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New technique induces egg growth in infertile women, and one gives birth

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Researchers at the Stanford University School of Medicine have identified a way to induce the ovaries of some infertile women to produce eggs.

Using the technique, clinicians at the St. Marianna University School of Medicine in Kawasaki, Japan, collected viable eggs from five women with a condition called primary ovarian insufficiency. One of these women has given birth to a healthy baby, and another is pregnant.

Twenty-seven women in Japan took part in the experimental study. The researchers were able to collect mature eggs for in vitro fertilization from five of them. Although it has not yet been tested in women with other causes of infertility, the researchers plan to investigate whether the technique can also help women with early menopause caused by cancer chemotherapy or radiation, and infertile women between the ages of 40 and 45.

The research will be published online Sept. 30 in the *Proceedings of the National Academy of Sciences.*

The technique, which the researchers refer to as "in vitro activation," or IVA, requires an ovary (or a portion of an ovary) to be removed from the woman, treated outside the body and then re-implanted near her fallopian tubes. The woman is then treated with hormones to stimulate the growth of specialized structures in the ovaries called follicles in which eggs develop.

"Women with primary ovarian insufficiency enter menopause quite early in life, before they turn 40," said Aaron Hsueh, PhD, professor of obstetrics and gynecology at Stanford and senior author of the study. "Previous research has suggested that these women still have very tiny, primordial primary and secondary follicles, and that even though they are no longer having menstrual cycles they may still be treatable. Our results obtained with our clinical collaborators in Japan make us hopeful that this is a group of patients who can be helped."

Women are born with hundreds of thousands of primordial follicles, each containing one immature egg. Usually, only one follicle develops to maturity each month and releases an egg into the fallopian tube for possible fertilization. About 1 percent of women of reproductive age in this country experience primary ovarian insufficiency, meaning that their ovaries don't produce normal amounts of estrogen or release eggs regularly.

Hsueh has been studying ovarian biology for some time. In 2010, he was awarded $1.4 million from the California Institute for Regenerative Medicine to study the maturation of human eggs for stem cell derivation.

The new study builds on earlier work demonstrating that a signaling pathway consisting of several proteins, including one called PTEN, controls follicle growth in the ovary. In 2010, Hsueh showed that blocking the activity of PTEN in mouse and human ovaries was enough to stir dormant follicles into growing and producing mature eggs. (Most follicles remain dormant for years or decades to conserve a woman's finite egg supply.)

"For patients with primary ovarian insufficiency, egg donation is the only option for bearing a baby," said Kazuhiro Kawamura, MD, PhD, associate professor of obstetrics and gynecology at the St. Marianna University School of Medicine. Kawamura is a lead author of the study

and headed the clinical aspects of the research. All the patients received treatment in Japan.

"These patients are eager to find a way to become pregnant with their own eggs," Kawamura said. "I have collaborated with Dr. Hsueh since 2010, working on ways to wake up these dormant follicles. When I was successful in obtaining mature human eggs from large, developed follicles after blocking PTEN activity, I gained confidence that this approach could work clinically."

Valerie Baker, MD, associate professor of obstetrics and gynecology and chief of Stanford's division of reproductive endocrinology and infertility, said, "Although there are too little data available about this experimental treatment to guarantee any kind of success rate, the approach does look quite promising for women who have run out of eggs."

Baker, who is also the director of Stanford's Program for Primary Ovarian Insufficiency, was not involved in the current study but is working with Hsueh to continue investigating the experimental treatment in Japan and at Stanford.

The successful birth represents a combination of two treatments known to induce follicle growth. It's been known for decades that mechanically disrupting the ovary through cutting or even drilling small holes in it can stimulate the development of arrested follicles, and this approach was used in the past to treat women with a condition known as polycystic ovary syndrome. (Women with the syndrome have absent or irregular menstrual cycles and may be infertile; it affects 5-10 percent of women of reproductive age.) But it's been a mystery as to why this works.

Yuan Cheng, PhD, a postdoctoral scholar in Hsueh's lab and another lead author of the paper, answered this question in the study by

demonstrating that cutting the ovary into pieces disrupts a growth-arrest pathway called Hippo. The Hippo pathway was originally identified in flies but is shared by many animals. Hippo signaling is known to modulate the growth of many organs in the body—keeping them just the right size for each species. In the ovary, the Hippo pathway appears to help ensure that only a few follicles at a time are growing to better conserve a woman's supply of eggs.

Hsueh and his colleagues then wondered what would happen if ovaries activated through fragmentation were also treated with a substance to modulate the PTEN pathway they inhibited in their 2010 work. In experiments first in laboratory mice and then in human ovarian fragments, the researchers showed that the two treatments together had an additive effect, activating many more follicles than either treatment alone.

"Human females have about 800,000 very small, primordial follicles at birth," Hsueh said. "Most of them remain dormant, and only about 1,000 start to grow each month. One of these reaches maturity each month to produce an egg each menstrual cycle. It's not known exactly how the follicles are selected for development, or why these follicles stop developing in women with primary ovarian insufficiency. But our treatment was able to awaken some of the remaining primordial follicles and cause them to release eggs."

Hsueh and Cheng initially conducted their experiments in laboratory mice and then, in collaboration with Kawamura, turned to frozen portions of human ovaries. After the 2010 work, Kawamura began to collaborate with St. Marianna professor Bunpei Ishizuka, MD, PhD, an expert on primary ovarian insufficiency who is also a corresponding author of the paper. Kawamura, Ishizuka and their colleagues used minimally invasive procedures to remove both ovaries from each of 27 women with primary ovarian insufficiency. The women's average age

was 37, and they had stopped menstruating an average of 6.8 years prior to the procedure. The researchers found that ovaries from 13 of the women contained residual follicles.

Next, the ovaries were mechanically fragmented and treated with drugs to block the PTEN pathway. Small pieces were then transplanted laparoscopically near the fallopian tubes of the women from whom they were derived, and the women were monitored with weekly or biweekly ultrasounds and hormone-level tests to detect follicle growth.

Follicle growth was observed in eight of the women, all of whom had exhibited signs of residual follicles prior to transplantation. These eight were treated with hormones to stimulate ovulation; five women developed mature eggs that were collected for in vitro fertilization. The eggs were fertilized with sperm from the partners of the women, and the resulting four-cell embryos were frozen and then transferred into the uterus.

One woman received one embryo but failed to become pregnant. Another received one embryo and is pregnant. The third received two embryos and established a successful pregnancy that resulted in a single, apparently healthy baby boy. The other two women are preparing for embryo transfer or undergoing additional rounds of egg collection.

"Although I believed, based on our previous research, that this IVA approach would work, I monitored the pregnancy closely and, when the baby was in a breech presentation, I performed the caesarean section myself," said Kawamura. "I could not sleep the night before the operation, but when I saw the healthy baby, my anxiety turned to delight. The couple and I hugged each other in tears. I hope that IVA will be able to help patients with primary ovarian insufficiency throughout the world."

The researchers are planning to study the experimental treatment in women who are infertile for other reasons. Hsueh is also interested in investigating ways to control the Hippo and PTEN pathways with drugs, rendering ovary removal unnecessary. However, the researchers speculate it will be several years before IVA can become a routine procedure like in vitro fertilization. But they are excited about the idea of giving hope to desperate patients.

"When I first saw the data, my eyes lit up," said Baker, who is the medical director of the Stanford Fertility and Reproductive Medicine Center. "These women and their partners come to me in tears. To suddenly learn at a young age that your childbearing potential is gone is very difficult. This technique could potentially help women who have lost their egg supply for any reason."

More information: Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1312830110

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