

FRONTIERS OF FERTILITY

TIME
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MAKING BABIES OUGHT TO BE the easiest thing you'll ever do—indeed, it ought to be a hard thing *not* to do. The evolutionary game is rigged so that it's fun, the kind of fun you want to have even when offspring aren't on your mind. Our body cycles make parenthood a constant possibility: women are ready to conceive every month, and men are pretty much ready to go any second. And the product of all that happy activity—a chubby, cuddly, cooing baby—is something we're hardwired to find irresistible.

But things, of course, aren't always so simple. The human reproductive system may be a prolific thing, but it's also a very fragile thing, and there is a lot that can go wrong with it. In the U.S. alone, more than

years of trying, according to figures released last year by the World Health Organization.

Given the powerful, primal hold baby-making has on us, the inability to perform so straightforward a genetic job can be deeply painful. "My husband and I would look around, and everyone we knew was having kids," says Cindy Flynn, 35, an IT worker at a Sacramento nonprofit. "We struggled so hard to get pregnant. Building a family should not be so difficult."

For now, it still is, but the outlook is getting decidedly brighter. Scientists are steadily refining and improving assisted-reproduction techniques. They're harvesting better eggs, using fewer drugs to do it and selecting more vigorous sperm that have a better chance of producing a baby. They're monitoring embryos while they're still in

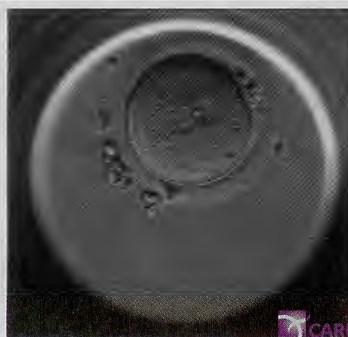
experimental.' Today I can often say, "There is at least a 2-out-of-3 chance you are going to have a baby out of this process.' It is becoming the most exciting field, with the most gratifying outcomes you can imagine."

Boosting the Odds

IMPROVING THE OUTLOOK FOR FERTILITY patients starts with improving the art of IVE, which is not just expensive and less than reliable but a true physical grind. Women must first endure a month's worth of hormonal dosings, including two or three shots a day in the final stretch, all of which can lead to headaches, restlessness, irritability and hot flushing. The dosing pushes the ovaries to hyperovulate, producing up to a dozen ova at once, which are retrieved via laparoscope through an incision in the pelvis. Even after

BABY'S FIRST PICTURES

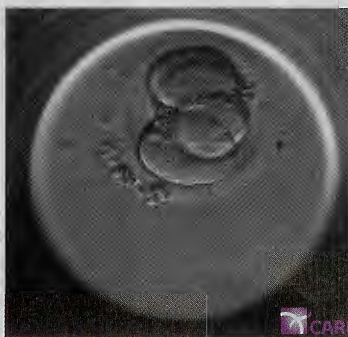
Time-lapse images like these can help identify which embryos are the most viable



16 HOURS AFTER FERTILIZATION
Fertilized zygote with sperm and egg nuclei



30 HOURS
Fertilized egg divides into two cells



45 HOURS
Egg divides into four cells and soon eight



59 HOURS
The eight cells begin to compact

7 million women have received treatment for infertility, spending more than an estimated \$5 billion per year. For the past 10 years, the average billed cost for a single in vitro fertilization (IVF) cycle is \$12,400—something infertile couples must pony up on their own since most insurance companies don't cover infertility treatments—and just one cycle is usually not enough. According to the U.S. Centers for Disease Control and Prevention, only 42% of assisted-reproduction cycles lead to a live birth when the woman is younger than 35. The figure drops to 22% by age 40, 12% by 42 and just 5% by 44. Outside the U.S., the odds are no better, and the number of people who need help is far greater: an estimated 48.5 million couples worldwide are unable to conceive after five

the lab in ways that were impossible before. Perhaps most tantalizing, they are working to engineer human stem cells so that eggs and sperm can be produced in the lab using raw cellular material taken from the parents. This would lead to a baby that was entirely, genetically theirs, the product of an ordinary union of egg and sperm—nothing short of a last-ditch miracle for people who, without this help, might have been unable to produce any healthy egg or sperm at all.

"Twenty years ago I would often tell a patient, 'I am sorry. There is nothing we can do,'" says Dr. Craig Niederberger, head of the department of urology at the University of Illinois at Chicago College of Medicine. "Fifteen years ago I would have been saying, 'There is something I can do, but it's very

all that, there's no guarantee the eggs will be viable; many immature ones that the ovaries would never have released on their own are shoved out prematurely by the drugs.

"Every time a patient goes through conventional IVF, the number of eggs designated as waste is about 90%," says Dr. John Zhang, founder and director of the New Hope Fertility Center in New York City.

Not all sperm are created equal either. The average male produces 76 million sperm per ejaculation; the lower limit for conception is 18 million. For IVE, the quality of sperm is judged in the lowest-tech way possible: a lab technician looks at them through a microscope. This method has just the limitations you might expect.

"A sperm has a head, a midpiece and a

tail,” says Niederberger, “and there’s a lot you can find that looks wrong. You would think if you can find the best-looking sperm, it would also be the healthiest one, but that is absolutely not correct. The vast majority of sperm—up to 96%—look abnormal, and the exact shape of a sperm doesn’t necessarily equate to its success.”

This is increasingly problematic as doctors turn away from the original IVF method of simply mixing an egg and a semen sample in a dish and adopt a more exacting approach known as intracytoplasmic sperm injection (ICSI), in which a single, especially handsome sperm is selected, lifted by the tail and injected directly into the egg. That practically guarantees fertilization, but if the technician was fooled by looks and rejected more

cycle, the women also use a nasal-spray version of Synarel, a drug that’s usually used to treat endometriosis but in this case helps trigger egg release. Eggs are then retrieved and fertilized as in traditional IVF.

“The physiologic changes the body experiences in mini IVF are close to the natural cycle, without excessive drugs,” says Zhang. Starting with fewer embryos can also help mitigate the ethical issues raised when unused ones are frozen and stored in clinics, with little or no prospect of ever being implanted but little or no appetite on the part of anyone involved to destroy them.

Not everyone is sold on the promise of mini IVF. Some critics suggest that the odds of producing a successful pregnancy with mini IVF are actually lower than with traditional IVF, but so far there have

and to do that without destroying them in the process. One method is to use something called Raman spectroscopy, which involves beaming laser energy of a particular frequency at the head of the sperm; the beam scatters back in readable patterns that reveal clues to the interior structure. The technique isn’t quite ready for wide use, but it’s getting close. “People are studying various frequencies along the electromagnetic spectrum to interrogate the sperm in a nondestructive way,” says Niederberger. “This holds a lot of promise.”

Even assuming the very best sperm can be matched with the very best egg, doctors still have to determine which of the several embryos that are often created in any one IVF cycle is the most viable one to transfer to the womb. That remains a highly



84 HOURS

Blastocyst cavity forms to spur embryo growth



92 HOURS

Cells increase as cavity starts filling with fluid



97 HOURS

In final blastocyst stage, the cavity is filled



112 HOURS

The full cavity will form the amniotic fluid of the fetus

viable candidates—what fertility experts dub “overcalling” sperm—it may doom a pregnancy before it can even get started.

All of this explains the growing interest in an approach called mini IVF, which Zhang’s and other clinics are promoting. As its name suggests, mini IVF strips the familiar in vitro regimen down in a way that makes it both less arduous and, its proponents say, more effective. Rather than endure a month of hormonal carpet bombing, women take a 12-day course of Clomid, an oral drug that blocks the body’s estrogen receptors and promotes egg maturation. This causes the ovaries to produce only three to five comparatively viable eggs rather than a dozen often immature ones. In the final day or two of the

been few long-term studies to crunch the numbers. And though the drug regimen is less intensive, for some women Clomid brings on physical and emotional side effects similar to standard IVF hormone treatment. Zhang just completed a five-year look at mini-IVF success rates that he is submitting for publication and promises will be a “time bomb”—presumably the good kind—in the field. But he’s one of the method’s pioneers. Other, more disinterested experts may offer a more measured assessment when they see his data.

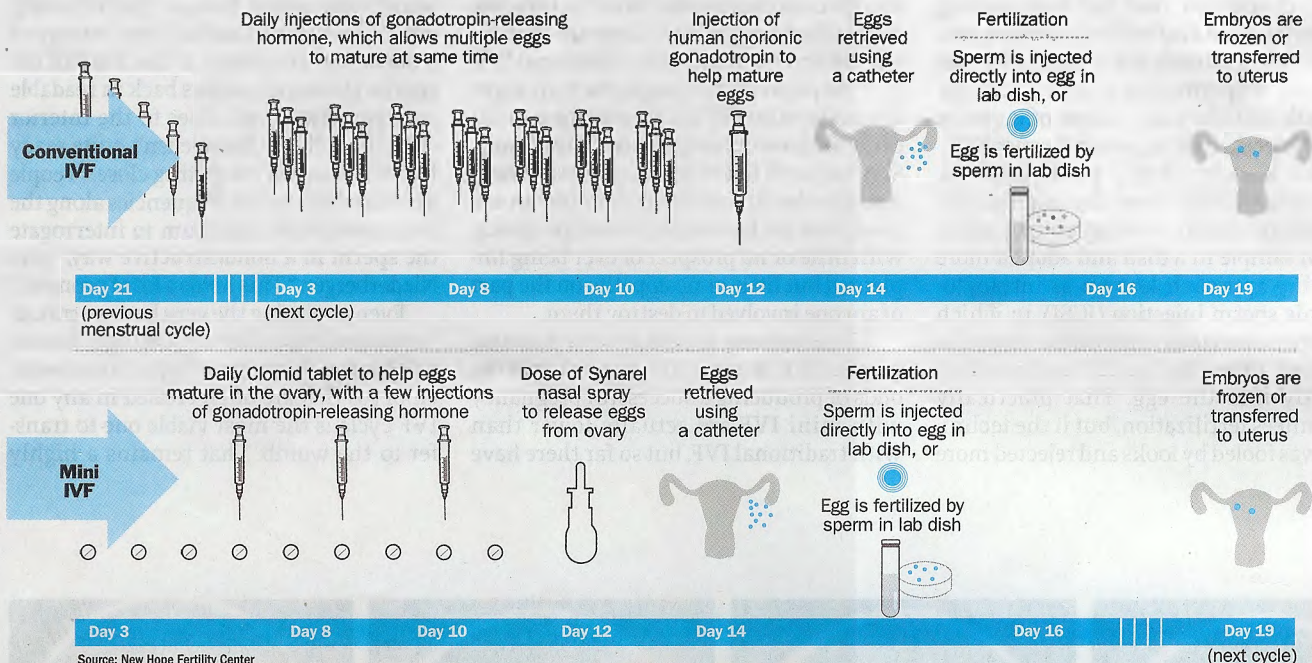
The job of selecting the best sperm for conception in any type of IVF is also seeing some advances. The trick is to look not just at the sperm cells but inside them to get a sense of how their DNA is packaged—

subjective matter that depends, again, simply on which one looks the best. “Identifying the single best embryo for implantation is one of the challenges of the last decades in assisted reproduction,” says Dr. Zev Rosenwaks, director of the Center for Reproductive Medicine at New York–Presbyterian Hospital/Weill Cornell Medical Center.

At Rosenwaks’ clinic, doctors are addressing that challenge with a time-lapse photography system that snaps pictures of growing embryos every 10 to 20 minutes for the first few days of incubation. Subtle differences in the way they divide can provide clues to which embryos are the strongest. Similar techniques were tried in the past, but the pictures were taken manually by lab technicians, which required opening the incubator

A NEW APPROACH TO IVF

In vitro fertilization is an ordeal that often does not produce a baby. Mini IVF involves fewer shots—and may be more effective



several times a day, exposing the embryos to blasts of room-temperature air and contaminants. The new cameras peer through glass into the sealed incubator and fire off their pictures automatically. “We have increased pregnancy rates across the board while decreasing the likelihood of multiple [births],” says Rosenwaks. “Whether the woman is younger or older, in every category we have improved pregnancy rates by 15% to 20%.”

This process too faces some early challenges—principally ones of access. There are more than 400 fertility clinics in the U.S., but only a few dozen so far have a system like Rosenwaks’. Not only does that exclude an overwhelming share of patients; it also means the 15%-to-20% improvement rate could be a premature boast, depending on how other clinics fare if they adopt the new technology.

Further out on the developmental frontier are stem cells. For decades it was assumed that girls are born with all the eggs they will ever have and can produce no more during their lives. In 2012 that wisdom was overturned when Jonathan Tilly, director of reproductive biology at Massachusetts General Hospital, announced that the ovaries harbor stem cells that, with the right chemical coaxing, could be made to mature into eggs.

Tilly accomplished that egg-growing feat—after a fashion—by harvesting stem

cells from ovaries removed during sex-reassignment surgery, growing them in a dish, repackaging them in a bit of the original ovarian tissue and transplanting the entire little bundle into a lab mouse so that it would receive a steady blood supply. (Implanting it in a woman would have raised ethical issues.) When Tilly extracted the cells, they had indeed matured into what at least appeared to be fully mature ova. Not even Tilly pretends that his method is safe or practical—at least not yet—but as a proof-of-concept study, it shows promise. The threshold requirement for parents conceiving via IVF, after all, is at least one healthy sperm meeting one healthy egg. If you don’t have that, all the improvements in the world in embryo monitoring and implantation do you no good.

Investigators at Newcastle University in England had similar success on the male side of the equation in 2009, using embryonic stem cells to create living, swimming, healthy-looking sperm—though the researchers have no idea if the sperm are viable, and British law prevents them from attempting fertilization and implantation to find out for sure. Since then, they have been working on ways to sidestep the use of embryonic stem cells and all the ethical issues they raise by creating stem cells from the skin cells of the infertile men, which could then develop into sperm.

Expanding the Choices?

THE MORE THE MEDICAL OPTIONS EXPAND, the more some doctors—and couples—wrestle with the implications. Fertility counselors, when framing patients’ choices, remind them that they can continue to try to conceive or they can choose to adopt or live child-free. That’s a word that’s carefully chosen with the intention of replacing the bleaker-sounding *childless* and capturing the notion of an upside for a loving couple living a free and relatively unencumbered life.

For those who decide to turn to science to boost their fertility, cost is no small issue. Assisted reproduction remains expensive and is typically not covered by insurance. Under the Affordable Care Act—a.k.a. Obamacare—basic gynecologic and obstetric care are covered, but infertility treatment isn’t. The law does increase the available deduction for those treatments from 7.5% of pretax income to 10%. (For people who adopt, there is a tax credit of \$13,360.)

In a perfect world, money wouldn’t stand in the way of having a child, but in a perfect world, neither would fertility problems. Basic as the reproductive drive might be, a lot of things have to go just right for a healthy baby to be the result. For a growing number of parents-in-waiting, more is starting to go right than wrong. —WITH REPORTING BY ALEXANDRA SIFFERLIN/NEW YORK ■