fertile field

CANCER PATIENTS HAVE MORE OPTIONS THAN EVER FOR PRESERVING THEIR FERTILITY. NOW, IF THEY ONLY KNEW ABOUT THEM.

BY ANNA DUBROVSKY

WHEN CHRISTINE HANLON LEARNED THAT her 9-year-old son had cancer, the no-nonsense legal assistant put her research skills to work. By the time of Dylan's first chemotherapy treatment at St. Joseph's Children's Hospital of Tampa, Florida, Hanlon had a good handle on the side effects. Then the oncologist threw her for a loop.

"He came into the room and said: 'There's one more thing I need you to know. There's a risk of infertility,'" she recalls. "He could see by the look on my face that I was surprised," but that was the start and end of the conversation.

Infertility is a common, recognized side effect of cancer treatment. That's because chemotherapy and radiation, which target rapidly dividing cancer cells, often damage bystanders like cells in the testes and ovaries. Yet many cancer patients are not made aware of their infertility risk. A study published in the September issue of the journal *Cancer* found that nearly 40 percent of women diagnosed with cancer between the ages of 18 and 40 were not informed that treatment could affect their ability to have children. Prepubescent patients are even less likely to receive infertility counseling. When patients are informed of the risk, they're often left with the impression that nothing can be done.

That's a terrible shame because recent years have seen great advances in fertility preservation among cancer patients. For men and boys who have gone through puberty, fertility preservation can be as simple as providing a semen sample to be frozen and stored for future use. Women of reproductive age can opt for egg freezing or embryo freezing. These are well-tested, reliable options.

There are no well-tested, reliable options for boys like Dylan, who do not yet produce sperm, and girls whose eggs have not yet matured. But as Christine Hanlon discovered through her own research, there are experimental ones. In January 2011, four months after beginning chemotherapy treatments, Dylan flew to Pittsburgh to become what he calls a "guinea pig." He checked into Children's Hospital of Pittsburgh of UPMC, where pediatric urologist Glenn Cannon, MD, surgically removed a sample of testicular tissue. The sample was cryopreserved, or frozen, in the hope that when Dylan is ready to become a father, doctors can extract spermatogonial stem cells — the precursors of sperm — and inject them back into his testes to stimulate sperm production.

Dr. Kyle Orwig

"I do not think there is another fertility preservation program in the country that is as comprehensive as ours." DR. ORWIG

Testicular tissue freezing is offered at only a handful of medical centers around the world. Even fewer accept patients who have already started a fertility-threatening course of treatment. Dylan's trip to Pittsburgh was not in vain. After his biopsy at Children's Hospital, a portion of his tissue sample was sent to Magee-Women Research Institute, where Kyle Orwig, PhD, confirmed that spermatogonial stem cells were still present.

"I do not think there is another fertility preservation program in the country that is as comprehensive as ours because we provide options for men, women, boys, and girls," says Dr. Orwig, director of the Fertility Preservation Program in Pittsburgh. Established in 2010, the multidisciplinary program brings together scientists from Magee-Womens Research Institute, fertility specialists from the Center for Fertility and Reproductive Endocrinology at Magee-Womens Hospital of UPMC, and pediatric oncologists and

← When Christine Hanlon learned that cancer treatment could make her son, Dylan, infertile, the pair traveled to Pittsburgh for an experimental fertility-preserving procedure. Photo by Lauren Cintron.

WANT TO HELP?

Philanthropy plays an important part in supporting cutting-edge fertility research. It can also make a world of difference for patients who cannot afford fertility-preserving procedures. To make a donation toward research or patient care, please visit www.mwrif.org/donate or use the enclosed remittance envelope.

Turn to page 24 to learn how one Magee nurse is using her retirement savings to support fertility research.

urologists from Children's. They have a dedicated phone line (412.641.7475) that patients and physicians can call to learn about the reproductive consequences of medical treatments and options for preserving fertility. Since the program's inception, they have provided fertility counseling to about 300 patients. More than half of those patients proceeded with sperm banking, egg or embryo freezing, or an experimental option like testicular tissue freezing.

The Fertility Preservation Program has frozen and stored testicular tissue from nine prepubescent boys. Testicular tissue freezing is also available to men who are too ill from cancer to provide a good semen sample for cryopreservation.

The program also offers ovarian tissue freezing for prepubescent girls and women ineligible for egg or embryo freezing. Doctors remove part or all of an ovary and freeze tissue that contains immature eggs. The tissue can later be transplanted to its original site. Though still experimental, ovarian tissue transplantation has been successfully tested in women, with about 30 pregnancies reported worldwide.

Physician education is a big part of the program's mission. Many oncologists are not only unaware of the latest advances in fertility preservation but also loath to recommend standard procedures like sperm banking. "There is a terrible misconception that fertility preservation procedures will cause a significant delay to cancer treatment," Dr. Orwig says. In reality, sperm banking requires just a short office visit. Women who wish to freeze eggs or embryos typically take fertility drugs to prompt the release of multiple eggs and then undergo an egg-harvesting procedure, a process that can take several weeks. But the process can be short-circuited, Dr. Orwig says, and even a few weeks' delay in cancer treatment is often deemed acceptable by oncologists.

He and his colleagues in the Fertility Preservation Program have held educational sessions for doctors at cancer centers in Pittsburgh and around the country. They also developed a trifold "cheat sheet" that doctors can tuck into a lab coat pocket. It lists different cancer treatments and their risk of fertility damage.

If cancer specialists gloss over infertility risk, it's because they're focused on saving lives. Cancer, after all, is the second leading cause of death among Americans. But it's no longer a death sentence. Doctors can find cancer earlier and treat it more effectively than ever before, which means the chances of survival are higher

Dylan at Camp Boggy Creek, a camp for seriously ill children, while he was battling a bone cancer called Ewing's sarcoma

than ever. The number of cancer survivors in the United States increased from 3 million in 1971 to 11.7 million in 2007. The five-year survival rate is now 67 percent, up from 49 percent in the 1970s. Children diagnosed with cancer have an even higher five-year survival rate: 83 percent, up from 58 percent in the 1970s.

The encouraging survivorship statistics make fertility counseling all the more important. "Surveys show that fertility status is at the very top of the list of things that affect the psychological wellbeing of cancer survivors," Dr. Orwig says. "It's very important to them."

LATEST FINDINGS

Now 12, Dylan is cancer free. He loves playing Xbox LIVE games with his friends. Last year the Make-A-Wish Foundation fulfilled his wish of visiting the Texas headquarters of video game developer Gearbox Software.

He also loves kids, says his mom.

Spermatogonial stem cell transplantation — the procedure that may one day allow him to have kids of his own — is not yet in practice. But Dr. Orwig and other fertility researchers have good reason to believe it will work. They have tested the procedure in a range of animals, including rats, pigs, dogs, and goats.

For the past several years, Dr. Orwig has been developing a monkey model of men and boys rendered infertile by chemotherapy. In a study published late last

year, he and his team took tissue samples from the testes of adult and prepubescent male monkeys before treating the monkeys with chemotherapy drugs known to impair infertility. A few months after chemotherapy treatment, the researchers transplanted each monkey's own spermatogonial stem cells back into his testes. Sperm production was established in nine out of 12 adult monkeys and three out of five prepubescent monkeys after they reached maturity. The researchers also showed that sperm arising from transplanted stem cells could successfully fertilize eggs to produce embryos.

Published in the journal *Cell Stem Cell,* the study provides the best evidence yet that stem cell transplantation could restore fertility in humans. Monkey testes are anatomically and physiologically similar to human testes. "I am quite confident that the transplantation technique we used in the monkey will transfer directly to humans with minimal, if any, modifications," Dr. Orwig says. "We are actively thinking about and moving toward human application."

Among the questions that remain to be answered is when to reintroduce the spermatogonial stem cells. "That's one of our active areas of research now," Dr. Orwig says. "In our monkey experiment, we put the cells back pretty soon, but for a human, you can imagine that it might be better to wait until they're designated a cancer survivor. Some people think the time to do it might be when they're ready to have kids, even if that's 20 years later. My feeling is that if the testis isn't making sperm for a long period of time, it might not be a very hospitable environment to transplant into. But I am not positive about that; we have to test it."

A bigger question is whether testicular tissue samples taken from cancer patients might be contaminated with cancer cells. "The worst thing we could do is put a cancer back into a survivor," he says. "That would destroy our whole field."

Dr. Orwig and team are hard at work on eliminating that risk. In a study scheduled for publication in the April 2013 issue of the *Journal of Clinical Investigation,* they contaminated human testis cells with a leukemic cancer, and then showed that they could separate cancer cells from healthy stem cells. "We still have work to do, but it appears at least possible to weed out the cancer cells," he says.

Dr. Orwig believes spermatogonial stem cell transplantation will be a viable option by the time Dylan is ready to start a family — if not much sooner. "It's exciting that the stuff we started out doing in mice years ago may actually have an impact on human medicine," he says. "The environment here at Magee-Womens Research Institute is ideal for translating lab bench research toward the clinic. There are not many places in the country where you have a top-notch research institution with such close ties to outstanding hospitals."

One of his goals as director of the Fertility Preservation Program is to export the testicular tissue freezing technology developed in Pittsburgh to medical centers around the country. That way boys like Dylan wouldn't have to travel hundreds of miles for the procedure.

"Any place that treats children with cancer should have the means to offer this option," says Christine Hanlon. She thought long and hard before taking Dylan to Pittsburgh because she didn't want to subject him to any more medical procedures than necessary, but she has never regretted the decision. "The day after the procedure, we were walking through the airport, and I said, 'Dylan, I hope I made the right decision for you. I hope you're not mad.' He said, 'No, mama, you made the right decision.' "

RECRUITMENT

Study for preserving fertility before cancer treatment

The Fertility Preservation Program in Pittsburgh is conducting a clinical trial for preserving fertility in young cancer patients, including boys who do not yet produce sperm and girls whose eggs are not yet mature. Participants must be:

- Females age 1 to 40 with two ovaries or males over the age of 1 with two testes
- Newly diagnosed with a cancer that requires chemotherapy or radiation treatment and puts them at high risk for infertility

The program will cover the costs of harvesting, processing, and freezing testicular or ovarian tissue.

For more information, call the Fertility Preservation Program's dedicated phone line at 412.641.7475.