Mixed blessing? Donating eggs is a time-consuming and uncomfortable business.

obtained eggs from his female subordinates.

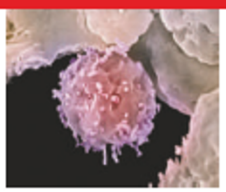
On 30 June, the ISSCR task force released draft guidelines at its annual meeting in Toronto. The guidelines embrace most of the principles proposed by the National Academies last year. But they differ on the issue of egg donation. The task force leaves the door open for a more liberal policy on compensation by stating simply that stem-cell research projects should be reviewed by a local oversight body, which must ensure "there are no undue inducements or other undue influences for the provision of human materials". What constitutes 'undue' is left to the local oversight bodies.

George Daley, a biologist at Harvard Medical School who chaired the task force, says that this is the best consensus the task force was able to achieve, because scientists and ethicists on the task force disagree so sharply about how egg donors should be treated (see 'Research volunteers or organ donors?).

The guidelines are seen as an important first step nonetheless, and are now open to public comment until 1 September, when the ISSCR will finalize the document.

"These are going to be seen as the rules set by scientists themselves, from the inside out," says Kevin Eggan of the Harvard Stem Cell Institute. "It's very useful for scientists to show that they have thought about these issues." ■

Erika Check



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DISCUSS
The pros and cons of egg donation on our Newsblog
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Health effects of egg donation may take decades to emerge

In 1989, a healthy 32-year-old woman offered her infertile younger sister some of her healthy eggs, and with them the chance to have a baby. Doctors at the Cromwell IVF and Fertility Centre in London gave the donor hormones that made a batch of eggs in her ovary mature, and collected six eggs for fertilization. Three embryos were transferred to the younger sister and two were frozen. One baby girl was born.

Five years later, the doctors contacted the egg donor to ask whether to discard her frozen embryos. They discovered that she had been diagnosed with late-stage colon cancer that spread to her skull. She died just before her thirty-ninth birthday.

Doctors don't know if the fertility drugs caused or accelerated the woman's cancer. But the possibility prompted Cromwell infertility specialist Kamal Ahuja to report the case as a reminder of how little is known about the risks of donating eggs (K. E. Ahuja and E. G. Simons, *Hum. Reprod.* 13, 227–231; 1998). "It shook us all up," he says.

Specialists in reproductive medicine say there is insufficient information about the long-term risks of drugs used to stimulate ovulation, a practice that has become more common in the past 25 years, with the proliferation of *in vitro* fertilization (IVF) and assisted reproduction. But some studies have suggested the drugs may be linked to the development of certain cancers.

The question is receiving renewed scrutiny now that scientists are asking healthy women to donate their eggs for stem-cell research — exposing them to the potential risks of ovulation stimulation without the end result of a baby (see Editorial, page 601). To discuss the issue, the California Institute of Regenerative Medicine (CIRM) in San Francisco has convened a meeting of experts to be held next month. Britain's Human Fertilisation and Embryology Authority (HFEA) will also tackle the issue in a forthcoming consultation on egg donation for research.

"This discussion should emphasize long-term risk assessment rather than money."

The uncertainty makes it even more difficult to reach a consensus on whether women who donate eggs should be compensated, and if so by how much (see 'Ethicists and biologists ponder the price of eggs'). "This discussion should emphasize long-term risk assessment rather than money," Ahuja says.

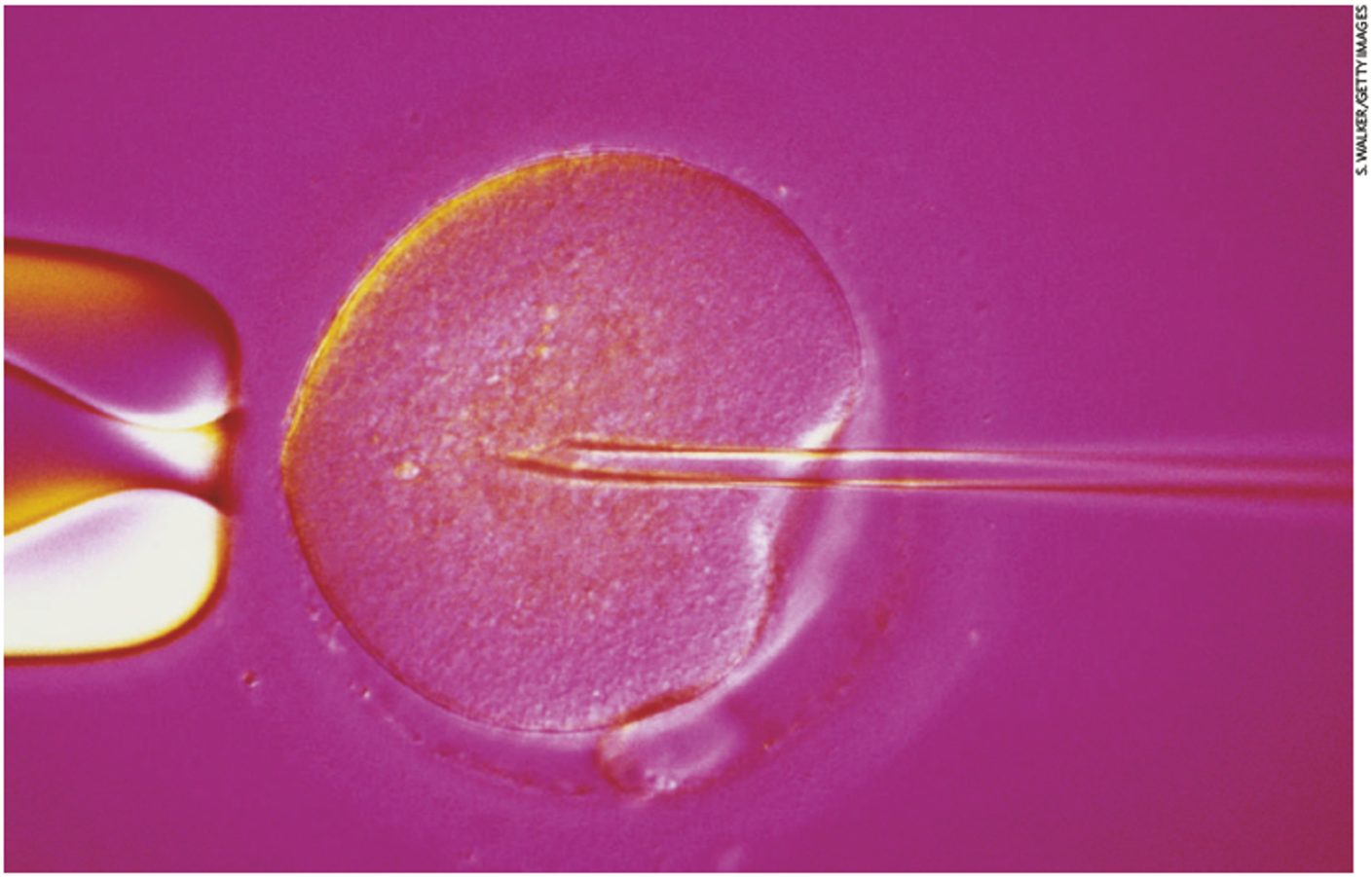
During ovulation stimulation for IVF or egg donation, women are given drugs that encourage the ovary to ripen several eggs simultaneously, rather than the one egg normally ovulated each month (see 'What egg donation involves', overleaf). Doctors know that this can have side effects ranging from moodiness to infection. The most serious is ovarian hyperstimulation syndrome, which seriously affects about 6% of women receiving the drugs. Thirty or more eggs start to develop at once and fluid leaks out of blood vessels and collects in the abdomen, causing nausea, bloating and very occasionally kidney failure or even death.

There is little information on how frequently ovulation stimulation has tragic side effects, says obstetrics and gynaecology professor Didi Braat of Radboud University Medical Centre in Nijmegen, the Netherlands, because doctors are often reluctant to report such cases and rarely have to. But deaths are thought exceptional: in a study reported at this year's meeting of the European Society for Human Reproduction and Embryology, Braat and her colleagues found only six deaths clearly linked to IVF from the medical records of some 100,000 women who underwent the procedure between 1984 and 2006.

So some specialists are more worried about the long-term risks of fertility drugs. In the 1990s, for example, studies pointed to a link between fertility drugs and breast or ovarian cancer, although it's not clear how cancer would be promoted. One study suggested that women who took an ovulation-stimulating drug called clomiphene citrate for more than a year had 11 times the risk of developing ovarian tumours compared with the general population (M. A. Rossing *et al. N. Engl. J. Med.* 331, 771–776; 1994).

But these studies are controversial. It might be infertility, not fertility drugs, that predisposes women to disease. Other aspects of women's reproductive lives influence ovarian and breast cancer — pregnancy is thought to protect against tumours, for example. And ovarian cancer is so rare that it's hard to get a large enough sample to spot any connection.

Louise Brinton at the US National Cancer Institute in Bethesda, Maryland, and her colleagues tried to control for these factors in one



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Next generation: the techniques of assisted reproduction have become increasingly commonplace in the past 25 years.

of the most comprehensive studies so far. They collected the medical records of more than 12,000 women who received ovulation-stimulating drugs between 1965 and 1988. The team did not find statistically significant increases in breast and ovarian cancer, but did find that the women were around 1.8 times more likely to develop uterine cancer (M. D. Althuis *et al. Am. J. Epidemiol.* **161**, 607–615; 2005).

Such studies have reassured many specialists that the risks of ovulation stimulation are insignificant. But Brinton and others studying the issue say the picture is still incomplete. Brinton's study involved mainly women who took clomiphene citrate, rather than the gonadotropin hormones introduced for IVF in the 1980s. Researchers have only had a decade or so to study significant numbers of women taking the newer drugs, but extra cancers may not appear until the women reach 50 or 60.

Researchers also don't know whether studies on infertile women can be generalized to egg donors, who are typically younger and healthier. Epidemiologist Mary Croughan at the University of California, San Francisco, has unpublished data suggesting donors are at lower risk of cancer. But "it's important to follow these women into the future", she says.

She and other experts want more extensive studies to follow up women who have had IVF treatment or donated eggs. There is at least one large study of the long-term effects of ovarian stimulation under way in the Netherlands. But it's unclear who will drive the effort, particularly when private fertility clinics may have little interest in finding out the potential risks of the drugs they use. Ahuja suggests that an authority such as Britain's HFEA could coordinate such an investigation.

What egg donation involves

- In one typical protocol, women take a gonadotropin-releasing hormone agonist daily for 1–2 weeks, which stops the pituitary from stimulating ovulation.
- They then inject gonadotropins such as follicle stimulating hormone to trigger the development of several egg-containing follicles.
- A third hormone triggers final maturation of the eggs.
- Eggs are collected with a needle inserted through the wall of the vagina into the ovary.

Some argue that the researchers asking women for eggs should help pin down the health risks. "There is some kind of ethical obligation there," says Mildred Cho of the Stanford University Center for Biomedical Ethics in California. The September CIRM meeting will focus on these risks and discuss what relevant data might be collected in the course of the institute's research.

"It's important for people to understand in the consent process that we don't know as much as we should about what those risks are," says Cho. Kevin Eggan of the Harvard Stem Cell Institute, for example, says that his group tells egg donors of the risks, and that they cancel the procedure if women show signs of ovarian hyperstimulation syndrome.

If the risks aren't made clear upfront, one well-publicized tragedy could kill efforts to find donors, adds John Buster, professor of obstetrics and gynaecology at Baylor College of Medicine in Houston, Texas. "If a woman has a cardiac arrest while giving eggs for stem-cell research, it won't go down too well." ■

Helen Pearson