



WHEN COUPLES GET PREGNANT

the old-fashioned way, sperm and egg meet in the fallopian tubes. The embryo then floats

in the woman's reproductive tract for several days before implanting in the wall of the uterus, where it's nourished and exposed to signals telling it when and how to grow. With ART, sperm and egg meet in a dish and create an embryo that grows in a liquid medium made up of salts, amino acids and other nutrients. But it gets no signals from the uterus.

In the 1960s, with hopes of supplying growth signals and mimicking a natural environment, scientists developed a technique called co-culture for growing mouse embryos on reproductive-tract cells. The embryos seemed to mature better, pregnancy rates seemed to improve, and researchers soon started growing human embryos on cells from African green monkeys, cows and rats. Suddenly, science-fiction-sounding fears of cross-pollination between humans and animals became a reality: Human embryos were intermingling with other species, then being implanted into women's wombs where their blood—and potentially diseases from the animal that helped them grow—eventually entered the mother's system. By 1989, without human testing or follow-up studies into long-term effects, fertility clinics began offering co-culture to a select group of patients. Some scientists thought using animal cells went too far, so a few, like Larry Barmat, now at Abington Reproductive Medicine in Abington, Pennsylvania, developed a method for growing embryos using pieces of the mother's uterus. But it wasn't until March 2002 that the FDA caught up and sent letters warning infertility clinics to stop animal co-culture without approval.

Co-culture, the FDA said, is a form of xenotransplantation—the transfer of organs and cells between species—and the agency has

jurisdiction over any human tissues exposed to animal tissues. With co-culture, the FDA worries that the embryo, the mother and her family may contract infectious diseases like HIV or countless animal viruses unknown to humans. Since many of these viruses lie dormant for years, a lack of symptoms does not mean the risk has ended.

But the FDA didn't ban co-culture. Instead, clinics must fill out an Investigational New Drug (IND) application, which can take anywhere from 30 days to many years for approval (so far none have been OKed). For all co-culture children and their families, the FDA recommends lifelong monitoring, reporting unusual symptoms and never donating blood or tissues. But because it's only a recommendation, clinics aren't required to do this. They also don't have to tell patients about recent data on ICSI, IVF and other common procedures. At Saint Barnabas Medical Center in Livingston, New Jersey, where the McNamara embryos were grown using co-culture, reproductive endocrinologist David Sable said he couldn't comment on whether his clinic would implement the FDA's recommendations with former patients like the McNamaras. I was the first person to tell Bill, Susan and several others about the latest co-culture and ART concerns.

Co-culture isn't the only infertility treatment making the FDA nervous. In July 2001, the agency started requiring INDs for two new procedures—nuclear transfer and cytoplasmic transfer. These technologies both aim to revitalize infertile eggs by combining them with healthy ones. In both cases, the resulting eggs have the female donor's cytoplasm—which provides necessary nutrients and growth factors—and the mother's nucleus, which houses the genes for everything from hair color to height. So in theory, after fertilization, any resulting baby will be the mother and father's genetic offspring, not the cytoplasm donor's. But the cytoplasm contains mitochondria,

small organelles important in aerobic activities like walking and exercising. Since mitochondria have their own DNA, combining cytoplasm from two women's eggs means the resulting children could inherit DNA from two mothers. Nuclear transfer hasn't yet produced any children, but cytoplasmic transfer led to 17 babies at Saint Barnabas (and several at other clinics) before the FDA stepped in, saying the techniques amount to gene manipulation, which it strictly regulates. Of the 17 born at Saint Barnabas, two inherited mitochondria from both mother and donor. Researchers worry this might cause problems science has never seen, because these are the first humans with DNA from three parents—mother, father and egg donor.

Fertility doctors are in a difficult position. For one thing, many aren't completely aware of the risks. "When you go into this field," says Gabriella Gosman, a fertility specialist at Magee-Womens Hospital in Pittsburgh, "no one tells you how it came about. I was shocked to find out ART developed without testing and research." In addition, there's the emotional needs of patients. "I'm as concerned about safety as anyone," says Sable. "I sit across the desk from people who've been through years of unsuccessful fertility treatments. They're looking for any answer I can give them. The most important thing is helping couples get pregnant."

Noguchi of the FDA is quick to point out that these newer technologies only account for a small fraction of ART procedures, and that concerns over their safety don't mean all ART is out of control. "We have looked," he says, choosing his words carefully. "There is not enough scientific data one way or the other to say whether the long- or short-term risks of procedures like ICSI are marked enough to warrant more vigorous oversight." Now, he says, it's up to scientists to find more data linking routine ART to birth defects.

