



Thanks to Brigham and Women's IVF program, the dream of having a child came true for Gina and Peter Princi when their son, Kyran, was born last year.

Building healthy families

—one baby at a time

Like most couples, Gina and Peter Princi did not anticipate needing the help of fertility specialists when they decided that they were ready to have a baby. But, in the spring of 2004, Gina suffered a frightening ectopic pregnancy—the implantation of an embryo outside of the uterus. She underwent emergency surgery, and tests later revealed that her fallopian tubes were blocked, preventing eggs from traveling through to the uterus. Her physician suggested in vitro fertilization, or IVF.

“I was really down,” recalls Gina. “I felt like having a baby was the one thing my body should be able to do.”

At the suggestion of Gina’s mother, and friends who had been through IVF, the couple made an appointment with Elizabeth Ginsburg, MD, at

South Shore Hospital, one of four satellite locations of the Brigham and Women’s Hospital Center for Reproductive Medicine. “Dr. Ginsburg’s reputation preceded her, and we immediately felt like we were in good hands,” says Gina. “She was very thorough and her confidence put me at ease. On the way home, Peter said, ‘I know we’re going to have a baby.’”

He was right. The Princis’ first IVF cycle, in which one embryo was transferred, resulted in pregnancy. Their son, Kyran Charles, named after Peter’s grandfather Charles Kyran, was born on April 13, 2006, and is now a happy, strong-willed 1-year-old.

“Kyran means the world to us,” says Gina. “We are so grateful to Dr. Ginsburg and everyone who helped us through the IVF process.” ▶▶

IVF RESEARCH AT BWH: MORE PREGNANCIES, FEWER “MULTIPLES”

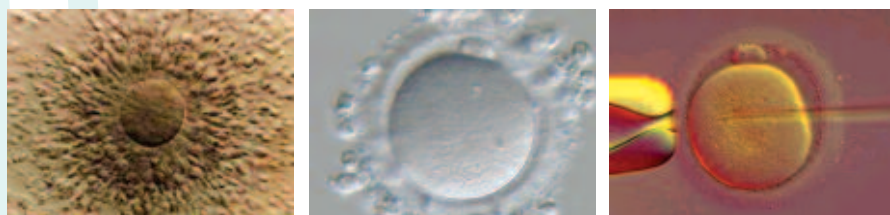
BY AMY TRUMBULL

SPERM MEETS EGG

Women starting IVF usually take fertility drugs to stimulate the ovaries to produce more eggs. Several eggs are harvested, and the cells around the egg (left) are removed (center) to facilitate fertilization. The eggs are then mixed with a concentrated sperm solution in the laboratory. If the man's sperm count is low, an embryologist can inject a sperm into the egg (right), a process called intracytoplasmic sperm injection.



Kerry Kelleher, BS, uses a microscope to check for fertilized eggs.



Courtesy of BWH Assisted Reproduction Laboratory

The science of conception

In vitro fertilization—fertilization that occurs outside of the body—was a revolutionary concept in 1978 when the first “test-tube baby” was born in England.

“IVF patients tend to be anxious,” says Ginsburg, the medical director of Assisted Reproductive Technologies at BWH. “They’ve been trying to conceive for at least a year without success—the definition of infertility—and some have

several eggs with a hollow, ultrasound-guided needle.

Several hours later, an embryologist combines the eggs with a concentrated sperm solution. If the man’s sperm count is low, the embryologist injects a sperm

“IVF is a delicate balancing act between maximizing the chance of pregnancy by implanting more embryos and minimizing the chance of multiple gestations.”

Pioneered for women like Gina who have blocked, damaged or missing fallopian tubes, IVF is now relatively common, accounting for 1 percent of the babies born in the U.S. It’s also an effective therapy for women whose infertility is caused by endometriosis, immunological problems or other factors, and for couples whose fertility problems stem from low sperm counts. The first choice for some patients, IVF is a last resort for others.

been trying for many years, exhausting all other options. IVF can be physically and emotionally taxing. We try to provide patients with as much information and support as possible.”

When a woman starts IVF, she usually takes daily injections of hormones and medications that stimulate multiple eggs, or oocytes, to mature inside the ovaries; normally, just one matures and is released each month. Physicians then harvest

into each egg (see images above).

Over the next three days, the fertilized eggs divide repeatedly to form eight-celled embryos. (Often, however, developing embryos have fewer or more cells.) Knowing that not every embryo will thrive in the womb, embryologists face two critical decisions: How many embryos—and which ones—should be transferred into the woman’s uterus?

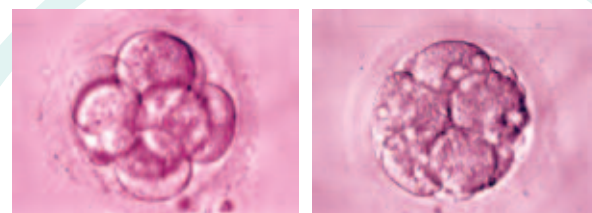
A GROWING EMBRYO

The fertilized egg (left), called a zygote, divides several times (center and right) over the next three days. The resulting ball of cells—usually eight in number, though there can be more or fewer—is called an embryo.



Semen can be preserved for future infertility-related treatments, including IVF. Vials are filled with semen that has been diluted with cryoprotectant to protect the sperm during freezing. The vials are slowly cooled, then frozen and stored in tanks of liquid nitrogen.

Alix PPI



EMBRYO EVALUATION

Embryos are evaluated under a microscope to identify those most likely to result in a successful pregnancy. A promising embryo (left) displays cells with good symmetry and minimal fragmentation. A poor embryo candidate with multiple fragments is shown on the right. Based on the quality of the embryos, the woman's age, and several other factors, physicians determine how many embryos—and which ones—to transfer to the uterus.

A balancing act

Embryologist Catherine Racowsky, PhD, HCLD, who directs the hospital's Assisted Reproductive Technologies Laboratory, explains: "IVF is a delicate balancing act between maximizing the chance of pregnancy by implanting more embryos and minimizing the chance of multiple gestations, particularly high-order multiple gestations."

High-order multiple births—triplets or more—garner media attention and capture the public's imagination, especially when six or seven babies are born. But having multiples, even twins, poses significant health risks. Mothers face an increased chance of developing gestational diabetes, anemia and hypertension; the chances of miscarriage also rise. Tiny siblings born prematurely, common in high-order multiple births, may suffer from impaired vision and hearing, developmental delays, mental retardation and respiratory distress. Some, including at least four of the six babies born 18 weeks

premature to a Minnesota couple in June, do not survive.

(Despite these risks, IVF patients often ask to have several embryos transferred to maximize the odds of pregnancy and avoid the burden and expense of future IVF cycles. Massachusetts and a handful of other states mandate full insurance coverage of IVF, but in states without such laws, a single IVF cycle can cost \$15,000 or more. Physicians in those states may also have to try other remedies before recommending IVF, such as surgery to open blocked fallopian tubes.)

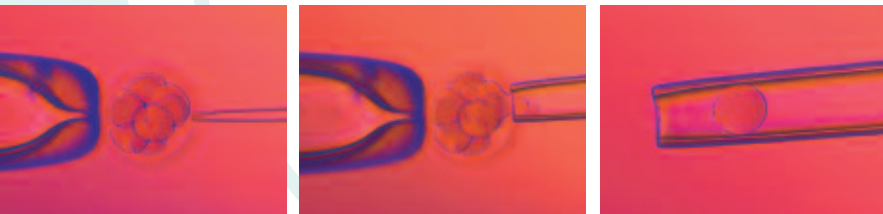
In addition to educating patients, the trick to lowering the risk of multiples, says Racowsky, is tailoring the approach to each patient's situation. Soon after arriving at BWH in 1997, she began analyzing data from thousands of IVF cycles to develop an algorithm for determining the number of embryos to transfer to the uterus. Among the variables factored in: a woman's age, her level of follicle-stimulating hormone, the number of high-

quality embryos available, and the number of previous IVF cycles she's had.

Racowsky's algorithm, which has been fine-tuned over the years and is in its 15th iteration, improves on the general guidelines issued by the Society for Assisted Reproductive Technology, the field's professional organization. Since 1998, it has helped increase the BWH program's pregnancy rate by 3 percent while reducing the rate of triplets or more from 12 percent to 2 percent. The impressive results can be attributed, in part, to a greater emphasis on single-embryo transfers for women with favorable chances of getting pregnant.

GENETIC SCREENING

A patient and her physician may decide to remove a cell from the embryos for genetic testing, especially if there's a high risk of a specific hereditary disorder, such as Tay-Sachs disease. Genetic screening can also check for chromosomal disorders, such as Down's syndrome. Once screened, normal embryos can be transferred to the uterus. Here, an embryo membrane is punctured (left) and a single cell is drawn out (center and right) with a pipette.



Pascal Goetgheluk/Science Photo Library



Gina (shown here) and Peter Princi hope to have a second child through IVF, making 1-year-old Kyran a big brother.

Larry Maglott

Before they settle on how many to move into the womb, Racowsky and her team evaluate the embryos and identify those most likely to result in a successful pregnancy. To find the hardiest ones, they examine them under a microscope, counting the number of cells in each and not-

and IVF cycle combine to advance the field. “We’re all here because we love the academic environment,” says Racowsky of her team. “Research is an important part of our work, and I’d like to think we’re improving different aspects of IVF.”

In a recent study, Racowsky and

“We are also pushing the field forward by looking beyond the success of the procedure itself to the health of babies conceived through IVF in all stages of their lives,” says Racowsky.

For example, the team is studying how different culture media influence

“We are pushing the field forward by looking beyond the success of the procedure itself and thinking about the health of babies conceived through IVF in all stages of life.”

ing the symmetry of the cells and any cell fragmentation (see images on page 5). The embryo—or embryos—of choice are generally transferred from the petri dish to the uterus three days after fertilization. From there, it’s a matter of wait-and-see.

Advancing the field

The size of the BWH program and the extensive data collected on each patient

Ellice Leiberman, MD, DrPH, dean of Faculty Affairs at Harvard Medical School and former director of clinical and epidemiologic research for Obstetrics and Gynecology at BWH, found a direct connection between the number of cells in an embryo on day 3 and the baby’s birth weight, a common indicator of health. That finding now helps to guide embryo selection.

embryonic development. These solutions aid in the very early stages of development by providing amino acids, glucose and other nutrients to the embryo, and by mimicking the natural environment of a woman’s reproductive system. Racowsky and her colleagues use two types of media in the lab, randomly assigning embryos to each. They then try to track which ones develop into fetuses. They

also plan to screen media using mass spectrometry. Looking at changes in the media—the nutrients consumed and the waste products left behind—could yield clues about fetal development.

Brigham and Women's physicians are interested, too, in investigating the effect that removing a cell on day 3 for genetic testing has on the health of the embryo and its chance of implantation. Research thus far suggests that it poses no harm, though data remains limited. Any potential risks must be weighed against the chances of transferring embryos that harbor a genetic problem or specific hereditary disorder. Brigham and Women's physicians are constantly trying to determine which patients would be best served by genetic testing.

In fact, personalized care for each patient, and each couple, is a hallmark of the BWH IVF program. "We try to look philosophically at each patient's situation and our medical protocols reflect that," says Mark Hornstein, MD, director of Reproductive Endocrinology and Infertility. "We have a large number of protocols compared to many programs, a reflection of our individualized approach."

As for Gina and Peter Princi, they have found joy in parenthood and hope to have a second child through IVF. "We couldn't have found a better place, and a better doctor, to help us bring Kyran into the world. We feel very lucky." ♦



Mark Hornstein, MD

Frank Steman

BWH IVF program celebrates 25 years of happy "birth" days

Since in vitro fertilization was first offered at Brigham and Women's in 1982, the program has grown tremendously. Every year, nearly 15,000 patients struggling with infertility are treated at the Center for Reproductive Medicine and its satellite offices. Many of them opt for IVF—the center's physicians perform more than 1,900 IVF procedures a year, making it one of the largest academic IVF programs in the country. More than 7,000 babies (as of the end of 2005) have made their way into the world thanks to the BWH program.

Comprehensive services are available at all five of the center's locations—BWH, South Shore Hospital, North Shore Medical Center, and Newton-Wellesley Hospital in Massachusetts, and Exeter Hospital in New Hampshire. Specially trained nurses head up patient education efforts, and social workers lead support groups and work one-on-one with patients as needed. Consultations, blood work and diagnostic testing can be completed at the satellites; IVF patients need to travel to Boston only for egg retrieval and embryo transfer procedures.

"It is a tremendous benefit for patients to have high-quality fertility care close to their home or workplace," says Mark Hornstein, MD, director of Reproductive Endocrinology and Infertility at BWH and president-elect of the national Society for Assisted Reproductive Technology.

Educating assisted reproduction specialists and embryologists is another priority. Hornstein and his colleagues Elizabeth Ginsburg, MD, and Catherine Racowsky, PhD, HCLD, currently mentor four fellows in Reproductive Endocrinology and Infertility and work closely with Obstetrics and Gynecology residents and medical students. Like Hornstein, both Ginsburg and Racowsky are national leaders in the field. Ginsburg is vice president of the Society for Assisted Reproductive Technology, and Racowsky is a board member of the American Society for Reproductive Medicine.

But what really makes the program such a success, its leaders say, is the strong partnership between physicians and embryologists. "This is a unique medical field," says Racowsky, director of the hospital's Assisted Reproductive Technologies Laboratory. "It requires trust and close collaboration between the laboratory and clinic. We work fantastically as a team." ♦



Larry Maglott

Elizabeth Ginsburg, MD



Frank Steman

ART LAB STAFF

Professionals in the Assisted Reproductive Technologies Laboratory include (front row, from left) Courtney McAuley, BS; Lydia Hualin Shi, MD, MS; Christine Sullivan, BS; Technical Director Kathy Jackson, BS, ELD; Director Catherine Racowsky, PhD, HCLD; Wana Popal, MS; Beverly Decoste, BS; (back row, from left) Behran Bogale, BS; Heather Slater, BS; Liben Zhu, MD; Gena Ratiu, MD; Tommy Waugh, BNS, TS; and Kerry Kelleher, BS.