IVF Patient Information

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

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

Embryo development usually proceeds along the following schedule:

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

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

Embryo transfer

After a few days of development, the embryo transfer takes place, or the embryos are frozen for transfer later on. One or more embryos are placed in the uterus using a thin tube called a catheter. Ultrasound may be used to help guide the catheter. The number of embryos to transfer is an important decision. A woman's age and the quality of the embryo affect both the chance for pregnancy as well as the chance for multiple embryos to implant. If multiple embryos implant, a multiple pregnancy (twins, triplets, or more) can result. In some cases, an embryo can split into two (identical twins) after transfer.

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

RECOMMENDED LIMITS ON THE NUMBER OF EMBRYOS TO TRANSFER

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

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

IVF Patient Information

Intracytoplasmic Sperm Injection (ICSI)

ICSI involves the direct injection of a single sperm into the interior of an egg using an extremely thin glass needle. This lets the sperm enter the egg without having to break through the shell around the egg (the *zona pellucida*). For it to work, the sperm must be healthy, and the egg must be mature. ICSI is a good choice when the sperm count, movement, or quality is poor. Live birth rates are very close to those of IVF for men with normal sperm counts.

ICSI may be associated with a slightly higher risk of birth defects. It is hard to know if the increased risk is due to the ICSI procedure itself or to defects in the sperm. The risk of birth defects after ICSI is still quite small (4.2% compared with 3% in children conceived naturally). Most recent studies have not detected any differences in the development of children born after ICSI, regular IVF, or natural conception. Children conceived by ICSI have slightly more problems with their sex chromosomes (the X and Y chromosomes) than children conceived by IVF alone, but only by a very small margin (0.8% to 1.0% for ICSI pregnancies compared to 0.2% for IVF pregnancies). The reason for the difference is not clear. It may be caused by the ICSI procedure itself, or by the father.

Cryopreservation

Sometimes there are normally developing embryos left after embryo transfer. Additional normal-appearing embryos can be frozen for future use. In some cases, it may be planned for all embryos from an IVF cycle to be frozen.

Benefits of freezing:

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

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

IVF Patient Information

Risks to the Woman

Ovarian Hyperstimulation Syndrome (OHSS)

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

OHSS occurs at two stages:

- early, 1 to 5 days after egg retrieval (as a result of the hCG trigger); and
- late, 10 to 15 days after retrieval (because of the hCG if pregnancy occurs).

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

Risks of Pregnancy

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

Risks of Pregnancy with IVF

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

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

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

IVF Patient Information

Risks to Your Baby

Overall Risks

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

IVF single babies are often born about 2 days earlier than naturally conceived babies. They are about 5% more likely to weigh less than 5 pounds, 8 ounces (2,500 grams) than a naturally conceived single baby. IVF twins are not born earlier or later than naturally conceived twins.

Birth Defects

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

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

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

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

Risks of a Multiple Pregnancy

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

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

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

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

IVF Patient Information

Additional Information

General IVF overviews available on the internet

www.reproductivefacts.org
www.cdc.gov/art/
www.sart.org/
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 Maternal Obesity

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.

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.

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.

Birth Defects

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.2015.4934IVF