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Do Assisted Reproductive Techniques Increase the Risk of Birth Defects?

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About 15% of couples in developed countries meet the clinical definition of infertility by not becoming pregnant after trying for one year. In some cases, these couples are normal and just need more time, but in other cases, there is a problem for which medical attention may be helpful. Causes of infertility affect three general features of the reproductive process:

- Normal ova may not be ovulated, or ova may not be ovulated normally;
- Normal sperm may not be introduced into the female genital tract or may not survive once they are introduced;
- There may be an obstruction in the genital tract, preventing the ova and the sperm from reaching one another.

Assisted reproductive techniques (ART) include the use of hormones or hormone-like compounds to induce ovulation, medical or surgical treatment of men, direct injection of sperm into the female genital tract, or in vitro fertilization (IVF) followed by transfer of the resulting embryo or embryos into the uterus.

IVF harvests ova from the ovaries through a needle placed into the ovary through the vagina. The ova are mixed with sperm in a laboratory dish. The resultant embryo is placed into the uterus through the cervix. Sometimes embryos are frozen for later implantation in the uterus during a cycle that has not been artificially stimulated with hormones. Variations on IVF include gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT). These techniques are similar to IVF; however, in GIFT, the ovum and sperm meet before fertilization in the fallopian tube, rather than a laboratory dish. The fallopian tube is where the ovum and sperm would join under normal circumstances, but in GIFT, the ovum and the sperm are injected into the fallopian tube together, through a thin instrument inserted into the belly through a tiny incision. In ZIFT, the fertilized ovum, called a zygote, is placed into the fallopian tube. Thus, fertilization has occurred in the laboratory, but early development happens in the fallopian tube, which may provide a more natural environment. With intracytoplasmic sperm injection (ICSI), a spermatozoon is injected directly into the ovum using a microscopically tiny pipette. The technique is otherwise exactly like IVF. ICSI eases the job for the sperm by ferrying it across the zona pellucida, a jelly-like layer that surrounds the ovum.

The first baby after IVF was born in 1978. In the decades since then, more than 5 million babies have been born using IVF or related techniques. There is concern that ART may increase the risk of an abnormal pregnancy. These concerns are based on two categories of possible issues: 1. the medications or physical procedures that are involved could injure a normal gamete or embryo, or 2. an abnormal gamete, ordinarily incapable of fertilization, will be helped to achieve fertilization and will give rise to a child with birth defects.

Experimental animal studies and livestock breeding programs support the safety of these techniques, but there is evidence from some studies in humans that the incidence of abnormal pregnancy outcome is increased, although not to a large extent. The highest birth defect incidence that has been described has been about a 33% increase in the background rate of birth defects. Such an increase, if real, would mean that instead of a background rate of 20–40 affected children per 1000 live births, there would be 26–53 affected children per 1000 live births. Even under the worst-case scenario of a birth defect rate of 53 per 1000 live births, 947 of 1000 children would not have a birth defect.

Here are other outcomes that have been studied in pregnancies conceived through assisted reproduction:

Miscarriage

Accurate miscarriage rates are almost impossible to determine because many miscarriages occur so close to the time of an expected menstrual period that a woman would never have suspected that she was pregnant. Miscarriage occurs in at least 30% of all pregnancies, but only about half of those pregnancies are recognized by the woman. In a group of women undergoing fertility treatments, detailed monitoring of hormone levels will catch even very early pregnancies, and an episode of bleeding that might be considered as a late menstrual period might be identified as a pregnancy loss. So the reason that miscarriage rates among women undergoing fertility treatments appear higher than in the general population may be because it is closer to the true rate. Women undergoing infertility treatments tend to be older and may have significant predisposing factors contributing to an increased pregnancy loss rate.

Ectopic Pregnancy

Sometimes an embryo implants outside the uterus, usually in the fallopian tube. In early pregnancy, fingerlike projections called chorionic villi dig into the tissue where the embryo is implanted, in order to set up the placenta. When a pregnancy occurs outside the uterus, the invading villi can erode into blood vessels, causing bleeding that can be life-threatening. Ectopic pregnancies may result from scarred fallopian tubes that trap the fertilized ovum before it can pass freely into the uterus. There are studies suggesting that assisted reproductive techniques increase the risk of ectopic pregnancies, but keep in mind that these techniques are used in women who may already have a higher rate of tubal damage.

Chromosome and Imprinting Abnormalities

An abnormal chromosome number occurs commonly in early pregnancies. In pregnancies that miscarry, about two thirds have an abnormal number of chromosomes, which is presumed to be the reason for the subsequent miscarriage. A naturally-conceived pregnancy that miscarries very early would not be checked for chromosome abnormalities. It has been noted that chromosomal abnormalities appear to be more common in embryos created through assisted reproductive techniques that involve fertilization in the laboratory, compared to the general population; however, when embryos are placed into women without pre-testing, chromosome abnormalities at birth are not increased. It appears likely, then, that chromosomally abnormal embryos are largely eliminated by natural processes.

Imprinting refers to an epigenetic process in which DNA or its associated histone proteins are marked by covalent binding with a small molecule such as a methyl group based on the parent of

origin of the affected gene. Imprinting defects include Prader- Willi and Angelman syndromes, associated with developmental delay, hypotonia and severe intellectual disability, ataxia, and seizures and Beckwith-Wiedeman syndrome, associated with macrosomia (an abnormally large body), omphalocele (a defect in the abdominal wall at the umbilicus), and other clinical features. DNA methylation occurs during the development of sperm and oocytes, and ART techniques are believed by some researchers to interfere with normal methylation. It is not known, however, whether imprinting abnormalities are increased by assisted reproductive techniques, or whether they are associated with the underlying infertility problems.

Multiple Gestations

Hormone-like medications that induce ovulation may cause more than one egg to be released in a cycle, resulting in twins, triplets, and higher-order multiple gestations. The rate of twins in the general population is about 1%, but between 8 and 25% of pregnancies achieved with ovulation induction result in twins. The rate of triplets in the general population is about 0.01%. With some ovulation induction medications, the rate for triplets can reach a few percent. With optimal monitoring of the induced ovulation cycle, quadruplets and higher do not occur very often. IVF, GIFT, and ZIFT have the potential for producing high order multiples (more than two babies at once) if more than one embryo or zygote is placed in the woman's reproductive tract. Multiple embryos may be used in order to increase the chance that at least one of them will implant and develop. Fertility doctors now recommend implanting no more than one or two embryos at a time, in order to avoid multiples of a higher order than twins, which would result in higher risk pregnancies.

Although having many babies at one time may sound like an efficient way for a couple to complete its family, multiple gestations are associated with pregnancy risks, including increased birth defects. The most important risk is prematurity, because the more babies there are in the uterus; the earlier in pregnancy the uterus will sense that it is overfull. Labor may start weeks before the babies are due. Prematurity is an important cause of death and disability in children arising from these pregnancies.
For videos showing how assisted reproductive techniques work, try these links:

https://www.youtube.com/watch?v=GeigYib39Rs
http://www.advancedfertility.com/aspiration.htm
https://www.youtube.com/watch?v=uXsCngh89fI

Suggested Reading

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