozen embryos are stored at -196°C or approximately- 400° F (below zero). Prior to ART you and your partner must sign a consent form indicating what we should do with any additional embryos. Current choices are disposal or cryopreservation for future use. We will store your embryos for a maximum of two years. After that time they must be transferred to a long-term storage facility. During that time you must keep us informed of your current address at least annually. Policies on cryopreservation may vary from center to center.

As with cryopreserved semen, many embryos do not survive cryopreservation and thawing. Those that do survive may function less well than do fresh embryos; that is, they may implant and produce ongoing pregnancies at a somewhat lower rate than fresh embryos.

We will usually transfer up to four embryos during this procedure. Embryos can be transferred successfully during an artificial cycle in which you take Lupron, estrogen, and progesterone.

Cryopreserved embryo transfer

For patients undergoing cryopreserved embryo transfer we can create an artificial cycle. This involves treatment with Lupron, estrogen patches, and progesterone. This treatment is well established. If you have been pregnant since your initial freezing of the embryos, a repeat trial transfer or uterine measurement will need to be done. In addition, blood work, physical examination, Pap smear, cervical culture, and hysterosalpingogram must be updated or have been performed within one year of he procedure.

The frozen embryo transfer involves four steps:

1. Hormonal therapy including Lupron, estrogen patches (in some cases pill or injection), and progesterone (injection or vaginally)

2. Embryo transfer will be scheduled when hormonal tests confirm that the uterus is ready to receive the embryos. This occurs approximately 18 days after estrogen patches are started. Progesterone supplementation

will be continued.

3. A pregnancy test is performed 10 days after embryo transfer.
4. Follow-up consultation.

Hormonal Therapy

It takes two menstrual cycles to prepare the uterus for embryo transfer. Oral contraceptives may or may not be used. Daily subcutaneous injections of Lupron will be taken to prevent ovulation during the cycle in which you will receive your embryos. Next, estrogen patches will be used to thicken the lining of the uterus. You will have been on estrogen patches approximately 18 days at the time of embryo transfer. Blood work and ultrasound will be done to confirm that the uterus is ready for you to receive your embryos. Progesterone injections will be started approximately three to four days before the embryo transfer. Estrogen patches and progesterone will be continued until pregnancy status is known. The IVF team will provide you with a detailed calendar as well as instructions.

Embryo Transfer

Embryo transfer is usually performed on the fourth day of progesterone therapy. Two to four embryos will be transferred during each frozen embryo transfer cycle. However, this number is flexible and your physician will discuss this issue with you.

The actual procedure is identical to the transfer of embryos following in vitro fertilization-embryo transfer with fresh embryos. A small plastic catheter is passed gently through the cervix into the uterus. The embryos are deposited into the cavity along with a small amount of fluid. You will be discharged after resting for two hours. No anesthesia is required. However, we do give you an oral dose of Valium, which will be taken approximately one hour before the transfer procedure.

Hormonal Studies/Pregnancy Test

We will perform a serum pregnancy test 10 days after the embryo transfer. We also measure serum progesterone. We will be repeating the pregnancy test every two to four days. If the test is negative, progesterone will be discontinued and a period usually starts within a few days.

Follow-up Consultation

If the pregnancy test is positive, we will perform a vaginal sonogram approximately three weeks later. At this point, we are usually able to identify the number of embryos and can often see a heart beat. If the procedure is unsuccessful, you should schedule a post IVF consultation with your physician to discuss further treatment options.

Donor Oocyte Therapy

In recent years, with the standardization of IVF-ET techniques and the development of ICSI (intracytoplasmic sperm injection) for severe sperm disorders, it has become clear that the single most important factor in predicting

the success of IVF-ET is the age of the female partner. For patients under 30, success rates of 30~50% per oocyte retrieval can legitimately be expected; for patients over 40, realistic success rates are only 5% to at most 15%. Oocytes from younger women possess greater fertility potential, and this potential is utilized in donor oocyte therapy. In this therapy, oocytes from another woman (the donor) are fertilized with the patient's (the recipient) husband's sperm, and the resultant embryos are placed in the recipient's uterus. The oocytes are stimulated and retrieved from the donor using routine IVF-ET techniques. The donor may be known to and recruited by the recipient (non-anonymous donation), or instead may be unknown to the recipient, having been recruited by the IVF-ET program (anonymous donation). Anonymous oocyte donation may occur in two forms. A woman who needs IVF in order to conceive may volunteer to share half of her oocytes with a recipient. These women typically have compromised fallopian tubes, pelvic adhesions, or a husband who has a severe male factor requiring ICSI. This method provides half of the oocyte complement for each the donor and the recipient. In the event of an odd number of oocytes, the recipient obtains the extra egg since she has absorbed the major financial burden. The donor will pay for her own prerequisites in this type of donation agreement. Another form of anonymous donation occurs when a young woman donates all of her oocytes to a recipient during a particular cycle. This woman is not trying to achieve pregnancy and will therefore be reimbursed for her time and effort. In this case the recipient is responsible for all prerequisite costs for the oocyte donor as well as the cycle. Each recipient couple must decide the type of donor with whom they are most comfortable. In cases where a young (less than 33 years old) donor is utilized, high success rates, comparable to those achieved in women of similar age using their own oocytes, can be expected.

Candidates for Donor Oocyte Therapy

There are four main indications for donor oocyte therapy.: 1) ovarian failure. This can be due to a wide variety of different causes, including radiation, chemotherapy, surgical removal of the ovaries and a variety of disease states which cause or are associated with ovarian failure; 2) women who carry some serious genetic disease who wish to diminish the chance that the disease will be passed on to their offspring; 3) women whose age is sufficiently advanced so that their fertility potential is impaired significantly; abd 4) women who have had poor quality embryos during previous IVF cycles.

Laboratory Testing and Genetic Screening

A short time before initiating a treatment cycle, the oocyte donor undergoes a very thorough battery of tests for sexually transmitted diseases. Obviously, by screening for sexually transmitted diseases, we seek to minimize the chances that such a disease will be passed from the donor to the recipient (and possible fetus) by the oocyte donation process. Despite these thorough precautions, a very small risk of transmission of disease from donor to recipient remains. In addition to sexually transmitted disease testing, the donor's blood type will be determined. The donor's blood type may be a factor in making the match between donor and recipient (see below).

All donors have a very thorough evaluation of their medical and family history. The donor is required to fill out a multi-page form detailing her family history. The IVF personnel and a genetic counselor for the oocyte donation program review this form and other aspects of the donor's genetic and medical history prior to acceptance of the

donor into the program. The genetic counselor sometimes recommends additional testing for the donor. Even with this intensive screening, there remains a small risk that a baby resulting from the oocyte donation process will suffer from a genetic disease. Overall, a baby conceived through oocyte donation will have the same risk of birth defect, trivial or catastrophic, genetic or nongenetic, as the human population as a whole, namely 3~5%.

Matching Donor and Recipient

We understand that choosing to receive donated oocytes carries with it a simultaneous sacrifice of hope for pregnancy with one's own oocytes, and this can be a feeling of great loss. There are probably many characteristics that you hope your oocyte donor will possess, and you probably desire that your oocyte donor will possess many of your own characteristics. The IVF team do what it can to assist you in selecting a donor who meets your most important expectations, but you must understand that we will always face certain limitations. One requirement of most anonymous donation program is that anonymity be maintained. In order to accomplish this, we are limited in the amount of information that we can give you about the donor. We cannot tell you much more than donor's height and weight, hair color and eye color, race, blood type, age and duration of formal education. We also give you as much family medical history as we know. You have the right to be as specific as you like about the characteristics of the donor, but you need to understand that the more specific you are, the longer the entire process may be delayed. Obviously, if your criteria are extremely specific and detailed, we may never find a donor who meets your expectations. It is the impression of the oocyte program that women who agree to donate their oocytes tend to be upbeat, energetic, resilient and altruistic. If they did not have these personality characteristics, they probably would not be willing to undergo the discomfort and risks involved in oocyte donation and IVF in the first place. Thus, to at least a small extent, the process of oocyte donation tends to select from women with these favorable personality characteristics. Most donors are women who are attempting conception through IVF themselves.

The blood type of the recipient, donor and recipient's husband are factors that can play some role in the matching process. Blood typing at its most basic level is defined by two separate typing systems. One is referred to as the ABO system. Four different types exist in this system, A, B, AB, and O. The other basic blood typing system is the Rh type. Only two Rh types are common, positive and negative. Thus, a routine blood type is described as one of the four ABO types and one of the two Rh types. The main element of the blood typing system, which has the potential to affect the health of a pregnant woman's baby, is the Rh-negative type. Serious compromise of a baby's health can occur when an Rh-negative woman is carrying an Rh-positive fetus. With modern obstetrical treatment, such complications are uncommon, but they still exist. There are two ways an Rh-negative woman can have an Rh-positive baby. One is if the father of the baby is Rh positive, and the baby inherited Rh positivity from the father. The other way this can happen is if an Rh-negative woman receives an oocyte from a donor who is Rh positive, and the genetic makeup of the oocyte confers Rh positivity on the resulting fetus. Thus, practically speaking, the main situation in which the blood type of the egg donor can pose increased risk for the recipient is when both the recipient and her husband are Rh negative. In this circumstance, the use of an Rh positive donor would expose the recipient's fetus to a risk of Rh incompatibility that would not have existed had the woman used her own eggs or received eggs from an Rh negative donor.

Differences in ABO type between mother and fetus pose little risk to the health of the fetus. Therefore, use of an oocyte donor whose oocyte might produce a pregnancy, which is different from ABO type of the recipient and husband, is not such a serious medical matter. Although ABO incompatibility is of negligible importance medically, we understand that to some recipient couples it may still be an important factor to match, so that genetically impossible differences in ABO type between parents and child are not revealed later in life.

Treatment of the Oocyte Donor

In general, stimulation of the oocyte donor's cycle is brought about using a similar regimen of drugs that a woman using her own oocytes for in vitro fertilization-embryo transfer is commonly given. Late in the cycle which precedes ovarian stimulation, the donor is started on daily treatment with one of two drugs, Lupron or Synarel, usually the former. Daily injections of Lupron will continue for a total of nearly three weeks. After the donor's period has started, daily intramuscular injections of a pharmaceutical gonadotropin preparation, such as FSH and HMG, will be added to the daily Lupron injections. Various brands of these hormones can be used. Generally, the donor will receive daily gonadotropin injections for a total of seven to twelve days. During the time that the donor is receiving the gonadotropin injections, she will have frequent vaginal ultrasound examinations and blood drawing for determination of estradiol (E2) level. When ultrasound and blood testing indicate that development of the follicles (follicles are the ovarian structures that contain the oocytes) is optimum, the donor receives an intramuscular injection of a different pharmaceutical medication called human chorionic gonadotropin (hCG). Two days (35 hours) after hCG injection, oocyte retrieval is performed. We will need a sperm specimen from the recipient's partner on the day of the retrieval, because the oocytes are inseminated on this day. Transfer of fertilized eggs (embryos) to the recipient's uterus is generally performed three days after the oocyte retrieval. Sometimes embryo transfer is delayed until five days after oocyte retrieval, based upon recommendations by the embryologist and physician team.

Treatment Regimen for Recipients

In general, we try to arrange for recipients to have a "fresh" as opposed to frozen embryo transfer. In order to do this, the recipient's cycle must be manipulated to synchronize her with the donor. A combination of two or three hormonal medications is used to modify the recipient's cycle.

Recipients who have regular menstrual cycles and bleeding on their own will take a medication which suppresses their own cycle. Sometimes oral contraceptives will be used to precede Lupron or Synarel administration. A few days before the recipient's period is expected to start, she is started on Lupron to suppress her natural cycle. A short time after her period starts the recipient will begin taking estrogen patches in addition to the Lupron. The formulation of estrogen that works best for our purposes, is the Vivelle 0.1 patch or its equivalent. This is applied to the abdomen or buttocks for absorption through the skin. These patches are changed every other day. The recipient will take Lupron and estrogen patches while waiting for the donor's cycle to come into synchrony with hers. When the donor's cycle has "caught up" with the recipient's, a simulated (artificial) 28 day menstrual cycle will be created in the recipient with the hormonal medications. To do this, the recipient takes an increased dose of patches as the donor stimulates. We perform blood tests for hormone levels and/or an ultrasound as oocyte

retrieval approaches to ensure an appropriate response. Lupron treatment will continue throug- hout this time. On the morning after oocyte retrieval, progesterone treatment is begun. Progesterone is given usually as a daily intramuscular injection of a preparation of progesterone in oil. The day before embryo transfer, Lupron is discontinued. The recipient will continue taking Vivelle and progesterone at least until the day her pregnancy test is performed. Fresh embryo transfer will be performed 3~5 days after oocyte retrieval. A sensitive blood pregnancy test will be performed on the 10th day after embryo transfer. If the recipient is pregnant, patches and progesterone treatment will be continued through the twelfth week of pregnancy.

Recipients who have complete ovarian failure and have no spontaneous menstrual cycles will not have to take Lupron, but otherwise will take the same regimen of medications just described.

In most instances a "trial cycle" is not performed to evaluate endometrial lining prior to the actual synchronized cycle. It has been our experience that endometrial thickness and hormonal levels during most patients' artificial hormone cycle are adequate for implantation. In the rare instance that the physicians feel that the endometrial lining is not adequate for embryo transfer, a recommendation for freezing embryos and doing a trial cycle prior to embryo transfer is made. This has proven to be a policy that is both cost effective and time saving for the recipient without compromising success rate.

Gestational Carriers

In some instances a couple may require the assistance of a gestational carrier to achieve a successful pregnancy. Gestational carriers differ from true surrogates in that they have no genetic link to the baby they will carry. The commissioning couple themselves will provide the embryo through IVF. As with oocyte donation, the best statistics occur when the embryos are transferred during a fresh cycle, requiring that the women and her gestational surrogate be synchronized as with oocyte donation. Some states have laws that address surrogacy and you should have this checked out. For example, Florida law requires that a woman have a medical indication for a gestational carrier to be utilized. The most common indications include a woman who has congenital absence of the uterus, prior surgery to remove her uterus, severe scarring of the uterine cavity, or a medical history that precludes pregnancy. In addition to meeting the medical requirement, a separate legal contract is required before treatment can begin. Programs may or may not have ready access to a group of potential gestational carriers. Generally, however, they can provide resources for investigation. Once a gestational carrier has been identified and the medical and legal prerequisites completed, treatment can proceed.

QUESTIONS AND ANSWERS

Q. Does ART damage the ovaries?

A: There is no evidence to suggest that laparoscopy and/or oocyte retrieval damages the ovaries. There is one report that suggests that infertile women who take fertility drugs and do not get pregnant have an increased risk of ovarian cancer. However, the study did not collect information on the type of drugs used, and the control (comparison) population may not have been selected accurately. The fertility drugs used in ART have been in use over 30 years, and other studies have suggested no increased risk. In most cases, the age of menopause does not

appear to be altered after ovarian stimulation.

Q: Why is the success rate with ART so low?

A: Studies of human reproduction indicate that for a couple with proven fertility, the likelihood of conception is only 20% per month. ART affords couples with infertility factors similar chances for conception.

Q: We're concerned about multiple births from ART. Should we just have one embryo transferred?

A: Any time more than one embryo is transferred, the chance for multiple pregnancy exists. In fact, about 25% of births from ART are twins, a rate much greater than in the general population (1 in 80 pregnancies). Triplets and quadruplets have also been conceived through ART. However, the majority of ART pregnancies (70%) are singletons, and the chance of any pregnancy with ART increases with the number of embryos or oocytes transferred. Success rates appear to peak on average with transfer of three or four embryos. We will discuss the options and implications of transferring fewer than four embryos, but in general we will not recommend transferring just one. In some programs, selective reduction is available to couples who conceive multiple gestations. Your physician can provide you with more information about this procedure. Identical twins can also occur with ART, the result of two babies from one egg.

Q: Is there an increased chance of birth defects if I become pregnant through ART?

A: No. The risk of congenital anomalies in children conceived through ART is the same as the risk in the general population. Chromosome abnormalities, such as Down's syndrome also occur at a rate similar to the general population.

Q: I had my tubes tied (tubal ligation) several years ago. Would I be a candidate for IVF?

A: Although surgical reversal of tubal sterilization might be a better option, IVF-ET is still a consideration, especially in older women or in couples with male factor infertility. The success rate is greater for ligation reversal than for a single cycle of IVF-ET, although the results of IVF-ET are obtained more rapidly than ligation reversal. If ligation reversal has been attempted and has failed, IVF-ET represents the best option. Cost and other factors (such as type and location of the ligation) involved in surgical reversal must be considered when making this decision.

Q: Does insurance cover the procedure?

A: Unfortunately, most insurance plans do not cover ART procedures. Some programs cover portions of the therapy. The IVF staff can help you determine your level of coverage. We strongly recommend you do this prior to starting ART therapy.

Q: How many days does the entire procedure take?

A: The entire procedure takes approximately six weeks. However, we only need to see you intensively over a two-week period. These details are discussed in the "Step by Step" sections. -

Q: Can we have intercourse while attempting ART?

A: Yes. We recommend that the man abstain from ejaculating for at least 48 hours preceding egg retrieval. This precaution assures that the semen sample for ART is of optimal quality. Near the time of egg retrieval, the ovaries can be enlarged and tender, which can make intercourse uncomfortable.

Q: What if I ovulate before the retrieval?

A: Virtually all cases of premature ovulation are now prevented by the use of GnRH analogs. In rare cases in which Lupron or Synarel are not used, we perform an ultrasound prior to retrieval to make sure the follicles are intact. In the uncommon case of ovulation, we will not perform retrieval because the quality of the remaining oocytes is adversely affected.

Q: Will scar tissue around my ovaries make it impossible to retrieve oocytes?

A: No, the oocyte can usually be retrieved by transvaginal aspiration even when the ovaries are covered with scar tissue. In rare cases, scarring pulls the ovaries out of the normal pelvic position. This condition can be identified with ultrasound before ART is undertaken.

Q: How much activity is recommended after ET?

A: We recommend a fairly quiet 24 hours after ET. Thereafter, most patients resume their normal routines. Strenuous exercises, running, etc. should be avoided until a pregnancy test has been performed.

Q: After embryo transfer, how long must we wait until we have intercourse without risk to the embryo?

A: No one knows for sure. We recommend abstinence for a minimum of 48 hours after transfer.

Cancellation

The IVF cycle will be cancelled if specific criteria occur:

1. Abnormal screening hormonal levels
2. Lack of proper stimulation
3. Failure of estradiol to increase by 20% daily or less than four adequate sized follicles (>20 mm) on ultrasound before retrieval day
4. Decline in estradiol level the morning after hCG administration (by 20% from the maximum).
5. LH surge prior to hCG administration plus a drop in estradiol
6. Lost follicles the day of retrieval
7. With a flare stimulation, Pattern D: Cycle may be changed to the Luteal Lupron Protocol, the Microdose Lupron Protocol, or a GnRH Antagonist Protocol

Financial Information

Costs for an ART cycle vary from program to program. Cycle prices vary according to the type selected. Before initiating ART, you should discuss financial arrangements with the billing personnel.

Additional expenses may include loss of wages from time missed at work and expenses incurred due to travel and/or accommodations. In addition, the medications utilized in ART procedures (human menopausal gonadotropins, hCG and GnRH analogs) are very expensive. All of these factors must be considered in determining the financial feasibility of participation in an ART program.

Programs offering ART are sensitive to the tremendous financial investment that couples make to participate in their program. We continuously strive to keep our costs manageable, and we continue to seek funded research protocols in which ART costs for the participants may be defrayed. In addition, through the efforts of our professional organizations, we are actively working at both the state and national levels to try to obtain insurance coverage for ART.

"LOOK FOR HYPERSTIMULATION"

Ovarian hyperstimulation syndrome is associated with an exuberant ovarian response to HMG or FSH. This can occur rarely in patients ovulating spontaneously or in women taking clomiphene. In this condition, the ovaries enlarge suddenly, and fluid (called ascites) leaks into the abdominal cavity, with or without pain. Fluid may accumulate around the lungs (called pleural effusion). It is estimated that severe hyperstimulation syndrome will occur in 0.4% to 2.0% of women taking these medications.

When moderate to severe hyperstimulation occurs, a number of problems within the body may follow. Urine output may decrease as fluid is transferred into the abdominal cavity and kidney function may be impaired. When this occurs, admission to the hospital is required to treat your fluid balance and maintain an adequate urine output. In addition, this dehydration can lead to blood clots to the lungs or other organs which may be life threatening.

To monitor your status and to detect early severe hyperstimulation syndrome, we ask that you do the following:

1. Measure your weight (no shoes and use the same scale) at the same time each day beginning after your hCG shot.
2. Call us if:
   a. your weight increases by two pounds
   b. your urine output seems to decrease or you seem excessively thirsty
   c. your abdomen seems to enlarge or to be bloated
   d. if you have vomiting, diarrhea, or increasing abdominal pain
   e. if you have further questions