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INFORMED CONSENT FOR IVF ADVERSE OUTCOMES

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).
 - 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.

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○ *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.

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

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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.