

Overlake Reproductive Health

Informed Consent for Assisted Reproduction:

*In Vitro Fertilization,
Intracytoplasmic Sperm Injection
Assisted Hatching
Embryo Freezing*

By signing below you are indicating which components of IVF treatment you agree to undertake in your upcoming treatment cycle. Also, you should initial each page to indicate that you have read and understand the information provided, regardless of consenting to that particular procedure. If you do not understand the information provided, please speak with your treating physician, or clinic representative. There are a few locations within the consent form where you are being asked to make a decision. Please initial your choice and sign where requested.

Patient Name: _____ & _____

Chosen Elements of Treatment:

	Patient Signature	Partner signature	Date
In-Vitro Fertilization (Including egg retrieval & medication administration)	_____	_____	_____
Use of Donated oocytes from ID# _____	_____	_____	_____
Insemination by partner sperm	_____	_____	_____
Insemination by donor sperm ID# _____	_____	_____	_____
Intracytoplasmic Sperm Injection (ICSI)	_____	_____	_____
Assisted Hatching	_____	_____	_____
Embryo Transfer (# of embryos to be decided on transfer day)	_____	_____	_____
Embryo Cryopreservation	_____	_____	_____

Signed and sworn before me on this _____ day of _____, 20____

Signature of Notary Public

Printed name of Notary Public

Expiration date of Notary Public appointment

We consent to the transfer of _____ embryos on day _____ of culture _____

Physician/Witness _____

Patient initials: _____ Partner Initials: _____

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OVERVIEW

In Vitro Fertilization (IVF) has become an established treatment for many forms of infertility. The main goal of IVF is to allow a patient the opportunity to become pregnant using her own eggs and sperm from her partner or from a donor. This is an elective procedure designed to result in the patient's pregnancy when other treatments have failed or are not appropriate.

This consent reviews the IVF process from start to finish, including the risks that this treatment might pose to you and your offspring. While best efforts have been made to disclose all known risks, there may be risks of IVF which are not yet clarified or even suspected at the time of this writing.

An IVF cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Insemination of eggs with sperm
- Culture of any resulting fertilized eggs (embryos)
- Placement ("transfer") of one or more embryo(s) into the uterus
- Support of the uterine lining with hormones to permit and sustain pregnancy

In certain cases, these additional procedures can be employed:

- Intracytoplasmic sperm injection (ICSI) to increase the chance for fertilization
- Assisted hatching of embryos to increase the chance of embryo attachment ("implantation")
- Embryo Cryopreservation (freezing)

Note: At various points in this document, rates are given which reflect what are believed to be U.S. national averages for those employing IVF treatments. These include items such as pregnancy rates, Cesarean delivery rates, and preterm delivery rates. These rates are not meant to indicate the rates of these outcomes within individual practices offering IVF, and are not to be understood as such. Individual practices may have higher or lower pregnancy and delivery rates than these national averages, and also higher or lower risks for certain complications. It is appropriate to ask the practice about their specific rates.

Also note that while this information is believed to be up to date at the time of publication (2008), newer reports may not yet be incorporated into this document.

Outline of Consent for IVF

A. Technique of In Vitro Fertilization

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 - a. medications
 - b. transvaginal oocyte retrieval
 - c. in vitro fertilization and development
 - d. embryo transfer
 - e. luteal support
2. Additional elements and their risk
 - a. intracytoplasmic sperm injection
 - b. assisted hatching
 - c. embryo disposition
 - d. cryopreserved embryo storage
 - e. donated or research embryo fate

B. Risks to woman

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2. oocyte retrieval
3. pregnancy

C. Risks to offspring

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3. multiple pregnancy

D. Ethical / religious concerns

E. Psychosocial risks

F. Legal considerations and legal counseling

G. Alternatives to IVF

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A. Technique of IVF

1. Core elements and their risk

a. Medications for IVF Treatment

- The success of IVF largely depends on growing multiple eggs at once
- Injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose
- Additional medications are used to prevent premature ovulation
- An overly vigorous ovarian response can occur, or conversely an inadequate response

Medications may include the following (not a complete list):

- **Gonadotropins or injectable “fertility drugs”** (Follistim®, Gonal-F®, Bravelle®, Menopur®): These natural hormones stimulate the ovary in hopes of inducing the simultaneous growth of several oocytes (eggs) over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some of them also contain LH (luteinizing hormone) or LH like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Luveris®, recombinant LH, can also be given as a separate injection in addition to FSH or alternatively, low-dose hCG can be used. These medications are given by subcutaneous or intramuscular injection. Proper dosage of these drugs and the timing of egg recovery require monitoring of the ovarian response, usually by way of blood tests and ultrasound examinations during the ovarian stimulation.

As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be there an allergic reaction to these drugs. The intent of giving these medications is to mature multiple follicles, and many women experience some bloating and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2.0 % of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see full discussion of OHSS in the Risks to Women section which follows]. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in blood vessels.

Even with pre-treatment attempts to assess response, and even more so with abnormal pre-treatment evaluations of ovarian reserve, the stimulation may result in very few follicles developing, the end result may be few or no eggs obtained at egg retrieval or even cancellation of the treatment cycle prior to egg retrieval.

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

- **GnRH-agonists (Leuprolide acetate)** (Lupron®): This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for 1-3 months. The primary role of this medication is to prevent a premature LH surge, which could result in the release of eggs before they are ready to be retrieved. Since GnRH-agonists initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way for more than 20 years. Potential side effects usually experienced with long-term use include but are not limited to hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. No long term or serious side effects are known. Since GnRH-a are oftentimes administered after ovulation, it is possible that they will be taken early in pregnancy. The safest course of action is to use a barrier method of contraception

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(condoms) the month you will be starting the GnRH-a. GnRH-a have not been associated with any fetal malformations however you should discontinue use of the GnRH-a as soon as pregnancy is confirmed.

- **GnRH-antagonists (*Ganirelix Acetate* or *Cetrorelix Acetate*)** (Antagon®, Cetrotide®): These are another class of medications used to prevent premature ovulation. They tend to be used for short periods of time in the late stages of ovarian stimulation. The potential side effects include, but are not limited to, abdominal pain, headaches, skin reaction at the injection site, and nausea.
- **Human chorionic gonadotropin (hCG)** (Profasi®, Novarel®, Pregnyl®, Ovidrel®): hCG is a natural hormone used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort.
- **Progesterone, and in some cases, estradiol:** Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg retrieval in some women, the ovaries will not produce adequate amounts of these hormones for long enough to fully support a pregnancy. Accordingly, supplemental progesterone, and in some cases estradiol, are given to ensure adequate hormonal support of the uterine lining. Progesterone is usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories) after egg retrieval. Progesterone is often continued for some weeks after a pregnancy has been confirmed. Progesterone has not been associated with an increase in fetal abnormalities. Side effects of progesterone include depression, sleepiness, allergic reaction and if given by intra-muscular injection includes the additional risk of infection or pain at the application site. Estradiol, if given, can be by oral, trans-dermal, intramuscular, or vaginal administration. Side effects of estradiol include nausea, irritation at the injection site if given by the trans-dermal route and the risk of blood clots or stroke.
- **Oral contraceptive pills:** Many treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to suppress hormone production or to schedule a cycle. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or stroke.
- **Other medications:** Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with egg retrieval or embryo transfer. Antibiotic use may be associated with causing a yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, and allergic reactions. Anti-anxiety medications or muscle relaxants may be recommended prior to the embryo transfer; the most common side effect is drowsiness. Other medications such as steroids, heparin, low molecular weight heparin or aspirin may also be included in the treatment protocol.

b. Transvaginal Oocyte Retrieval

- Eggs are removed from the ovary with a needle under ultrasound guidance
- Anesthesia is provided to make this comfortable
- Injury and infection are rare

Oocyte retrieval is the removal of eggs from the ovary. A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A long needle, which can be seen on ultrasound, can be guided into each follicle and the contents aspirated. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa egg-supporting cells. Rarely the ovaries are not accessible by the transvaginal route and laparoscopy or transabdominal retrieval is necessary. These procedures and risks will be discussed with you by your doctor if applicable. Anesthesia is generally used to reduce if not eliminate discomfort. Risks of egg retrieval include:

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

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

Trauma: Despite the use of ultrasound guidance, it is possible to damage other intra-abdominal organs during the egg retrieval. Previous reports in the medical literature have noted damage to the bowel, appendix, bladder, ureters, and ovary. Damage to internal organs may result in the need for additional treatment such as surgery for repair or removal of the damaged organ. However, the risk of such trauma is low.

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

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

c. In vitro fertilization and embryo culture

- Sperm and eggs are placed together in specialized conditions (culture media, controlled temperature, humidity and light) in hopes of fertilization
- Culture medium is designed to permit normal fertilization and early embryo development, but the content of the medium is not standardized.
- Embryo development in the lab helps distinguish embryos with more potential from those with less or none.

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

A few hours after eggs are retrieved, sperm are placed in the culture medium with the eggs, or individual sperm are injected into each mature egg in a technique called Intracytoplasmic Sperm Injection (ICSI) (see below). The eggs are then returned to the incubator, where they remain to develop. Periodically over the next few days, the dishes are inspected so the development of the embryos can be assessed.

The following day after eggs have been inseminated or injected with a single sperm (ICSI), they are examined for signs that the process of fertilization is underway. At this stage, normal development is evident by the still single cell having 2 nuclei; this stage is called a zygote. Two days after insemination or ICSI, normal embryos have divided into about 4 cells. Three days after insemination or ICSI, normally developing embryos contain about 8 cells. Five days after insemination or ICSI, normally embryos have developed to the blastocyst stage, which is typified by an embryo that now has 80 or more cells, an inner fluid-filled cavity, and a small cluster of cells called the inner cell mass.

It is important to note that since many eggs and embryos are abnormal, it is expected that not all eggs will fertilize and not all embryos will divide at a normal rate. The chance that a developing embryo will produce a pregnancy is related to whether its development in the lab is normal, but this correlation is not perfect. This means that not all embryos developing at the normal rate are in fact also genetically normal, and not all poorly developing embryos are genetically abnormal. Nonetheless, their visual appearance is the most common and useful guide in the selection of the best embryo(s) for transfer.

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

- Fertilization of the egg(s) may fail to occur.
- One or more eggs may be fertilized abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos will not be transferred.
- The fertilized eggs may degenerate before dividing into embryos, or adequate embryonic development may fail to occur.
- Bacterial contamination or a laboratory accident may result in loss or damage to some or all of the eggs or embryos.

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- Laboratory equipment may fail, and/or extended power losses can occur which could lead to the destruction of eggs, sperm and embryos.
- Other unforeseen circumstances may prevent any step of the procedure to be performed or prevent the establishment of a pregnancy.
- Hurricanes, floods, or other 'acts of God' (including bombings or other terrorist acts) could destroy the laboratory or its contents, including any sperm, eggs, or embryos being stored there.

Quality control in the lab is extremely important. Sometimes immature or unfertilized eggs, sperm or abnormal embryos (abnormally fertilized eggs or embryos whose lack of development indicates they are not of sufficient quality to be transferred) that would normally be discarded can be used for quality control. You are being asked to allow the clinic to use this material for quality control purposes before being discarded in accordance with normal laboratory procedures and applicable laws. None of this material will be utilized to establish a pregnancy or a cell line unless you sign other consent forms to allow the clinic to use your eggs, sperm or embryos for research purposes. Please indicate your choice below:

_____/we hereby CONSENT to allow the clinic to utilize my/our immature or unfertilized eggs, left-over sperm or abnormal embryos for quality control and training purposes before they are discarded.

Patient	Partner (if applicable)	Date
_____	_____	__/__/____

_____/we hereby DO NOT CONSENT to allow the clinic to utilize my/our immature or unfertilized eggs, left-over sperm or abnormal embryos for quality control and training purposes. This material will be discarded in accordance with normal laboratory procedures and applicable laws.

Patient	Partner (if applicable)	Date
_____	_____	__/__/____

d. Embryo transfer

- After a few days of development, the best appearing embryos are selected for transfer
- The number chosen influences the pregnancy rate and the multiple pregnancy rate
- A woman's age and the appearance of the developing embryo have the greatest influences on pregnancy outcome
- Embryos are placed in the uterine cavity with a thin tube
- Excess embryos of sufficient quality that are not transferred can be frozen

After a few days of development, one or more embryos are selected for transfer to the uterine cavity. Embryos are placed in the uterine cavity with a thin tube. Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. Although the possibility of a complication from the embryo transfer is very rare, risks include infection and loss of, or damage to the embryos.

The number of embryos transferred influences the pregnancy rate and the multiple pregnancy rate. The age of the woman and the appearance of the developing embryo have the greatest influence on pregnancy outcome and the chance for multiple pregnancy. While it is possible, it is unusual to develop more fetuses than the number of embryos transferred. It is critical to discuss the number to be transferred before the transfer is done.

In an effort to help curtail the problem of multiple pregnancies (see multiple pregnancies), national guidelines published in 2006 recommend limits on the number of embryos to transfer (see Tables below). These limits differ depending on the developmental stage of the embryos and the quality of the embryos and take into account the patient's personal history.

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Recommended limits on number of 2-3 day old embryos to transfer

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1 or 2	2	3	5
unfavorable	2	3	4	5

Recommended limits on number of 5-6 day old embryos to transfer

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1	2	2	3
unfavorable	2	2	3	3

In some cases, there will be additional embryos remaining in the lab after the transfer is completed. Depending on their developmental normalcy, it may be possible to freeze them for later use. (See section 2.c. for an in-depth discussion of embryo cryopreservation).

e. Hormonal support of uterine lining

- Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support
- Progesterone, given by the intramuscular or vaginal route, is routinely given for this purpose

Successful attachment of embryos to the uterine lining depends on adequate hormonal support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. However, in IVF cycles, this support is not always adequate. Therefore, progesterone is routinely given, and some clinics also prescribe estradiol. Progesterone is given by the intramuscular or vaginal route. Estradiol is given by the oral, vaginal, or intramuscular route. The duration of this support is from 2 to 10 weeks.

2. Additional Elements and their risk

a. Intracytoplasmic Sperm Injection (ICSI)

- ICSI is used to increase the chance of fertilization when fertilization rates are anticipated to be lower than normal
- Overall success rates with ICSI are slightly lower than for conventional insemination
- An increased risk of genetic defects in offspring is reported
- ICSI will not improve oocyte defects

The use of ICSI provides an effective treatment for male factor infertility. The negative effects of abnormal semen characteristics and sperm quality on fertilization can be overcome with ICSI if viable sperm are available because the technique bypasses the shell around the egg (zona pellucida) and the egg membrane (oolemma) to deliver the sperm directly into the egg. ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle. ICSI allows couples with male factor infertility to achieve fertilization and live birth rates close to those achieved with in vitro fertilization (IVF) using conventional methods of fertilization in men with normal sperm counts. ICSI can be performed even in men with no sperm in the ejaculate if sperm can be successfully collected from the epididymis or the testis.

Reports on the risk of birth defects associated with ICSI (compared to those associated with conventional fertilization in IVF cycles) have yielded conflicting results. The most comprehensive study conducted thus far, based on data from five-year-old children, has suggested that ICSI is associated with an increased risk of certain major congenital anomalies. However, whether the association is due to the ICSI procedure itself, or to inherent sperm defects, could not be determined because the study did not distinguish between male factor conditions and other causes of infertility. Note that even if there is an increased risk of congenital malformations in children conceived with ICSI, the risk is relatively low (4.2% versus ~3% of those conceived naturally). The impact of ICSI on the intellectual and motor development of children conceived via ICSI also has

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been controversial. An early report suggested that development in such children lagged significantly behind that of children resulting from conventional IVF or those conceived naturally. However, more recent studies from larger groups, using standardized criteria for evaluation, have not detected any differences in the development or the abilities of children born after ICSI, conventional IVF, or natural conception.

The prevalence of sex chromosome abnormalities in children conceived via ICSI is higher than observed in the general IVF population, but the absolute difference between the two groups is small (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). The reason for the increased prevalence of chromosomal anomalies observed in ICSI offspring is not clear. Whereas it may result from the ICSI procedure itself, it might also reflect a direct paternal effect. Men with sperm problems (low count, poor motility, and/or abnormal shape) are more likely themselves to have genetic abnormalities and often produce sperm with abnormal chromosomes; the sex chromosomes (X and Y) in the sperm of men with abnormal semen parameters appear especially prone to abnormalities. If sperm with abnormal chromosomes produce pregnancies, these pregnancies will likely carry these same defects. The prevalence of translocations (a re-arrangement of chromosomes that increases the risk of abnormal chromosomes in egg or sperm and can cause miscarriage) of paternal origin and of de novo balanced translocations in ICSI offspring (0.36%) also appears higher than in the general population (0.07%).

Some men are infertile because the tubes connecting the testes to the penis did not form correctly. This condition, called congenital bilateral absence of the vas deferens (CBAVD), can be bypassed by aspirating sperm directly from the testicles or epididymis, and using them in IVF with ICSI to achieve fertilization. However, men with CBAVD are affected with a mild form of cystic fibrosis (CF), and this gene will be passed on to their offspring. All men with CBAVD, as well as their partners, should be tested for CF gene mutations prior to treatment, so that the risk of their offspring having CF can be estimated and appropriate testing performed. It is important to understand that there may be CF gene mutations that are not detectable by current testing and parents who test negative for CF mutations can still have children affected with CF.

Some men have no sperm in their ejaculate because their testes do not produce adequate quantities (non-obstructive azoospermia). This can be due to a number of reasons such as prior radiation, chemotherapy or undescended testicles. In some men, small deletions on their Y chromosomes lead to extremely low or absent sperm counts. Testicular biopsy and successful retrieval of viable sperm can be used to fertilize eggs with ICSI. However, any sperm containing a Y chromosomal microdeletion will be transmitted to the offspring. Thus the risk that male offspring might later manifest disorders including infertility is very real. However, men without a detectable deletion by blood testing can generate offspring having a Y chromosome microdeletion, because the chromosomes in the sperm may not be the same as those seen when tested by a blood test.

If it is in the opinion of the Laboratory that Intracytoplasmic Sperm Injection (ICSI) is required to ensure fertilization, then it is understood that my consent is expressly given with my consent to undergo IVF - unless expressly noted by me in **writing** prior to the egg retrieval, and delivered in person to the Laboratory Director.

b. Assisted Hatching

- **Assisted Hatching involves making a hole in the outer shell (zona pellucida) that surrounds the embryo**
- **Hatching may make it easier for embryos to escape from the shell which surrounds them.**

The cells that make up the early embryo are enclosed within a flexible membrane (shell) called the zona pellucida. During normal development, a portion of this membrane dissolves, allowing the embryonic cells to escape or “hatch” out of the shell. Only upon hatching can the embryonic cells implant within the wall of the uterus to form a pregnancy.

Assisted hatching is the laboratory technique in which an embryologist makes an artificial opening in the shell of the embryo. The hatching is usually performed on the day of transfer, prior to loading the embryo into the transfer catheter. The opening can be made by mechanical means (slicing with a needle or burning the shell with a laser) or chemical means by dissolving a small hole in the shell with a dilute acid solution.

Some programs have incorporated artificial or “assisted hatching” into their treatment protocols because they believe it improves implantation rates, and ultimately, live birth rates although definitive evidence of this is lacking.

Risks that may be associated with assisted hatching include damage to the embryo resulting in loss of embryonic cells, or destruction or death of the embryo. Artificial manipulation of the zygote may increase the rates of monozygotic (identical) twinning which are significantly more complicated pregnancies. There may be other risks not yet known.

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c. Embryo disposition

- Freezing of viable embryos not transferred after egg retrieval provides additional chances for pregnancy.
- Frozen embryos do not always survive the process of freezing and thawing.
- Freezing of eggs before fertilization is currently much less successful than freezing of fertilized eggs (embryos).
- Ethical and legal dilemmas can arise when couples separate or divorce; disposition agreements are essential.
- It is the responsibility of each couple with frozen embryos to remain in contact with the clinic on an annual basis.

Freezing (or “cryopreservation”) of embryos is a common procedure. Since multiple eggs (oocytes) are often produced during ovarian stimulation, on occasion there are more embryos available than are considered appropriate for transfer to the uterus. These embryos, if viable, can be frozen for future use. This saves the expense and inconvenience of stimulation to obtain additional eggs in the future. Furthermore, the availability of cryopreservation permits patients to transfer fewer embryos during a fresh cycle, reducing the risk of high-order multiple gestations (triplets or greater). Other possible reasons for cryopreservation of embryos include freezing all embryos in the initial cycle to prevent severe ovarian hyperstimulation syndrome (OHSS), or if a couple were concerned that their future fertility potential might be reduced due to necessary medical treatment (e.g., cancer therapy or surgery). The pregnancy success rates for cryopreserved embryos transferred into the human uterus can vary from practice to practice. Overall pregnancy rates at the national level with frozen embryos are lower than with fresh embryos. This, at least in part, results from the routine selection of the best-looking embryos for fresh transfer, reserving the 'second-best' for freezing. There is some evidence that pregnancy rates are similar when there is no such selection.

Indications:

- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures
- To increase the chance of having one or more pregnancies from a single cycle of ovarian stimulation
- To minimize the medical risk and cost to the patient by decreasing the number of stimulated cycles and egg retrievals
- To temporarily delay pregnancy and the risks of OHSS occurs by freezing all embryos, when this risk is high.

Risks of embryo cryopreservation: There are several techniques for embryo cryopreservation, and research is ongoing. Traditional methods include “slow,” graduated freezing in a computerized setting, and “rapid” freezing methods, called “vitrification.” Current techniques deliver a high percentage of viable embryos thawed after cryopreservation, but there can be no certainty that embryos will thaw normally, nor be viable enough to divide and eventually implant in the uterus. Cryopreservation techniques could theoretically be injurious to the embryo. Extensive animal data (through several generations), and limited human data, do not indicate any likelihood that children born of embryos that have been cryopreserved and thawed will experience greater risk of abnormalities than those born of fresh embryos. However, until very large numbers of children have been born following freezing and thawing of embryos, it is not possible to be certain that the rate of abnormalities is no different from the normal rate.

Because of the possibility of you and/or your partner’s separation, death or incapacitation, it is important to decide on the disposition of any embryo(s), fresh or cryopreserved that remain in the laboratory. Since this is a rapidly evolving field, both medically and legally, the clinic cannot guarantee what the available or acceptable avenues for disposition will be at any future date.

Embryos are understood to be your property, with rights of survivorship. No use can be made of these embryos without the consent of both partners (if applicable).

In the event of divorce or dissolution of the marriage or partnership, the ownership and/or other rights to the embryo(s) will be as follows:

- a) All embryos are to be discarded
- b) All embryos are to be donated to medical research
- c) All embryos are to be transferred to _____ (insert name of recipient partner)

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In the event of the death or incapacitation of one partner, the embryo(s) will be as follows:

- a) All embryos will discarded
- b) All embryos will be donated to medical research
- c) All embryos are to be transferred to the surviving partner

In the event of death or incapacitation of both partners the embryo(s) will be as follows:

- a) All embryos are to be discarded
- b) All embryos are to be donated to medical research
- c) We have selected another disposition for our frozen embryos and have indicated as such in our will

Patient	Partner (if applicable)	Date
_____	_____	__/__/____

d. Cryopreserved embryo storage

The Clinic will only maintain cryopreserved embryos for a period of 5 years. After that time, any cryopreserved embryos must be:

- 1) Thawed and transferred
- 2) Donated to research
- 3) Discarded or
- 4) Transferred to another storage facility

Additionally, maintaining embryo(s) in a frozen state is labor intensive and expensive. There are fees associated with freezing and maintaining cryopreserved embryo(s). Patients/couples who have frozen embryo(s) must remain in contact with the clinic on an annual basis in order to inform the clinic of their wishes as well as to pay fees associated with the storage of their embryo(s). In situations where there is no contact with the clinic for a period of 2 years or fees associated with embryo storage have not been paid for a period of 2 years and the clinic is unable to contact the patient after reasonable efforts have been made, the embryo(s) will be considered to be abandoned and may be destroyed by the clinic in accordance with normal laboratory procedures and applicable law.

I/We understand that before I (the patient) reach 56 years of age (DATE __/__/__), the cryopreserved embryo(s) must be:

- 1) Thawed and transferred
- 2) Donated to research
- 3) Discarded or
- 4) Transferred to another storage facility

If no disposition has occurred by the above date, I/we hereby waive any and all interest in said cryopreserved embryo(s) and the cryopreserved embryo(s) shall become the sole and exclusive property of the clinic. In this event I/we elect to: (please initial your choice)

	patient	partner
1) Discard the cryopreserved embryo(s)	_____	_____
2) Donate the cryopreserved embryo(s) for research	_____	_____

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e. Donated or research embryo fate

In certain situations, donating embryo(s) for research or to another couple may not be possible or may be restricted by law. While efforts will be made to abide by your wishes, no guarantees can be given that embryo(s) will be used for research or donated to another couple. In these instances, if after 1 year no recipient or research project can be found, or your embryos are not eligible, your embryo(s) will be discarded by the lab in accordance with laboratory procedures and applicable laws.

B. Risks to the Woman

1. Ovarian Hyperstimulation Syndrome

To increase the number of eggs that develop, a series of hormone shots are given. The hormones used in this regimen are known to have, or suspected of having a variety of side effects, some minor and some potentially major.

The most serious side effect of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). Its symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure, or death. The severe cases affect only a very small percentage of women who undergo in vitro fertilization—0.2 percent or less of all treatment cycles—and the very severe are an even smaller percentage. Only about 1.4 in 100,000 cycles has led to kidney failure, for example. OHSS occurs at two stages: early, 1 to 5 days after egg retrieval (as a result of the hCG trigger); and late, 10 to 15 days after retrieval (as a result of the hCG if pregnancy occurs). The risk of severe complications is about 4 to 12 times higher if pregnancy occurs which is why sometimes no embryo transfer is performed to reduce the possibility of this occurring.

2. Cancer

Many have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical significance, but it is at least possible that use of fertility drugs may indeed cause some increased risk of uterine cancer.

3. Risks of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions (see Table below from the Executive Summary of a National Institute of Child Health and Human Development Workshop held in September 2005, as reported in the journal *Obstetrics & Gynecology*, vol. 109, no. 4, pages 967-77, 2007). Some of these risks stem from the higher average age of women pregnant by IVF and the fact that the underlying cause of infertility may be the cause of the increased risk of pregnancy complications. There may be additional risks related to the IVF procedure per se, but it is difficult to assign the relative contributions.

Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
Placenta previa	2.4%	2.9 (1.5--5.4)
Placental abruption	2.2%	2.4 (1.1--5.2)
Gestational diabetes	6.8%	2.0 (1.4--3.0)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

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In this table, the Absolute risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a relative risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the “Confidence Interval”) indicate the range in which the actual Relative Risk lies.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Of note, IVF twins do as well as spontaneously conceived twins. Triplet (and greater) pregnancies deliver before 32 weeks (7 months) in almost half of cases.

Additionally, while embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone or concurrently with a normal intra-uterine pregnancy. These abnormal pregnancies oftentimes require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy. Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding and injury to any internal organs.

C. Risks to Offspring

- IVF babies may be at a slight increased risk for birth defects
- The risk for a multiple pregnancy is significantly higher for patients undergoing IVF, even when only one embryo is transferred
- Multiple pregnancies are the greatest risk for babies following IVF
- Some risk may also stem from the underlying infertile state, or from the IVF techniques, or both

1. Overall risks.

Since the first birth of an IVF baby in 1978, more than 3 million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for IVF babies as compared to naturally conceived babies.

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under 5 pounds nine ounces (2500 grams) is 12.5% vs. 7% in naturally conceived singletons.

2. Birth Defects.

The risk of birth defects in the normal population is 2-3 %. In IVF babies the birth defect rate may be 2.6-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects.

Imprinting Disorders. These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies approximately 4% of children with the imprinting disorder called Beckwith-Weidemann Syndrome were born after IVF, which is more than expected. A large Danish study however found no increased risk of imprinting disorders in children conceived with the assistance of IVF. Since the incidence of this syndrome in the general population is 1/15,000, even if there is a 2 to 5-fold increase to 2-5/15,000, this absolute risk is very low.

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Childhood cancers. Most studies have not reported an increased risk with the exception of retinoblastoma: In one study in the Netherlands, five cases were reported after IVF treatment which is 5 to 7 times more than expected.

Infant Development. In general, studies of long-term developmental outcomes have been reassuring so far; most children are doing well. However, these studies are difficult to do and suffer from limitations. A more recent study with better methodology reports an increased risk of cerebral palsy (3.7 fold) and developmental delay (4 fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

Potential Risks in Singleton IVF Pregnancies

	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)
Preterm birth	11.5%	2.0 (1.7--2.2)
Low birth weight (< 2500 g)	9.5%	1.8 (1.4--2.2)
Very low birth weight (< 1500 g)	2.5%	2.7 (2.3--3.1)
Small for gestational age	14.6%	1.6 (1.3--2.0)
NICU admission	17.8%	1.6 (1.3--2.0)
Stillbirth	1.2%	2.6 (1.8--3.6)
Neonatal mortality	0.6%	2.0 (1.2--3.4)
Cerebral palsy	0.4%	2.8 (1.3--5.8)
Genetic risks		
-imprinting disorder	0.03%	17.8 (1.8--432.9)
-major birth defect	4.3%	1.5% (1.3--1.8)
-chromosomal abnormalities (after ICSI):		
-of a sex chromosome	0.6%	3.0
-of another chromosome	0.4%	5.7

In this table, the Absolute risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a relative risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the "Confidence Interval") indicate the range in which the actual Relative Risk lies.

3. Risks of a Multiple Pregnancy

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Others include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Triplets and above increase the risk to the mother of more significant complications including post-partum hemorrhage and transfusion.

Prematurity accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations. Moreover, IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus or mother. No excess perinatal or maternal morbidity has been described resulting from a "vanishing" embryo.

Demise of a single fetus in a twin pregnancy after the first trimester is more common when they share a placenta, ranging in incidence from 0.5% to 6.8%, and may cause harm to the remaining fetus.

Multiple fetuses (including twins) that share the same placenta have additional risks. Twin-twin transfusion syndrome in which there is an imbalance of circulation between the fetuses may occur in up to 20% of twins sharing a placenta. Excess or insufficient amniotic fluid may result from twin-to-twin transfusion syndrome. Twins sharing the same placenta have a higher

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frequency of birth defects compared to pregnancies having two placentas. Twins sharing the same placenta appear to occur more frequently after blastocyst transfer.

Placenta previa and vasa previa are more common complications in multiple gestations. Abruption placenta also is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries. Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity and chronic lung disease) as well as those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. Rearing of twins and high-order multiples may generate physical, emotional, and financial stresses, and the incidence of maternal depression and anxiety is increased in women raising multiples. At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons. It is not clear to what extent these risks are affected by IVF per se.

The Option of Selective Reduction: Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. The greater the number of fetuses within the uterus, the greater is the risk for adverse perinatal and maternal outcomes. Patients with more than twins are faced with the options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, or reducing the number of fetuses in an effort to decrease the risk of maternal and perinatal morbidity and mortality. Multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates profound ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggest that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%.

In general, the risk of loss after MFPR increases if the number of fetuses at the beginning of the procedure is more than three. While there is little difference between the loss rates observed when the final number of viable fetuses is two or one, the loss rate is higher in pregnancies reduced to triplets. Pregnancies that are reduced to twins appear to do as well as spontaneously conceived twin gestations, although an increased risk of having a small for gestational age fetus is increased when the starting number is over four. The benefit of MFPR can be documented in triplet and higher-order gestations because reduction prolongs the length of gestation of the surviving fetuses. (This has been demonstrated for triplets; triplets have a 30-35% risk of birth under 32 weeks compared to twins which is 7 to 10%)

D. Ethical and Religious Considerations in Infertility Treatment

Infertility treatment can raise concerns and questions of an ethical or religious nature for some patients. The technique of in vitro fertilization (IVF) involves the creation of human embryos outside the body, and can involve the production of excess embryos and/or 'high-order' multiple pregnancy (triplets or more). We encourage patients and their spouses or partners who do desire to consult with trusted members of their religious or ethics community for guidance on their infertility treatment.

E. Psychosocial Effects of Infertility Treatment

A diagnosis of infertility can be a devastating and life-altering event that impacts on many aspects of a patient's life. Infertility and its treatment can affect a patient and her spouse or partner medically, financially, socially, emotionally and psychologically. Feelings of anxiousness, depression, isolation, and helplessness are not uncommon among patients undergoing infertility treatment. Strained and stressful relations with spouses, partners and other loved ones are not uncommon as treatment gets underway and progresses.

Our health care team is available to address the emotional, as well as physical, symptoms that can accompany infertility. In addition to working with our health care team to minimize the emotional impacts of infertility treatments, patients may also consider working with mental health professionals who are specially trained in the area of infertility care.

While it is normal to experience emotional ups and downs when pursuing infertility treatment, it is important to recognize when these feelings are of a severe nature. If you experience any of the following symptoms over a prolonged period of time, you may benefit from working with a mental health professional:

- loss of interest in usual activities

Patient initials: _____ Partner Initials: _____

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- depression that doesn't lift
- strained interpersonal relationships (with partner, family, friends and/or colleagues)
- difficulty thinking of anything other than your infertility
- high levels of anxiety.
- diminished ability to accomplish tasks
- difficulty with concentration
- change in your sleep patterns (difficulty falling asleep or staying asleep, early morning awakening, sleeping more than usual for you)
- change in your appetite or weight (increase or decrease)
- increased use of drugs or alcohol
- thoughts about death or suicide
- social isolation
- persistent feelings of pessimism, guilt, or worthlessness
- persistent feelings of bitterness or anger

Our health care team can assist you in locating a qualified mental health professional who is familiar with the emotional experience of infertility, or you can contact a national support group such as RESOLVE, (www.resolve.org, Tel. 1-888-623-0744) or The American Fertility Association (AFA), (www.theafa.org, Tel: 1-888-917-3777).

F. Legal Considerations and Legal Counsel

The law regarding embryo cryopreservation, subsequent thaw and use, and parent-child status of any resulting child(ren) is, or may be, unsettled in the state in which either the patient, spouse, partner, or any donor currently or in the future lives, or the state in which the ART Program is located. We acknowledge that the ART Program has not given us legal advice, that we are not relying on the ART Program to give us any legal advice, and that we have been informed that we may wish to consult a lawyer who is experienced in the areas of reproductive law and embryo cryopreservation and disposition if we have any questions or concerns about the present or future status of our embryos, our individual or joint access to them, our individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.

G. Alternatives to IVF

There are alternatives to IVF treatment including gamete Intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) or tubal embryo transfer (TET) where eggs and sperm, fertilized eggs or developing embryos, respectively, are placed into the fallopian tube(s). Using donor sperm, donor eggs, adoption or not pursuing treatment are also options. Gametes (sperm and/or eggs), instead of embryos may be frozen for future attempts at pregnancy in an effort to avoid potential future legal issues relating to disposition of any cryopreserved embryos. Sperm freezing, but not egg freezing, has been an established procedure for many decades. Egg freezing is considered an experimental procedure at this time.

H. Reporting Outcomes

The 1992 Fertility Clinic Success Rate and Certification Act requires the Centers for Disease Control and Prevention (CDC) to collect cycle-specific data as well as pregnancy outcome on all assisted reproductive technology cycles performed in the United States each year and requires them to report success rates using these data. Consequently, data from my/our IVF procedure will be provided to the CDC, and to the Society of Assisted Reproductive Technologies (SART) of the American Society of Reproductive Medicine (ASRM). The CDC may request additional information from the treatment center or contact me/us directly for additional follow-up. Additionally, my/our information may be used and disclosed in accordance with HIPAA guidelines in order to perform research or quality control. All information used for research will be de-identified prior to publication. De-identification is a process intended to prevent the data associated with my/our treatment being used to identify me/us as individuals.

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References:

General IVF overviews available on the internet

<http://www.sart.org/>; <http://www.cdc.gov/art/>; <http://www.resolve.org/site/PageServer>

Number of Embryos to Transfer

Guidelines on number of embryos transferred. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S51-S52.

Culturing Embryos to the Blastocyst Stage

Blastocyst culture and transfer in clinical-assisted reproduction. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S89-S92.

Intracytoplasmic sperm injection

Genetic considerations related to intracytoplasmic sperm injection (ICSI). The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S103-S105.

Embryo hatching

The role of assisted hatching in in vitro fertilization: a review of the literature. A Committee opinion. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Fertil Steril 2006; 86 (suppl 4): S124-S126.

Ovarian Hyperstimulation

Ovarian hyperstimulation syndrome. The Practice Committees of the American Society for Reproductive Medicine. Fertil Steril 2006; 86 (suppl 4): S178-S183.

Risks of pregnancy

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Risks to offspring

Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Obstet Gynecol 2007; 109(4):967-77.

Multiple pregnancy associated with infertility therapy. The Practice Committees of the American Society for Reproductive Medicine Fertil Steril 2006; 86 (suppl 4): S106-S110.

Imprinting diseases and IVF: A Danish National IVF cohort study. Lidegaard O, Pinborg A and Anderson AN. Human Reproduction 2005; 20(4):950-954.