

EGGS ON ICE

Technical advances are driving a boom
in egg freezing, which promises to let women
put off pregnancy indefinitely.
But will the science live up to the hype?

By Liza Mundy

Photographs by Jamie Chung



EQUIPMENT for in vitro fertilization includes syringes for injectable medications, petri dishes, sperm vials, and more.

SPRIGHTLY YELLOW SEEMS TO BE THE HUE OF CHOICE FOR CORPORATE wellness chains designing a logo to attract health-minded women. There is the cleansing grapefruit of SoulCycle, the happy buttercup of Drybar. And last year vans started materializing at busy pedestrian spots in Manhattan and Los Angeles that sported the shade of sunflowers. These vans are mobile fertility clinics, inviting women to pop in and learn how to safeguard their reproductive germ line by freezing their eggs. “Own your future,” the ads on the side promise. “Your fertility, understood.”

The vehicles are emissaries of Kindbody, a boutique fertility practice that courts the same clientele that frequents spin classes and blow-dry bars. It is one of a small but growing number of outfits that offer fertility services, including retrieving a woman’s eggs, or oocytes, to be frozen for later use. Because eggs are one of the most important factors in female fertility, and both their quality and quantity declines with age, banking eggs promises to lengthen a woman’s window of fertility and postpone the decision of whether to have kids. As a rival service, Extend Fertility, puts it, “Women have more options today than ever before. And we’re giving you one more—the option to start your family when you’re ready.”

The appearance of boutique egg-freezing outfits is one of the most high-profile—but not the only—recent developments in assisted reproductive technology, which is the science (and commerce) of helping people have the babies they want. These stand-alone clinics exist thanks to a convergence of female financial empowerment, venture capital backing and real medical progress. And it is not just mobile clinics behind the push. Egg freezing is on the rise at gold-standard fertility clinics, such as the one at the University of Southern California. There, according to clinic director Richard Paulson, it accounts for almost 40 percent of egg-retrieval cycles—in which women inject themselves with hormones to stimulate their ovaries to release multiple eggs, and doctors then collect those eggs while the women are under anesthesia. (The other 60 percent of cycles at the clinic involve women undergoing infertility treatment who intend to use the eggs soon.)

Ultimately these providers are making the case that egg freezing has come far enough to justify the \$10,000-plus bet women place by investing in the procedure and medications not covered by insurance (that price tag does not include the storage fees women must pay yearly to keep the eggs on ice). This confidence stems from significant breakthroughs in the science of fertility and conception made over the past decade, notably a process that allows doctors to flash-freeze eggs. Physicians have also come a long way in the science of in vitro fer-

tilization (IVF)—the process that comes after egg freezing—which unites a thawed egg (or a fresh one) with a sperm for conception in a petri dish and then grows the resulting embryo to the point where it can be put back inside a woman’s uterus to implant.

All this amounts to a sea change in the science of making babies, one that suggests, in theory, that women are not bound by the traditional notion of the ticking biological clock. Yet in practice, the reality is more complicated. Women must consider other factors besides their eggs, such as their overall health and the health of the sperm they plan to use, in deciding when to get pregnant. And just how good of a bet these new technologies truly are remains to be determined: the vast majority of frozen eggs at clinics have yet to be thawed. The question remains: Will they all be viable? Can science really safeguard fertility for later?

THE FREEZING BOOM

IN SOME PLACES, such as the San Francisco Bay Area, the rise in egg freezing is linked in part to nearby tech companies such as Facebook and Google, which now (and with some fanfare) cover the procedure for employees. In Silicon Valley, egg freezing has become part of the benefits package a prudent career woman may consider availing herself of, a kind of 401(k) for future family formation. The boom also stems from other converging trends. One is the millennial generation’s comfort with social media; boutique clinics have strong presences on Instagram and Twitter, as do a growing number of traditional clinics. Even online dating—which has sold the hope that much messiness of the human heart can be solved by downloading an app—has an impact. “Women have said to me, instead of looking at every date as ‘Is this someone I could marry?’ they can set that aside,” says Marcelle Cedars, director of the University of California, San Francisco’s Center for Reproductive Health.

The rise in freezing also bespeaks a public inured to paying a monthly fee for products. What egg freezing is—among other things—is one more paid-subscription service, like Netflix or Zipcar. Oocytes, once frozen, must be



Liza Mundy is a journalist, a senior fellow at the New America foundation and a former staff writer for the *Washington Post*. She is author of four books, most recently the *New York Times* best seller *Code Girls: The Untold Story of the American Women Code Breakers of World War II* (Hachette Books, 2017).



VITRIFICATION DEVICES such as the S-Cryolock (shown) help to freeze eggs and embryos almost instantly to prevent damage.

kept frozen until used. After a woman goes through the not easy or cheap process of having eggs retrieved, she will be powerfully motivated to continue paying the storage fee, which can be as much as \$500 or \$1,000 a year. Every batch of eggs in liquid nitrogen represents an income stream for years, for the clinic and its investors.

But the freezing trend is also the outcome of science. Asked to reflect on stages of progress in the field, Paulson casts his mind back to when in vitro was in its infancy. The first IVF baby was Louise Brown, born in 1978, now a mother herself. The technology for the scheme was nonexistent to the point where doctors had to fashion their own utensils to retrieve eggs and incubate embryos; when the late gynecologist Patrick Steptoe and the late physiologist Robert Edwards were performing the experiments that would result in Brown's birth, they kept embryos

warm in a pouch created in the skin of a living rabbit.

Into the 1980s IVF patients could expect, at best, a 10 to 15 percent delivery rate. "We were able to help a handful of people," says Alan Penzias, an associate professor at Harvard Medical School and a doctor at Boston IVF. "But not the majority. Most people failed."

The retrieval of eggs—the well-protected female germ line—has always been hard. The 1980s saw basic techniques developed and refined; at first, doctors had to perform laparoscopic surgery to extract a single egg the instant it was ovulated. They learned to administer hormones that could cause eggs to ovulate in greater quantity and at a more predictable time and to retrieve them vaginally, with a needle that pokes through to the ovaries. The 1990s were—unexpectedly—the decade of the man. Male-factor infertility—slow or misshapen sperm or low sperm count—is a common reason couples



INSTEAD of growing embryos in incubators in the lab, the INVOcell device can be inserted into a patient's vagina to incubate them there.

may be unable to conceive. For a long time the only "cure" for male-factor infertility was sperm donation. Then, in 1992, scientists in Belgium announced the first live birth after using ICSI—intracytoplasmic sperm injection—in which a single sperm is injected into the egg. ICSI was a disruptive technology that cured male-factor infertility, for couples who can afford it.

For more than half a century it has been almost ridiculously easy to freeze sperm, which are stripped-down DNA missiles. The first reported human birth from frozen sperm occurred back in 1953. Not so for the egg, which is among the largest cells in the body and difficult to freeze well. Eggs are mostly water, meaning ice crystals can form, with sharp edges that damage organelles and other delicate structures. For years freezing an egg entailed dehydrating it to the fullest extent possible, then introducing tiny amounts of cryoprotectant, a kind of antifreeze that aims to prevent crystals from forming. Everything was done very slowly. "It would be this painful process that would take about two to three hours," says Amy Sparks, an embryologist at the University of Iowa, who remembers the agony of ratcheting down the temperature bit by bit. This technology enabled the first human birth from a frozen embryo in 1984; the first birth from a frozen oocyte was reported two years later, in 1986. But for eggs, freezing remained both difficult and damaging: the upshot often was like what happens when you thaw ice cream and refreeze it: icy granulation. "When it thaws, all of a sudden the water from those crystals has nowhere to go and causes damage to the cell," Sparks says.

Then, about 10 years ago, came the most important recent scientific breakthrough in assisted reproductive technology. Vitrification—from *vitrum*, Latin for "glass"—

is the ability to freeze eggs (and embryos) breathtakingly fast. The procedure involves larger quantities of cryoprotectant than earlier methods and a direct plunge into liquid nitrogen, which triggers "ultrarapid cooling," minimizes the formation of ice crystals and almost instantly transforms the egg into a glasslike state. "In the past 10 years the impact of vitrification ... has really transformed the field in ways that we could not have foreseen," says Serena Chen, director of the clinic at Saint Barnabas Medical Center in New Jersey.

Vitrification is akin to pushing the "pause" button, Chen says; when the time comes, the laboratory pushes "play" and commences rapid thawing. The results are so show-stopping that in 2018, the ethics committee of the American Society for Reproductive Medicine (ASRM)—which up to that point had declined to recommend social use of the technology—issued a paper saying egg freezing "for women attempting to safeguard their reproductive potential for the future" could now be considered "ethically permissible." In short: egg freezing has gone mainstream. Clinics disagree over whether frozen eggs are as viable as fresh, but most experts, including Paulson and Sparks, say they are very, very close. And there is no question that eggs frozen when a woman is 32 are better than fresh eggs retrieved from the same woman at 42.

But even great eggs, just like sex, do not always make a baby. Cedars explains to patients that they should not wait to use frozen eggs until their early 40s, because if they do not work, the old-fashioned method might not either. Yet here lies a quandary—if women cannot wait until their fresh eggs have declined, what is the point of freezing in the first place?

IVF STRIDES

VITRIFICATION is not the only advance helping to buoy the promise of egg freezing. Other elements of IVF have seen major improvements, such as the new standard of growing an embryo for five days in the lab before transferring it back to a woman. A decade ago embryos were often transferred at the three-day stage, when they consisted of just eight cells. Human embryos now arrive in the uterus as "blastocysts," with roughly 100 cells, which are more mature and robust and have a much greater chance of success. According to CDC data from 2016, for women younger than 35, nearly 50 percent of fresh embryos transferred at day five resulted in a live birth as compared with 34.4 percent of embryos transferred at day three. For women between 35 and 37, the percentages were 42.1 for day five versus 28.6 for day three.

Success rates are also getting better because labs can now closely replicate the chemical environment of the fallopian tube, where embryos spend their first five or so days when pregnancy happens naturally. Labs have gotten much better at regulating the amounts and concentrations of nitrogen, oxygen and carbon dioxide. Current incubators also feature more solid-state technology that requires less opening and closing of doors so that embryos can rest undisturbed.

The ability to develop embryos to the blastocyst

stage means embryologists can more easily recognize the best of the batch before deciding which to try to implant. These judgment calls are also improved by a process called preimplantation genetic selection. Back in the three-day-embryo era, if scientists wanted to gauge the genetic health of an embryo, they had to pry one cell from an eight-cell mass, a lab procedure so harrowing that Sparks still has “nightmares” about it. Now it is much easier to use lasers to grab a couple of cells from the part of the blastocyst that will create the placenta—the less vital section than the one that is destined for the fetus.

All in all, embryologists’ improved ability to freeze and test embryos amounts to “a huge change,” Penzias says. About 10 years ago, frozen embryos had a 10 percent lower success rate than fresh. “Now we’re talking about parity,” he says. The improved odds mean, in theory, that whether women are using embryos created from eggs retrieved the same month or from those frozen years before, clinics can transfer just one embryo at a time rather than the two or three that used to be the norm. For 14 years it has been the University of Iowa’s policy that if a woman is younger than 38, has no prior failed transfers at the clinic and has at least a single good-looking blastocyst (a five-day-old embryo), then one is “all they get,” Sparks says. These trends have reduced the prevalence of twins, and especially of triplets and higher-order multiples, which are much riskier pregnancies than carrying singletons, for both babies and moms. At the University of Iowa, the rate of twin birth used to be 40 percent in 2001; now it is under 5 percent. Industrywide, according to the CDC, the portion of transfers involving a single embryo has more than tripled, from 12 percent in 2007 to 40 percent in 2016. Equally important: the percentage of fresh single-embryo transfers resulting in a live birth increased from 21 percent in 2007 to 37 percent in 2016.

These innovations are just the beginning. A new invention allows a woman to incubate embryos inside a device inserted in her vagina rather than an incubator in the lab. And even more radical technologies are on the horizon: Mitochondrial replacement therapy, for instance, is a controversial procedure that can eliminate the risk of genetic mitochondrial disease by injecting the nucleus of a mother’s egg into an egg from a woman without the disease whose nucleus has been removed but whose mitochondria remain. The procedure is banned in the U.S., out of concerns about mixing the DNA of two women, but is being developed in England. The day is also coming, Paulson says, when it will be possible to use stem cell technology to manufacture sperm and eggs from normal body cells, such as skin cells. Although it sounds like science fiction, the procedure would involve no changes to a cell’s DNA, so that part, at least, is less worrisome than mitochondrial transfer. With this technology, women would no longer need to bank eggs. “At 45, you can still have an egg made out of your skin cells,” Paulson says. It sounds wild, but so did IVF 40 years ago. “It’s going to happen.”

TICKING CLOCKS

IT IS A FACT THAT A WOMAN is born with all the oocytes she will have; over time her ovarian reserve diminishes, as does the quality of her eggs.

Talking about this subject has always been fraught. Back in 2001, when the ASRM launched an ad campaign partly about age-related infertility, the National Organization for Women attacked it as coercive and antifeminist. Chen says this reaction does women a major disservice; older eggs are more likely to be chromosomally abnormal, with a higher risk for miscarriage and the grief that follows. She adds that egg freezing is often depicted as elective and narcissistic, “kind of like plastic surgery or getting a cute Mini Cooper.” But women face many pressures, particularly in their mid-30s, when each year of delayed childbearing means an increase in earning power. “It’s not about women just being selfish and trying to work on their careers,” Chen says. “The truth is, a lot of people just haven’t found the right partner.”

Still, Chen shares concerns about the commercialization of a technology that originally aimed to help cancer patients preserve fertility during treatment. Jake Anderson-Bialis, co-founder of the consumer education Web site FertilityIQ, worries that women do not realize taking hormones and then undergoing retrieval is not a minor lunch-hour-type procedure. And there is still no guarantee the eggs will result in a live birth. The backlash could be huge if many of the women now freezing their eggs later attempt to use them, only to find out their investment failed. The dirty secret of the fertility industry, up to now, has been multiple births; going forward, Anderson-Bialis says, “if there’s going to be a black eye, it’s egg freezing.” By this, he means the danger that the eggs, once thawed, will not be viable—a potentially devastating outcome to women sold on the promise of egg freezing. Cedars agrees that some women are too bullish on what technology can accomplish. “We have to repeatedly say to patients, ‘There’s not a baby in the freezer,’” she says. “‘There is the potential for a baby.’” ■

MORE TO EXPLORE

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