Embryo Selection No Longer a 'Beauty Contest'

BY BETSY BATES
Los Angeles Bureau

UNIVERSAL CITY, CALIF. — Preimplantation genetic diagnosis is making embryo selection more of a science and less of a blastomere "beauty contest," David L. Hill, Ph.D., told colleagues at a meeting of the Obstetrical and Gynecological Assembly of Southern California.

"We used to line up all the embryos and say, 'These two or three look pretty good to me. Let's go,' " said Dr. Hill, director of the ART Reproductive Center in Beverly Hills, Calif. "It was essentially a beauty contest."

Embryologists are increasingly realizing that chromosomally abnormal embryos can appear to be developing properly and look quite normal at the blastocyst stage. As an example, he showed an embryo at days 3, 4, and 5 that were diagnosed with monosomy 13 using advanced preimplantation genetic diagnosis (PGD) technology.

"Monosomy 13 would never lead to a live birth. But it still can make an absolutely beautiful blastomere. We could easily select that very nice-looking embryo … lowering the implantation rate [for that patient] and possibly leaving a healthy embryo behind."

Other normal-appearing blastocysts were shown to have trisomy 21 and monosomy 18; trisomy 13; or mosaicism 18.

These days, a five-cocktail probe can test blastocysts for autosomal trisomies such as Down syndrome; autosomal monosomies; X and Y numerical disorders such as Turner's syndrome and Klinefelter's syndrome; and translocations using fluorescent in situ hybridization (FISH).

The classic screen assesses chromosomes 13, 18, 21, X, and Y.

Other chromosomes can be added to the screening panel, and polymerase chain reaction technology can be used to custom-design probes for more than 200 specific hereditary diseases.

The FISH technique potentially extends the usefulness of PGD far beyond couples with a known familial disease to those concerned about miscarriage or birth defects associated with advanced maternal age or a history of recurrent pregnancy loss.

The natural aneuploidy rate in human embryos is very high, Dr. Hill explained.

Recent 5-chromosome panel FISH examinations of embryos from his center's in vitro fertilization program found an aneuploidy rate of 38% among 317 embryos from infertile women aged 37 or younger, 45% among 382 embryos from infertile women aged 38 or older, and 36% of 53 embryos from healthy, fertile ovum donors whose average age was 30.

In PGD, as in traditional in vitro fertilization, embryos are also assessed for morphology and growth before they are transferred. But perhaps because more is known about the chromosomal makeup of transferred embryos, the pregnancy rate following PGD appears to be higher than with normal in vitro fertilization.

Dr. Hill compared pregnancy rates among 441 non-PGD patients and 146 PGD patients who underwent in vitro fertilization at his institution. The average maternal age in both groups was identical, 37.

Although fewer embryos were transferred in PGD cases (2.4 vs.3.1), the pregnancy rate was signficantly higher after PGD (44% vs. 33%).

Among women aged 38 or older, the pregnancy rate was higher for 54 PGD patients, compared with 238 non-PGD patients (37% vs. 30%), although the number of PGD patients was too small for the difference to achieve statistical significance.

The accuracy of PGD-FISH can vary, Dr. Hill and his colleagues have found.

He noted the diagnosis is made from a single cell plucked from a six-cell embryo, and that he and his colleagues are "very conservative when we read the FISH signals."

Signal overlap or split signals can be misleading, so he says he errs on the side of caution. "Your heart may want you to call it a normal embryo—you want this couple to have a good transfer." But your head tells you, this is just not suitable.

In limited cases, an embryo with a chromosomal abnormality can self-correct, discarding the incorrect copies of a chromosome. Mosaicism can also occur.

Finally, some abnormalities are more likely than others to be misdiagnosed. Monosomies and trisomies are rarely falsely diagnosed. Recently, 146 embryos diagnosed by FISH as abnormal were studied as their development progressed in Dr. Hill's lab. Further analysis confirmed 122 were abnormal, for a positive predictive value of 83% and a negative predictive value of 81%, he said. ■