

RANDY S. MORRIS M.D.
BOARD CERTIFIED REPRODUCTIVE ENDOCRINOLOGY
AND INFERTILITY

INFORMED CONSENT FOR IVF AND IVF LABORATORY PROCEDURES

Overview

Eggs are removed from the ovaries of a female (oocyte retrieval) and are placed in a laboratory setting. Sperm are added to the eggs using various techniques (fertilization). Fertilized eggs (zygotes) are placed in special growth promoting solutions (media). The zygotes undergo a process of cell division to form embryos (embryo culture). Embryos are then placed in the uterus in the hopes of producing a pregnancy (embryo transfer).

Methods of fertilization

- **Standard insemination**

The eggs and sperm are placed in close proximity in a small amount of growth media. The sperm are allowed to use the normal mechanisms for attaching to and penetrating an egg.

- **Intracytoplasmic sperm injection (ICSI)**

A single sperm is isolated and drawn into a specially designed glass pipette with a sharp tip. The pipette is inserted through the wall of the egg into its center (the cytoplasm). The sperm is released and the pipette is withdrawn. This technique was initially performed for couples in whom severe male factor is thought to be a contributing cause for infertility or previous treatment failures. Today, many programs opt to use ICSI to reduce the risk for spontaneous failed fertilization

Embryo culture

The developing embryo is in need of various substances for nutrition. Some of these substances are provided by the solution that the embryos are grown in (media). At different stages of development, the embryo has different needs so different media may be used. **Media may contain biologically derived materials.** During this time, the embryos are kept at a controlled temperature and atmosphere in an incubator. Embryos are inspected during this time to assess for normal development. Currently, it is possible to culture embryos for five to six days at which time they may reach the blastocyst stage.

Assisted Hatching (AZH, zona drilling, hatching)

The early embryo is surrounded by a protein shell called the zonae pellucidae. Before the embryo can attach itself to the wall of the uterus, the embryo must break out of this shell (hatching). There is some evidence that creating a small gap in the zonae will increase the likelihood for implantation. Gaps can be created by applying chemicals to dissolve the zonae or by mechanical means.

Preimplantation Genetic Diagnosis (PGD)

The study of the genes or chromosomes of an embryo in the laboratory setting prior to transfer to the uterus. **The techniques related to PGD are still considered investigational. We encourage all patients who have undergone PGD to have prenatal testing, as this is the current standard of care.**

- **Polar Body Biopsy** The first polar body is produced from the division of the egg after the final injection of hCG is given. Upon penetration of the egg by the sperm (fertilization), but prior to the joining of the sperm's genetic material with the egg's genetic material, the egg undergoes another cell division, producing the second polar body. Once implantation occurs, the polar bodies disintegrate and are not part of the developing fetus. By testing the first and second polar bodies, the genetic make-up of the egg, and maternal genetic contribution in the resultant embryo, can be determined. Removal and genetic analysis of the polar bodies occurs on the first and second day after aspiration. In some instances, it is necessary to confirm a diagnosis made on polar body analysis by performing blastomere biopsy. In these situations, it may be necessary to perform blastomere biopsy for further genetic analysis.
- **Blastomere Biopsy** (also known as embryo biopsy) Following fertilization, the zygote begins to divide. On the third day following the egg retrieval, the embryo is at the blastomere stage (4 to 8 cells). A cell may be carefully removed for genetic analysis. After removal of the cell(s), the developing embryo is placed back into the culture dish and genetic analysis is performed separately on the removed cell(s). At this early point of embryo development, all of the cells are equivalent and thus, removal of a cell from the embryo at this stage does not appear to remove anything critical for normal development. The embryo compensates for the removed cell and should continue to divide following blastomere biopsy.

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Risks during IVF and laboratory procedures

- *A woman may have an insufficient response to medications to allow for egg retrieval.*
- *Upon egg retrieval, eggs may not be obtained from every follicle aspirated. Occasionally, no eggs may be obtained.*
- *The embryologist may fail to identify eggs from the follicular fluid*
- *The eggs retrieved may be abnormal and therefore unusable.*
- *The male partner may fail to produce a semen specimen or produce sperm of sufficient quantity for fertilization*
- *Despite obtaining eggs and sperm, the eggs may fail to fertilize or fertilize normally and therefore be unusable*
- *The eggs or embryos may be damaged from micromanipulation procedures (ICSI, AZH, PGD)*
- *The embryos generated may fail to develop (cleavage arrest) or fail to develop normally*
- *Loss or damage to eggs, sperm or embryos may occur as a result of laboratory and clinical handling, equipment failure or acts of god*
- *The physician may fail to transfer the embryos into the uterus.*
- *Apparently normal embryos may fail to implant normally in the uterus after uterine transfer.*

Possible adverse outcomes from IVF

The most common risk of IVF is multiple pregnancy. There is some evidence to suggest that even after controlling for multiple pregnancies, IVF cycles may have a higher incidence of various complications of pregnancy compared to conception naturally. This remains controversial since most of these studies have significant methodological weaknesses that limit interpretation of their results. In addition, there is accumulating evidence that infertility is a significant risk factor for adverse outcomes even if couples conceive without treatment.

- **Antepartum complications** (those occurring before labor and delivery)
In some studies, IVF pregnancies showed more instances of gestational diabetes, preterm labor, placenta previa (where the placenta covers the uterine opening), vaginal bleeding and stillbirth. Other studies have also indicated a higher risk of pre-eclampsia (a problem of high blood pressure in pregnancy).
 - *Miscarriage:* Pregnancies that occur from assisted reproduction may result in miscarriage. There is no good evidence that the rate of miscarriage is affected by the use of IVF laboratory techniques. However, as many as 1 in ten singleton deliveries from IVF may be the result of a spontaneous loss of one fetus from a twin pregnancy (spontaneous reduction). Spontaneously reduced pregnancies may place babies at greater risk for low birth weight, very low birth weight, pre-eclampsia and neonatal death.
 - *Ectopic pregnancy:* It is possible that embryos placed in the uterus can migrate out of the uterus and implant in an abnormal location (ectopic pregnancy). Unless treated properly, ectopic pregnancies can result in severe morbidity and even death. Recent data indicate that 0.9-2.3% of IVF pregnancies are ectopic. This rate is similar to that seen in the general population.
 - *Multiple pregnancy:* Transferring multiple embryos to the uterus increases the risk for multiple pregnancies. The more embryos transferred the higher the risk. There is some evidence that culturing an embryo to the blastocyst stage may increase the likelihood of monozygotic (identical) twinning. The risk of complications of pregnancy or adverse outcomes is higher with multiple pregnancies than with singleton pregnancies. These include, but are not limited to, preterm delivery, gestational diabetes, hypertensive disorders, birth defects and fetal or neonatal death.
- **Adverse outcomes of labor and delivery**
Some studies suggest that IVF babies were less likely to go into labor on their own and more likely to be delivered by cesarean section. This included both emergency cesarean sections and elective cesarean sections.
- **Fetal and infant outcomes**
 - *Low Birth weight*
Birth weight is related to the fetal age at delivery. A low birth weight (LBW) baby is commonly defined as a baby with a birth weight less than 2500 gram (5 pounds 8 ounces). A very low birth weight (VLBW) baby has a birth weight less than 1500 grams (3 pounds 5 ounces).

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- Cause
The primary risk factor is that development of the placenta is insufficient to meet the demands of the fetus, resulting in malnutrition of the developing fetus. There are two main categories of LBW babies: those that are born prematurely and those which were not premature but are nonetheless small. IVF babies showed an increase in the risk of VLBW and LBW possibly of both causes.
- Impact
Babies who are VLBW have a 25% chance of dying before age 1. LBW babies have about a 2% chance of dying before age one (1/4 of 1% higher than normal weight babies). Various studies have also suggested that babies born with LBW or VLBW may be at increased risk for various problems such as mental retardation, cerebral palsy, poor motor skills and lower intelligence. As an adult such problems as obesity, diabetes, and lower intelligence have been reported.
- *Perinatal mortality*
Perinatal mortality is defined as the death of a fetus after the 20th week of pregnancy but before delivery (antenatal death) plus the death of a baby up to 28 days after birth (neonatal death). IVF babies were more likely to experience perinatal death than spontaneously conceived babies.
- *Congenital abnormalities (birth defects)*
The risk of birth defects in the general population is usually cited at 1-3% of all births. The risk is higher with multiple pregnancies. Pregnancies that occur from assisted reproduction cycles may also have birth defects. There have been studies that suggest that the risk of birth defects may be higher in babies born from IVF even when controlling for the rate of multiple births.
A recent study from Finland found an increased risk of birth defects in singleton boys conceived from IVF. The risk for girls from multiple pregnancies was decreased.
Another recent study from Iowa also found an increased risk of birth defects in babies from IVF of about 30%. If there were truly a 30% greater chance of birth defects in IVF babies, than the overall incidence of birth defects in IVF babies would be from 1.3% to 3.9% of IVF births.
 - Chromosomal abnormalities
Normal human beings have 23 pairs of chromosomes. Embryos commonly have an abnormal number of chromosomes. These are called aneuploidies. As a woman gets older, she produces an increasing number of embryos with chromosome abnormalities.
In 2002, a study published in the New England Journal of Medicine suggested that the rate of chromosome abnormalities in babies may be higher than that seen in the general population. However, a 2005 study in the United States was unable to find an increase in the risk for chromosome abnormalities from IVF.
The use of ICSI to fertilize eggs has been linked with a higher incidence of sex chromosome abnormalities in male offspring. Currently, this is thought to be due to transmission of chromosome abnormalities from the father rather than an effect of the ICSI per se.
Some studies have found that couples with certain types of problems may have a higher rate of chromosome abnormalities than expected. For example, one recent study showed that couples with recurrent miscarriage produce a higher rate of chromosome abnormalities.
 - Gene imprinting disorders
Genes are the functional part of chromosomes - they are responsible for specific functions in the body. Genes typically come in pairs with one member of the pair being inherited from the mother and one member from the father. Normally, the genes from both the mother and father function equally. With imprinted genes, however, only one member of the gene pair is functional and this is determined by the parent of origin. Maternal imprinting means that for a particular gene only the copy received from the mother functions.

Imprinted genes have evolved over time in mammals to fine-tune the growth of the fetus. Paternally expressed genes generally enhance growth, whereas maternally expressed genes appear to suppress growth.

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Disruptions in the normal pattern of imprinting may result in human diseases. Recent studies have suggested that babies born from IVF may have a higher rate of certain rare imprinting disorders. Since these disorders are very rare, it has been difficult to determine if there is a true association with IVF. Investigators have used rare disease registries to help identify possible risk factors for imprinting disorders.

Some experts now believe that IVF is associated Beckwith-Wiedeman Syndrome (BWS). BWS is characterized by a triad of pre- and/or post-natal overgrowth, macroglossia (large tongue) and anterior abdominal wall defects. In addition, about 7% of BWS children develop a tumor, most commonly Wilms' tumor. The incidence of BWS in the general population is estimated at 7.2 cases per 100,000 births. Some estimates suggest that IVF increases the risk 3-4 fold. If true, this would give an incidence of 21.6-28.8 cases per 10,000 births.

This data was based on upon physician's investigation of patients in the BWS registry. They found that 4.6% of the children in the registry were conceived from IVF whereas, in the United States during that time period, IVF made up 0.8% of all births.

Some experts have noted however, that parents who have undergone IVF are more connected to the medical system and are therefore more likely to have their children added to the registry. This may then account for the skewed results.

There were a few isolated reports of babies born from IVF having a rare form of another imprinting disease called Angelman syndrome. However, a 2006 British study was unable to confirm an association. The British study was also unable to find a link to another imprinting disorder known as Prader-Willi Syndrome.

A 2005 study Danish study examined 442,349 singleton non-IVF and 6052 IVF children. The investigators were unable to find an increase in the incidence of any imprinting disorders.

- Lack of long term follow up
The first human birth using in-vitro fertilization occurred in 1978. The first babies born after ICSI or AZH occurred in 1994 and 1989 respectively. The first babies born after PGD occurred in 1991. Consequently, there is no long-term data in humans on the effect of any of these procedures.

We acknowledge that we have read the above consent in its entirety and have had any questions answered completely and to our satisfaction.

We understand the risks, consequences, and potential benefits of in-vitro fertilization.

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