

Research & Books

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Researchers Detour Around Stem-Cell Rules

Thwarted by regulations on egg donation for research, scientists craft new ways to manufacture embryos

By BIJAL TRIVEDI

James A. Byrne sits in a waiting room at the Stanford Fertility & Reproductive Medicine Center with an incubator next to him. At about 4 p.m., an embryologist hands Mr. Byrne three tubes, each containing a single egg freshly harvested from a young woman's ovaries.

These particular eggs are too immature for the in vitro fertilization procedure, but Mr. Byrne thinks they may help his experiments. He places them in the incubator, rushes to his black Honda Civic, and plugs the incubator into the cigarette lighter. Then he speeds away.

Mr. Byrne, a postdoctoral fellow at Stanford University's Institute for Stem Cell Biology and Regenerative Medicine, studies stem cells. Like hundreds of other researchers worldwide, his ultimate goal is to use cloning to develop embryonic stem cells that are genetically matched to patients. In theory, these cells could enable scientists to grow any of the body's 200 or so cell types and replace a patient's diseased or damaged tissue without the threat of immune rejection. But these much-hyped therapies remain distant goals because the raw materials needed to develop such technologies — namely human eggs — are in short supply.

To stay in the game, researchers like Mr. Byrne are engaging in all sorts of cellular alchemy to find alternatives to fresh oocytes, or egg cells, and transform them into embryonic stem cells. Some are using a combination of animal and human cells, while others are trying eggs unfit for human fertilization.

Researchers are exploring such paths because they must weave through a complicated landscape of political and ethical constraints. Several states, including California and Massachusetts, have encouraged stem-cell science, but they have enacted laws that prohibit researchers from paying women for donating eggs for medical research. Other states are considering such bans, and a Louisiana law blocks compensation for any egg donation, even for IVF purposes.

High Costs, High Risks

On the open market, human eggs can fetch thousands of dollars, but the price comes with real costs for donors.

Women who wish to donate must give themselves two daily injections of fertility hormones that will, over

the course of a few weeks, cause 10 to 20 eggs to mature in their ovaries instead of just one. Then there are weekly blood tests, doctor's appointments, a dozen or so ultrasounds to monitor the number and size of the eggs, psychological evaluations, and finally surgery under anesthesia to retrieve the eggs. Ethicists wonder whether donors will suffer any long-term consequences from these procedures.

Kelly, a 24-year-old from San Diego who asked that her surname not be used, is undergoing her sixth and final cycle of egg donation for IVF purposes and says she knows the procedure entails significant risks. The most common side effect is ovarian hyperstimulation syndrome — nausea and vomiting, fluid in the abdomen, breathing difficulties, and, in the worst cases, blood clots or kidney failure.

But women who donate eggs for reproductive procedures generally take home from \$5,000 to \$10,000 per egg-donation cycle. Over two years, Kelly will have made a total of \$48,000 from her six donations.

Some politicians, scientists, and ethicists say such high prices will induce poor women to donate eggs simply for the money. The International Society for Stem Cell Research and the National Academy of Sciences have recommended that women not receive compensation beyond minimal expenses when they donate eggs for research. But a growing number of legal scholars, scientists, and ethicists say the current policy is too restrictive. The American Society for Reproductive Medicine released a report in August that recommended paying for eggs donated for research.

"Not compensating for research seems illogical," says Robert G. Brzyski, an associate professor of obstetrics and gynecology at the University of Texas Health Science Center at San Antonio and chair of the society's ethics committee. He says all egg donors are exposed to the same risk, whether they are doing it for research or for a fertility procedure.

Research participants undergoing an MRI, or those donating blood, bone marrow, or other tissues, are compensated financially, says Kathy L. Hudson, director of the Genetics and Public Policy Center, in Washington. "To not do so for women undergoing hormonal stimulation and invasive oocyte retrieval for research is just plain unfair."

Research on Hold

The restrictions on compensation have put the brakes on some embryonic stem-cell research. In June 2006, Harvard University scientists received the go-ahead to begin cloning experiments and put out a call for egg donors to fuel the program. To date, because of the state law against compensation, not a single woman has donated eggs.

Robert Lanza, vice president for research at Advanced Cell Technology, had the same experience. His company gave up its own recruitment program after a hundred or so advertisements yielded only one appropriate donor who contributed about five eggs.

"It essentially shut down our ...program," says Dr. Lanza. He also complained that the law was unclear as to what constitutes "reasonable costs incurred in connection with the donation."

"Can we compensate for cab fare? A mistake could mean substituting stem cells for jail cells," says Dr. Lanza, who added that he has spent more time in the past year talking with lawyers than doing research.

Richard O. Hynes, a professor of cancer research at the Massachusetts Institute of Technology and co-chair

of the National Academy of Sciences committee that prepared the academy's "Guidelines for Human Embryonic Stem Cell Research," said the committee continues to discuss the issue of payment for oocyte donation, but no decisions have been made. "There are strong opinions on both sides of the issue," he says.

Mr. Hynes is not convinced that scientific progress has been hindered by the no-compensation rule.

Researchers would particularly like to use these donated eggs in a branch of stem-cell research known as therapeutic cloning. That procedure could, potentially, generate embryonic stem cells matched to a patient, and raise the possibility of treating conditions like diabetes and Alzheimer's disease. More immediately, proponents say the technology offers a unique way to study those diseases.

In animal studies, scientists have created embryonic stem cells by removing the DNA from an egg and replacing it with DNA from an adult donor cell — such as a skin cell — in a process called somatic-cell nuclear transfer. Once the adult DNA is inserted into the empty egg, the genetic material is reprogrammed and essentially reverts to its embryonic state. When this re-engineered egg begins to divide, it forms a small ball of cells called a blastocyst, from which embryonic stem cells can be harvested.

Recycling Programs

Without fresh donor eggs, scientists are looking for new ways to reprogram adult DNA. Stanford's Mr. Byrne is hoping that he can transform the immature "junk oocytes" he collected into the coveted mature oocytes.

In September, Mr. Byrne tested his idea when he picked up the immature eggs at the clinic and rushed them back to his lab. He bathed the eggs in a brew of hormones. Several hours later, to his surprise and delight, the eggs matured enough for use in therapeutic-cloning research, he says.

"This is very encouraging," says Mr. Byrne. He now hopes to expand his collecting to nine other clinics in the vicinity, which together might yield between 20 and 40 eggs per week.

Although he is essentially recycling waste from the IVF clinics, Mr. Byrne stresses that this wasn't an easy path. "We still had to jump through a lot of hoops to get the stuff that ends up in the trash," he says. Before the discarded eggs are released, the women must sign a consent form that specifically says that their eggs will be used for the nuclear-transfer research, not just for medical research.

Dr. Lanza at Advanced Cell Technology is also studying the use of immature eggs collected from in vitro fertilization centers. But other scientists are trying even more exotic approaches to get around the shortage of eggs for research.

Kevin Eggan, an assistant professor of molecular and cellular biology at Harvard, and colleagues are exploring abnormal eggs as potential sources. In experiments with mice, his team tested a technique that uses fertilized eggs, called zygotes, which were fertilized by two sperm cells. When that happens, the eggs have too many chromosomes and cannot develop beyond the one-cell stage. Mr. Eggan's team then removes the DNA from the abnormal egg and replaces it with DNA from a donor cell, using nuclear transfer. This new egg now has the correct number of chromosomes and continues to develop into a blastocyst.

Mr. Eggan's team showed that this blastocyst can either be implanted in the uterus of a foster mother to produce a healthy mouse or can be used to produce embryonic stem cells. In vitro fertilization clinics

throughout the country discard abnormal zygotes, yet if Mr. Eggan's work in mice can be translated to humans, abnormal zygotes could represent another valuable tool salvaged from the IVF clinics' cellular scrap heap.

Debating Compensation

In Britain the Human Fertilisation and Embryology Authority recently approved two measures that may help researchers overcome the shortage of donated human eggs. The first allows the creation of cytoplasmic hybrids, or "cybrids," in which researchers substitute animal eggs for human eggs. The idea is that once researchers remove the DNA from the animal egg, the remaining jellylike substance inside, called cytoplasm, will mimic the cytoplasm in human eggs — which contains the chemicals necessary to reprogram mature human DNA to its embryonic state. These cybrid embryos could then be used to generate embryonic stem cells for medical research.

In another move, Britain's Medical Research Council agreed to back a program that offers discounted in vitro fertilization to women who agree to give half the eggs collected during the procedure to stem-cell researchers.

Alison P. Murdoch, a professor of reproductive medicine at the University of Newcastle Upon Tyne, said her team had turned to the egg-sharing program after other means of increasing the supply had failed.

Dr. Murdoch had tried using eggs that failed to be fertilized during IVF, but those did not have the capacity to reprogram a nucleus. "If we are actually going to make progress in reprogramming, then we need fresh eggs," she says.

These policies have generated mixed reactions in the United States. Ms. Hudson, of the Genetics and Public Policy Center, argues that the program exploits women who may be otherwise unable to afford in vitro fertilization and are desperate to have a baby. Every egg taken from a woman "is one fewer embryo she has to make a baby," she added.

Marcy Darnovsky, associate executive director of the Center for Genetics and Society, in Oakland, Calif., thinks egg sharing is problematic because "it's difficult to set up a fire wall between doctors whose primary responsibility is to the woman — the patient — and the researchers, whose primary motivation is to get the eggs for the research."

"It's not great that everyone in this whole cycle of events stands to benefit financially but the woman who is providing the eggs," adds Ms. Darnovsky. "But the only thing crazier than that is paying women ... because women who need the money are going to be putting themselves at risk." She argues that it is bad enough that egg-donation companies target young women on college campuses and says that paying women to donate eggs for research would only raise demand and make the situation worse. "We support reimbursement only," she says.

In the front lines of stem-cell research, the scientists themselves sometimes disagree about what is best. Many researchers have called for compensating women to donate eggs for research, but there are some who have held back.

Renee A. Reijo Pera, director of the Center for Human Embryonic Stem Cell Research and Education at Stanford University School of Medicine, says that while she believes that embryonic stem cells will help

many people, it is not certain that the work with the donated eggs will succeed. Without payment for eggs, researchers might discover alternative methods to reprogram DNA with genetic factors rather than oocytes or find other cell sources — such as those Mr. Byrne is using. She worries that payment might tempt women to donate eggs for the money. "So to me a woman has to be truly altruistic in her donation and realize there may not be a major, major benefit," she says.

Ms. Reijo Pera says that more such altruistic people may exist than researchers have found in the past. Even though the Harvard group was not successful in recruiting donors, Ms. Reijo Pera holds out hope for help from Californian women, and her team is seeking approval to start a study using eggs specifically given for research. "We believe our experience might be different — we do receive quite a lot of calls from women who want to donate," she says.

Mr. Byrne, of Stanford, takes a more liberal stance than his boss and says he supports compensating all women who donate their eggs for research. However, he is not holding his breath that donors will provide enough necessary oocytes for study. He will keep his incubator and Honda Civic ready to go.

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