Item 1

Patient Consent for Therapy
Human In Vitro Fertilization and Embryo Transfer

This is to certify that I, _____, hereby agree to a form of treatment known as In Vitro Fertilization and Embryo Transfer.

I have an infertility problem that is unresolved by conventional therapy. I understand that this procedure called in vitro fertilization (IVF) and embryo transfer (ET) provides means by which infertile couples may conceive and bear children. I have requested this therapy, and after detailed and complete discussion with my physician, I understand that the following is an outline of the steps required in this treatment, as well as the known risks, value, and potential benefits of this treatment. There may be other unknown risks involved.

1. **Purpose of Treatment:** The purpose of the treatment is to provide a means for achieving pregnancy when conventional treatments have failed or are unacceptable. Surgical and medical treatments have been tried with adequate periods of follow-up for pregnancy to occur and after thorough evaluation of coital, cervical, uterine, tubal, ovarian, peritoneal and male factors.

2. **Procedures to be Followed:** Ovulation stimulating agents including clomiphene citrate, human menopausal gonadotropin and follicle stimulating hormone, will be used to stimulate multiple egg production. A GnRH agonist may be used in conjunction with these drugs to down regulate ovarian function. Human chorionic gonadotropin (HCG) is used to trigger ovulation, assist in the maturation process of the eggs prior to egg retrieval, and contributes to luteal phase support. I will have blood samples collected and undergo ovarian ultrasound examination, a standard technique in which high frequency sound waves are used to form an image. The [illegible] recovery. Surgery is scheduled near the time of projected ovulation.

   The method of oocyte retrieval will be determined by the medical team and will be dependent upon the patient's medical history and anatomic status. One or more oocytes may be taken from my ovaries by one of the following means

   A. *Vaginal Aspiration Under Ultrasound Guidance:* Eggs are collected by means of vaginal ultrasound guided aspiration of ovarian follicles using a specially designed needle introduced through the vaginal wall under local anesthesia and/or intravenous sedation.

   B. *Laparoscopy:* (In rare instances) Introduction of a tube approximately 1/2 inch in diameter into the abdomen under general anesthesia.

My husband will provide a fresh ejaculate collected by masturbation. The egg(s) will be incubated with my husband's sperm.

After a period of about 72 hours, if fertilization takes place as planned, the resulting early embryo(s), will be placed into my uterus. This transfer will be made through my cervix via a small catheter.

Following embryo transfer, I will be at bed rest for several hours.

3. Reasons for Possible Failure: The following event(s) could prevent the establishment of a pregnancy.

A. The time of ovulation may be misjudged or may be unpredictable, or may not occur at all in the monitored cycle, thus precluding any attempt at obtaining an oocyte.
B. An attempt at egg retrieval may be unsuccessful.
C. The egg(s), if obtained, may not be normal.
D. My husband may be unable to obtain a semen specimen.
E. Fertilization may not occur.
F. Cleavage, or cell division, of fertilized egg(s) may not occur.
G. The embryo(s) may not develop normally.
H. It will not be possible to maintain the life of the embryo if the patient does not return for transfer.
I. Implantation may not occur.
J. Loss or damage of the fertilized egg(s) or embryo(s) may occur during the procedure.
K. There may be other reasons.

4. Discomforts and Risks: The following are some of the risks and discomforts associated with various procedures. One concern is failure of the procedure to produce a pregnancy. In 1994 569 IVF cycles, resulting in 157 live born deliveries. This reflects an overall pregnancy rate of 27.5% for all cycles initiated, which included patients in all age groups, diagnoses, male factor with and without assisted fertilization, and non male factor patients. In 1995 135 ongoing pregnancies resulted from 244 retrievals in patients who are less than 38 years old, and have no male factor. This is a pregnancy rate of 55.5%. In male factor patients in the same age group, the ongoing pregnancy rate was 39.5% per retrieval. In patients 38 years and older without male factor infertility, the pregnancy rate was 28.4% (27 out of 95 patients retrieved). When male factor infertility was present in this age group the ongoing pregnancy rate was 22.9% per retrieval (16 pregnancies out of 70 retrievals).

A major risk of this procedure is that the technique may not succeed and my husband and I will be disappointed. We may expect frustration, anxiety, and depression which may be severe.

Complications of some of the problems listed below may lead to serious permanent disability or death.

The following are some of the risks and discomforts associated with IVF and embryo transfer procedures.

A. *Blood drawing:* Mild discomfort and the possibility of developing a painful bruise at the needle site may occur. A blood clot in the vein may occur.

B. *Ultrasound:* This examination involves the use of a form of energy (sound waves) which at high energy levels may produce heat and tissue damage. At the extremely low energy levels utilized in diagnostic ultrasounds, no adverse effects have been observed to date.

C. *Medications:* The risks associated with taking hormones to stimulate multiple egg production are probably much less common than the known risks of pregnancy. Women may experience none to all of the following symptoms: Nausea, vomiting, slight weight gain or loss, breast tenderness and enlargement, occasional vaginal bleeding, yeast infections of the vagina,

vaginal discharge and wetness, hot flashes, night sweats, menstrual period cramping, headaches, fluid retention and mood swings. Much less common side effects include appetite changes, nervousness and fatigue, and changes in sex drive. More serious but rare side effects include hypertension (high blood pressure), gall bladder disease, blood clots developing in the legs, lungs, eyes, brain, heart or elsewhere, heart attacks and strokes.

Precautions regarding the potential risks of treatment with ovulatory agents must include uncertain risks of ovarian disease, including cancer. Even though these issues need to be addressed, available evidence still clearly supports the use of these drugs for fertility enhancement as an accepted standard of practice.

The risk of ovarian cancer for most women is 1% in their lifetime. The risk after use of ovarian stimulating drugs may increase to 3% according to some estimates. Ovarian cancer appears to have an inherited pattern, so that women with a maternal history of ovarian cancer can have risks as high as 50% for the disease. If you have ovarian cancer in your family, this would be an extremely adverse condition. Women who use these drugs will wish to be screened for ovarian cancer regularly as they age. There are no highly reliable methods of screening available at this time.

These findings do not prove that infertility drugs cause ovarian cancer, however they support other data which suggest an association between the agents and the disease. Currently, there are no specific guidelines which are available to guide women in terms of future surveillance for ovarian cancer.

Most patients will be given an antibiotic, usually Tetracycline. The use of Tetracycline may result in nausea, vomiting, diarrhea, loss of appetite, rashes [illegible] disease including reduced platelets or fractured red cells which occur with anemia or bleeding.

D. *Ovarian Hyperstimulation:* Ovarian cysts may develop, causing pain, internal bleeding, and severe disturbances of fluid and chemistry balances. This may require hospitalization. Blood clots are possible which could lead to strokes or other life threatening complications.

E. *Aspiration of Oocytes Under Ultrasonographic Guidance:* Pain of short duration is likely. There is a possibility of seeing blood in the urine for a day following the procedure. Perforation of blood vessels, bladder, bowel, bleeding from the ovary, and pelvic infection are possible.

F. *Laparoscopy/Laparotomy:* Infection of the incision site or pelvic organs. Perforation of bowel or bladder, internal bleeding, possible formation of scar tissue by attempted egg retrieval and/or manipulation of pelvic organs.

G. *Anesthesia:* Local or IV Sedation, if used, may cause numerous possible untoward reactions from various drugs and procedures.

H. *Embryo Transfer:* This procedure may cause discomfort and may lead to infection and/or ectopic (tubal) pregnancy.

I. *Risk to Potential Children:* There are theoretical risks of the procedure which potentially could damage the embryo and result later in defects in the child.

Superovulation has been implicated by one laboratory animal study and one human study as leading to an increased incidence of genetic defects. Other large studies have not confirmed these findings.

The normal filtering effect of the female reproductive tract selects against certain types of abnormal sperm. Since this filter is lost in IVF, abnormal sperm could be responsible for fertilization. Unusually high numbers of sperm reaching the egg may lead to multiple fertilization and potential genetic damage.

Although the early embryo is thought to be highly resistant to environmental damage, the laboratory culture conditions may induce previously unknown problems.

Use of natural progesterone can potentially increase the risk of congenital heart malformations from 8 in 10,000 births to 15 in 10,000 births.

There is no apparent increase of developmental defects in the published worldwide experience with humans in IVF.

I. *Multiple Pregnancies:* Replacement of more than one embryo increases the chance of pregnancy. However, the risk of multiple pregnancy increases as well, according to the most recent information. There is a 22% risk of having twins and an 11.7% risk of having triplets after 3 embryos are transferred. When 4 embryos are replaced, 1.3% of the pregnancies resulting are quadruplets, a 7% of the pregnancies are triplets, 18.9% of the pregnancies are twins. A procedure known as fetal reduction of pregnancy has been proposed for some women whose pregnancies involve 3 or more fetuses. More information on this controversial procedure is available on a personal basis.

Multiple pregnancies (twins or more) carry higher than normal risks for the birth mother for hypertension and other disorders, because of the extra fetuses. These pregnancies may lead to emotional and financial strain for the family and prolonged hospitalization of the birth mother before birth and of both the birth mother and infants after birth. Deaths of babies around the time of delivery and the number of babies born with long term handicaps are several times more common in multiple births than in single births. The major problem is that the babies are born before they are fully mature.

The following disorders are responsible for increased illness and death of infants: infection of the membranes sometimes due to premature rupture of the membranes, twin-to-twin transfusion syndrome, placental infarcts (portions of the placenta lose their blood supply), and premature separation of the placenta and compression of the cord. Also, higher numbers of birth defects occur in offspring of multiple-fetus pregnancies for reasons not fully understood.

An article in the American Journal of Obstetrics and Gynecology (Volume 172:679, 1995), outlines detailed analyses of 20 pregnancies delivered at a single institution in a year period. Fifteen of the pregnancies were the result of assisted reproductive technologies. The average gestational age at delivery was 30.7 weeks (10 weeks early). Sixteen (80%) underwent cesarean delivery. Of the four patients having vaginal delivery, two had previable fetuses (20 and 22 weeks gestation) and two had single fetal death with a viable triplet presenting first. Of the 60 fetuses, there

were six fetal deaths, three pregnancies with one death each, and one pregnancy with all triplets dying before birth. The average birth weight among surviving triplets was 1764 grams or approximately 3.8 pounds.

In a study conducted in Stockholm Sweden, it was found that 24 sets of triplets were born between 1986 and 1989. In one set born at 34 weeks gestation, one triplet died before delivery, in a second set born at 32 weeks gestation, one triplet died before delivery and in a third set born at 33 weeks gestation, one triplet died neonatally. In the study, 17 sets of surviving triplets at 4-6 years of age born at 33-36 weeks gestation were assessed for physical and mental development. At birth, none of the 51 triplets showed any malformations. No major physical disabilities were found. The strongest determinant of individual development seems to be birth weight. In a group of triplets born small for dates, the scores were significantly lower than those of their siblings. On the whole, at age 4-6 years, physical and mental development did not differ from what has been found in twins and singletons of the same age and with the same birth weight. Even with the most modern management, including cesarean section, the risk of extremely premature delivery is severe. Of 234 fetuses, 19 were stillborn, and 9 of these weighed less than one pound. 48 babies weighed less than 3 pounds at birth. 10 of those died. Of the 38 remaining infants, 4 (1.7% of all babies) had severe disabilities due to cerebral palsy. An additional 8 infants (3.4% of all babies) had mild abnormalities, predominantly muscle tone abnormalities or attention deficit disorders. Most of the infants in the study were normal.

The extent to which each of these risks is of importance is unknown and cannot be estimated with certainty. Future knowledge and understanding may be more complete, and deferral of this therapy to the future may be a safer course of action.

If pregnancy is successfully established, miscarriage, ectopic pregnancy, stillbirth, or birth defects may occur. I realize that there is insufficient information at this time as to whether the occurrence of these events is increased by the IVF procedure. In 1995, patients experienced 2.65% risk for ectopic pregnancy. Serial pregnancy, progesterone and/or estradiol hormone levels will be monitored by blood testing throughout the first 6 to 10 weeks of pregnancy. Vaginal ultrasound will be utilized to evaluate the growth, number and location of the fetus(es).

K. *Controversial Ethics:* Certain aspects of the ethics of this treatment are controversial. Some members of the community, including my own family or friends, may not approve of this treatment. This disapproval may damage interpersonal relations between me and my family and/or friends.

L. *Unknown Complications:* There may be other complications which have not been listed that may occur.

5. **Alternative Treatment Available:** All other possible alternative procedures for helping me become pregnant have been explained, offered, or attempted. Depending on the nature of my particular problem, alternative treatment measures might include major and minor surgery, medical therapy, or no treatment with further observation after previous therapy. My husband and I feel that these other treatments have been adequately attempted or are unacceptable.

6. **Disposition of Eggs or Embryos Unsuitable for Use:** In the event that I have unfertilized eggs, I understand that these may be subjected to scientific study. If

fertilization occurs with too many sperm or if embryos form but are not developing or not living, scientific study of these may be undertaken. Poor quality eggs and poor quality embryos which are not transferred into the uterus or tubes, or frozen for later use may be discarded.

7. Expectations of Compensation: I do not expect payment for expenses or compensation for injuries.

My consent to this treatment is purely voluntary. No inducements have been offered. My consent may be withdrawn at any time prior to the procedure, under the assumption that this will not affect either my present or future care.

I have been assured all information about me obtained during treatment will be handled confidentially and neither my identity nor specific medical details may be revealed by my doctor without my consent. Specific medical details may be revealed in professional publications or forms as long as my identity is withheld. Photographs taken during various procedures may be used professionally, as long as my identity is withheld.

I have read this form and understand it fully. I understand that some of the language in this consent form may be technical. I have been given an opportunity to ask any questions I may have. All questions and inquiries have been answered to my satisfaction. I have been informed that I may contact the office of
regarding further questions about this treatment and my rights as a patient. I am 18 years of age or older.

Patient's Signature _____ Date _____

Witness' Signature _____ Date _____

Husband's Consent

I _____, certify that I understand the nature of the proposed therapy and consent to its performance. While most of the procedures will be carried out on my wife, I consent to the use of my sperm, which I will provide by masturbation.

Husband's Signature _____ Date _____

Witness' Signature _____ Date _____

I, the undersigned, have defined and fully explained the treatment involved to the patient named above and her husband, and I have answered all of their questions.

Physician's Signature _____ Date _____

1/8/99