

In Vitro Fertilization Process & Risks

An IVF cycle typically includes the following steps or procedures:

- Taking medicine to grow several eggs at once
- Removing the eggs from the ovary or ovaries
- Mixing eggs and sperm together so the eggs will be fertilized
- Growing any resulting fertilized eggs (embryos) in the lab
- Placement ("transfer") of one or more embryo(s) into the uterus
- Taking hormone medications to help you have a successful pregnancy

Sometimes, other IVF steps may be included:

- Injecting individual sperm into each egg, called intracytoplasmic sperm injection
- Cryopreservation (freezing) of eggs or embryos that are not transferred to the uterus
- Genetic testing of the embryos for abnormal genes or number of chromosomes.

Medications for IVF Treatment

- The success of IVF largely depends on growing several eggs at once.
- Injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose.
- Other medications are used to keep ovulation from happening too soon.
- Sometimes the ovaries respond too strongly—and sometimes not enough.

Here are some medicines commonly used in an IVF cycle:

- **Gonadotropins, or injectable "fertility drugs"** (Follistim®, Gonal-F®, Menopur®, Bravelle®, low dose hCG or human chorionic gonadotropin): These are all natural hormones that help the ovary to grow several eggs (oocytes) at once over 8 or more days. These injections may be given either just under the skin or directly into muscle.

Taking any medicine in an injection can cause bruising, redness, swelling, or pain at the injection site. In rare cases, there may be an allergic reaction. Some women have bloating or minor discomfort as the ovaries briefly become enlarged. About 1% of women will develop Ovarian Hyperstimulation Syndrome (OHSS) [see "Risks to the Woman" section]. Other side effects can include headaches, weight gain, feeling tired, mood swings, nausea, or clots in blood vessels.

Sometimes, especially when testing prior to the IVF cycle has shown that the woman has a lower number of eggs available, the medications may not help multiple eggs to grow. There may be very few or even no eggs harvested at the egg retrieval procedure, or the cycle may be canceled before egg retrieval can be attempted.

- **GnRH-agonists (leuprolide acetate) (Lupron®) or (Synarel):** Lupron medication is an injection. There are two forms of the drug. One is a short-acting form that needs to be injected daily, and the other is a long-acting form that lasts for 1-3 months. Leuprolide is often given to help prevent the release of eggs (by ovulation) before they can be retrieved. Leuprolide can also be used to start the growth of eggs, or trigger the final stages of their growth. Leuprolide is approved by the FDA (U.S. Food and Drug Administration), but not approved for use in IVF. Still, because it has been studied in IVF patients, the medicine has been used in IVF for more than 20 years. Synarel is a nasal spray most commonly used for suppression of endometriosis but works in the same way as Lupron during an IVF cycle.

Leuprolide and Synarel can cause a number of side effects. These include hot flashes, vaginal dryness, nausea, headaches, and muscle aches. Some women may retain fluid or feel depressed, and long-term use can result in bone loss. Since Leuprolide is taken as an injection, skin reactions can also occur where the injection is given. No long term or serious side effects are known. If Leuprolide is given in a cycle after ovulation has occurred, you should use condoms for birth control in that month. Leuprolide has not been linked with any birth defects, but it should be stopped if you become pregnant while taking it.

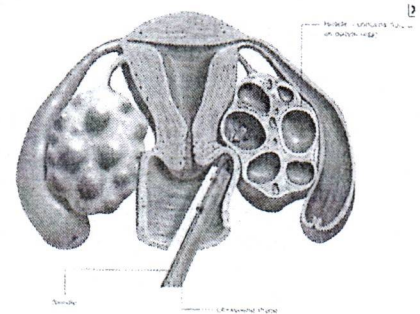
- **GnRH-antagonists (ganirelix acetate or cetrotorelix acetate)** (Ganirelix®, Cetrotide®): These drugs are used to prevent premature ovulation. Side effects may include stomach pain, headaches, skin reactions where the shot is given, and nausea.
- **Human chorionic gonadotropin (hCG)** (Profasi®, Novarel®, Pregnyl®, Ovidrel®): hCG is a natural hormone used in IVF to help the eggs become mature and ready to harvest and be fertilized. This drug must be taken at just the right time is to retrieve mature eggs. Side effects can include breast tenderness, bloating, and pelvic pain.
- **Progesterone, and in some cases, estradiol:** These two hormones are normally produced by the ovaries after ovulation. In some women, after egg retrieval, the ovaries will not produce enough of these hormones to support a pregnancy. Adding them helps improve your chances of getting pregnant and staying pregnant. Progesterone can be taken as a daily intramuscular injection (injection into muscle, most commonly in the hip). It can also be taken by placing a suppository (Endometrin®, Crinone®, Prochieve®, Prometrium®, or pharmacist-compounded suppositories) directly into the vagina as frequently as three times per day after egg retrieval. Progesterone is often continued for some weeks after you become pregnant. Progesterone has not been shown to cause birth defects. Side effects of progesterone can include depression, sleepiness, or an allergic reaction. The intra-muscular injection can cause infection or pain at the injection site. Estradiol can be taken by pill, in a patch, as an intramuscular shot, or as a vaginal suppository. Side effects of estradiol include nausea, irritation at the site of the injection or patch, and the risk of blood clots or stroke.
- **Oral contraceptive pills (birth control pills):** Your doctor may ask you to take birth control pills for 2 to 4 weeks before starting hormone stimulation injections. This is done to slow down hormone production or to schedule a treatment cycle. Side effects include bleeding, headache, breast tenderness, nausea, and swelling. There is also a risk of blood clots or, very rarely, stroke.
- **Growth Hormone:** This medicine is used in some regimens in hopes of improving embryo quality. It is given as a daily injection, and may cause some local irritation.
- **Testosterone or DHEA:** This medicine is used in some treatments in hopes of increasing the number of growing eggs. It is often given as a pill, patch, or cream, for one to three months before ovarian stimulation begins.
- **Clomid or Letrozole:** These medicines are used in some treatments to increase the number of growing eggs or reduce the estrogen level in the bloodstream. Short-term side effects in some women include headache, hot flashes, or increased moodiness. They are taken by mouth in pill form.
- **Coenzyme Q10:** This medicine is often recommended to improve egg quality, and is taken by mouth for one to three months before ovarian stimulation begins.
- **Other medications:** Antibiotics may be given for a short time during the treatment cycle. This may reduce the risk of infection from egg retrieval or embryo transfer. Antibiotic use may

cause a number of side effects, including vaginal yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, or allergic reactions. Your doctor may suggest using anti-anxiety medications or a muscle relaxant before the embryo transfer. The most common side effect of these medicines is drowsiness. Other medicines such as steroids, heparin, low molecular weight heparin, or aspirin may also be recommended.

Transvaginal Oocyte (Egg) Retrieval

- Eggs are removed from the ovary with a needle under ultrasound guidance.
- Anesthesia is given to make this more comfortable.
- Complications such as injury and infection are rare.

Oocyte retrieval is the removal of eggs from the ovary. Before removing the eggs, the doctor will look at your ovaries using an ultrasound probe placed into the vagina. A long needle, which can be seen on ultrasound, can be attached to the ultrasound probe. Guiding the needle into the ovaries, the doctor will draw out fluid, eggs, and egg-supporting cells. Very rarely, the ovaries cannot be reached through the vagina. In that case, the eggs might be removed by guiding the needle through the belly, or by inserting a viewing tube (laparoscope) through the belly button to reach the eggs. Anesthesia is generally used to reduce or eliminate pain.



Risks of egg retrieval:

Infection: Bacteria from the vagina may be transferred into the pelvis or ovaries by the needle. This can cause an infection of nearby organs. The incidence of infection after egg retrieval is very small (less than 0.1%). If you do get an infection, you may be given antibiotics. Severe infections sometimes require surgery to remove infected tissue. Infections can reduce your chance of getting pregnant in the future. Antibiotics may be used before the egg retrieval to help reduce the chance of infection. Still, there is no way to remove the risk completely.

Bleeding: The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels. There are also other blood vessels nearby. This means that small amounts of blood may be lost while removing the eggs. The risk of major bleeding is small (< 0.1%). Major bleeding may require surgery to stop, and could result in the removal of an ovary. Only rarely is a blood transfusion needed. If bleeding occurs and is not noticed (also rare), it can lead to death.

Trauma: Even with ultrasound guidance, nearby organs can be damaged. This includes damage to the intestines, appendix, bladder, ureters, and ovary. In some cases, a damaged organ may need to be fixed or removed through surgery. Still, the risk of damage during egg retrieval is very low.

Anesthesia: The use of anesthesia while removing eggs can cause an allergic reaction or low blood pressure. It can also cause nausea or vomiting. In rare cases, use of anesthesia has resulted in death.

Failure: Sometimes no eggs are found during the retrieval process. In other cases, the eggs are not normal, or are of poor quality. These situations can prevent you from having a successful pregnancy.

In vitro fertilization and embryo culture

- Sperm and eggs are placed together in a petri dish.
- The dish is kept under special conditions to promote fertilization.
- The fluid in the dish (culture medium) helps the sperm fertilize the egg and helps embryos to grow. Each clinic may have its own blend of fluids in which to grow the embryos.
- In most cases, the embryologist chooses the best embryos for pregnancy by the way they look under a microscope.

After eggs are retrieved, they are transferred to the embryology laboratory where they are kept in conditions that support their growth. The eggs are placed in small dishes or tubes containing "culture medium," which is special fluid to support development of the embryos. The fluid is made to resemble the conditions in the Fallopian tubes and uterus. The eggs are then placed into incubators, which keep the temperature, humidity, gas, and light at just the right levels.

Three to four hours after the eggs are retrieved, sperm are placed in the culture medium with the eggs. In some cases, individual sperm are injected into each mature egg in a technique called Intracytoplasmic Sperm Injection (ICSI) (see "ICSI" section). The eggs are then returned to the incubator, where they remain to develop and grow. They are inspected at intervals over the next few days, to check their progress.

Embryo development usually proceeds along the following schedule:

- *Day 1:* This is the day that the eggs and sperm come together, and we can check for signs of fertilization. At this stage, the normally fertilized egg is still a single cell with 2 nuclei, called a 2PN or zygote.
- *Day 2:* Normal embryos will divide into 2 to 4 cells.
- *Day 3:* Normally developing embryos will continue to divide and contain 4 to 8 cells.
- *Day 4:* The cells of the embryo begin to merge to form a solid ball of cells called a morula (named because it looks like a mulberry).
- *Day 5:* Normal embryos now have 100 cells or more, and are called blastocysts. It has an inner fluid-filled cavity and a small cluster of cells on the inside called the inner cell mass.

It is important to understand that many eggs and embryos are abnormal. This means that some eggs will not fertilize, and some embryos will not divide at a normal rate. Some embryos may stop growing. Even if your embryo(s) develop normally in the lab, you still may not get pregnant. Some embryos end up being genetically abnormal. Testing for genetic abnormalities is possible ("preimplantation genetic testing, or "PGT"), but genetic testing is not routinely done. The best embryo(s) for transfer are usually selected by the way they look under the microscope.

We take great care of all eggs, embryos, and sperm in the lab. Still, there are many reasons why pregnancy may not happen with IVF:

- The eggs may fail to fertilize.
- One or more eggs may fertilize abnormally. This can lead to an abnormal number of chromosomes in the embryo. These abnormal embryos cannot be transferred.
- The fertilized eggs may fall apart before dividing into embryos, or the embryos may not develop normally.
- Rarely, the eggs or embryos may be harmed by contact with bacteria in the lab.
- In spite of having backup systems in place, lab equipment may fail or power may be lost. Both can lead to the destruction of eggs, sperm, and embryos.

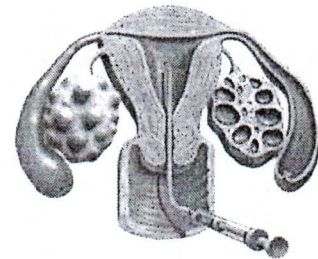
- A lab accident or human error can happen and can lead to embryo loss.
- Other unplanned events may prevent any step of the process from being performed or prevent a pregnancy from occurring.
- Hurricanes, floods, or other “acts of God,” including bombings or other terrorist acts, could destroy the laboratory or its contents, including any sperm, eggs, or embryos.

Quality control is the process of running tests to ensure that lab conditions are the best they can be to help embryos grow. Systems in the lab are frequently checked to make sure conditions are optimal. Sometimes immature or abnormal eggs, or embryos that have not developed normally, can be used for quality control checks before they are discarded. None of the material that would normally be discarded--blood, tissues eggs, sperm or embryos--will be used to create a pregnancy or a cell line.

Embryo transfer

- After a few days of development, the best-developed embryos are chosen for transfer.
- The number of embryos transferred affects the pregnancy rate and the risk of twins or other multiple pregnancies.
- The woman’s age and the quality of the developing embryo(s) have the greatest effect on pregnancy outcome.
- Embryos are placed in the uterus using a thin tube.
- Extra, normally developing embryos that are not transferred can be frozen for future use.

After a few days of development, the embryo transfer takes place, or the embryos are frozen for transfer later on. One or more embryos are placed in the uterus using a thin tube called a catheter. Ultrasound may be used to help guide the catheter. It can also confirm placement through the cervix and into the uterus. Although this is a simple process, there are some very rare risks. These risks include infection, loss of the embryo(s), or damage to the embryo(s). Not all embryos become pregnancies, and not all pregnancies are normal or grow in the correct place - tubal pregnancies can occur.



The number of embryos to transfer is an important decision. A woman’s age and the quality of the embryo affect both the chance for pregnancy as well as the chance for multiple embryos to implant. If multiple embryos implant, a multiple pregnancy (twins, triplets, or more) will result. In some cases, an embryo can split into two (identical twins) after transfer. Before the transfer, it is critical to discuss with your doctor how many embryos to transfer.

Guidelines for the maximum number of embryos to transfer are given below.

RECOMMENDED LIMITS ON THE NUMBER OF EMBRYOS TO TRANSFER

| | Age: <35 | 35-37 | 38-40 | 41-42 | > 42 |
|---------------------------------|----------|-------|-------|-------|-----------|
| Cleavage-stage embryos | | | | | |
| • Normal # chromosomes | 1 | 1 | 1 | 1 | 1 |
| • From Egg Donor <35 | 1 | 1 | 1 | 1 | 1 |
| • Other favorable* | 1 | 1 | ≤3 | ≤4 | Not known |
| • All others | ≤2 | ≤3 | ≤4 | ≤5 | Not known |
| Blastocyst-stage embryos | | | | | |
| • Normal # chromosomes | 1 | 1 | 1 | 1 | 1 |
| • From Egg Donor <35 | 1 | 1 | 1 | 1 | 1 |
| • Other favorable* | 1 | 1 | ≤2 | ≤3 | Not known |

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|--------------|----|----|----|----|-----------|
| • All others | ≤2 | ≤2 | ≤3 | ≤3 | Not known |
|--------------|----|----|----|----|-----------|

*Other favorable = any ONE of these criteria: Fresh cycle: expectation of 1 or more high-quality embryos available for cryopreservation or previous live birth after an IVF cycle; FET cycle: availability of vitrified day-5 or day-6 blastocysts, Euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.

Hormonal support of the uterine lining

- For pregnancy to occur, the embryo(s) must attach to the lining of the uterus. This process is called *implantation*.
- Implantation has a better chance of happening if you take extra progesterone hormone.

The most important hormones to support implantation are progesterone and estrogen. Normally, the ovaries make these hormones to support pregnancy. However, in IVF cycles, retrieving the eggs causes reduced production of progesterone and estrogen by the ovaries. Therefore, in most cases, progesterone and sometimes estrogen are routinely taken. Progesterone is most commonly taken as an injection or as a vaginal suppository. Estrogen can be given as pills, an injection, vaginal suppositories, or a skin patch. Progesterone and/or estrogen are usually continued for several weeks to help support the pregnancy.

Additional Elements

Intracytoplasmic Sperm Injection (ICSI)

- In some cases, fertilization will not happen when eggs and sperm are placed together in a lab dish. Injecting a sperm into each egg (ICSI, or intracytoplasmic sperm injection) can help fertilization occur.
- ICSI does not guarantee normal fertilization.
- There may be an increased risk of genetic problems in children born from ICSI.
- ICSI will not improve any defects in the eggs.

ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle. This lets the sperm enter the egg without having to break through the shell around the egg (the *zona pellucida*). For it to work, the sperm must be healthy, and the egg must be mature.

ICSI is a good choice when the sperm count, movement, or quality is poor. Live birth rates are very close to those of IVF for men with normal sperm counts.

ICSI may be associated with a slightly higher risk of birth defects. It is hard to know if the increased risk is due to the ICSI procedure itself or to defects in the sperm. The risk of birth defects after ICSI is still quite small (4.2% compared with 3% in children conceived naturally). Experts are still debating the impact of ICSI on the mental and physical development of children. Most recent studies have not detected any differences in the development of children born after ICSI, regular IVF, or natural conception.

Children conceived by ICSI have slightly more problems with their sex chromosomes (the X and Y chromosomes) than children conceived by IVF alone, but only by a very small margin (0.8% to 1.0% for ICSI pregnancies compared to 0.2% for IVF pregnancies). The reason for the difference is not clear. It may be caused by the ICSI procedure itself, or by the father. Men with sperm problems such as very low count and low motility are more likely to have genetic abnormalities. They often

produce sperm with abnormal chromosomes, especially with abnormal sex chromosomes (X and Y). If sperm with abnormal chromosomes produce pregnancies, the pregnancies will likely carry the same defects. Translocations (a re-arrangement of chromosomes that can cause miscarriage or birth defects) may be more common after ICSI.

Some men with extremely low sperm counts or no sperm have small deletions on their Y chromosomes. In some of these cases, sperm can be obtained to fertilize eggs with ICSI. Any sperm containing a Y chromosome microdeletion will pass on the deletion to any male child. These male children will also carry the microdeletion and may be infertile. A Y chromosome microdeletion can often, but not always, be detected by a blood test. This is because the chromosomes in the sperm may not always be the same as those seen when tested in the blood.

Some men are infertile because the tubes connecting the testes to the penis did not form correctly (congenital bilateral absence of the vas deferens [CBAVD]). These men can still father children, but sperm must be taken directly from the testicles or the tubes next to them. This sperm is then used in ICSI. These men have a mild form of cystic fibrosis (CF), which can be passed on to their children. Men with CBAVD and their partners should be tested for CF gene mutations before treatment. However, some CF mutations may not be detected by current tests, so that some parents who test negative for CF mutations can still have children affected by CF.

Preimplantation Genetic Testing (PGT)

- Preimplantation genetic testing of embryos requires removal of one or more cells from the embryo (*embryo biopsy*).
- This test is most often done on Day 5 or Day 6 of embryo development, but it may be done sooner in some circumstances.
- The cells removed from the embryo may be sent to an off-site lab for the testing, while embryos remain in storage at the clinic.
- In most cases, the tested embryos will need to be frozen (cryopreserved) while the test is being run.
- Test results can be incorrect.

There are several reasons that some patients choose to do PGT. Current reasons include:

- determining whether the embryo has the incorrect number of chromosomes ("PGT-A").
- determining whether the embryo has a structural rearrangement of its chromosomal material ("PGT-SR").
- determining whether the embryo has a specific disease-causing mutation ("PGT-M")
- determining the gender of the embryo.

PGT does not guarantee that a pregnancy will occur, even if embryo testing is normal. Factors other than the genes also influence pregnancy rates.

Screening the embryo's chromosomes, or testing for one specific genetic disease, does not guarantee that the embryo will be healthy and free of other disorders. For example, some common disorders that cannot be checked with PGT are autism and diabetes. Some birth defects can also occur even if chromosome screening is normal. An example of this would be a cleft lip or palate (failure of the lip and upper mouth to join properly).

It is always a possibility that PGT will show that there are NO normal embryos available to transfer.

Risks of embryo biopsy

- **Damage.** There is a small risk of damage to the embryo. This may result in no healthy embryos available to transfer.
- **No result.** The test may not give a result. Sometimes, there is not enough genetic material retrieved to run the test. It may be possible to repeat the biopsy and try again to test the embryo.
- **Misdiagnosis.** The test may give the wrong result, and say that a normal embryo is actually abnormal, or that an abnormal embryo is actually normal. The accuracy of testing is determined by the off-site lab. Most testing is very accurate, so the chance of misdiagnosis is low. Furthermore, since not all embryos are made up of cells with identical genetics (“mosaicism”), it is possible that accurate test result does not reflect the genetics of the entire embryo. Consequently, the current recommendation is to confirm the result in early pregnancy.

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 be released from the shell and implant in the uterus.**

The cells that make up the early embryo are coated with a membrane (shell) called the zona pellucida. Normally, as the embryo grows, this shell melts away. This lets the embryo be released or “hatch” from the shell. Only after hatching can the embryo implant in the uterus for the pregnancy to continue.

Assisted hatching makes it easier for the embryo to escape the shell. This is done on the lab, by making a small hole in the shell with a needle, a laser, or with chemicals. The procedure is usually done on the day of transfer, before putting the embryos into the transfer catheter.

Some programs use assisted hatching because of the belief that it improves implantation and birth rates. There is no absolute evidence of this, however. In most cases, assisted hatching is believed to be helpful in women who are over 38 years old when their eggs are harvested, or if they have failed to get pregnant in a previous IVF cycle. It can also be done when the shell around the embryo is extra thick. The thickness of the shell is checked on all embryos before embryo transfer.

Assisted hatching does have some risks. Very rarely, the embryo can be damaged, lose cells, or even be destroyed. There is also a higher chance of having identical twins if the embryos are cleavage stage (Day 3), which is a riskier pregnancy. There may also be other risks not yet known.

Cryopreservation

- **Freezing of eggs and embryos provides other chances for pregnancy in the future.**
- **Frozen eggs and embryos do not always survive the process of freezing and thawing.**
- **Freezing of eggs before fertilization does not work as well as freezing of embryos.**
- **Ethical and legal questions can arise when couples separate or divorce. It is vital to agree on what will be done with remaining eggs or embryos in those cases.**
- **A person or couple with frozen eggs or embryos MUST be in touch with the clinic once a year.**
- **There are usually yearly fees for keeping embryos or eggs frozen.**

Sometimes there are normally developing embryos left after embryo transfer. Additional normal-appearing embryos can be frozen for future use. In some cases, it may be planned for all embryos from an IVF cycle to be frozen (for example, when PGS is used). On the other hand, some women may wish to freeze their eggs because they are not ready to conceive now, or because they are planning to have therapy such as cancer treatment that could damage their eggs.

Benefits of freezing:

- Saves you from going through ovarian stimulation again if you need eggs or embryos in the future.
- Lets you transfer fewer embryos in the fresh cycle, and keep the others for a frozen cycle. This can reduce the risk of a multiple pregnancy (twins, triplets, or greater).
- Lets you freeze all embryos in the fresh cycle to prevent over-stimulation of the ovaries.
- Lets you freeze embryos while waiting for test results from PGS or PGD.
- Protects you if your future fertility is at risk because of surgery or other treatments such as cancer therapy.

There are different ways to freeze embryos. The most common are “slow” freezing and “rapid” freezing (called *vitrification*). You should know that embryos do not always survive the freezing and thawing process. There is always a risk that no embryos will survive. If this happens, the transfer will have to be cancelled. Studies of animals and humans indicate that children born from frozen embryo cycles do not have any greater chance of birth defects than children born after fresh embryo transfers. However, until very large numbers of children have been born from frozen embryos, it is not possible to be absolutely certain that there are no increased risks.

Risks of freezing:

The process of cryopreservation (freezing), storage, and thawing can damage cryopreserved eggs or embryos, and not all eggs and embryos will be successfully cryopreserved, or, if cryopreserved, successfully thaw, fertilize (if eggs), or be available for further treatment or implantation.

It is also possible that cryopreserved eggs and embryos may be damaged, destroyed, lost or fail to develop, and therefore be unavailable for further treatment or implantation, due to a number of potential factors, including, but not limited to: patient-specific differences in tolerance of gamete freezing; accidents; power outages; mechanical or equipment failure (including but not limited to loss of nitrogen or other tank failures); materials (including vials, straws and other containers used to freeze and store the samples and their labels); changes of any applicable law or regulations; human error; labelling errors; inventory record loss; natural and man-made disasters; sabotage; transportation or shipping accidents or other events which may be beyond the control of Carolinas Fertility Institute (CFI) or its laboratory. In accordance with its protocols, CFI makes reasonable efforts to handle and maintain its patients' eggs and embryos, including, but not limited to maintenance and monitoring of its equipment, materials and laboratory. Despite such efforts, I understand that as a result of one or more of these potential factors, my eggs and/or embryos may become unavailable for further treatment or implantation, or that the likelihood of a pregnancy resulting from any treatment or implantation may be reduced.

NOTE: In some cases, the clinic may not own or operate the laboratory responsible for cryopreservation or storage of your eggs or embryos and, therefore, cannot be responsible for laboratory processes beyond its knowledge and control. If this is true for your treatment, you may be asked to sign further documents with the laboratory. In the event my eggs or embryos are damaged, lost or destroyed, are otherwise unavailable for further treatment or implantation, or fail to result in a pregnancy, I hereby agree not to sue and agree to hold harmless, the CFI, and any of CFI's physicians, employees, or agent except in the event of willful misconduct or gross negligence on the part of CFI, or any of CFI's physicians, employees, contractors or agents.

Some clinics do not offer long-term storage, so will ship your embryos to another facility after a period of time. In the event the embryos are lost, damaged or destroyed during transport, are otherwise unavailable for further treatment or implantation, or fail to result in a pregnancy, I hereby agree not to sue and agree to hold harmless, CFI, and any of CFI’s physicians, employees, or agent except in the event of willful misconduct or gross negligence on the part of C, or any of CFI’s physicians, employees, or agents.

If you choose to freeze eggs or embryos, you MUST complete the Cryopreservation, Storage and Disposition of Embryos (or Eggs) Agreement before freezing. This statement must also be notarized. The statement explains the choices you have for disposing of the eggs or embryos in a variety of situations that may arise. You can submit a new statement later if you change your mind about your choices. For frozen embryos, any change requires that both parties – you and your partner-- agree in writing to the change. Be sure to let us now if you change your address. You must also pay storage fees as they come due.

Risks to the Woman

Ovarian Hyperstimulation Syndrome (OHSS)

This is the most severe side effect of stimulating the ovaries. Signs of OHSS include increased ovarian size, nausea, vomiting, and a buildup of fluid in the stomach. You may also have trouble breathing. In some cases, OHSS increases the level of red blood cells, and causes kidney and liver problems. In the most severe cases, it can cause blood clots, kidney failure, or death. All of these complications occur very rarely (in only 0.2% of all treatment cycles).

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 (because of the hCG if pregnancy occurs).

The risk of severe problems from OHSS is much higher if you become pregnant. For this reason, your doctor may suggest that your embryos be frozen for later use instead of transferring them in the fresh cycle. A frozen transfer can be done later, when there is no risk of OHSS.

Cancer

There is some concern that using fertility drugs can cause breast, ovarian, or uterine cancer. These cancers are more common in women with infertility, so it is difficult to know whether the reason for the cancer is the infertility itself or use of the drugs. In current studies that take into consideration the increased risk of cancer due to infertility, there does not seem to be an increased risk of cancer due to the fertility drugs alone. More studies need be done to confirm whether there is an association of cancer with use of fertility drugs.

Risks of Pregnancy

Getting pregnant through IVF comes with certain risks. This is partly because women using IVF are often older than those who might get pregnant on their own. In addition, the cause of the infertility itself may be to blame. There may be other risks linked to IVF that are not known at this time. Please see the table below for certain known risks.

Risks of Pregnancy with IVF

| | Singleton Pregnancies | Twin Pregnancies |
|--|-----------------------|------------------|
| | | |

| | Incidence in IVF Pregnancies (%) | Risk compared to other infertile women | Risk compared to fertile women | Incidence in IVF Pregnancies (%) | Risk compared to other infertile women | Risk compared to fertile women |
|-------------------------------------|----------------------------------|--|--------------------------------|----------------------------------|--|--------------------------------|
| Gestational diabetes | 8.2% | No difference | 41% higher | 10.7% | No difference | 23% higher |
| Pregnancy-induced hypertension | 12.6% | No difference | No difference | 25.5% | No difference | 15% higher |
| Placental complications | 5.2% | 95% higher | 281% higher | 4.9% | No difference | 83% higher |
| Primary cesarean delivery | 32.2% | 10% higher | 20% higher | 65.4% | 8% higher | 17% higher |
| Low birthweight (<5.5 pounds) | 7.7% | 21% higher | 65% higher | 50.4% | No difference | No difference |
| Preterm birth (<37 weeks gestation) | 10.3% | 26% higher | 70% higher | 53.8% | No difference | 7% higher |

About 25% of IVF pregnancies are multiple pregnancies (twins, triplets, or greater) in 2015, of which less than 1% are triplets or more. Identical twins occur in less than 5% of all IVF pregnancies. Identical twins may happen more often after blastocyst (Day 5 or 6) transfers. Multiple pregnancies in general have an increased risk of pregnancy problems. In addition to early delivery, problems include pre-eclampsia (high blood pressure and protein in the urine), excess bleeding with delivery, and diabetes of pregnancy (gestational diabetes). Problems with the placenta (afterbirth) are also more common. Other problems more common with multiple pregnancy include gall bladder problems, skin problems, and the need for extra weight gain.

In IVF, embryos are transferred directly into the uterus. Still, tubal, cervical, or abdominal pregnancies can sometimes occur. These abnormal pregnancies may need to be treated with medication or surgery. Abnormal pregnancies within the uterus can also occur.

Risks to Your Baby

- IVF babies may be at a slightly higher risk for birth defects and genetic defects.
- IVF has a greater chance of multiple pregnancy, even when only one embryo is transferred.
- A multiple pregnancy is the greatest risk to your baby when using IVF.

Overall Risks

The first IVF baby was born in 1978. Since then, more than 5 million children around the world have been born through IVF. Studies have shown that these children are quite healthy. In fact, some experts believe having a child through IVF is now just as safe as having a child naturally. Still, one must be careful when making this claim. Infertile couples do not have normal reproductive function. This means that a baby they have through IVF may have more health problems than a baby conceived naturally.

IVF single babies are often born about 2 days earlier than naturally conceived babies. They are about 5% more likely to weigh less than 5 pounds, 8 ounces (2,500 grams) than a naturally conceived single baby.

IVF twins are not born earlier or later than naturally conceived twins.

The risks of freezing have been checked in animal tests over several generations. Human data has also been checked. There is no proof that children born from frozen and thawed embryos or frozen and

thawed eggs have any more health problems than those born from fresh embryos. Still, it is hard to know for sure if the rate of health problems is the same as the normal rate.

Birth Defects

The risk of birth defects through normal birth is about 4.4 %, and it is about 3% for severe birth defects. In IVF babies, the risk for any birth defect is about 5.3%, while the risk for a severe birth defect is about 3.7%. Most of the increased risk with IVF seems to be due to older mothers and to having infertility. No higher risk is seen in frozen embryo or donor egg cycles.

Imprinting Disorders. These are rare disorders caused by whether the genes from the mother or the genes from the father are working. Studies do not agree on whether these disorders are associated with IVF. Even if they are, these disorders are extremely rare (1 out of 15,000 people).

Childhood cancers. Most studies do not suggest any extra risk, except for retinoblastoma (a cancer behind the eye). One study did report an increased risk after IVF treatment, but further studies did not find an increased risk.

Infant development. Most studies of long-term developmental outcomes have been reassuring so far. Most children are doing well. However, these studies are hard to do, and they have some limitations. A more recent study using better methods shows an extra risk of cerebral palsy and developmental delay. However, this arose mostly from prematurity and low birth weight that was a result of multiple pregnancy.

Risks of a Multiple Pregnancy

More than 30% of IVF pregnancies are multiple pregnancies (twins, triplets, or greater). Identical twins occur in less than 5% of all IVF pregnancies. Identical twins may happen more often after blastocyst (Day 5) transfers, and with assisted hatching after cleavage stage (Day 3) transfers.

Early delivery accounts for most of the extra problems associated with babies from multiple pregnancies. IVF twins deliver an average of three weeks earlier than IVF single babies, and they weigh about 2 pounds less than IVF single babies. Triplet (and greater) pregnancies deliver before 32 weeks (7 months) in almost half of cases. Fetal growth problems and unequal growth among the fetuses can also result in perinatal illness and death before or shortly after delivery.

Multiple fetuses that share the same placenta, such as most identical twins, have additional risks. Twin-to-twin transfusion syndrome, where the circulation is not equal between the fetuses, may occur in up to 20% of twins who share a placenta. Twins sharing the same placenta have a higher frequency of birth defects compared to twins with two placentas. Death of one fetus in a twin pregnancy after the first trimester is more common with a shared placenta; this may cause harm to the remaining fetus.

Other problems babies can face include cerebral palsy, retinopathy of prematurity (eye problems that result from early delivery), and chronic lung disease. No one knows how much multiple pregnancies affect neurological or behavioral development, even when none of the other problems occur.

Fetal death rates for single pregnancies are 4.3 per 1,000. For twins, that number is higher at 15.5 per 1,000; and for triplets, the fetal death rate is 21 per 1,000. The death of one or more fetuses in a multiple pregnancy ("vanishing twin") is more common in the first trimester and may be happen in up to 25% of IVF pregnancies. Loss of a fetus in the first trimester does not usually affect the surviving fetus.

The Option of Multifetal Pregnancy Reduction (Selective Reduction): The more fetuses there are in the uterus, the greater the chance of a problem. Patients with twins or more have 3 choices:

- Continue on with the pregnancy (with all the risks that have already been stated),
- End the pregnancy.
- Reduce the number of fetuses (terminate one or more of the fetuses) to lower the health risks to mother and child.

Reducing the number of fetuses lowers the risk of early delivery. This can be a difficult decision to make. The main danger is losing the entire pregnancy. The odds of losing the entire pregnancy are about 1 in 100 (1%). The odds of losing the entire pregnancy are greater if there are more than 3 fetuses present before the procedure is done.

Ethical and Religious Considerations in Infertility Treatment

Infertility treatment can raise ethical or religious concerns for some patients. IVF involves the creation of embryos outside the human body. It can also involve the production of extra embryos, and can lead to a high number of fetuses (triplets or more). Patients who have concerns should speak with their counselor or religious leader, or with someone else they trust. This can be a helpful step in infertility treatment.

Psychosocial Effects of Infertility Treatment

Finding out that you or your partner is infertile or have a lower fertility can be very painful. Infertility and its treatment can affect your emotions, your health, your finances, and your social life. During treatment, you may feel anxious, helpless, depressed, or all alone. You may go through highs and lows. Be sure to notice if these feelings get severe. In some cases, you may want to seek the help of a mental health expert. Here are some of the warning signs you should watch out for:

- Losing interest in the things you usually like to do.
- Feeling depressed most of the time.
- Strained feelings with your partner, family, friends, or those with whom you work.
- Thinking about infertility all of the time.
- Feeling extremely anxious or nervous.
- Having trouble finishing tasks.
- Finding it hard to focus or concentrate.
- Having changes in your sleep patterns, such as having a hard time falling asleep or staying asleep, waking up early every morning, or sleeping more than normal.
- Having a change in your appetite or weight (increase or decrease).
- Using drugs or alcohol more than before.
- Thinking about death or suicide.
- Staying away from other people.
- Feeling negative, guilty, or worthless much of the time.
- Feeling bitter or angry much of the time.

Raising twins or higher multiples may cause physical, emotional, and financial stresses. The chance of having depression and anxiety is higher in women raising multiples.

Patients may consider working with mental health professionals who are specially trained in the area of infertility care, as well as with their health care team, to minimize the emotional impact of infertility treatments. National support groups are also available, such as RESOLVE, (www.resolve.org), or Path2Parenthood (www.path2parenthood.org.org).

Reporting Outcomes

In 1992, the Fertility Clinic Success Rate and Certification Act was passed. This law requires the Centers for Disease Control and Prevention (CDC) to gather information about IVF cycles and pregnancy outcomes in the U.S. each year. This information is used to calculate success rates which are reported each year.

We (the Clinic) will report the required information from your IVF procedure to the CDC. Since our Clinic is a member of the Society of Assisted Reproductive Technologies (SART) of the American Society for Reproductive Medicine (ASRM), it will also be reported to SART. Information reported to SART about your cycle may be used for research or quality assessment according to HIPAA guidelines; your name will never be connected to your cycle information in any research that is published by ASRM or SART.

Research Conducted by SART

Since 2006, the Society for Assisted Reproductive Technology has participated in a series of studies looking at the health of women and children after IVF. Many of these studies are still being conducted. The studies compare women who have not had trouble conceiving and their children with women who used IVF and their children. The studies also compare women who had trouble conceiving but did not do IVF, and their children, to women and their IVF children. IVF children who have siblings form another study group. They are compared with their siblings who were conceived with IVF, conceived with non-IVF fertility treatment, or conceived spontaneously. The items studied are problems related to pregnancy or birth, and the risk of birth defects. Children are also followed to find out if they have developmental delays, problems in school, or increased risk of childhood or adult cancer. You can see the results of many of these studies in the information given below. Results can also be found on the SART website (www.sart.org) under "Research".

ASRM / SART

Initials: ____/____

Additional Information

General IVF overviews available on the internet

www.reproductivefacts.org

www.sart.org/

www.cdc.gov/art/

www.resolve.org/site/PageServer

Effect of Woman's Age

Female age-related fertility decline. Committee Opinion No. 589. *Fertility and Sterility* 2014; 101:633-4.

Effect of Number of Oocytes Retrieved

Baker VL, Brown MB, Luke B, Conrad KP. Association of number of retrieved oocytes with live birth rate and birth weight: An analysis of 231,815 cycles of in vitro fertilization. *Fertility and Sterility* 2015; 103:931-8.

Effect of Infertility Diagnoses

Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcomes by infertility diagnoses with and without ART treatment. *Fertility and Sterility* 2015; 103:1438-45.

Luke B, Stern JE, Kotelchuck M, Declercq E, Cohen B, Diop H. Birth outcomes by infertility diagnosis: Analyses of the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). *Journal of Reproductive Medicine* 2015; 60:480-490.

Effect of Maternal Obesity

Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. *Human Reproduction* 2011; 26:245-252.

Obesity and reproduction: A committee opinion. Practice Committee of the American Society for Reproductive Medicine. *Fertility and Sterility* 2015; 104:1116-26.

Number of Embryos to Transfer

Elective single-embryo transfer. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. *Fertility and Sterility* 2012; 97:835-42.

Criteria for number of embryos to transfer: 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* 2013; 99(1):44-6.

Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of embryos to transfer: A committee opinion. *Fertility and Sterility* 2017; 107:901-3.

Culturing Embryos to the Blastocyst Stage

Blastocyst culture and transfer in clinical-assisted reproduction: 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* 2013; 99:667-72.

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.

Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion. Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. *Fertility and Sterility* 2012; 98:1395-9.

Wen J, Jiang J, Ding C, Dai J, Liu Y, Xia Y, Liu J, Hu Z. Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. *Fertility and Sterility* 2012; 97(6): 1331-1337 e4.

Embryo hatching

The role of assisted hatching in in vitro fertilization: a guideline. 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* 2014; 102:348-51.

Luke B, Brown MB, Wantman E, Stern JE. Factors associated with monozygosity in assisted reproductive technology (ART) pregnancies and the risk of recurrence using linked cycles *Fertility and Sterility*, 2014; 101:683-9.

Ovarian Hyperstimulation

Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. The Practice Committees of the American Society for Reproductive Medicine. *Fertil Steril* 2016;106;1634-47.

Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on Assisted Reproductive Technology (ART) treatment and outcome. *Fertility and Sterility* 2010; 94:1399-404.

Risks of pregnancy

Declercq E, Luke B, Belanoff C, Cabral H, Diop H, Gopal D, Hoang L, Kotelchuck M, Stern JE, Hornstein MD. Perinatal Outcomes Associated with Assisted Reproductive Technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). *Fertility and Sterility* 2015; 103:888-895.

Risk of borderline and invasive tumours after ovarian stimulation for *in vitro fertilization* in a large Dutch cohort. FE van Leeuwen, H Klip, et al. *Human Reproduction*, 2011;26(12):3456-65.

Luke B, Brown MB, Spector LG, Missmer SA, Leach RE, Williams M, Koch L, Smith Y, Stern JE, Ball GD, Schymura MJ. Cancer in women after assisted reproductive technology. *Fertility and Sterility* 2015; 104:1218-26.

Risks to offspring

Fauser BCJM, Devroey P, Diedrich K, Balaban B, Bonduelle M, Delemarre-van de Waal HA, Estella C, Ezcurra D, Geraedts JPM, Howles CM, Lerner-Geva L, Serna J, Wells D, Evian Annual Reproduction Workshop Group 2011. Health outcomes of children born after IVF/ICSI: A review of current expert opinion and literature. *Reproductive BioMedicine Online* 2014; 28:162-182.

Multiple pregnancy associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Practice Committees of the American Society for Reproductive Medicine *Fertil Steril* 2012; 97:825-34.

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

Amor DJ and Halliday J. A review of known imprinting syndromes and their association with assisted reproduction technologies. *Human Reproduction* 2008; 23:2826-34.

Bergh C, Wennerholm U-B. Obstetric outcome and long-term follow up of children conceived through assisted reproduction. *Best Practice & Research Clinical Obstetrics and Gynaecology* (2012), doi:10.1016/j.bpobgyn.2012.05.001.

Wennerholm U-B, Söderstöm-Anttila V, Bergh C, Aittomäki K, Hazekamp J, Nygren K-G, Selbing A, Loft A. Children born after cryopreservation of embryos or oocytes: A systematic review of outcome data. *Human Reproduction* 2009; 24:2158-72.

Kopeika J, Thornhill A, Khalaf Y. The effect of cryopreservation on the genome of gametes and embryos: principles of cryobiology and critical appraisal of the evidence. *Human Reproduction Update* 2015; 21:209-227.

Birth Defects

Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad PO. Congenital malformations in infants born after in vitro fertilization in Sweden. *Birth Defects Research (Part A)* 2010; 88:137-43.

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive Technologies and the risk of birth defects. *N Engl J Med* 2012;366:1803-13.

Boulet SL, Kirby RS, Reefhuis J, Zhang Y, Sunderam S, Cohen B, Bernson D, Copeland G, Bailey MA, Jamieson DJ, Kissin DM. Assisted reproductive technology and birth defects among liveborn infants in Florida, Massachusetts, and Michigan, 2000-2010. *JAMA Pediatrics* 2016; Published online April 04, 2016. doi:10.1001/jamapediatrics.2015.4934

IVF Treatment Plan

Patient name: _____ Date: _____
Spouse / partner name: _____ for IVF when? _____

Provider of Sperm.

We (I) plan to use sperm from:

- Spouse / partner
- Donor (specify name or number): _____
- Other (specify arrangement): _____

Initials: ____ / ____

Carrier of embryos.

We (I) plan to transfer the embryos into:

- Me, the intended parent
- A Gestational Carrier
----if known, her name: _____

Initials: ____ / ____

Method of Insemination.

We (I) acknowledge that we (I) have discussed the possibility of the need for ICSI with our (my) physician and understand, agree and consent that:

- ICSI *will be* used.
- ICSI *will not* be used.
- ICSI *will not* be used, unless the semen at time of egg retrieval is sub-optimal based on the best medical judgment of the ACRM staff, or the initial fertilization is poor. In these cases ICSI may be used. We (I) understand that we (I) will be notified if ICSI is performed.

Initials: ____ / ____

Initials: ____ / ____

Limit on Number Inseminated?

Regarding the number of eggs to expose to sperm, we (I) choose:

- Inseminate ALL Mature Eggs
- Inseminate SOME Mature Eggs

Number or fraction of eggs to be exposed to sperm: _____

Initials: _____ / _____

Plan for Eggs NOT Inseminated (if applicable).

Regarding the eggs not exposed to sperm for fertilization we (I) choose:

- Freeze for my later use (requires Disposition Declaration)
- Donate to:
 - Research
 - Another person or couple
- Discard. This disposal will follow ASRM Ethical Guidelines. These extra eggs will no longer be available for attempting a pregnancy.

Initials: _____ / _____

Plan for Embryos NOT Transferred.

Regarding the disposition of embryos not transferred, we (I) elect the following option:

- Freeze Excess Embryos (requires Disposition Declaration)
- Donate Excess Embryos to:
 - Research
 - Another person or couple
- Discard Excess Embryos. This disposal will follow ASRM Ethical Guidelines. These extra embryos will no longer be available for attempting a pregnancy.

Initials: _____ / _____

Plan for Preimplantation Genetic Testing / Screening.

We (I) choose:

- No genetic testing / screening of embryos
- Genetic testing of all blastocysts no matter how few are available
- Genetic testing of all blastocysts if enough are available to test (in consultation with embryology lab staff).

Initials: _____ / _____

Patient signature: _____

Partner / spouse signature: _____

WVFI Staff signature: _____

Date: _____

We (I) acknowledge that we have read and understood the information provided above regarding the IVF process and its risks, and agree to go forward with this treatment as our signatures below testify.

X

 Patient Signature _____ Date _____

 Patient Name _____ Date of Birth _____

Notary Public
 Sworn and subscribed before me on this ____ day of _____, _____.

 Notary Signature _____ Date _____

X

 Spouse / Partner Signature _____ Date _____

 Spouse / Partner Name _____ Date of Birth _____

Notary Public
 Sworn and subscribed before me on this ____ day of _____, _____.

 Notary Signature _____ Date _____

=====

Statement by Witness (must be employee of Clinic and at least 18 years of age)

I declare that the person who signed this document is personally known to me and appears to be of sound mind and acting of his or her own free will. He or she signed (or asked another to sign for him or her) this document in my presence.

Witness Name: _____
 Witness Signature: _____
 Date: _____