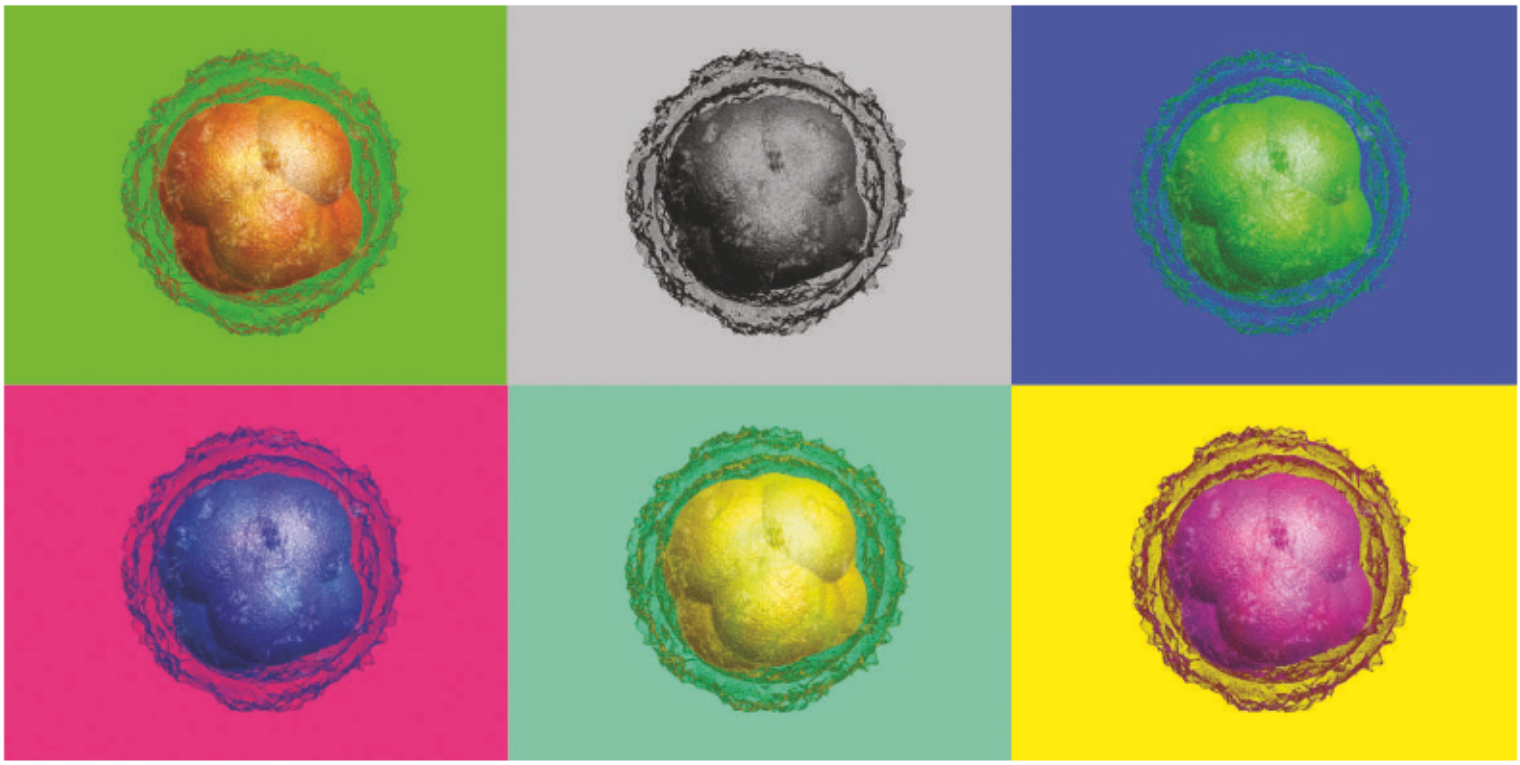


THE FIRST CUT

Extracting a cell from a budding human embryo can expose genetic defects, but does it actually help generate more healthy babies? **Bruce Goldman** investigates.

Suppose that one-eighth of you suddenly disappeared — but that within a few hours, your missing parts grew back and life carried on with no obvious sign of harm. Apart from wondering why it happened, you might worry whether your new body parts are proper replacements for the old. Is there something indefinable missing?

This year, more than 1,000 human embryos will begin their lives with just such a loss — and exactly the same nagging doubts will surround them. During a procedure called preimplantation genetic diagnosis (PGD), one cell is teased from the eight or so that comprise a three-day-old embryo. It is analysed for genetic abnormalities as an adjunct to *in vitro* fertilization (IVF). The results are meant to help doctors decide which embryos are free of genetic defects and should be placed in the mother's uterus.

PGD was first reported in 1990 for identifying and screening out male embryos that might carry a sex-linked disorder[1]. Since then, its popularity has risen on the coat-tails of IVF. An informal reporting system in Europe, which represents some two-thirds of all PGD activity in the continent, shows a jump from PGD tests in 131 IVF cycles in 1999 to 2,984 in 2003 (ref. 2).

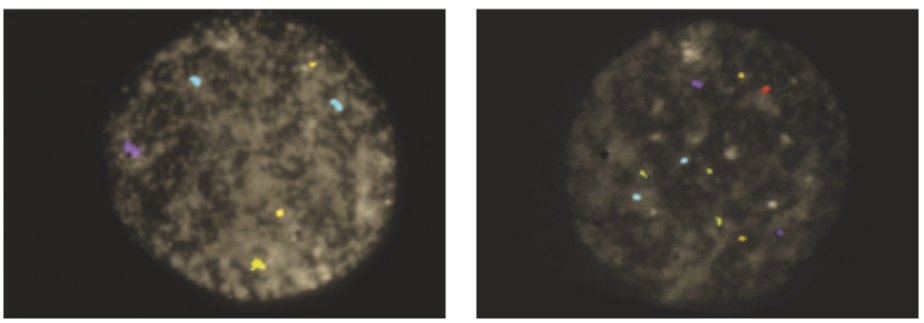
The goal of PGD is to foster life not interfere with it — but a number of researchers and clinicians find its soaring popularity unsettling. Many are concerned that a lot of PGD is being done for little benefit, because it may not boost the number of healthy babies. And some question whether removing a single cell — once assumed to be a harmless procedure — might subtly impair an embryo or the long-term health of the resulting children.

Health check

For prospective parents who could pass on a genetic condition such as cystic fibrosis, PGD has proved priceless. The only alternative to PGD would be to test several weeks into a pregnancy and, if positive, make the difficult choice of whether or not to abort the fetus.

But PGD has another, more controversial use: screening embryos for abnormal chromosome counts, or aneuploidy. The number of a woman's eggs carrying such defects rises rapidly with advancing age, and embryos with these faulty chromosomes are thought to be more likely to miscarry or produce babies with birth defects. Using aneuploidy screening in IVF should reduce the miscarriage rate and enable doctors to transfer fewer and healthier embryos into the uterus, improving pregnancy rates and cutting multiple births. Roughly two-thirds of more than several thousand PGD procedures in the United States are for aneuploidy screening[3], as are well over half in Europe[2].

There is good evidence that such screening can reduce the proportion of pregnancies lost in women who suffer from recurrent miscarriage — one study[4] showed a drop from 87%



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Normal (left) versus abnormal: PGD can identify extra chromosomes (green) in embryonic cells.

to 17% using the technique. But there is now intense debate about whether it helps increase the number of IVF attempts that go on to produce a 'take-home' baby.

One of the strongest advocates for routine aneuploidy screening is Yury Verlinsky, director of the Reproductive Genetics Institute in Chicago. "In the near future I hope all IVF will be done with PGD," he says. Verlinsky points to one of his own studies, in which his team compared what happened to hundreds of IVF recipients before and after undergoing aneuploidy screening. He found that with PGD the miscarriage rate fell from 68% to 28%, and the number who ended up with babies increased[5].

But other experts are critical of this and similar studies because the women were not randomly assigned to screening. And as there is no ongoing system for collecting PGD outcomes across the United States, "all the reporting is by individual laboratories publishing their own results", says Susannah Baruch, director of reproductive genetics at the Genetics and Public Policy Center (GPPC) in Washington DC. "They're really picking and choosing who they're looking at and what they're writing about."

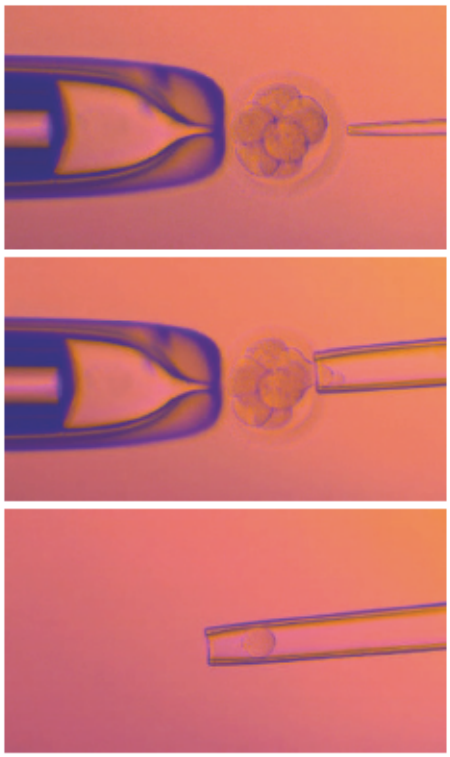
Babes in arms

In one Belgian study done with rigorous controls, women aged 37 or older were randomly assigned to receive aneuploidy screening during IVF. The women who had PGD gave birth to slightly fewer babies than the control group[6], a similar finding to many other studies. "There's a lot of controversy in the field as to how PGD should be appropriately applied," says Catherine Racowsky, director of the IVF lab at Brigham and Women's Hospital, Boston, Massachusetts. "It doesn't seem to be very helpful in improving overall pregnancy rates."

One reason is that older women produce only a limited number of eggs during IVF. Many of these generate the chromosomally faulty embryos that are identified and discarded after PGD, so there are few embryos left for use in each IVF cycle. The embryos that remain after PGD may be more likely to implant and produce a pregnancy, but this does not seem to compensate for the reduced number of embryos transferred.

Another problem is that some perfectly good embryos may be getting thrown out. In the past few years, embryologists have realized that as many as half of all human embryos exhibit 'mosaicism', in which the embryo is a patchwork of chromosomally normal and abnormal cells. The cell selected for PGD may have a different chromosome tally from the rest.

Recent studies have also suggested that these mosaic embryos tend to self-correct, or eliminate cells with aberrant chromosomes, notes Richard Scott of Reproductive Medicine Associates in West Orange, New Jersey. When Scott's lab took embryos that were abnormal on the third day of development and tested them again on day five, the researchers could no longer identify the abnormality in one-third of the embryos. So many embryos identified and eliminated using PGD would, quite possibly, develop as normal, another reason why PGD does not dramatically boost pregnancy rates.



P. GOETCHEUCK/SPL

On test: a single cell is extracted from an eight-cell embryo for PGD.

"We're probably overcalling the number of faulty embryos." — Robert Jansen

"We're probably overcalling the number of faulty embryos," says Robert Jansen, managing and medical director of Sydney IVF, which does close to half of all the PGD in Australia. "The risk, in an older woman, is that so many of her embryos are likely to screen as abnormal that all will be rejected, when one or more of them, if transferred, might have produced a healthy baby." Jansen and the directors of other fertility clinics have been cutting back on aneuploidy screening, and both the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology (ESHRE) are debating the technique's validity.

There is another concern clouding the use of PGD — the question of whether it is truly harmless. The traditional view among embryologists is that the first few cells of mammalian embryos are essentially equivalent: remove one or two, and the rest can ably fill the gap. But some recent studies have challenged that idea, and many now believe that even these early cells are predisposed to contribute in different ways to future tissues.

Earlier this year, Magdalena Zernicka-Goetz of the University of Cambridge, UK, and her colleagues established how four genetically identical embryonic cells acquire their own character[7]. Working with mouse embryos, she showed that the DNA packaging proteins called histones, which help control gene expression, have different levels of specific chemical tags in each cell — and that changing these tags changes the type of embryonic tissues to which that cell contributes.

Studies such as this raise questions about whether removing a cell during PGD leaves a molecular mark on the embryo that somehow affects its ability to develop, or affects the child's long-term health. "I would be very, very surprised if implantation rates overall were not compromised by the removal of a cell from the embryo," Racowsky says, perhaps because the removal has a metabolic cost that compromises its development.

A question of balance

And there the matter sits. Thousands of PGD babies have already been born without any obvious problems. But the oldest of these babies are just teenagers — and rare or subtle effects of the procedure, if they exist, may not become apparent until researchers collect together many more cases and until these children reach middle age or beyond.

Many PGD experts acknowledge the need for a large effort to collect data on the number and health of children born after PGD. In 2005, the GPPC convened a working group of reproductive endocrinologists, IVF doctors and PGD providers in the United States to discuss a voluntary data-collection system. "We're optimistic that it will be up and running within the next year or so," says Baruch. ESHRE already collects information on babies born after PGD and is in the process of setting up a study to follow these babies in more detail.

Meanwhile, patients are left in a quandary about whether the small, unproven risks are worth taking. To avoid having a child with a severe genetic disease, it is probably well worth undergoing PGD; but for aneuploidy screening the decision is less clear. At the very least, experts say, practitioners should spell out the risks and benefits of the procedure to would-be parents (and many already do just that).

Some researchers are seeking ways round the problem by trying to identify genetically abnormal embryos in less invasive ways, such as detecting secreted molecules or testing cells destined to become part of the placenta. "My view is that the less one perturbs an embryo, the better," says Racowsky. "We really do not know yet whether we're doing any harm in removing cells from early embryos." ■

Bruce Goldman is a science writer based in San Francisco.

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