

**Assisted Reproduction**

**Consent for Treatment**

# Consent for Assisted Reproduction

## In Vitro Fertilization, Intracytoplasmic Sperm Injection, Assisted Hatching, Egg Cryopreservation, Embryo Cryopreservation, and Preimplantation Genetic Testing

### INSTRUCTIONS:

**Please read this document carefully. If you do not understand the information provided, please speak with your treating physician. This material is being presented so you can make an informed decision regarding the elements of IVF treatment you agree to undertake in your upcoming IVF treatment cycle.**

### OVERVIEW

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

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

*An IVF cycle typically includes the following steps or procedures:*

- *Taking hormonal medications to grow several eggs at once*
  - *Removing the eggs from the ovary or ovaries*
  - *Mixing eggs with sperm together so the eggs can be fertilized*
  - *Growing any resulting fertilized eggs into embryos in the lab*
  - *Placement ("transfer") of one or more embryo(s) into the uterus • Taking hormonal medications to support a successful pregnancy*
- Sometimes other IVF steps may be included:***
- *Injecting individual sperm into each egg, called intracytoplasmic sperm injection (ICSI)*
  - *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*

### **Suboptimal stimulation response consent:**

There is a chance during any IVF treatment cycle that stimulation medication may not induce the desired response in number of mature follicles/oocytes (eggs) to move on to the transvaginal oocyte (egg) retrieval. In this case it may be medically indicated to convert to intrauterine insemination/timed intercourse or treatment cycle cancellation.

### **Important abstinence/contraception consent:**

For an IVF/embryo transfer cycle (including frozen embryo transfers), we advise that you abstain from intercourse or use condoms during your treatment cycle up to its completion when we have the result of a pregnancy test letting us know if the treatment was successful. This is to avoid a high risk multiple gestation pregnancy from a concurrent natural conception.

## **CORE ELEMENTS OF IVF, BENEFITS AND RISKS MEDICATIONS for IVF TREATMENT**

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

### **Gonadotropins, or injectable “fertility drugs”**

(Follistim®, Gonal-F®, Menopur®) These natural hormones stimulate the ovary over the span of 8 or more days, with the intentions of growing several oocytes (eggs). These hormonal medications are given by injection, either just under the skin or directly into muscle. Proper dosage of these drugs and the timing of egg retrieval require monitoring of the ovarian response, usually by way of blood tests and ultrasound examinations during the ovarian stimulation.

- *The success of IVF largely depends on growing several eggs at once*
- *Injections of gonadotropins, the natural hormones follicle stimulating hormone (FSH) and/or luteinizing hormone (LH), are used for this purpose*
- *Other medications may be used to prevent ovulation from happening too soon, before the eggs are retrieved surgically*
- *Sometimes the ovaries respond too strongly and sometimes not enough*

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

Sometimes, especially when testing prior to the IVF cycle has shown that the woman has a lower number of eggs (*diminished ovarian reserve*), the medications may result in very few follicles developing, the end result may be few or no eggs obtained at egg retrieval or even cancellation of the treatment cycle prior to egg retrieval.

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

### **GnRH-agonists: Leuprolide acetate (Lupron®)**

This medication is taken by injection. There are two forms of the medication: A short acting medication requiring daily injections and a long-acting preparation lasting for 1 to 3 months. It is the short-acting form that is used primarily in the IVF process. The primary role of this medication is to prevent premature spontaneous release of eggs before they are ready to be retrieved. Since GnRH-agonists (GnRH-a) initially cause a release of FSH and LH from the pituitary, they can also be used to start the growth of the follicles or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has been used in this way since 1988. Potential side effects experienced with long-term use include, but are not limited to, hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. No long term or serious side effects are known with short term use of this medication. Since GnRH-a injections may be started after ovulation, you should use contraception (either contraceptive pills or condoms) the month you will be starting the GnRH-a. GnRH-a have not been associated with any birth defects, however, it should be avoided if you might be pregnant.

### **Medications for IVF Treatment (continued) GnRH-antagonists: Ganirelix Acetate or Cetrorelix Acetate (Cetrotide®)**

These are another class of medications used to prevent premature ovulation. The potential side effects include, but are not limited to, abdominal pain, headaches, skin reaction at the injection site, and nausea.

**Human chorionic gonadotropin (hCG) (Profasi®, Novarel®, Pregnyl®, Ovidrel®)** hCG is a natural hormone used in IVF to induce the eggs to become mature and fertilizable. The timing of this medication is critical to retrieve mature eggs. Potential side effects include, but are not limited to, breast tenderness, bloating, and pelvic discomfort.

## **Progesterone, and in some cases, estradiol**

Progesterone and estradiol are hormones normally produced by the ovaries after ovulation. After egg retrieval in some women, the ovaries will not produce enough of these hormones to support a pregnancy. Adding them helps improve your chances of getting pregnant and staying pregnant. Progesterone is usually given by injection or by the vaginal route (Endometrin®, Crinone®, Prometrium®, or pharmacist-compounded suppositories after egg retrieval. Progesterone is often continued for some weeks after a pregnancy has been confirmed. Progesterone has not been associated shown to cause birth defects. Side effects of progesterone include depression, sleepiness, allergic reaction and, if given by intra-muscular injection, includes the additional risk of infection or pain at the application site. Estradiol, if given, can be by pill, patch, intramuscular, or vaginal suppository. Side effects of estradiol include nausea, irritation at the injection site if given by intramuscular injection and the risk of blood clots or stroke.

### **Oral contraceptive pills:**

Many treatment protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to slow down hormone production and synchronize egg production. Side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling and the risk of blood clots or stroke.

### **Other medications:**

Anti-anxiety medications or muscle relaxants may be recommended prior to the embryo transfer; the most common side effect is drowsiness. Other medications such as steroids, heparin, low molecular weight heparin or low dose aspirin may also be included in the treatment protocol.

## **TRANSVAGINAL OOCYTE (EGG) RETRIEVAL**

Oocyte retrieval is the removal of eggs from the ovary most often under anesthesia. **If under anesthesia the procedure is performed on an empty stomach, this means nothing to eat or drink after midnight the night before the procedure.** A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A long needle, which can be seen on ultrasound, is used to puncture each follicle and the contents aspirated. The aspirated material includes follicular fluid, oocytes (eggs) and granulosa (egg-supporting) cells. On occasion the ovaries are not accessible by the transvaginal route. These procedures and risks will be discussed with you by your doctor if applicable. Anesthesia is generally used to reduce, if not eliminate, discomfort.

It is important to recognize that not all follicles contain eggs. In general, 50-70% of follicles are likely to provide an egg. Follicles 15 mm and greater are the most likely to yield eggs. Not all eggs retrieved will be mature eggs which can be fertilized.

## **Risks of egg retrieval include:**

### ***Infection:***

Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can reduce your chances of getting pregnant in the future. Antibiotics are routinely administered before the egg retrieval procedure to reduce the risk of pelvic or abdominal infection. Despite the use of antibiotics, there is no way to completely eliminate this risk.

### ***Bleeding:***

The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels.

In addition, there are other blood vessels nearby. A small amount of bleeding is common and expected during egg retrievals. The risk of major bleeding problems has been estimated to be less than 0.1%. Major bleeding may require surgery and possibly loss of the ovary. The need for blood transfusion is possible, however the risk of this is very low. Although extremely rare, unrecognized bleeding can lead to death.

### ***Trauma:***

Even with ultrasound guidance, it is possible to damage nearby organs during the egg retrieval. This includes damage to the bowel, appendix, bladder, ureters, and ovary. Damage to internal organs may result in the need for additional treatment such as surgery for repair or removal of the damaged organ. However, the risk of such trauma is extremely low.

### ***Anesthesia:***

The use of anesthesia during the egg retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting and in rare cases, death. Complications are more likely to occur in those who have pre-existing medical diseases such as obesity, asthma, high blood pressure and heart disease.

### ***Failure:***

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

## IN VITRO FERTILIZATION and EMBRYO CULTURE

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

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

The day after the eggs have been inseminated, they are examined for signs that the process of fertilization is underway. At this stage, normal development is evident by the fertilized egg having 2 nuclei; this is called a *zygote*. Two days after insemination, normally developing embryos would have divided into between 2 to 4 cells. Three days after insemination, normally developing embryos would have divided into between 4 to 8 cells. Up to 5 to 7 days after insemination, normal embryos would have developed to the blastocyst stage, which is typified by an embryo that has 200 or more cells, an inner fluid-filled cavity and a small cluster of cells called the inner cell mass.

It is important to note that since many eggs and embryos are abnormal, it is expected that not all eggs will fertilize and not all embryos will divide at a normal rate. Some embryos may stop growing. Even if your embryo(s) develop normally in the lab you still may not get pregnant. This means that not all embryos developing at the normal rate are also genetically normal, and not all poorly developing embryos are genetically abnormal. Nonetheless, their visual appearance is the most common and useful guide in the selection of the most appropriate embryo(s) for transfer.

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

- *Fertilization of the egg(s) may fail to occur.*
- *One or more eggs may fertilize abnormally resulting in an abnormal number of chromosomes in the embryo; these abnormal embryos cannot be transferred.*
- *The fertilized eggs may fail to develop into embryos, or the embryos may not develop normally.*
- *Rarely, the eggs or embryos may be harmed by contact with bacteria.*
- *Laboratory accident or human error can occur which could lead to the loss of eggs, sperm and embryos.*
- *Other unforeseen circumstances may prevent any step of the procedure to be performed or prevent the establishment of a pregnancy.*

- *Hurricanes, tornadoes, floods, earthquakes, fires or other “acts of God” (including bombings or other terrorist acts) could destroy the laboratory or its contents, including any sperm, eggs, or embryos being stored there.*

Quality control is the process of running tests to ensure lab conditions are the best they can be to help embryos grow. 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 will be utilized to establish a pregnancy or a cell line unless you sign other consent forms to allow the clinic to use your eggs, sperm or embryos for research purposes.

## **EMBRYO TRANSFER**

One (or more) embryo(s) is/are selected for transfer to the uterine cavity. Embryos are placed in the uterine cavity with a thin tube (catheter). Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. Although the possibility of a complication from the embryo transfer is very rare, risks include infection and damage to or loss of the embryos. Not all embryos become pregnancies and not all pregnancies are normal or grow in the correct place. Tubal (ectopic) pregnancy can occur.

The number of embryos to transfer is an important decision. The age of the woman and the appearance of the developing embryo are two factors which have significant influence on the likelihood of pregnancy and the risk of multiple pregnancy. It is possible to develop more fetuses than the number of embryos transferred if one (or more) of the transferred embryo(s) split into “identical” twins. It is critical to discuss with your physician the number of embryos to be transferred before the transfer is done.

- *After a few days of development, the best developed embryo(s) is/are selected for transfer*
- *The number of embryos transferred influences the likelihood of pregnancy and the risk of multiple pregnancy*
- *The age of the woman who provided the oocytes (eggs) and the appearance of the developing embryo(s) have significant influence on pregnancy outcome*
- *Extra, normally developing embryos that are not transferred can be frozen for potential use in future*

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
<i>Cleavage-stage embryos</i>					
Normal # chromosomes	1	1	1	1	No limit
Other favorable*	1	1	≤3	≤4	No limit
All others	≤2	≤3	≤4	≤5	No limit
<i>Blastocyst-stage embryos</i>					
Normal # chromosomes	1	1	1	1	No limit
Other favorable*	1	1	≤2	≤3	No limit
All others	≤2	≤2	≤3	≤3	No limit

<sup>1</sup> 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.

In an effort to help curtail the problem of multiple pregnancies, national guidelines published in 2017 recommend the number of embryos to transfer (see Tables above). These guidelines differ depending on the developmental stage of the embryos and the appearance of the embryos, and take into account the patient's personal history.

In some cases, there will be additional embryos remaining in the lab after the transfer is completed. Depending on their developmental progress, it may be possible to freeze them for later use.

(See *Cryopreserved Embryo Storage* on pages 12 & 13).

## ADDITIONAL ELEMENTS OF IVF, BENEFITS AND RISKS

### Intracytoplasmic Sperm Injection (ICSI)

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

ICSI has been reported to be associated with a slightly higher risk of birth defects in some studies. However, it was unclear in those studies whether the association is due to the ICSI procedure *per se* or to inherent defects in the sperm from men who have severely abnormal sperm, thus requiring ICSI. The risk of birth defects after ICSI is quite small. (4.2% versus ~3% of those conceived naturally). Experts are still debating the impact of ICSI on the intellectual and motor development of children. Most recent studies have not detected any differences in the development or the abilities of children born after ICSI, conventional IVF, or natural conception.

The prevalence of sex chromosome abnormalities in children conceived via ICSI is higher than observed in the general IVF population, but the absolute difference between the two groups is small (0.8% to 1.0% in ICSI offspring vs. 0.2% in the general IVF population). The reason for the increased prevalence of chromosomal anomalies observed in ICSI offspring is not clear. It may be caused by the ICSI procedure itself, or the father. Men with sperm problems (low count, poor motility, and/or abnormal shape) are more likely themselves to have genetic abnormalities and often produce sperm with abnormal chromosomes; the sex chromosomes (X and Y) in the sperm of men with abnormal semen parameters appear especially prone to abnormalities. If sperm with abnormal chromosomes produce pregnancies, these pregnancies will likely carry these same defects. Translocations (a re-arrangement of chromosomes that can cause birth defects, or miscarriage) may be more common after ICSI.

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

Some men with extremely low sperm counts or no sperm may have abnormalities (microdeletions) in their Y chromosomes. Testicular biopsy and successful retrieval of viable sperm can be used to fertilize eggs with ICSI. However, any sperm containing a Y chromosome microdeletion will be transmitted to the male child. Thus the risk that male offspring might later manifest disorders including infertility is very real. However, men without a detectable deletion by blood testing can generate offspring having a Y chromosome microdeletion, because the chromosomes in the sperm may not be the same as those seen when tested by a blood test.

**Rescue ICSI:** In some cases, unexpectedly none of the eggs fertilize by regular insemination. When this lack of fertilization is discovered the next day, an attempt may be made to inseminate some of these unfertilized eggs with ICSI. Embryos resulting from rescue ICSI appear to have reduced potential for pregnancy and may have increased risk of genetic abnormalities.

## **ASSISTED HATCHING**

The cells that make up the early embryo are enclosed within a flexible shell called the *zona pellucida*. During normal development of the embryo, a portion of the *zona pellucida* dissolves, allowing the embryonic cells to exit or “hatch” out of the shell. Only upon hatching can the embryonic cells implant within the endometrium (lining of the uterus) to result in pregnancy.

Assisted hatching makes it easier for the embryo to exit the *zona pellucida*. The opening can be made by a needle, a laser, or with chemicals. Some clinics have incorporated artificial “assisted hatching” into their treatment protocols because they believe it improves the likelihood of pregnancy, and ultimately, live birth rates although definitive evidence of this is lacking.

Risks that may be associated with assisted hatching include (very rarely) damage to the embryo resulting in loss of cells, or destruction of the embryo. Artificial manipulation of the embryo may increase the rates of identical twinning which result in high risk pregnancies. There may be other risks not yet known.

## **GENETIC SCREENING TESTS**

Genetic carrier screening is done to determine if one or both parents may carry abnormal genes that may increase the chance that their child will have a specific genetic disease. For many genetic diseases, if someone has an abnormal gene, that person is considered a carrier for that genetic disease. If this abnormal gene is passed to the child, the child will usually not be affected with that genetic disease, but will also be a carrier for that genetic disease. If both parents are carriers of the abnormal gene for the same genetic disease, there is a 25% chance that their child will inherit one abnormal gene from each parent and be affected with the genetic disease. Genetic screening is typically done on one parent first, and if the first parent tests positive, then the other parent is tested.

The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Geneticists (ACMG) recommend routine screening for certain genetic diseases and additional screening when indicated due to ethnicity, family history or other known risk factors.

Two of the recommended standard genetic carrier screening tests are Cystic Fibrosis (CF) and Spinal Muscular Atrophy (SMA). There is no one genetic carrier test that detects all genetic diseases and, therefore, genetic carrier tests may only be done for specified genetic diseases and are usually performed on a blood sample. During the course of your evaluation and treatment you may consider screening for specific genetic disease(s) which may be indicated based on your medical history and/or family history to determine whether or not you are a carrier for that specific genetic disease(s). You may be asked to sign a consent to be tested or a waiver declining testing for CF, SMA and any other genetic screening tests recommended by your physician.

### **PREIMPLANTATION GENETIC TESTING (PGT)**

- *Preimplantation genetic testing of embryos requires removal of one or more cells from the embryo (embryo biopsy).*
- *The embryo biopsy 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 are sent to an off-site genetics laboratory for the testing, while embryos remain in storage at the clinic.*
- *In most cases, the tested embryos will need to be cryopreserved (frozen) while the genetic test is being done.*
- *Test results may be incorrect.*

Preimplantation Genetic Testing for a monogenic disease (PGT-M) is testing for a specific, known genetic disease. An example would be if two parents each carry a gene for cystic fibrosis or sickle cell anemia. Preimplantation Genetic Testing for a structural rearrangement in the chromosomes (PGT-SR) is testing for a structural chromosomal abnormality.

Preimplantation Genetic Testing for aneuploidy (PGT-A) is testing for an abnormal number of chromosomes in the embryo, and this test also provides information on the sex of the embryo (male or female).

PGT cannot guarantee that a pregnancy will occur, even if the genetic test result is normal. Factors other than the chromosomes and genes also influence the ability of embryos to implant to result in successful pregnancy.

Testing 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. Birth defects can occur even if chromosome testing is normal. An example of this would be a cleft lip or palate (failure of the lip and upper mouth to develop properly).

There is a possibility that PGT will show that there are NO normal embryos suitable to transfer.

#### **Risks of embryo biopsy**

- *Damage. There is a small risk of damage to the embryo. This may result in no viable embryos suitable for 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 genetics lab. Most testing is very accurate (~99%), so the chance of misdiagnosis is very low. Furthermore, since some embryos may contain cells with different genetics (“mosaicism”), it is possible that accurate genetic results of the cells biopsied and tested does not reflect the genetics of the entire embryo. Consequently, the current recommendation is to confirm the genetics of the fetus in early pregnancy.*

## **Sex Selection and Family Balancing**

PGT-A for determination of the sex of an embryo has multiple applications. There are certain genetic diseases that are caused by a mutation of a gene in the X chromosome. Because the normal male sex chromosome complement is XY, any gene mutation present on the X chromosome will result in the male individual being affected by the genetic disease, since there is not a complementary normal X chromosome to offset the expression of the mutated gene as there is in females (whose normal complement is XX). Hemophilia (a bleeding disorder), is an example of an X-linked disease. In this case, if a couple is at risk for passing Hemophilia on to their male offspring, they may choose to transfer only female embryos to avoid a male affected with the disease.

Another reason a couple may choose to determine the sex of their embryos is to balance their family. Couples who have one or more children of the same sex may wish to have a child of the opposite sex to “balance” their family. It is strongly recommended that couples who are planning to do sex selection or family balancing meet with a Boston IVF counselor or other appropriate psycho-social counselor prior to starting the treatment cycle.

## **CRYOPRESERVATION**

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

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

### **Benefits of cryopreservation:**

- *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 cryopreserve all embryos in the fresh cycle to prevent or reduce the risk of developing severe ovarian hyperstimulation syndrome (OHSS).*
- *Lets you cryopreserve embryos while waiting for genetic test results from PGT.*
- *Protects you if your future fertility is at risk because of surgery or other medical treatments that could damage your eggs.*

There are different ways to cryopreserve embryos. The most common are “slow freeze” and “rapid freeze” (called vitrification). Cryopreserved embryos do not always survive the freezing and thawing process. There is always a risk that none of the embryos will survive. If this happens, the planned frozen embryo transfer will have to be cancelled. Studies of animals and humans indicate that children born from cryopreserved embryos do not have any greater chance of birth defects than children born after transfer of embryos which have not been previously cryopreserved. However, until very large numbers of children have been born from cryopreserved embryos, it is not possible to be absolutely certain that there are no increased risks.

*If you choose to cryopreserve eggs or embryos, be sure to let us now if you change your address. You must also pay storage fees as they come due.*

### **Cryopreserved Embryo/Egg Storage**

*Options for cryopreserved embryo disposition provide that they can be:*

- *Thawed and transferred;*
- *Released to an outside embryo donation agency;*
- *Donated to research;* • *Discarded;*
- *Transferred to another storage facility.*

Additionally, maintaining cryopreserved embryos is labor intensive and costly. There are fees associated with cryopreserving and maintaining cryopreserved embryo(s). Patients/couples who have cryopreserved embryo(s) must remain in contact with Boston IVF on an annual basis in order to inform the clinic of their wish to maintain their cryopreserved embryos in storage, as

well as to pay fees associated with the storage of their embryo(s). Cryopreserved embryos will be maintained in storage until specific directives and authorization for those directives are provided. When the disposition has been decided, Boston IVF requires that a consent form specific to the method of disposition be signed and approved by the Laboratory Manager. Boston IVF reserves the right at its sole discretion to make decisions regarding the final disposition of cryopreserved embryos if fee obligations are not met.

### **Donated Reproductive Materials or Research Embryo Fate**

You may decide to donate your unused cryopreserved embryo(s) to research or to another infertile couple for reproductive purposes. In certain situations, donating embryo(s) for research or to another couple may not be possible or may be restricted by law, but every effort will be made to abide by your wishes. If after 5 years, no recipient couple or research project can be found, or your embryos are not eligible, your embryo(s) may be discarded by the lab in accordance with laboratory procedures and applicable laws. **In some cases, discarded sperm, eggs or embryos may be used for future studies conducting research that leads to a better understanding of infertility and to improve techniques used in the treatment of infertility – these discarded embryos will not be used for any other purposes.**

### **RISKS TO FEMALE 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 abdomen (belly). You may also have difficulty breathing. In some cases, OHSS increases the level of red blood cells, and may cause kidney and liver problems. In the most severe cases, OHSS may result in blood clots, kidney failure, or death. All of these complications occur extremely rarely (less than 0.2% of all IVF 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 when pregnancy results following embryo transfer).*

The risk of severe problems from OHSS is much higher if you become pregnant. For this reason, your doctor may suggest that all of your embryos be cryopreserved for later use instead of transferring them during the fresh IVF cycle. A frozen embryo transfer would 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 infertility or the drugs used for IVF. 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 *per se*. More studies need to 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 conceive on their own without infertility treatment. 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. They are given as “adjusted odds ratios,” which describes the size of the risk compared to women who conceived on their own, adjusted for other factors, such as race, ethnicity and parity. For example, the adjusted odds ratio (AOR) of 1.41 for gestational diabetes means it was seen 41% more often during pregnancy after IVF than in fertile women. The numbers in parentheses (the 95% confidence intervals) indicate the range of the risk; if the range includes 1, then the risk is not significantly elevated. For example, for gestational diabetes, the increased risk seen after IVF likely is somewhere between 15% lower and 134% higher.

### Risks of Pregnancy with IVF <sup>2, 3</sup>

	Singleton Pregnancies			Twin Pregnancies		
	Incidence in IVF Pregnancies (%)	Adjusted Odds Ratios (Women with IVF treatment compared to Fertile women)	Adjusted Odds Ratios (Women with IVF treatment compared to Subfertile women)	Incidence in IVF Pregnancies (%)	Adjusted Odds Ratios (Women with IVF treatment compared to Fertile women)	Adjusted Odds Ratios (Women with IVF treatment compared to Subfertile women)
Gestational diabetes	8.2 %	<b>1.41</b> (0.85, 2.34)	<b>0.89</b> (0.72, 1.09)	10.7 %	<b>1.23</b> (1.06, 1.43)	<b>0.88</b> (0.71, 1.09)
Pregnancy-induced hypertension	12.6 %	<b>1.22</b> (1.15, 1.28)	<b>1.08</b> (1.00, 1.18)	25.5 %	<b>1.15</b> (1.06, 1.26)	<b>0.99</b> (0.96, 1.02)
Placental complications	5.2 %	<b>2.81</b> (2.57--3.08)	<b>1.95</b> (1.67, 2.28)	4.9 %	<b>1.83</b> (1.45, 2.31)	<b>0.87</b> (0.62, 1.22)
Primary cesarean delivery	32.2 %	<b>1.20</b> (1.17, 1.24)	<b>1.10</b> (1.05, 1.15)	65.4 %	<b>1.17</b> (1.13, 1.21)	<b>1.08</b> (1.02, 1.15)
Low birthweight (<5.5 pounds)	7.7 %	<b>1.65</b> (1.53, 1.78)	<b>1.21</b> (1.08, 1.36)	50.4 %	<b>1.04</b> (1.00, 1.08)	<b>1.00</b> (0.94, 1.05)
Preterm birth (<37 weeks gestation)	10.3 %	<b>1.70</b> (1.60, 1.81)	<b>1.26</b> (1.14, 1.39)	53.8 %	<b>1.07</b> (1.03, 1.12)	<b>0.99</b> (0.94, 1.04)

<sup>2</sup> Luke B, Gopal D, Cabral H, et al. Pregnancy, birth, and infant outcomes by maternal fertility status: The Massachusetts Outcomes Study of Assisted Reproductive Technology. American Journal of Obstetrics and Gynecology 2017 (in press).

<sup>3</sup> Luke B, Gopal D, Cabral H, et al. Adverse pregnancy, birth, and infant outcomes in twins: Effects of maternal fertility status and infant gender combinations: The Massachusetts Outcomes Study of Assisted Reproductive Technology. American Journal of Obstetrics and Gynecology 2017 (in press).

Multiple pregnancies in general have an increased risk of problems during pregnancy. In addition to premature (early) delivery, problems for the mother include pre-eclampsia (high blood pressure and protein in the urine), diabetes of pregnancy (gestational diabetes), and excess bleeding at the time of childbirth. Problems with the placenta (afterbirth) are also more common. Other problems more common with multiple pregnancy include gall bladder problems during pregnancy, skin problems, and the need for extra weight gain.

In IVF, embryos are transferred directly into the uterus. However, tubal, cervical, or abdominal ectopic 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 July 1978. Since then, almost 8 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 embryo cryopreservation (freezing) have been checked in animal tests over several generations. Human data has also been checked. There is no proof that children born from cryopreserved and thawed embryos or cryopreserved 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 in babies conceived spontaneously (without medical treatment) is about 4.4 %, and it is about 3% for severe birth defects. In IVF-conceived 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 has been seen in cryopreserved embryo or donor egg cycles.

**Imprinting Disorders.** These are extremely rare disorders caused by whether the genes from the mother or the genes from the father are activated. 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 increased risk, except possibly 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, these problems arose mostly from prematurity and low birth weight that was a result of multiple pregnancy.

### **Risks of a Multiple Pregnancy**

In the past, more than 30% of IVF pregnancies were multiple pregnancies (twins, triplets, or greater). More recently, due to a concerted effort to transfer only one embryo at a time, less than 15% of IVF pregnancies are multiple pregnancies. 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.

Premature (early) births account 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. Premature birth associated with

multiple pregnancies may also affect neurological or behavioral development (eg. Autism, learning disabilities, etc), 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 professional. 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, financial & marital 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](http://www.resolve.org)) or Path2Parenthood ([www.path2parenthood.org](http://www.path2parenthood.org)).

## **Reporting Outcomes**

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

Information from your IVF procedure will be reported to the CDC. It will also be reported to the Society of Assisted Reproductive Technologies (SART) of the American Society for Reproductive Medicine (ASRM), if your clinic is a member of this organization. The CDC may ask for more information from the treatment center or contact you directly for additional followup. Information about your cycle may be used for research or quality control according to HIPAA guidelines. Your name will never be connected to your cycle information in any research that is published.

### **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](http://www.sart.org)) under “Research”.

## **Additional Information**

### **General IVF overviews available on the internet**

[www.reproductivefacts.org](http://www.reproductivefacts.org) [www.sart.org/](http://www.sart.org/) [www.cdc.gov/art/](http://www.cdc.gov/art/)  
[www.resolve.org/site/PageServer](http://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**

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

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.

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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