

Fertilization Method Is Linked to Gene Defect

Researchers Find Some Offspring From In Vitro Technique Have 'Inherited Infertility'

A popular fertility technique that allows men with defective sperm to sire babies has led to what scientists believe are the first clear cases of "inherited infertility," in which newborns carry the genetic glitch that seems to have caused their fathers' infertility.

Most children conceived by the technique apparently have not inherited the problem, and all appear normal in other respects. But the seemingly contradictory phenomenon of inherited infertility has some researchers worried that the technique can also pass along more serious birth defects that in the past would have been prevented by biology's natural safeguards.

The fertility technique, called intracytoplasmic sperm injection or ICSI, is the most aggressive developed to date in the burgeoning, largely unregulated field of assisted reproduction. It involves the injection of an individual sperm directly into a woman's egg in a laboratory dish. By relieving the sperm of the usual need to seek out and penetrate an egg under its own power, the technique allows fertilization even by sperm hobbled by the damage that made the fathers infertile.

Other kinds of in vitro fertilization techniques carry the theoretical potential to pass along fertility problems, but scientists believe the risk is greater for ICSI. That's because standard techniques, in which sperm and egg are mixed in a dish, requires those cells to have the modicum of good health needed to achieve fertilization on their own. Moreover, standard in vitro fertilization is mostly used for female infertility, which is almost always caused by blocked fallopian tubes or other non-heritable problems.

Holland and Japan recently banned certain ICSI procedures, citing concerns that sperm with one defect often have others. Doctors who use clearly infertile sperm, officials said, may pass other genetic defects to test tube babies.

Critics in this country are calling for improved counseling for prospective parents about ICSI's potential risks, and creation of a formal registry to track the health of ICSI offspring for decades.

Last December, researchers in Israel reported the first molecular evidence that some ICSI children had inherited the genetic defects that probably caused their fathers' infertility. A report in today's issue of the *New England Journal of Medicine* strengthens that conclusion.

"There is no question that we are passing on genetic defects that affect reproduction," said Jon L. Pryor, the University of Minnesota urologist and cell biologist who co-directed the new study. But on the question of what to do about that, consensus breaks down.

Pryor and others believe that infertile adults who desperately want a child should not be denied the option just because the resulting children may themselves be infertile. "I ask these patients, 'Now that you know, does it matter?'" he said. "They say, 'Oh, so our son would have the same problem that I have. Big deal.'"

Indeed, preliminary surveys have not found an increase in any other birth defects among ICSI children. But the technique is only about five years old.

"Most of the work done so far has been to screen for obvious birth defects postnatally and follow-up for two years," said Michael McClure, chief of reproductive sciences at the National Institute of Child Health and Human Development in Bethesda. "The question is if there is more subtle genetic damage," in any of the thousands of ICSI children worldwide.

Men are responsible for about half of all cases of infertility, usually defined as an inability to achieve pregnancy after a year of unprotected sex. In the majority of those cases, no cause can be found.

One identifiable cause, the prevalence of which has until recently been uncertain, is a defect in the father's Y chromosome—the one out of 46 chromosomes in every man that carries genes for sperm production and other instructions for making a male. It is this class of defect that researchers have found can be passed to offspring through ICSI.

The first such report, by Joseph Itskovitz-Eldor and Shahar Kol of the Rambam Medical Center in Haifa, Israel, published in the December issue of *Molecular Human Reproduction*, found that three of 30 sons of men who used ICSI had inherited a defect in the Y chromosome believed to be the cause of their fathers' infertility. (Girls do not inherit a Y chromosome from their father, so are not affected.)

To find out how common such defects are, Pryor and colleague Kenneth P. Roberts, also of the University of Minnesota, led a study that looked for Y chromosome deletions in 200 infertile men and 200 normal men. They used a genetic test developed by Madison, Wis.-based Promega Corp.

Seven percent of the infertile men—and nearly one in four of those with extremely low sperm counts—harbored such deletions, as compared to only 2 percent of the fertile men. The team concluded that Y chromosome deletions do not always cause a drop in sperm number but are a common cause of male infertility. The degree of infertility apparently depends on the size and location of the chromosome break.

"With the advent of intracytoplasmic sperm injections," the researchers conclude, "the potential for passing on these defects to offspring is real and should be considered when infertile couples are counseled about this procedure."

The debate over ICSI has gradually expanded since the first case report was published in 1992. Since then scientists have discussed the topic vigorously at international meetings and in the letters columns of medical journals.

The technique is the focus of a heated exchange in the February issue of the *Journal of NIH Research*, and will be addressed at a June workshop co-sponsored by the National Institutes of Health and the Washington-based National Advisory Board on Ethics in Reproduction.

No organization keeps track of how many ICSI procedures are performed in the United States each year, or how many result in births. About 500 to 600 were conducted at New York's Cornell University Medical Center last year alone—the largest ICSI center in the United States—at a cost approaching \$10,000 per effort.

Many fertility specialists think that fears of ICSI are overblown. "By the data so far in the literature . . . there does not seem to be an increase in birth defects," said Zev Rosenwaks, director of Cornell's Center for Reproductive Medicine and Infertility.

George Annas, a bioethicist at Boston University, agreed that "it's hard to justify banning a procedure just because it leads to infertility." At the same time, he said, "these are the same doctors who argue that infertility is horrible and you should spend all the money you can to overcome the problem."

Jairo Garcia, director of the Greater Baltimore Medical Center's fertility center and president of the Society for Assisted Reproductive

Technology, the professional organization that oversees artificial insemination clinics in the United States, said he was gratified by the early lack of evidence of miscarriages in ICSI mothers or congenital malformations in ICSI children.

Still, Garcia said: "There is concern among all the physicians who do reproductive techniques about the long-term repercussions of ICSI. There is no registry [of ICSI children] in America," he said, "and one thing we'd like to see from NIH is to institute this kind of registry."

The test for Y chromosome deletions could in theory be used to identify affected ICSI embryos before they are transferred to the mother, but is not now available for that use in clinics. Tests are available, however, to tell the gender of an embryo before transfer.

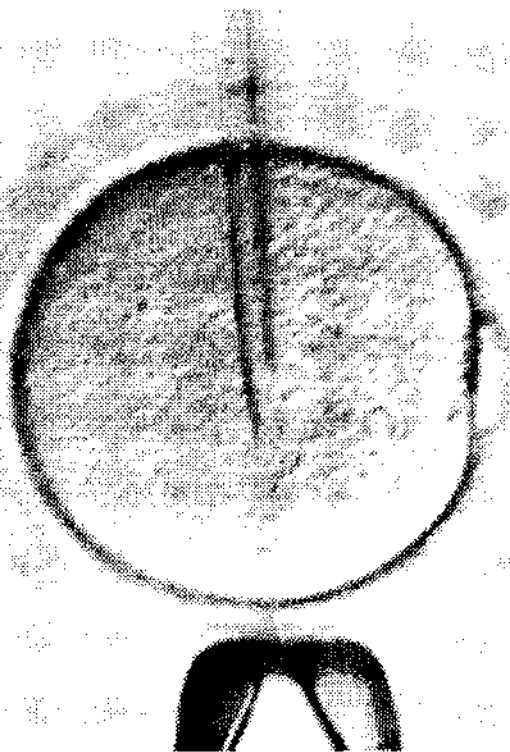
"Right now, the only way to definitely prevent having an infertile [ICSI] baby is to transfer just the females," Itskovitz-Eldor said. "And that has significant ethical and moral questions."

In Holland, a committee reporting to the Dutch ministry of health last June concluded "there is still a lot of uncertainty about possible damage to the health of any children who may result from ICSI, especially when sperm is used which has not been obtained naturally"—a reference to the practice of using immature sperm drawn directly from the testes of men who are incapable of producing mature sperm.

It is this use of immature sperm—a practice that accounts for 10 percent to 15 percent of ICSI efforts in this country—that is banned in Holland and Japan.

INTRACYTOPLASMIC SPERM INJECTION

A form of artificial insemination, known as intracytoplasmic sperm injection (ICSI), involves injecting an individual sperm directly into an egg in a laboratory dish. ICSI has raised concern that boys born to fathers who use the technique may inherit their father's infertility. There is also concern that ICSI may be more likely to produce babies with other genetic defects, although that has not yet been shown to have occurred. This image shows a pipette injecting a sperm into an egg from above while a second pipette at the bottom uses suction to hold the egg in place.



SOURCE: The Journal of NIH Research

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McClure said the meteoric rise in the use of ICSI despite lingering concerns was an example of what happens when a field of science goes largely unregulated and has the potential not only to benefit patients but also to bring vast profits to doctors and clinics.

There is a saying from Khalil Gibran, McClure said, that fertility specialists might take as a warning: "Parents are the bow that fires the arrow of the child into the future."

"We are firing arrows into the future," McClure said, "and we won't be there to see the outcome."