

WILL YOUR  
EMBRYOS  
MAKE  
THE GRADE?

EVER WONDER HOW FERTILITY DOCTORS FIGURE OUT WHICH EMBRYOS TO TRANSFER DURING IVF? HERE ARE THE CRITERIA THEY USE TO MAKE THIS ALL-IMPORTANT DECISION.



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Life as an in vitro fertilization (IVF) patient means you're pretty much in a constant state of suspense: How well am I responding to the drugs? How many follicles are there? How many eggs? How many of them fertilized? If you've gotten as far as the embryo transfer, you can add a new question: How good are my embryos? This is the time when the lab specialists at your fertility clinic evaluate your fledgling offspring to decide which one(s) should be plucked from the Petri dish and transferred into your womb.

This is an all-important step, since an embryo's report card determines to a large extent your chances of getting pregnant. In recent years, embryologists have become more adept at judging an embryo's potential to implant, which is one reason that IVF success rates, particularly for younger patients, have risen from 15 percent in the 1980s to more than 30 percent today. And scientists are developing even more sophisticated ways to evaluate embryos. "When we arm ourselves with these tools, we will see an increase in pregnancy rates because we'll be using more information to guide us," says Kathryn J. Go, Ph.D., scientific and laboratory director at the Reproductive Science Center of New England, a group of clinics in the Boston area.

## PASSING GRADES

IVF labs use a variety of embryo grading systems involving letters and/or numbers—an embryo might be labeled a "Grade 3" or a "4AA," for instance. But all of the scores are based on morphology, or what an embryologist can see through a microscope. The most important factor determining exactly how your embryos will be evaluated is whether you're scheduled for your embryo transfer at day 3 or day 5 following fertilization. Embryos transferred on the third day (a.k.a. "day-3 embryos") are graded according to different criteria from those transferred on day 5. Whether you have a day-3 transfer or a day-5 transfer depends on how many of your eggs fertilized, though embryo quality matters, too. If you have plenty of embryos, your doctor may wait until day 5 on the theory that the extra two days will weed out the weaker embryos. If you're short on embryos, though, a day-3 transfer may be in order, since some healthy embryos may not survive to day 5 and you wouldn't want to risk losing them.

Day-3 embryos are judged on three criteria. First is the rate of cell division. An embryo that has seven, eight, or nine cells is more likely to implant than an embryo with either fewer or more cells. "More than 10 is not a good sign. It means the embryos are developing faster than they should," says John Garrisi, Ph.D., laboratory director at the Institute for Reproductive Medicine and Science of Saint Barnabas in New Jersey. "Embryos with four or five cells on day 3 also have a low chance of implantation, about 10 to 15 percent, or about half that of

a seven- to nine-cell embryo, depending on the patient."

Embryologists next assess whether the size and shape of the cells are symmetrical. "An embryo that divides unevenly may not be up to snuff," explains Go. The third trait considered is fragmentation, the percentage of the embryo that has broken off into pieces during cell division. "Anything under 20 percent fragmentation is a good embryo," says Denny Sakkas, Ph.D., director of the

**IN THE SAME WAY THAT AN SAT SCORE MIGHT NOT TRULY GAUGE A STUDENT'S POTENTIAL, AN INDIVIDUAL EMBRYO'S SCORE DOESN'T ALWAYS ACCURATELY ASSESS ITS CHANCES OF IMPLANTING.**

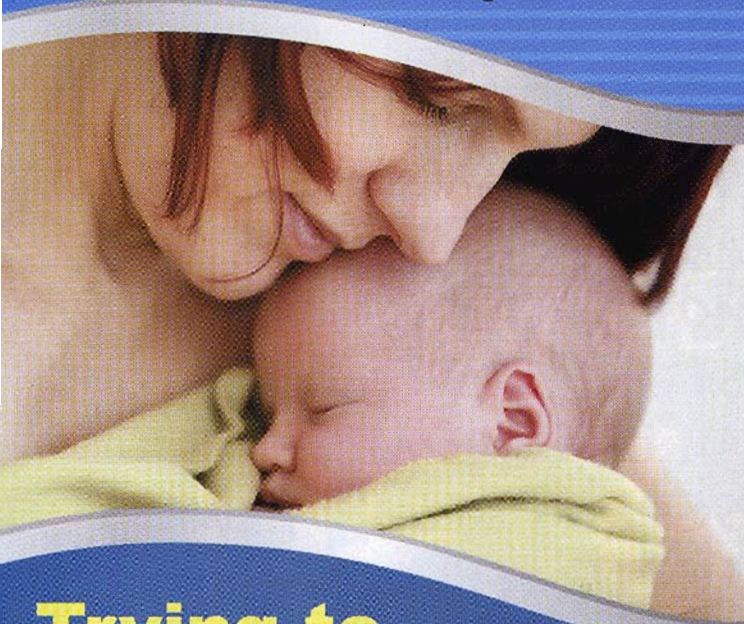
embryology laboratory at the Yale Fertility Center in New Haven, Connecticut. "Twenty to 40 percent is medium-quality. Fifty percent is poor." If a patient has no other embryos, though, some labs will transfer ones that have up to 50 percent fragmentation.

## ON THE FIFTH DAY

If you're transferring day-5 embryos—called blastocysts—evaluating them is completely different. "You can't count the cells anymore because around day 4, they compact and become like a ball," explains Sakkas. "By day 5, that ball starts to have fluid accumulating in the center." Embryologists first look at how much the embryo has expanded, typically giving it a rating from 1 to 6. A score of at least 3 or 4 is ideal. In addition, these specialists grade the quality of the outer-cell layer, the part of the embryo that will develop into the placenta, and the inner cell mass, which eventually becomes the baby. If these cells are tightly packed, they earn an A; if they're more loosely grouped, they get a B or C. A high-scoring day-5 embryo, for example, might be termed a grade 4AA, which means the embryo got an "A" for both the inner- and outer-cell layers.

If a patient doesn't have any top-drawer embryos, her physician may still decide to transfer lesser embryos. The chances of implantation are lower, but it does not mean that the embryo will develop into a less-than-

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stellar baby. "There's absolutely no correlation between embryo morphology and a baby's health," Garrisi stresses.

## WHAT WE'RE LEARNING

Though embryologists devote time and care to grading embryos, they caution that these ratings aren't the whole picture. In the same way that an SAT score might not truly gauge a student's potential, an individual embryo's score doesn't always accurately assess its chances of implanting. "We are judging the book only by its cover," says Go. "There's a whole universe of information that is not revealed to us."

The universe embryologists are exploring goes well beyond what can be seen under a microscope. They're now delving into genetics and protein synthesis to get more clues about an embryo's potential. So far, though, the only additional tool now in use to help labs select embryos is preimplantation genetic screening (PGS), an expensive technique that involves removing one or two cells from the embryo on day 3 and screening the cells for chromosomal disorders that might lead to Down syndrome, for example. This is the same process used in preimplantation genetic diagnosis (PGD); the difference is that PGD screens for specific diseases, such as cystic fibrosis, Duchenne muscular dystrophy, or Tay-Sachs.

In the early 1990s, when PGS first appeared on the scene, the technology seemed as if it would improve pregnancy rates by providing new information about how to select robust, healthy embryos for transfer. "But this turned out not to be a panacea for embryo selection," says Go. Not only is PGS very costly and invasive (on rare occasions, embryos can be destroyed), but it can result in a false positive or a false negative, and it can't detect as many disorders as the prenatal tests amniocentesis or chorionic villus sampling (CVS). At this point, PGS may be recommended mainly in cases where patients have had recurrent miscarriages and/or a family history of specific heritable diseases, but not as a general screen for embryo quality.

## STATE OF THE ART

Although PGS hasn't panned out as a way to significantly raise overall IVF success rates, experts are excited about other promising technologies. One is called metabolomics: Instead of analyzing the embryo itself, scientists evaluate the fluid in which the embryo is cultured. "Good embryos use the components in the fluid differently from embryos that are bad," says Yale University's Denny Sakkas, Ph.D., who also serves as chief scientific officer at Molecular Biometrics, a company that's developing an embryo evaluation test based on metabolomics.

Dr. Sakkas' company has tested the technique in 1,500 single-embryo transfers and expects it to be available in Europe next year and in the United States in 2010. "We've been able to show consistently that the higher the score [from the test], the greater the chance of establishing a pregnancy," he says, adding that he predicts this technology will improve IVF pregnancy rates by 10 to 20 percent and make it more likely that women will conceive in their first round of IVF. He also expects the test to increase the success rate for single-embryo transfers, thereby reducing the number of twins and triplets. "You can do it an hour before the embryo transfer, and it gives you something valuable to help

make the decision [about which embryo(s) to transfer]," he says.

In other labs, researchers are investigating the use of video, hoping that analyzing embryos over time—rather than checking in on them just once a day—will yield further clues about their quality. Meanwhile, researchers in Greece and Australia have discovered that embryos likely to implant have a distinct set of active genes that are turned off in non-viable embryos. By removing eight to 20 cells from day-5 embryos, the scientists identified the DNA fingerprint of embryos with good odds for implanting; they hope to refine the technique for use in IVF labs. "We will still have morphology assessment," says Sakkas, referring to the visual evaluation of embryos through a microscope, "but soon there will probably be another two or three tests that people will be using routinely that will give us much more information."

Embryologists emphasize, though, that no matter how skillful they become at

picking embryos, quality isn't all that affects a patient's chances of getting pregnant. "The transfer is critical," says Garrisi, noting that a smooth embryo

Like so much else about assisted reproduction, evaluating embryos is at least somewhat an art, not just a science. At Kathryn Go's lab, the scientists are regu-

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transfer, without trauma to the uterine lining, gives the embryos the best chance of implanting. The uterine environment—a thick enough lining, for example, and the right interplay of hormones—is important as well; even stellar embryos and a trouble-free transfer won't ensure success if the embryo doesn't have a good "home."

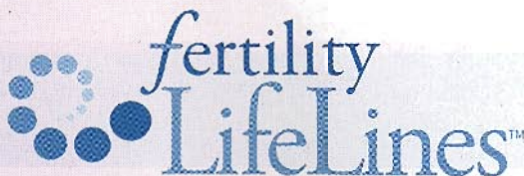
larly surprised about which embryos turn into healthy pregnancies. "An embryologist will come into the lab holding a picture of a baby that came from a slowly developing embryo that was not symmetrical and had a lot of fragments," she says. "It makes you humble before nature to know that a dreadful-looking embryo can turn into a beautiful baby."■

"When I found out I was not able to conceive naturally and my only option to start a family was to have IVF, I wanted information. Fertility LifeLines was a great resource to have; they sent me a whole packet of information about exactly how the treatments worked. I felt like I was moving forward."

"Fertility LifeLines was a wonderful resource for me and it was nice to know someone was there for me. It made a huge difference knowing that my husband and I were not alone and that there was a resource available to help us and make the journey a little easier."

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