Fertility specialist sees better-than-hoped for results from ovarian transplants

Samuel Kim, M.D., publishes his findings on cryopreserving ovarian tissue in the Journal of Assisted Reproduction and Genetics

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Cancer is always a crushing diagnosis. And for women who haven't hit menopause and girls in their teens or younger, it can be even more painful to learn that if they survive, the toxicity of cancer therapy will most likely wipe out their ability to bear children.

Over the last decade, one technique has garnered increasing interest as an option to restore fertility after cancer treatment: cryopreserving a patient's ovarian tissue by freezing it to sub-zero temperatures (-196°C) and, later, transplanting it back into her body.

"It's been done in lymphoma [both Hodgkin's and non-Hodgkin's], cervical cancer, Ewing's sarcoma and some breast cancers," says Samuel Kim, M.D., an associate professor in the department of obstetrics and gynecology at the University of Kansas Medical Center and director of the department's reproductive endocrinology division. "It enables hundreds of immature oocytes to be cryopreserved immediately — unlike freezing mature egg cells, which first requires stimulating the ovaries with fertility medication for one to two weeks. So it's a solution for young cancer patients who can't afford to delay treatment, but still wish to preserve their fertility prior to the sterilizing effects of cancer therapy."

Kim has spent most of the last decade following up on five of his patients who received ovarian transplants between 2001 and 2010. They underwent monthly blood tests to measure the levels and function of two reproductive hormones — estrogen and FSH (follicle stimulating hormone) — followed by ultrasounds. The women were monitored until their hormonal function ceased.

In a paper published in the June 2012 issue of the *Journal of Assisted Reproduction and Genetics* , Kim observed that it took between 12 to 20 weeks to restore hormonal function in all five women, while four required a follow-up transplant within two years. He also noted that hormonal function returned much faster the second time around.

"They probably retained some ovarian function from the initial transplant," he says, "which was augmented by the second."

Notably, one of the four patients received her follow-up ovarian transplant in 2004, and her grafts were still producing hormones seven years later. "The lifespan of ovarian grafts is longer than expected," Kim wrote in the journal article. In fact, seven years is, to his knowledge, the longest duration of ovarian function reported after transplanting frozen-thawed ovarian tissue in humans and "currently a world record," he says.

Reviving an old concept

Ovarian cryopreservation and transplantation is still relatively uncommon — Kim is one of just three clinicians in the U.S. with experience in this field. His peers are Kutluk Oktay, M.D., at New York Medical College, and Sherman Silber, M.D., at St. Luke's Hospital in St. Louis, Mo.

Yet the concept is hardly new. The first successful ovarian transplantation was reported over a century ago by Robert Tuttle Morris, M.D., in 1895. Medicine then was vastly different: endocrinology, or the study of our system of hormone-secreting glands, didn't exist as a specialty; the word "hormone" wasn't in the lexicon; and preserving organ function through freeze-thawing was not feasible. So beyond Morris's pioneering work, interest in ovarian transplantation waned for most of the 20th century because, Kim says, "there were no practical applications and no technologies to back it up."

Then in 1994, Roger Gosden, Ph.D., D.Sc., demonstrated that fertility could be restored in sheep through the grafting of frozen-thawed ovarian tissue. Kim was fascinated and promptly sought his tutelage in Leeds, U.K. It was a natural step forward from there to begin exploring the procedure's applicability in humans: By the mid-1990s, much was already known about egg and sperm culture and other assisted reproductive technologies, and the technology of cryopreservation had rapidly advanced since its debut in 1948.

Kim went on to carry out ovarian tissue transplants on four cancer survivors while at the University of Washington in Seattle and at Cedars-Sinai Medical Center in Los Angeles. In 2007, he joined the faculty at KU Medical Center and in 2010 performed Kansas' first ovarian transplant on Loraine Martin, who had Kim preserve some of her ovarian tissue prior to chemotherapy for Hodgkin's lymphoma 10 years earlier. Martin regained endocrine function, Kim says, and is currently undergoing additional fertility treatments.

The first baby conceived as the result of an ovarian transplant was born in 2004 and, by Kim's count, this procedure has so far produced 20 infants worldwide. With one exception, all the mothers are cancer survivors.

How it works

Obtaining and freezing ovarian tissue is fairly straightforward, Kim says. Via laparoscopy — surgery through small incisions in the pelvis, using a camera for visual guidance — he removes one ovary, which he then slices into thin sections for cryopreservation.

Transplanting thawed ovarian tissue, on the other hand, is more complex. It can be either orthotopic (where the ovary is normally located) or heterotopic (at a different site in the body), Kim explains, and each has its pros and cons. The orthotopic transplant essentially replaces a patient's missing ovary, increasing her likelihood of conceiving naturally. Surgically, however, it's a pretty invasive procedure.

For heterotopic transplants, Kim favors a site between the abdominal skin and the rectus muscle that's rich in blood vessels, ensuring that the newly grafted tissue gets enough oxygen. It's also much less invasive — patients require only local anesthesia — and immature egg cells can be easily retrieved, after which *in vitro* fertilization (IVF) and other assisted reproductive technologies take center stage. The main downside is that no pregnancies have yet been recorded with this method; all 20 babies born to date were conceived after orthotopic ovarian transplants.

Fortunately, Kim adds, both procedures can be done simultaneously — and most patients go for that option.

"Ovarian transplantation may be an old concept, but the technology is still new and there are many unanswered questions," he says. "We haven't found an optimal freeze-thawing method, or the best graft site. Nor do we have enough data on the quality of eggs retrieved from ovarian grafts."

The future of ovarian transplantation

Besides cancer survivors, women with other diseases requiring treatment with toxic drugs could benefit from an ovarian transplant, Kim says. Those born with Turner syndrome — characterized, among other things, by premature ovarian failure — may also benefit, as may women with endometriosis, where removing the entire ovary is sometimes necessary when treating cysts and adhesions associated with this severe disease.

"In such cases, the ovary itself can't be saved, but as long as there's some intact ovarian tissue left, it should be preservable," he says.

Currently president of the International Society for Fertility Preservation (ISFP), Kim stresses that ovarian transplantation is a potential method for *preserving* fertility, not treating infertility. Egg and

sperm donations notwithstanding, he reckons that "donor ovarian tissue" won't be added to the roster of assisted reproductive technologies for infertility anytime soon, simply because grafting foreign tissue is so complex and high doses of immunosuppressants are needed to prevent transplant rejection.

Media reports like *The Daily Mail*'s claim that "scientists can stop menopause with ovary transplants" shouldn't be taken too seriously, he adds. "I won't say that it's not a possible use," he says, "but it's definitely futuristic."

Right now, Kim says, the technology of ovarian tissue cryopreservation and transplantation shows promise and provides hope to preserve fertility, especially for cancer survivors. "Quite simply," he says, "it has a ways to go before we can remove the 'investigational' label and establish it as a standard procedure."

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