Columbia University Fertility Center
5 Columbus Circle PH
New York, NY 10019 | O: 646.756.8282 | Fax: 646.756.8281

DOB:

In Vitro Fertilization/ PGT

In Vitro Fertilization Consent

This "In Vitro Fertilization" (IVF) consent is intended to inform you about the IVF process at the Columbia University Fertility Center (the Fertility Center) in detail, including the risks to both patients and potential children. If you do not understand the information provided, please speak with your nurse or physician. Consent may be withdrawn at any time before embryos are created and requires a Columbia University Fertility Center witnessed directive. While this consent is comprehensive, there are circumstances that cannot be foreseen, that may have a negative effect on your cycle or stored material.

In Vitro Fertilization Process & Risks

In Vitro Fertilization (IVF) is a treatment that aspirates eggs from a female ovary or ovaries to be fertilized with pre-selected sperm; resulting embryos may be transferred, cryopreserved or biopsied and cryopreserved in an attempt to achieve a pregnancy either with this treatment cycle or at a later time. The majority of transfers at the CUFC are from cryopreserved embryos. A patient can use sperm provided by her partner or from a pre-selected sperm donor.

We will be testing all patients for COVID-19. The protocol is changing rapidly as information on this virus is changing rapidly. Speak to your care coordinator team concerning the latest protocol. Please be aware if you test positive at any time during the course of treatment the cycle may be delayed by a few weeks or cancelled.

An IVF cycle typically includes the following steps or procedures:

- Taking medication to grow several eggs at once.
- Under anesthesia, surgically removing the eggs from the ovary or ovaries.
- Mixing eggs and sperm together in the embryology lab so the eggs may be fertilized.
- Injecting individual sperm into each egg, called intracytoplasmic sperm injection (ICSI).
- Growing any resulting fertilized eggs (embryos) in the embryology lab.
- The choice of biopsy/ genetic screening and cryopreserving embryos for a future transfer.
- Assisted hatching embryos for biopsy or embryo transfer.
- Cryopreservation (freezing) of eggs or embryos for a future transfer.
- Placement ("transfer") of typically one embryo into the uterus, typically during a frozen embryo transfer.
- Taking hormone medications to help you have a successful pregnancy during and after your frozen embryo transfer cycle.

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.
- Other medications are used to keep ovulation from happening too soon.
- Sometimes the ovaries respond too strongly—and sometimes not enough.

Medications Commonly Used in IVF Cycles

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.

Gonadotropins, or injectable "fertility drugs": (Follistim®, Gonal-F®, Menopur®, 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. 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. 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 patients have bloating or minor discomfort as the ovaries briefly become enlarged. Other side effects can include headaches, weight gain, feeling tired, mood swings or nausea. About 1% of patients will develop a potentially dangerous syndrome called Ovarian Hyperstimulation Syndrome (OHSS). This condition is rare due to advances in IVF medications and cycle management, but is more likely in patients with very high AMH (ovarian reserve). While bloating and dehydration are common in most patients going through IVF, OHSS can include severe bloating, laboratory changes (involving electrolytes, liver function and/or kidney function), and/or increased risk of clots in blood vessels. [See full discussion of OHSS in the Risks to the Patient section which follows].

GnRH-agonists (leuprolide acetate) (Lupron®): This 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. Leuprolide can cause a number of side effects. These include hot flashes, vaginal dryness, nausea, headaches, and muscle aches. Some patients 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 cetrorelix 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 be aspirated and attempt to 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 patients, 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.

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 patients include headache, hot flashes, or increased moodiness. They are taken by mouth in pill form.
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.

Egg Retrieval and Risks

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, is attached to the ultrasound probe. Guiding the needle into the ovaries, the physician will draw out fluid, eggs, and egg-supporting cells. Anesthesia administered by an anesthesiologist will be used to reduce or eliminate pain; the anesthesia is considered conscious sedation or "twilight sleep" where you are breathing on your own and sleeping. After the retrieval you may feel mildly uncomfortable which is considered normal.

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 very rarely 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

The physician will aspirate fluid, eggs, and egg-supporting cells from the ovary; the aspirates are immediately transferred to the embryology lab to be processed by an embryologist. The eggs are placed in small petri dishes containing "culture medium," which is specially developed media to support egg growth. 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 appropriate levels to support embryo development. 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 continue to develop and grow. They are assessed at various intervals over the next few days, to check their progress.

- Sperm and eggs are placed together (or ICSI is performed).
- 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.
- Embryos remain in controlled culture conditions throughout their time in the embryology laboratory and are inspected at regular intervals.

- The embryologist chooses the best embryos for transfer, for biopsy or cryopreservation by the way they look under a microscope (embryo assessment).

Embryo Development

Embryo development typically proceeds along the following cleavage (dividing) schedule:

- *Day 0:* This is retrieval day (or egg thaw day), the day the eggs and sperm will be placed together or ICSI performed.
- *Day 1*: This is the day that the eggs and sperm have already come together, and we will check for signs of fertilization. Not all eggs fertilize and some fertilize abnormally. At this stage, the normally fertilized egg is still a single cell with 2 nuclei, called a 2PN or zygote.
- *Day 2*: Typically, embryos will divide into 2 to 4 cells (the embryos are not checked on this day).
- *Day 3*: Normally developing embryos will continue to divide and usually 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 (the embryos are not checked on this day).
- *Day 5/6/7*: 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. An embryo that makes it to the blastocyst stage does not automatically mean it is a chromosomally normal embryo. Approximately half of all fertilized embryos reach this stage but it can vary from none to all embryos in a given cycle.

<u>It is important to understand that for any age group, many eggs and embryos are abnormal.</u> This means that some eggs will not fertilize, some embryos will not divide at a normal rate or may simply stop dividing. Even if your embryos develop according to the normal cleavage schedule, they may not be genetically normal. It is possible to biopsy embryos ("preimplantation genetic screening"), to identify an embryo with a normal number of chromosomes; even genetically normal embryos may not be healthy and will not produce a pregnancy. Unless genetic testing is done, the embryos that look the best under the microscope are chosen for transfer.

<u>There are many reasons why pregnancy may not happen with IVF</u>

- 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 or cryopreserved.
- The fertilized eggs may not divide, or the embryos may not develop normally.
- In spite of having backup systems in place, lab equipment may fail or power may be lost. Anticipated (hurricane, blizzard) or unforeseen disasters (floods, building shutdown, acts of terrorism, pandemic) may prevent clinical activities at the Fertility Center; both can lead to the destruction of eggs, sperm, and embryos.
- A lab accident or human error can happen and can lead to tissue lost.
- Other unforeseen events may prevent any step of the process from being performed or prevent a pregnancy from occurring.

<u>Quality Control</u>: The process of running tests to ensure that lab conditions are the best they can be to help eggs fertilize and 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 (and can never result in a normal pregnancy), 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.

Intracytoplasmic Sperm Injection (ICSI)

Intracytoplasmic sperm injection or 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 ICSI 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 if not equal to those of IVF for men with normal sperm counts.

In some cases, fertilization will not happen when eggs and sperm are placed together in a petri dish. Injecting a single sperm into each egg (ICSI, or intracytoplasmic sperm injection) can help fertilization occur. ICSI does not guarantee normal fertilization.

- The egg may be damaged or destroyed during the ICSI process.
- There may be a slight increased risk of genetic problems in children born from ICSI.
- ICSI will not improve any defects in the eggs.

Reports on the risk of birth defects associated with ICSI (compared to those associated with conventional fertilization in IVF cycles) have yielded conflicting results. 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 relatively low (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 sperm. 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), and may pass on this gene 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.

Embryo Transfer

Embryos can be transferred during a fresh cycle at day 1 to day 5 of development. Typically, at the CUFC the embryos are frozen for transfer at a future date. Usually one embryo is placed in the uterus using a thin tube called a transfer catheter. Ultrasound is used to help guide the catheter and to help confirm placement through the cervix and into the uterus. Although this is a simple process, and does normally not require anesthesia, there are some very rare risks. These risks include infection, loss of the embryos, or damage to the embryos. Not all embryos become pregnancies, and not all pregnancies are normal or grow in the correct place – tubal pregnancies can occur. Very rarely the physician cannot perform the transfer and the embryos may be transferred under anesthesia.

- Embryos can be transferred on any day of embryo development, but at the CUFC morphologically normal appearing embryos are routinely cryopreserved for transfer at a future date; embryos that are/ or are not biopsied are routinely cryopreserved at the blastocyst stage development day 5 to day 7.
- You will discuss with your physician the number of embryos to thaw and transfer before the transfer event. Typically, one blastocyst stage embryo is transferred.
- If preimplantation genetic screening has been performed, one euploid (normal) embryo will be transferred during a thawing cycle.
- If you transfer more than one embryo you proceed with the knowledge that you are at risk for becoming pregnant multiple implantation (twins or greater attaching to the lining of the uterus).

Hormonal Support of the Uterine Lining

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.

Assisted Hatching

The cells that make up the early embryo are coated with a membrane (outer shell) called the zona pellucida. Normally, as the embryo grows, this shell becomes very thin so the embryo can "hatch" from its shell. Only after hatching can the embryo implant in the uterus. Assisted hatching makes it easier for the embryo to escape the shell. This is done in the lab, by making a small hole in the shell with a laser. The procedure is usually done on the day of the frozen embryo transfer, before putting the embryos into the transfer catheter. During a biopsy cycle, all normally fertilized developing embryos will be assisted hatched for potential biopsy. 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 embryo is hatched. There may also be other risks not yet known.

- Assisted hatching involves making a small hole in the outer shell (zona pellucida) that surrounds the embryo.
- Assisted hatching will be used for all developing embryos in an embryo biopsy cycle.
- Hatching may make it easier for embryos to be released from the shell and implant in the uterus.
- Assisted hatching is performed on all oocytes/embryos after they are thawed before transfer.

Cryopreservation

- At the CUFC most cycles are cryopreservation cycles without a fresh transfer.
- Embryos can be cryopreserved on any cycle day, but typically embryos that reach the blastocyst stage on day 5, 6, or 7 and are normal appearing may be biopsied and cryopreserved or cryopreserved without embryo biopsy for a future frozen embryo transfer cycle. After embryo biopsy, embryos are cryopreserved to await genetic testing results and may be transferred during a frozen embryo transfer cycle.
- Fertility preservation can be achieved when eggs or embryos are frozen and banked (stored) for short or long periods of time; the eggs or embryos can be thawed when the person or couple are ready to attempt a pregnancy.
- Frozen eggs and embryos do not always survive the process of freezing and thawing.
- Studies on 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.
- Legal questions can arise when couples terminate their relationship (e.g. divorce) or one both contributor(s) to the embryo passes away. <u>It is vital to agree on what will be done with cryopreserved embryos remaining in storage beforehand by signing an embryo disposition consent before embryos are cryopreserved.</u> It is suggested you also have a written plan for your cryopreserved embryos.
- A person or couple with frozen eggs or embryos <u>MUST</u> stay in touch with the Fertility Center. If it is greater than 3 years with no patient communication, despite the Fertility Center attempting to contact the person or couple, it will be assumed the cryopreserved material has been abandoned and may be discarded without additional consenting.
- Cryopreserved material should not be stored indefinably at the Fertility Center, it is recommended if your infertility treatment is complete that the oocytes or embryos are transported to a commercial storage facility or you sign a disposition form to donate or discard the cryopreserved material.
- As cryopreserved storage at the Fertility Center is limited, the stored eggs or embryos in storage may be transported to a long-term storage facility on your behalf. You will be contacted concerning details of this transport.
- There are annual fees to store cryopreserved gametes (eggs and sperm) and embryos.

Columbia University Fertility Center
5 Columbus Circle PH
New York, NY 10019 | O: 646.756.8282 | Fax: 646.756.8281

DOB:

If you choose to freeze embryos, you MUST complete this section on embryo donation. It is vital to agree on embryo donation before the IVF procedure to satisfy regulatory requirements. Please choose one disposition choice below**. By signing to donate, this does not mean you are required to donate, but your embryos will be eligible to donate**.

_____**I/we are considering** donating my/our cryopreserved embryo(s) to another person/couple. I/we understand to satisfy regulatory requirements for embryo donation, the contributors to the embryo (unless donor) will need additional blood testing and complete a simple questionnaire either the week before or the week after the egg retrieval. The third-party reproduction team will guide you through this process to make it as simple as possible. **Embryo(s) cannot be donated to a person/couple without this additional testing and a completed questionnaire.**

_____I/we **DO NOT** wish to donate to another person/couple. **I/we understand without the additional regulatory testing** before embryos are created we will not be able to donate to another person/couple.

++
By signing below, I/We acknowledge the above selection:

_____	_____	_____
Patient	Partner (if applicable)	Date

Risks of Freezing

In accordance with its protocols, the Fertility Center makes reasonable efforts to manage and properly maintain its patient's cryopreserved material (eggs, sperm and embryos), including, but not limited to storage tank maintenance and monitoring, continual monitoring of the storage tanks via an alarm system with remote capability, and 24 hour embryology surveillance. There is a slight risk that the cryopreservation process (freezing/ storage and thawing) can damage an embryo (the CUFC experience is that ~ 97% of frozen blastocysts survive thawing/warming). 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.

There are circumstances out of the Fertility Center's control that could have harmful effects on your cryopreserved materials:

- Natural and man-made disasters.
- Loss of power to 5 Columbus Circle or New York City.
- Equipment failure (including but not limited to loss of nitrogen or other tank failures).
- Transportation or shipping accidents.

In the event my cryopreserved donor eggs or embryos are damaged, lost or destroyed, are otherwise unavailable for further treatment or implantation, or fail to result in a pregnancy, I/we hereby agree not to sue and agree to hold harmless, the Fertility Center, Columbia University and any of its physicians, employees, or agents.

Risks to the Patient

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). Your physician may suggest freezing embryos for a future transfer.

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: 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.

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.

Maternal Risks	**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)

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.

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.

Risks of Multiple Gestation

Historically more than 25% of IVF pregnancies were multiple gestation (multiple pregnancies), at the Columbia University Fertility Center we have successfully lowered our multiple gestation rate by performing single embryo transfers; in 2019 less than 4% of IVF pregnancies were multiples. Identical twins occur in less than 5% of all IVF pregnancies, identical twins may happen more often after blastocyst (Day 5/6/7) transfers.

Multiple gestation in general has an increased risk of pregnancy problems. The most important maternal complications associated with multiple gestation are premature delivery ("early delivery" accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations), pre-eclampsia (high blood pressure and protein in the urine), diabetes of pregnancy (gestational diabetes), excessive bleeding at delivery and placental disorders are more common. Other problems more common with multiple pregnancy include gallbladder 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.

Placenta previa and vasa previa are more common complications in multiple gestations. Abruptio 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.

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. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. 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. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

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

Risks to Your Baby

IVF babies may be at a slightly higher risk for birth defects and genetic defects, IVF has a slightly increased risk of multiple pregnancy, even when only one embryo is transferred.

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. 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.

Birth Defects: The risk of birth defects through normal birth is about 4.4 %, and it is about 3% for severe birth defects; no higher risks are 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.

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 some complications. 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. 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.

Consent for Preimplantation Genetic Testing for Aneuploidy (PGT-A)

Preimplantation Genetic Testing (PGT) of embryos. This portion of the consent pertains to the specific procedures, risks, benefits and results of PGT.

Trophectoderm biopsy is the primary method of embryo biopsy. Since trophectoderm cells are extra-embryonic tissue, they do not become part of the fetus but do become part of supporting structures, such as the placenta and membranes. The advantage of this method is ~5 trophectoderm cells can be removed from the embryo for analysis. Trophectoderm biopsy takes place at the blastocyst stage on day 5, day 6 or day 7 of embryo development. For this procedure to be performed, all normally dividing embryos will undergo assisted hatching on day 3. There must be at least one fully expanded, morphologically normal blastocyst on day 5, day 6 or day 7 for trophectoderm biopsy to be performed. After the biopsy is performed, the blastocysts will be cryopreserved for possible future embryo transfer.

PGT-A Results

Euploid: Normal number of chromosomes per cell. This embryo is recommended for transfer.

Aneuploid: Abnormal number of chromosomes per cell. This embryo is not recommended for transfer.

Mosaic: This embryo is predicted to have some cells with an abnormal number of chromosomes and some with a normal number of chromosomes. These embryos are not recommended for transfer. However, apparently normal live births have been reported from the transfer of embryos with a mosaic result. There is still limited experience with transfer of mosaic embryos and no long-term data. This embryo may be considered for transfer if no euploid embryos are available and the risks have been thoroughly explained by your physician and/or genetic counselor.

No Result: No DNA, no result or degraded DNA – a reliable result could not be obtained from these embryos. These embryos can be transferred with an untested status or the embryo can be re-biopsied, re-frozen and sent for analysis. This would require a follow-up conversation with your physician.

Euploid (normal) embryos and mosaic embryos
Will remain in cryopreserved storage.

DOB:

Disposition of abnormal embryos

Please select and initial A, or B, or C concerning disposition of abnormal embryos.

A. Continue to store all embryos in cryopreserved storage, no matter what the result even if classified as abnormal. Storage fees may apply.

B. Donate to research or discard (discard if cannot be used for research).

C. Discard only.

++

By initialing below, I/We acknowledge the above selection:

_____ _____

Patient Initials Partner Initials (if applicable)

PGT Risks of the Procedure

Damage to the embryo during the biopsy procedure may result in a decrease in the embryo's ability to develop and/or implant. The risk of damage from biopsy is uncertain but one publication found no significant impact from trophectoderm biopsy (Scott RT, Upham KM, Forman EJ, et. al. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. *Fertil Steril* 2013;100:624-30)

- Embryos may not progress to the blastocyst stage of development by day 5, day 6 or day 7 and will not be biopsied.
- The DNA from the biopsy may be affected during transport to the outside laboratory.
- There is a 3-5% risk of a cryopreserved blastocyst not surviving cryopreservation or thawing.
- None of the embryos may be eligible for transfer and aneuploid embros will not be transferred.
- The genetic testing of the embryo may be inaccurate or inconclusive.

Additionally, given that testing is not perfect and only the trophectoderm layer is sampled, please understand that prenatal non-invasive and/or invasive genetic testing is strongly recommended. Invasive methods such as chorionic villous sampling or amniocentesis may be recommended and are associated with a risk of pregnancy loss (<1%).

The laboratory will only release the results of the screening tests to my/our doctor or to his/her agent unless otherwise authorized by you as required by law.

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 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.

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".

Regulatory Inspections

The Fertility Center is licensed by the New York State Department of Health, accredited by the American Association for Accreditation of Ambulatory Surgery Facilities and is registered with the Food and Drug Administration (FDA). These agencies inspect the Fertility Center regularly to maintain licensure and accreditation. All program records must be made available to regulatory inspectors during the course of an inspection.

Columbia University Fertility Center
5 Columbus Circle PH
New York, NY 10019 | O: 646.756.8282 | Fax: 646.756.8281

DOB:

In Vitro Fertilization/ PGT

Informed Consent

Signing this consent indicates that the consent has been read in its entirety, all of your questions have been answered and the information is understood. If you have questions or concerns or require additional clarification, please contact your physician/ nurse team before signing. This consent is valid for one year from the date it is signed. This consent may be rescinded at any time by any of the signed parties. In the event that any of the signed parties withdraw from participation, then this consent is nullified and will require consultation with a Columbia University Fertility Center physician and the resigning of all pertinent consents.

Additional consents will be signed at the time of the retrieval and will include procedure and anesthesia consents.

Partner Name _____
(If applicable)

Signatures:

Patient: _____ Date: _____

Partner: _____ Date: _____
(If applicable)