



STOPPING THE CLOCK?

Will the mainstreaming of egg freezing offer women more choice about when to have children—kind of like the Pill in reverse—or delude them with a false sense of security? Penn physicians, researchers, and patients weigh in on this issue and some broader implications of advances in fertility techniques. By Caren Lissner

This past fall, just before Thanksgiving, a 37-year-old College alumna we'll call "Jessica" went to a fertility clinic and froze her eggs. (She doesn't want her real name or identifying details used, because of the sensitive nature of her decision and because she hasn't told all of her friends about it.) She'd been thinking about egg freezing—technically, oocyte cryopreservation—since she was 35, she says. She has always wanted children, but she knew that a woman's fertility declines steeply as she approaches 40, since the quantity and quality of the eggs in her ovaries diminish.

Not currently dating, unwilling to "pick someone just to get married," and not certain she could raise a child on her own, she saw freezing her eggs now, in hopes of one day combining them with sperm in a laboratory through in vitro fertilization (IVF), as her best option. With a relatively new egg-freezing technique called *vitrification*, she may have a success rate of nearly 50 percent.

Jessica began preparing for the procedure in September, undergoing ultrasounds and blood tests, injecting herself with hormones for three weeks, and paying \$10,000 out of pocket (her insurance only covered some of the tests). During the procedure, which takes less than an hour, patients undergo anesthesia. A

doctor uses ultrasound to guide a needle through the vagina and into the ovaries. Doctors hope to extract 10 to 15 eggs, although they may harvest as many as 45 or as few as none depending on the woman's age and response to medications. After a recovery of an hour or two, the woman can go home.

Jessica believes it was worth it.

"I highly recommend it to any single woman," she says. "I don't feel as stressed about dating, and I feel more relaxed. I don't feel like the clock is ticking. When you do this, you've stopped the clock."

Alan Copperman C'85 believes it may someday be commonplace for young women and even teenagers to take a medical test to determine whether they should freeze their young eggs for future baby-making. Copperman—director of the Division of Reproductive Endocrinology and Infertility at New York's Mount Sinai Medical Center and co-director of Reproductive Medicine Associates, a fertility practice in the city—has appeared on news programs like *20/20* to discuss fertility and hosts seminars about egg freezing that draw capacity crowds. Copperman contends that egg freezing and similar breakthroughs will change society the way the birth-control pill did in the 1960s.

"I do foresee a day when there will be genomic tests done of young women in their teens or their twenties to know whether they are destined to be fertile into their fourth decade of life and beyond, or whether they will have reproductive issues and should consider electively freezing their eggs," Copperman says. "The birth-control pill once freed up women to not get pregnant when they didn't want to, and now this technology will help them get pregnant when they want to."

A history and sociology of science major at Penn (with minors in chemistry and biology), Copperman says his academic background "helped me understand the historical significance of what we're doing now. If you understand the history of the birth-control pill, the liberties it gave women decades ago, I see a societal parallel."

The difficulty of getting pregnant at 40 wasn't a pressing concern back when the Pill was first helping remake society in the 1960s. In 1970, a woman's average age at marriage was 20.8, according to the US Census (for men, it was 23.2). By 2010, it was 26.1 for women and 28.2 for men. The age of first births climbed as well during that period, going from 21.5 to 25.4, according to the Centers for Disease Control & Prevention. From 1970 to 2006, the percentage of first births to women over 35 increased eightfold. In fact, the number of births to women ages 35 to 39 has risen 57 percent from 1990 to 2006, according to the CDC.

The range of social factors driving this trend—from women's desire to establish themselves professionally to men's reluctance to commit to marriage to the dim

economic prospects of recent years—have been extensively (even exhaustively) covered in the media. But women's bodies haven't gotten the memo.

Women are born with one to two million eggs, and at the start of menstruation, perhaps 400,000 remain. As women proceed through their twenties and thirties, many of the remaining eggs become damaged. When a woman ovulates in a given month and the egg is one of the damaged ones, it may stop her from getting pregnant at all, or she may miscarry, or she may give birth to a child with a birth defect. According to the American Society for Reproductive Medicine (ASRM), a 30-year-old woman trying to get pregnant has a 20 percent chance of succeeding in a given month. By age 40, her chance is "less than 5 percent."

Since the birth of the first test-tube baby in 1978, IVF has come to provide an infertility-treatment option for some couples who can afford it or whose medical insurance covers it. In 2010, American fertility clinics conducted 146,693 cycles of IVF. Older women can use IVF to get pregnant with donor eggs from younger women. Or, if they use their own eggs, doctors can isolate the most healthy-looking ones for implantation. Still, for women 41-42 who used their own eggs in 2010, the average success rate with IVF at American clinics was only 12.5 percent per cycle. For women under 35, the rate was 41.7 percent.

It's no wonder doctors would like younger women to be able to freeze their eggs for use later—if the process works reliably.

Egg freezing was first used in the 1980s

to help women cancer patients whose fertility might be compromised due to chemotherapy; but fewer than half of the eggs were able to survive the thawing process.

However, in the last few years, two things changed to push egg freezing into the mainstream.

First, clinics around the world have moved from the traditional slow-freezing technique to vitrification—a more rapid, more successful process that means, literally, changing a substance into glass. Scientists first place the egg into a solution that dehydrates it. Then they rapidly freeze it. When the eggs are warmed up, they survive at a rate of over 90 percent. With the old method, ice crystals often formed, damaging the cell membranes.

In 2010, doctors announced astounding success rates in a presentation at the 26th annual meeting of the European Society of Human Reproduction and Embryology in Rome. When 600 women underwent IVF with either frozen or fresh eggs, the pregnancy rate was 43.7 percent for vitrified eggs, slightly higher than 41.7 percent with fresh eggs. The fact that a frozen egg was as good as a fresh egg for IVF was big news.

The second boost came last fall. Because of the past failures, the ASRM had labeled egg freezing an "experimental" procedure in 2008, meaning that institutional review boards overseeing clinics and universities developed strict guidelines for how the procedure could be offered and how patients would be monitored. But back in October, after a year of review, the ASRM dropped the "experimental" designation—meaning that hundreds more clinics will offer the procedure as a first-line treatment just like IVF, with less stringent guidelines.

Samantha Pfeifer M'86, associate professor of obstetrics and gynecology, chaired the ASRM Practice Committee that recommended the change. Pfeifer works out of Penn Fertility Care, the Perelman School of Medicine's fertility clinic, which is one of eight centers nationwide funded by the National Institutes of Health for clinical infertility research. Several of the doctors on staff are active with the ASRM.

Pfeifer had been involved with the group for several years when she was nominated to chair the practice committee. "The process of generating a document is incredibly precise," she says. "I really enjoyed being in that environment, with great minds putting together information in that field."

She sees both pluses and minuses with regard to the impending popularity of the procedure, which the changed designation will likely spur. "The first concern was, is the technique successful? We didn't feel like we could recommend or advocate a technique where fewer than 50 percent of the eggs survived. It wasn't until vitrification and further experience with the technique that we got good rates of survival. We saw studies that showed a 90 percent survival rate in young women," she says.

"The second thing is that, the egg may survive, but did you destroy the genes, the material in the egg? Studies showed the

mitotic spindle [which segregates chromosomes] was not significantly disrupted."

The fact that the pregnancy rate and live-birth rates were the same for fresh and frozen egg donors "was very powerful information," she adds. "The last thing was information on birth defects, since there have only been about 1,000 babies reported born from frozen eggs. There does not seem to be an increased risk of birth defects."

On the other hand, Pfeifer does express some concerns about the uncontrolled spread of the procedure, particularly to practices that have little history with it. "Every program is going to start doing egg freezing now. It's a great opportunity for patients, but also a moneymaker. In the beginning, some centers will not be very good at it," she says. "Every procedure has a learning curve. Patients need to be aware that they just started doing this, and things have to be sorted out. Patients have to be counseled about the risks and benefits, and about what they are getting into."

For example, Pfeifer wonders whether clinics would counsel older patients that their success rates will be much lower than for younger women freezing their eggs. Many of the studies on egg freezing were done with eggs from women under 30.

Clarisa Gracia GM'04, associate professor of obstetrics and gynecology, was also on the committee. Gracia is on the faculty of the Center for Research on Reproduction and Women's Health and is the primary researcher into egg and ovarian tissue freezing for cancer patients at Penn Fertility Care. When it comes to elective egg freezing, she is a bit hesitant, and counsels her patients accordingly.

Since Penn began performing egg vitrification in 2009, "we've seen more and more healthy women who are freezing their eggs because they don't have a partner," Gracia explains. "They're in their mid-30s and they're worried they'll be over 40 when they meet their partner, and they're not going to be able to get pregnant. I don't encourage it. We will do it, but the only way to guarantee having a baby is to get pregnant. I would say, 'Would you want to use donor sperm and have a baby now?'"

She acknowledges that some women aren't ready to have a child on their own. "There's no perfect solution," she says. "Most women in their mid-30s are probably going to have a partner and get pregnant on their own within the next five years,

considering the statistics on women under 40 getting married, and they may not be able to use those [frozen] eggs. And the cost of the procedure is a lot.”

But women have been hit with a flurry of magazine and newspaper articles over the last 10 years that practically scolded them for waiting too long to do something about their fertility. In an infamous 2008 *Atlantic Monthly* essay called “Marry Him,” a fortysomething single mom exhorted her women readers to “settle” for “Mr. Good Enough” so they could have children at a young age. (The latest round in this ongoing cultural argument was launched in December with a story in *The New Republic* built around writer Judith Shulevitz’s experiences as an older parent, as well as some troubling research on potential children’s health effects and adverse social impacts associated with what the cover line teased as “The Grayest Generation.”)

“Society is tough on women,” Gracia says. “We expect them to do everything and have babies, and it’s hard, unless society changes so that women can find a partner and get pregnant earlier, which is really the root of the problem.”

Penn bioethicists have long examined the ethical issues surrounding fertility treatments, considering questions that arise about the use of frozen eggs, embryos, and other aspects of the procedures, as well as the appropriate level of regulation over access to treatments, such as age limits or other restrictions.

In 2004, a paper coauthored by Art Caplan, then head of Penn’s Center for Bioethics, along with Dominic Sisti GGS’00 and Andrea Gurmankin G’00 Gr’03, reported the results of a questionnaire mailed to 341 American IVF clinics to find out what they did with their extra frozen embryos. The answers varied among discarding, donating, and keeping them indefinitely. Caplan, now affiliated with New York University, says that egg freezing leads to similar types of questions: “Can a frozen egg be used three generations from now? Can you sell the eggs if you choose not to use them?”

Interestingly, newer egg-freezing techniques have been promoted in European countries as an ethical alternative to the practice of single women fertilizing their eggs with donor sperm and freezing the embryos, which yielded better results

than the old slow-freezing method for eggs. Europeans generally find it more morally acceptable to deal with excess eggs than excess embryos.

Despite any ethical questions, many women, and couples, are grateful for the assistance provided by infertility treatments.

After Meesh Joslyn Pierce W’93 WG’98 got married at 36, she and her husband suffered from unexplained infertility. She underwent IVF and intrauterine insemination to conceive her two boys. She has five friends who have frozen their eggs, she says, and knows “three

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or four” single women who decided to have children on their own. One of the single moms made the choice after battling breast cancer at 39.

“She didn’t want to wait any longer,” Pierce says.

Michael Friedman C’94 and his wife Deena, who live in Massachusetts, struggled with reproductive issues in their early thirties, endured unsuccessful infertility treatments, and spent two and a half years trying to navigate the red tape of foreign adoption. In 2009, the couple brought home twins—a boy and a girl—conceived using a surrogate in India.

And certainly, for many infertility is a major life trauma. In “Recovery from Traumatic Loss,” her doctoral dissertation in the School of Social Policy and Practice, Marni Rosner GrS’12 examined the psychological effects on women who ended up childless after fertility treatments. Besides the potential heartbreak of not having their own children to love and receive love from, they face a lifetime of being left out of motherly rites of passage (like seeing their children get married), of exclusion from their peer group who are raising children, and the “‘death’ of their desired future”—a severe loss not validated or acknowledged by others. For the 12 women Rosner studied, it took an average of 3-4 years “to fully emerge

from feeling like being infertile was their primary identity,” she writes.

Rosner and her husband began trying for kids when she was 39, and she was surprised to find herself “devastated” when doctors told her that her hormone levels indicated a low chance of success with IVF. At her therapy practice in New York, she has talked to patients considering egg freezing, which she thinks is “fantastic.” She doesn’t want a host of new regulations for fertility procedures, but believes that counseling should be required for those undergoing treatment, considering the emotional impact.

“It does take the pressure off of women to find someone right away,” she says of egg freezing. “It’s not a guarantee. There needs to be a lot of education around it. I have younger women who are talking about this. They haven’t met partners yet. One met a partner but was at that age where, do you want to put pressure on the relationship to have a baby soon if you’re not ready?”

Right now, doctors at Penn Fertility Care are looking at ways to improve the success rates of all reproductive treatments, studying the effects of fertility medications, and looking at how egg and egg-tissue cryopreservation can preserve the fertility of young cancer patients. While reproductive medicine can be controversial, and society may not be used to the idea of women having more choices about when to have children, Pfeifer believes it’s “a gift” to be able to give couples and single people options through modern techniques.

“I think it’s a very exciting field of medicine,” she says. “It’s important to be cautious and look at the data and [make sure] that we’re doing things that are safe and benefiting patients, but it does offer great hope to people, and it’s great technology.” ♦

Caren Lissner C’93 is working on the *Someday Mom Book* for busy women who want to know their options for the future. Her website is carenlissner.com.