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Progress in the Search for a Better Embryo

IVF Clinics Hone Methods To Identify the Most Viable; 'Looks Can Be Deceiving'

By Amy Dockser Marcus

FERTILITY CLINICS are making progress in perhaps the most difficult, and important, challenge they face: how to choose, among all the embryos growing in the lab, the one most likely to result in a pregnancy.

The goal is to improve the chances of pregnancy—and simultaneously reduce the number of multiple births—by searching for certain molecular markers and by monitoring an embryo's secretions for signs that a particular embryo has promise. That, in turn, would allow doctors to put fewer embryos back into the uterus. The search for viable embryos has also been aided by improvements in lab techniques that are allowing more clinics to grow, and observe, embryos in a petri dish for longer periods of time.

Last week, the effort got a boost when a team of infertility specialists at the Sher Institutes for Reproductive Medicine, whose main headquarters are in New York, and the Millenova Laboratory in Chicago reported that they had found an important molecular marker. According to the paper published in the journal Reproductive BioMedicine Online, embryos that produce and release higher amounts of the molecule sHLA-G—which is important to the development of a pregnancy—are more likely to implant in a uterus. Though the technique isn't likely to be widely adopted until further testing is done, the Sher Institutes are now using it at the seven Sher clinics around the country.

Traditionally, the quest for a viable embryo has been a kind of beauty contest for cells, with doctors evaluating options largely by how they look under a microscope. Indeed, they commonly describe embryos as "beautiful," "pretty" or "attractive." Good candidates are those with numerous round cells that are even, not fragmented, and are light in shading. Darker shading can indicate that the cell isn't thriving. But recent studies have indicated that, depending on the age of the woman, anywhere from 10% to 80% of embryos that look good under the microscope can still be genetically abnormal, leading doctors to search for another way.

"It turns out that looks can be deceiving, even in an embryo," says David K. Gardner, scientific director of the Colorado Center for Reproductive Medicine in Englewood, Colo., who is running trials of some newer methods.

The drive to find new techniques also comes as the Society for Assisted Reproductive Technology, a national fertility-clinic association, is considering revising its guidelines on the number of embryos transferred back into a uterus during in-vitro fertilization. Currently, for instance, the group recommends no more than two embryos at a time for women who have a favorable prognosis and are under age 35 (younger women generally have higher-quality eggs, and have time to try again if the procedure fails). But many clinics transfer multiple em-

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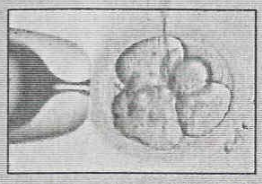
Beauty Contest

Some key methods fertility clinics are using to choose the best embryo



- **Method:** Morphological Assessment
  How It Works: Look under the microscope at the embryo after five days growing in the lab. The cells should be round, not fragmented, a light color, and be numerous.
- **Method:** Molecular Markers
  How It Works: Measure amounts of various molecules the embryo produces or uses that appear to be connected to successful implantation.
- **Method:** Preimplantation genetic diagnosis
  How It Works: A cell from the embryo is removed and examined for chromosomal abnormalities.

Choosing the Best Embryo

Some fertility clinics developing different methods to find the most viable embryo

CLINIC	WEB SITE	METHOD	COMMENT
Boston IVF Waltham, Mass.	www.bostonivf.com	Embryonic gene expression	Tests have been done in mouse models, and soon trials will start on human embryos.
Center for Reproductive Medicine and Infertility New York, N.Y.	www.ivf.org	Improved morphological assessment	The clinic says it has a 70% success rate of embryo implantation using criteria it developed.
Coastal Fertility Medical Center Irvine, Calif.	www.coastalfertility.com	Preimplantation genetic diagnosis	Not every chromosome can be checked, and procedure carries a certain risk to the embryo.
Colorado Center for Reproductive Medicine Englewood, Colo.	www.colocrm.com	Molecular markers	Several markers are in clinical trials right now; results will be known by the end of the year.
Sher Institutes for Reproductive Medicine New York, N.Y.	http://haveababy.com	Molecular markers	The institute says its method is already being used in every one of its seven clinics around the country.

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Fertility Clinics Refine Methods

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bryos, even in young women, in the hopes of improving their odds. This can result in multiple births that pose significant health risks to the mother and babies, including premature labor and low birth weight.

In addition to the one described in last week's paper from the Sher Institutes, there are a number of emerging methods for spotting viable embryos. In one, which also involves searching for markers, scientists put an embryo in a petri dish filled with growth liquid, leaving it there for four hours, taking it out, and then working out how much lactate the embryo produced. Embryos that produce too much lactate have little chance of turning into a pregnancy, says Dr. Gardner of the Colorado Center, which is running a trial of the technique. "Abnormal embryos have abnormal metabolisms," he says. The results of the trial should be available by the end of the year.

Less far along in the research process is an approach being studied by Denny Sakkas, Hugh Taylor and a team at Yale University School of Medicine in New Haven. The team reported last year in the Fertility and Sterility journal that good-quality embryos produce molecules that send signals to a gene in the mother. This gene, known as HOXA-10, plays a role in getting the uterus ready to accept an embryo. There is still a way to go before this marker would be used in a clinic. Dr. Sakkas says the team hasn't been able to pin down the identity of the particular molecule.

All this isn't to say that good looks don't count anymore. Zev Rosenwaks, director of New York's Center for Reproductive Medicine and Infertility, says his group is searching for molecular markers but also focusing on improving how scientists go about assessing an embryo's attractiveness under the microscope.

The ability to grow embryos in a petri dish for longer periods of time is making an important difference. Waiting until an embryo is five days old, rather than the traditional three days, before implanting allows the doctors to study the embryo longer and not make such quick assessments on the best embryo to choose. Dr. Rosenwaks says that by carefully watching and grading the embryo's evolving appearance over five days, his team is able to predict with 70% accuracy which embryo will turn into a successful pregnancy. "So far, there is no molecular marker that has been any better than this," Dr. Rosenwaks says.

Amid the concern over multiple births and IVF, the average number of embryos being put back in a woman's body has dropped, from 3.0 per patient under age 35 in 1999 to 2.8 in 2001. And there has been a steady decline in the percentage of triplets born to women 35 and under, from 9.4% in 1999 to 8.1% in 2001, according to the Centers for Disease Control and Prevention.

Still, the overall percentage of multiple births in IVF patients has gone up, to 36% in 2001, a significant number especially when compared with the 3% rate of multiple births in the general population. The new guidelines from SART, the national clinic group, will suggest that doctors at least discuss the possibility with patients of only transferring back a single embryo.

"The holy grail for IVF is a single embryo transfer leading to a single baby being born," says Robert Stillman, medical director of Shady Grove Fertility in Washington and chairman of the Council of Physicians and Scientists, a group of fertility clinics.

Lawrence Werlin, medical director of Coastal Fertility Medical Center in Irvine, Calif., says that a technique called preimplantation genetic diagnosis (PGD) is the best way to achieve this goal. His center is starting a trial in June with 160 women who will receive only two embryos back. Half of the women will have their embryos screened before transfer for chromosomal abnormalities using PGD, which involves taking out a cell from the embryo and studying it for potential genetic problems.

Techniques like PGD have drawbacks. Coastal Fertility charges $3,500 for the procedure, adding to what is already a high price tag for fertility treatments. And removing a cell carries a risk of harming the embryo.

Efforts have also been made at giving embryos a kind of face lift, a technique that involves removing fragmented, less-attractive cells from the embryo to improve its overall appearance, at least under the microscope. "The problem is that while the embryos become better looking, it doesn't make them any more normal," Coastal Fertility's Dr. Werlin says.

For patients like Sara Niewinski, the effort to find the "best" embryo is already making a difference. The 30-year-old St. Petersburg, Fla., woman says that she and her husband transferred four embryos back to her uterus during a previous attempt at IVF. Despite the fear of a multiple birth, she says, "we didn't think we could get pregnant without that many embryos."

But this time, doctors at the Sher Institutes tested the couple's embryos for the sHLA-G molecular marker, and one of them had it. "The marker gave us confidence," she says. The couple agreed to transfer back only two embryos this time. They will learn later this week if Ms. Niewinski is pregnant.